HETEROCYCLIC COMPOUNDS

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Volume 1

Three-, Four-, Five-, and Six-Membered Monocyclic Compounds Containing One O, N, and S Atom

Edited by

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PREFACE

Shortly after the conclusion of World War II, the editor, in common with many of his colleagues, considered the advisability of the preparation of one or more monographs dealing with specialized phases of the chemistry of heterocyclic compounds. After many discussions with persons interested in this broad general field, the original plan was abandoned. The almost unanimous feeling of those with whom the matter was discussed was that a definite need existed for a detailed treatment of the chemistry of these interesting compounds which would concentrate on the chemical principles involved rather than attempt to give an encyclopedic coverage of the field. It was further felt that such a treatment should be the result of a common effort of specialists in the particular fields to be discussed. Obviously, despite the many similarities between the chemistry of the heterocyclic compounds and the chemistry of the aliphatic and aromatic substances, sufficient divergencies appear between the various classes of compounds so that an adequate treatment of the heterocycles appears to be beyond the capabilities of any one chemist, however great his individual capacity may be. It was therefore decided that the symposium type of book would be best adapted to the ends in view, and with some misgivings I undertook the editorship of such a series.

In this, the first volume of the series, the chemistry of the monocyclic heterocycles containing one oxygen, sulfur, or nitrogen atom in three-, four-, five-, or six-membered rings is presented. This rather arbitrary choice of ring systems perhaps requires comment. The inclusion of ethylene oxide and ethylenimine was made in the belief that the chemistry of these increasingly important substances properly belongs in any treatment of heterocyclic compounds. The recent interest in the chemistry of β-lactams in connection with the structure of penicillin serves as justification for a discussion of the chemistry of azete. The less important heterocycles containing more than six-membered rings as well as those containing hetero atoms other than oxygen, sulfur, and nitrogen will be dealt with in a later volume of the series.

Throughout this volume, no attempt has been made to list all the derivatives of the various substances under discussion. Likewise, de-

tailed tabulation of physical properties of the derivatives of the heterocycles has been avoided, except when inclusion of such data serves to emphasize a chemical principle. For those in search of such detailed data, the various handbooks are excellent sources. In general, no pretense of an exhaustive literature coverage is claimed. Rather, effort has been directed toward citation of the more recent or important references, in particular toward those articles in which historical or critical reviews are presented. During the period that necessarily elapsed between preparation of the manuscript and the appearance of the book, much new material has appeared in the literature. This has been incorporated in the text when possible, but necessarily it has not been practical to include all such new information. Attention has been concentrated on the chemical principles dealing with the syntheses, properties, and reactions of the compounds under discussion, with the view always in mind of bringing the reader the latest information available, together with a critical evaluation of the published data. If, in the course of such treatment, certain contributions have been neglected, the editor can only plead his case on the grounds of striving to keep the entire series within a reasonable number of volumes.

Throughout this volume and subsequent ones, two guiding principles will be kept in mind. If a given field has been the subject of adequate and critical discussion in available book form recently, this field will be the subject of somewhat less extensive treatment in the present volumes. The material presented will be discussed from the standpoint of modern organic chemistry. On the other hand, although the newer concepts of theoretical organic chemistry are introduced as an aid in the understanding of the reactions and properties of the substances under discussion, every effort has been made to avoid wild flights of theoretical speculations.

In this and the other volumes of the series, no detailed treatment of the chemistry of the alkaloids will be given. This decision was arrived at with some misgivings. However, it was felt that, since adequate discussions of these most important natural products are available elsewhere, no particular end, other than increasing the size of the series, would be served by inclusion of such a discussion. Therefore the chemistry of the alkaloids will be introduced only when some particular chemical principle of the parent substance can best be illustrated by reference to the alkaloids.

Throughout the series, the general practice of omitting hydrogen atoms from cyclic formulas will be followed unless the inclusion of

such hydrogen atoms is definitely indicated. In all cyclic formulas double bonds will be written. It is thus hoped that no confusion will ensue through omission of the concomitant hydrogens in cyclic structures.

The problem of nomenclature is serious, although in the present volume no particular difficulties are apparent. The general practice of indicating at the head of a chapter the system of nomenclature and numbering adopted, together with alternate systems, will be followed.

It is a pleasure to acknowledge the hearty cooperation of my friends throughout the world for the encouragement given me in undertaking the editorial task involved in the preparation of this series. Particular acknowledgment is due to the various contributors to this volume. Without their efforts, the book would not have been possible. To my colleagues and to many graduate students at Columbia I owe a large debt for their devotion of much time and effort in reading certain portions of the manuscript and for many fruitful discussions. Finally, to my wife, who has been an understanding partner in the editing, proofreading, and indexing, I am most grateful.

ROBERT C. ELDERFIELD
Editor

New York 27, N. Y.
January, 1950

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CHAPTER 1

ETHYLENE AND TRIMETHYLENE OXIDES

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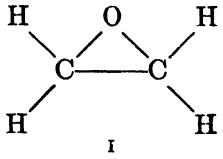
ETHYLENE OXIDES

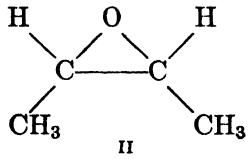
Introduction

One of the simplest classes of heterocyclic compounds is that of the ethylene oxides (1,2-epoxides), which contain a strained ring of two

carbon atoms and one oxygen atom. Electron diffraction studies on ethylene oxide (I) (oxirane) and the *cis*- and *trans*-2,3-epoxybutanes (II and III) show the expected internuclear distances (C—C 1.54 A, C—O 1.43 A, C—H 1.05 A [1,2]) but distorted bond angles; thus, the



I



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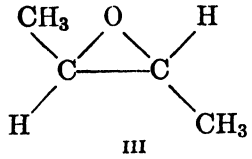
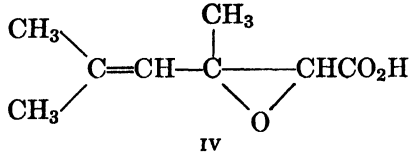


III

bond angle of oxygen is reduced to 67°, and the 109° 28′ tetrahedral value of carbon becomes 57° 26′ and 117° 28′. Dipole moment measurements of ethylene and propylene oxides give values of 1.88×10^{-18} e.s.u.[3,4]

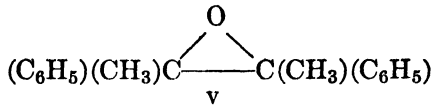
The transition in C—C bond type from ethylene to cyclopropane is gradual, and certain features of the ethylenic linkage remain in the cyclopropane ring. This situation has a parallel in the cyclic ethers. The phenomenon of hyperconjugation [5] due to alkyl substitution in an olefin extends to substituted cyclopropanes, and a similar effect appears to exist in the three-membered heterocycles.[6] In ethylene oxides this has a marked effect on the rate of oxide formation. As an olefinic linkage or carbonyl group can conjugate with another double-bond or aryl group, so also can a three-membered ring.[7,8] Several observations have been made of the similarity of the absorption spectra of conjugated molecules which have an ethylene oxide ring to the spectra of the corresponding molecules with an olefinic linkage or carbonyl group in its place. Measurements are available for such substances as IV [9]



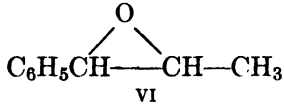
IV

1 Brockway and Cross, *J. Am. Chem. Soc.*, **58**, 2407 (1936); **59**, 1147 (1937).
2 Ackermann and Mayer, *J. Chem. Phys.*, **4**, 377 (1936).
3 Hibbert and Allen, *J. Am. Chem. Soc.*, **54**, 4115 (1932).
4 Allen and Hibbert, *J. Am. Chem. Soc.*, **56**, 1398 (1934).
5 Mulliken, Rieke, and Brown, *J. Am. Chem. Soc.*, **63**, 41 (1941).
6 Winstein and Grunwald, *J. Am. Chem. Soc.*, **70**, 828 (1948).
7 Carr and Burt, *J. Am. Chem. Soc.*, **40**, 1590 (1918).
8 (*a*) Klotz, *J. Am. Chem. Soc.*, **66**, 88 (1944); (*b*) Rogers, *ibid.*, **69**, 2544 (1947).
9 Heilbron et al., *J. Chem. Soc.*, 727 (1942).

and V.[8] Similar observations have been made with carotenoid oxides.[10] Comparison of the spectra of acetophenone and 1-phenyl-1,2-epoxypro-



V



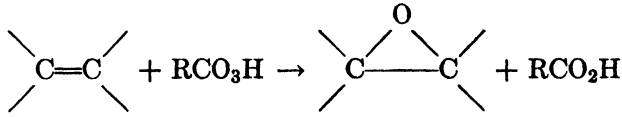
VI

pane (VI) shows closely similar curves with maxima shifted 20–30 mμ toward the ultraviolet for the oxide.[11]

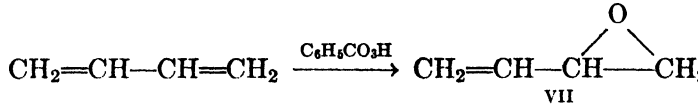
The ethylene oxides, with the strained three-membered ring, are the most reactive of the oxides and, in general, far more reactive than ordinary ethers. The open-chain ether analogs are characterized by inertness to a wide variety of reagents; the ethylene oxides, on the other hand, are susceptible to attack by almost all known nucleophilic reagents.

Methods of Formation

Oxidation of Olefins. Olefins are converted to ethylene oxides readily, usually in satisfactory yields, by treatment with an organic peracid in solution according to the equation



Most frequently, perbenzoic acid [12–17] has been used. Thus, butadiene may be converted to the monoöxide [17] (VII), and similarly perbenzoic



VII

10 Hunter and Krakenberger, *J. Chem. Soc.*, 1 (1947).

11 Campbell, Linden, Godshalk, and Young, *J. Am. Chem. Soc.*, **69**, 880 (1947).

12 Böeseken and Elsen, *Rec. trav. chim.*, **47**, 694 (1928).

13 Swern, Findley, and Scanlan, *J. Am. Chem. Soc.*, **66**, 1925 (1944).

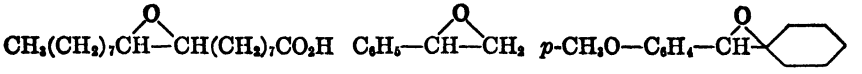
14 Hibbert and Burt, *J. Am. Chem. Soc.*, **47**, 2240 (1925); *Org. Syntheses*, **8**, 102 (1928).

15 Prileschajew, *Ber.*, **59**, 194 (1926); **42**, 4811 (1909).

16 Ruzicka and Bosshard, *Helv. Chim. Acta*, **20**, 244 (1937).

17 Pummerer and Reindel, *Ber.*, **66**, 335 (1933).

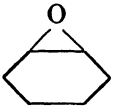
acid converts oleic acid to the oxide [13] (VIII), styrene to the corresponding oxide [14] (IX), and anisalcyclohexane to X.[18] It is sometimes



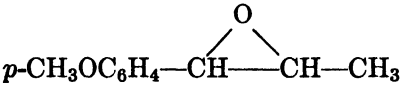
VIII IX X

possible to generate the perbenzoic acid within the reaction mixture from benzaldehyde and air or oxygen.[18]

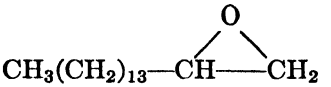
Peracetic acid [19–22] is effective in the conversion of an olefin to an oxide and is used considerably. Thus, cyclohexene gives the oxide (XI), anethole the oxide (XII), and 1-hexadecene the oxide [22] (XIII).



XI



XII



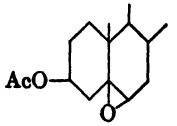
XIII

Peracetic acid is commonly prepared from hydrogen peroxide and used in glacial acetic acid solution. One of the difficulties of the per-acid method of converting an olefin to the oxide is the tendency for reaction of the oxide with the carboxylic acid present. This is especially troublesome when the solvent is a carboxylic acid, such as acetic acid, the oxide being in part transformed to glycol ester.[21,23] With performic acid in formic acid solution, the entire product appears to be glycol ester.[22]

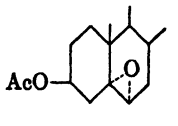
Another difficulty of the per-acid method is the relative instability of per-acids toward long storage. Monoperphthalic acid perhaps best avoids the difficulties of the per-acid method.[24–26] Thus, this reagent converts linaloöl [27] to the monoöxide, 1-phenylpropene-1 to the

18 Tiffeneau et al., *Compt. rend.*, **201**, 277 (1935); **195**, 1284 (1932).
19 Arbusow and Michailow, *J. prakt. Chem.*, [2] **127**, 92 (1930).
20 Böeseken and Jacobs, *Rec. trav. chim.*, **55**, 786 (1936).
21 Findley, Swern, and Scanlan, *J. Am. Chem. Soc.*, **67**, 412 (1945).
22 Swern, Billen, and Scanlan, *J. Am. Chem. Soc.*, **68**, 1504 (1946).
23 Böeseken and Schneider, *J. prakt. Chem.*, [2] **131**, 285 (1931).
24 Böhme, *Ber.*, **70**, 379 (1937); *Org. Syntheses*, **20**, 70 (1940).
25 Chakravorty and Levin, *J. Am. Chem. Soc.*, **64**, 2317 (1942).
26 Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947).
27 Naves and Bachmann, *Helv. Chim. Acta*, **28**, 1227 (1945).

oxide [28,29] (VI), cholesteryl acetate to the mixture of stereoisomeric oxides [25] (XIV and XV) (only A and B rings are shown), and 1-(2-bi-

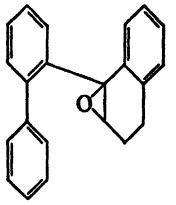


XIV



XV

phenyl)-3,4-dihydronaphthalene to the corresponding oxide [30] (XVI).



XVI

The rate of reaction of olefinic compounds is quite sensitive to the number and kind of substituents on the ethylenic carbon atoms. Thus, simple alkyl-substituted olefins give a relative rate sequence for reaction with peracetic acid approximately as follows.[26]

$$H_2C{=}CH_2,\ 1 < RCH{=}CH_2,\ 24 < RCH{=}CHR,\ 500 \cong$$
$$R_2C{=}CH_2,\ 500 < R_2C{=}CHR,\ 6500 < R_2C{=}CR_2$$

Alkyl groups increase reactivity, tetramethylethylene displaying a rate too high for measurement. α-Aryl groups are also rate-enhancing in general. The cyclic olefins display rates comparable to the open-chain analogs.

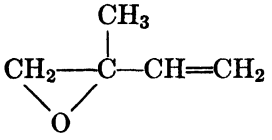
When the ethylenic linkage is conjugated with a carboxyl, carboalkoxy, or carbonyl group, the reaction with a per-acid is either quite slow or fails completely. This occurs with such substances as cinnamic, crotonic, maleic, and fumaric acids.[31,32] Actual rate constants show approximately

$$C_6H_5CH{=}CHCH_3,\ 500 > C_6H_5CH{=}CHCO_2H,\ 1$$

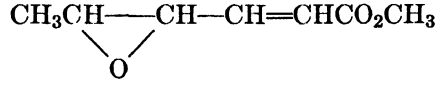
28 Stevens, Allenby, and DuBois, *J. Am. Chem. Soc.*, **62**, 1424 (1940).
29 Akawie, Doctoral Dissertation, University of California at Los Angeles, 1947.
30 Bradsher and Rapoport, *J. Am. Chem. Soc.*, **65**, 1646 (1943).
31 Böeseken and de Graaf, *Rec. trav. chim.*, **41**, 199 (1922).
32 Böeseken, *Rec. trav. chim.*, **45**, 838 (1926).

The general reactivities have been interpreted by Swern on the basis that alkyl substitution enhances and carboxyl substitution depresses the nucleophilic or electron-donor character of the olefin, the per-acid being an electrophilic or electron-seeking reagent. A substitute interpretation can be based on the relative amounts of stabilization of the oxide and parent olefin by conjugation and hyperconjugation involving substituents. On this basis, an α-alkyl or α-aryl group stabilizes the transition state for formation of oxide more than the olefin.

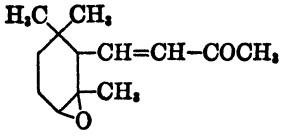
The behavior toward per-acids of compounds with more than one olefinic linkage is quite in line with the general indications from observed reaction rates. Thus, isoprene gives the monoöxide [17] (XVII), methyl 2,4-hexadienoate gives the monoöxide [33] (XVIII), and α-ionone yields the monoöxide [34] (XIX).



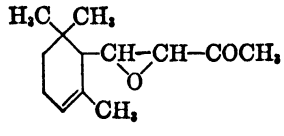
XVII



XVIII



XIX



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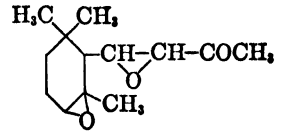


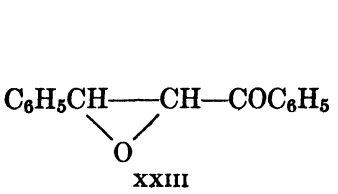
XXI

Because of the low reaction rate, reaction with a per-acid is not a general preparative method for attack on olefinic linkages conjugated with a group such as the carbonyl. For example, no reaction is observed between *m*-nitrobenzalacetophenone (XXII) and perbenzoic

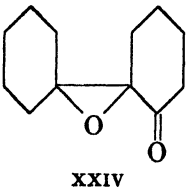
$$\underset{\text{XXII}}{m\text{-}O_2NC_6H_4CH{=}CHCOC_6H_5} \xrightarrow{C_6H_5CO_3H} \text{no reaction}$$

acid.[15] For such α,β-unsaturated carbonyl compounds, hydrogen peroxide in basic medium is useful.[35] Thus, benzalacetophenone yields the oxide [35] (XXIII), cyclohexylidenecyclohexanone [36] yields XXIV, and 1-mesityl-1-mesitoylethylene yields the oxide (XXV).[37]

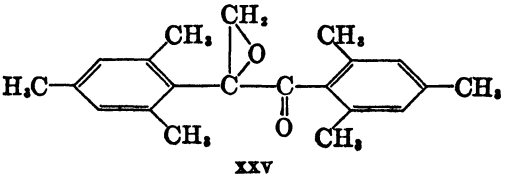
33 Heinänen, *Suomen Kemistilehti*, **11B**, 2 (1938) [*C. A.*, **32**, 2908 (1938)].
34 Karrer and Stürzinger, *Helv. Chim. Acta*, **29**, 1829 (1946).
35 Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).
36 Reese, *Ber.*, **75**, 384 (1942).
37 Fuson et al., *J. Org. Chem.*, **10**, 69 (1945).



XXIII

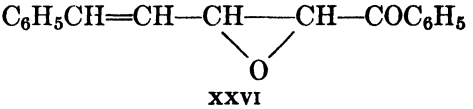


XXIV



XXV

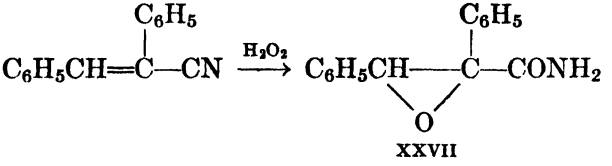
The alkaline peroxide reagent appears to react specifically with the α,β-olefinic linkage if others are available. Thus, cinnamalacetophenone gives the oxide [35] (XXVI), whereas α-ionone yields the oxide [34]



XXVI

(XX), different from the one obtained with perphthalic acid. The ionone bisoxide (XXI) may be prepared by reaction of XX with perphthalic acid or of XIX with alkaline peroxide.

Sometimes hydrogen peroxide will convert an α,β-unsaturated nitrile to an oxide, as illustrated by the conversion of α-phenylcinnamonitrile to the α,β-diphenylglycidamide [38] (XXVII).



XXVII

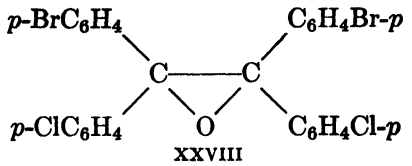
There are rare instances of oxide formation in the oxidation of olefins with other reagents. Thus, chromic anhydride in glacial acetic acid can produce ethylene oxides from tetraarylethylenes.[39–41] For example, di-*p*-bromophenyl-di-*p*-chlorophenylethylene yields the oxide [41] (XXVIII), and tetra-*p*-nitrophenylethylene yields XXIX.[40] Oxide

38 Murray and Cloke, *J. Am. Chem. Soc.*, **56**, 2749 (1934).

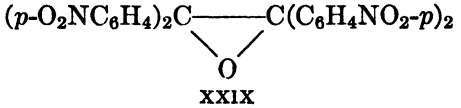
39 Behr, *Ber.*, **5**, 277 (1872).

40 Biltz, *Ann.*, **296**, 219 (1897).

41 Bockemüller and Janssen, *Ann.*, **542**, 166 (1939).



XXVIII

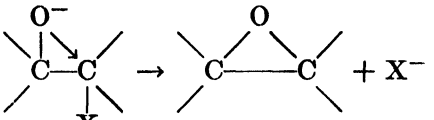


XXIX

formation occurs with a low yield in the oxidation of the 5,6 double bond of several sterols with potassium permanganate in acetic acid.[42]

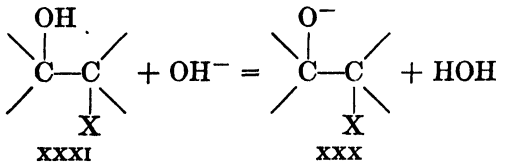
The vapor-phase oxidation of ethylene at elevated temperatures with air or oxygen over a silver catalyst produces ethylene oxide.[43,44]

Dehydrohalogenation of Substituted Alcoholate Ions. A group of methods for formation of the ethylene oxide ring involves a substituted alcoholate ion (XXX) which is converted to an ethylene oxide. In



XXX

the most common of these methods, the dehydrohalogenation of a halohydrin (XXXI) with a base such as sodium or potassium hydroxide or sodium methoxide, the intermediate (XXX) is in equilibrium with the halohydrin according to the equation



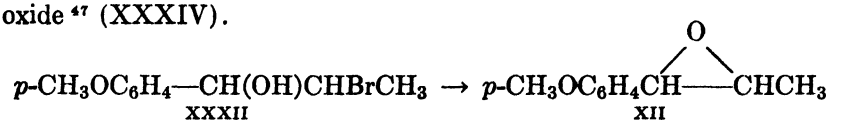
XXXI XXX

the rate-determining step being the conversion of XXX to the oxide.[45]

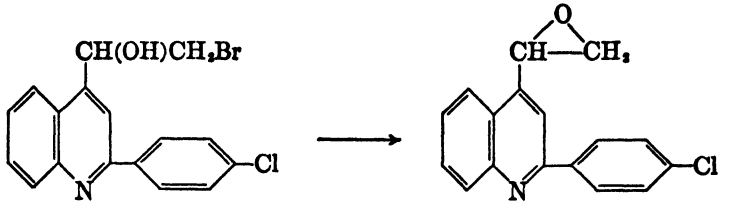
The over-all reaction of a halohydrin with alkali to produce the oxide is rapid and quantitative at room temperature, and, because halohydrins are readily prepared, this method has been much used. Thus, anethole bromohydrin[46] (XXXII) yields the oxide (XII), and

42 Ehrenstein and Decker, *J. Org. Chem.*, **5**, 544 (1940).
43 Ryerson and Oppenheimer, *J. Phys. Chem.*, **48**, 290 (1944).
44 McBee, Hass, and Wiseman, *Ind. Eng. Chem.*, **37**, 432 (1945).
45 Winstein and Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939).
46 Hoering, *Ber.*, **38**, 2296, 3458, 3464, 3477 (1905).

the bromohydrin (XXXIII) yields the quinoline-subsituted ethylene oxide [47] (XXXIV).

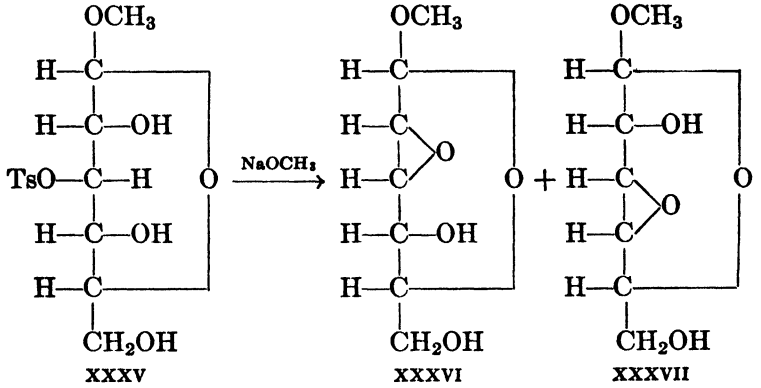


XXXII XII



XXXIII XXXIV

Completely analogous to the dehydrochlorination of a halohydrin is the conversion of a β-hydroxyalkyl toluenesulfonate to an ethylene oxide. In this case, X in formula XXX is $OSO_2C_6H_4CH_3$. This reaction is of considerable utility in the carbohydrate field. For example, 3-*p*-toluenesulfonyl-α-methylglucoside (XXXV) is converted by sodium methoxide to a mixture of 2,3-anhydro-α-methylalloside (XXXVI) and 3,4-anhydro-α-methylalloside [48,49] (XXXVII).



XXXV XXXVI XXXVII

The closing of the ring with the expulsion of X^- from the substituted alcoholate ion (XXX) is an intramolecular example [45,50] of the usual bimolecular displacement [51] symbolized by

$$Y:^- + R:X \rightarrow Y:R + :X^-$$

47 Winstein et al., *J. Am. Chem. Soc.*, **68**, 1831 (1946).

48 Peat and Wiggins, *J. Chem. Soc.*, 1088, 1810 (1938).

49 Ohle and Wilcke, *Ber.*, **71**, 2316 (1938).

50 Winstein et al., *J. Am. Chem. Soc.*, **70**, 816 (1948).

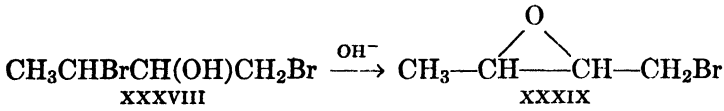
51 Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940, Chapters V and VI.

in which the nucleophilic agent $Y:^-$ displaces $:X^-$ from RX. The effect of alkyl substitution on the rate of oxide formation from a halohydrin can be seen from the rate sequence [52]

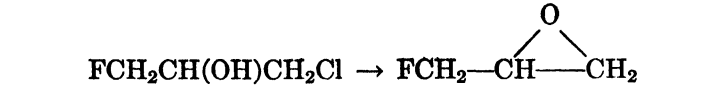
$$HOCH_2CH_2Cl,\ 0.31 < HOCH_2CHClCH_3,\ 1.7$$
$$< CH_3CH(OH)CH_2Cl,\ 6.5$$
$$< (CH_3)_2C(OH)CH_2Cl,\ 78 \cong HOCH_2CCl(CH_3)_2,\ 77$$
$$< (CH_3)_2C(OH)CHClCH_3,\ 424$$
$$< CH_3CH(OH)CCl(CH_3)_2,\ 633$$
$$< (CH_3)_2C(OH)CCl(CH_3)_2,\ 3600$$

It is clear that methyl substitution on either carbon atom of ethylene chlorohydrin is rate-enhancing. Though the primary propylene chlorohydrin is more reactive than the secondary, the secondary is more reactive than ethylene chlorohydrin. The main effect of alkyl substitution appears to be on the rate of ring closure from intermediate XXX, the closure of a small ring being favored by such substitution.[6]

The beneficial effect of alkyl substitution on oxide ring closure is seen in the tendency toward formation of the more substituted oxide if there are competing halogen atoms. Thus, the halohydrin (XXXVIII) is reported [53] to yield mainly the oxide (XXXIX) on treatment with base. Similarly, the halohydrin (XL) yields mainly



the oxide (XLI).[54] When there are different competing halogen atoms in a halohydrin, the ordinary reactivity rule, RI>RBr>RCl>RF, applies. Thus, 1-fluoro-3-chloropropanol-2 yields epifluorohydrin,[55]



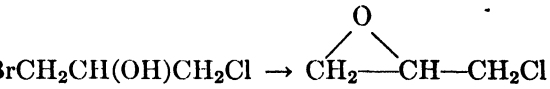
[52] Nilsson and Smith, *Z. physik. Chem.*, **166A**, 136 (1933).

[53] Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 713 (1941) [*C. A.*, **36**, 404 (1942)].

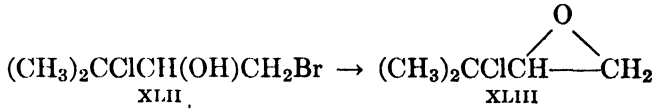
[54] Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 931 (1945) [*C. A.*, **40**, 6415 (1946)].

[55] Knunyantz, *Compt. rend. acad. sci. U.R.S.S.*, **55**, 223 (1947) [*C. A.*, **41**, 5855 (1947)].

1-bromo-3-chloropropanol-2 yields mainly epichlorohydrin,[56] and it has been reported that the halohydrin (XLII) with a tertiary chlorine



and a primary bromine yields mainly the oxide (XLIII), bromine being displaced rather than chlorine even though displacement of chlorine would yield the most substituted oxide.[54]



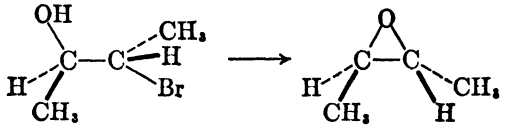
XLII XLIII

The closure of the trimethylene oxide ring is very much slower than that of the ethylene oxide ring. Thus, for example, comparison of the rates of reaction with base of trimethylene chlorohydrin and propylene chlorohydrin gives the approximate relative rates.[57]

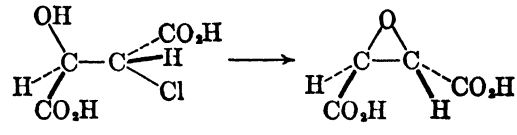
$$CH_3CH(OH)CH_2Cl,\ 10^4 > HOCH_2CH_2CH_2Cl,\ 1$$

It is a good general rule that the ethylene oxide ring is preferred even when other hydroxyl groups are available.

Just as bimolecular nucleophilic displacements on carbon proceed with a steric result of Walden inversion, so is there inversion of configuration of the carbon atom losing the halogen in the closure of an oxide ring.[45,58-60] Thus, the closing is a *trans* closure. In this way, the *erythro* halohydrins, 3-bromo-2-butanol [45] (XLIV), chloromalic acid [59] (XLV), and stilbene bromohydrin [60] (XLVI), yield cleanly the *trans*

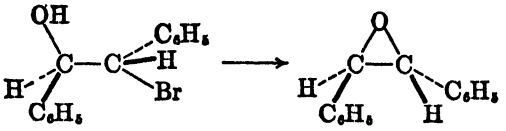


XLIV



XLV

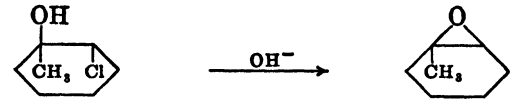
56 Abderhalden and Eichwald, *Ber.*, **48**, 1847 (1915).
57 Evans, *Z. physik. Chem.*, **7**, 337 (1891).
58 Lucas and Gould, *J. Am. Chem. Soc.*, **63**, 2541 (1941).
59 Kuhn and Ebel, *Ber.*, **58**, 919 (1925).
60 Reulos, *Compt. rend.*, **216**, 774 (1943); **218**, 795 (1944).



XLVI

oxides. Conversely, the analogous *threo* halohydrins [45,59,60] yield *cis* oxides. When the *erythro*-3-bromo-2-butanol is racemic, the *trans*-2,3-epoxybutane is naturally racemic, but, when the bromohydrin is resolved, active *trans* oxide is obtained from it.[61] On the other hand, *cis*-2,3-epoxybutane is internally compensated and cannot be prepared in an optically active modification, even from optically active *threo*-3-bromo-2-butanol.

The nature of the ring closure in the formation of an ethylene oxide from a halohydrin is further shown by the difference in behavior of *cis*- and *trans*-halohydrins of cyclic olefins. For example, the *trans*-chlorohydrins, 1-methyl-2-chlorocyclohexanol [62] (XLVII) and indene chlorohydrin [63] (XLVIII), give rise smoothly to the oxides. These



XLVII

XLVIII

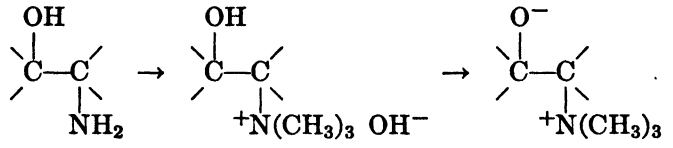
oxides are *cis* oxides and are the only ones known to result from such reactions.[59,64] The closure is thus a *trans* closure, and Walden inversion occurs. On the other hand, the analogous *cis*-chlorohydrins, if they followed the same mechanism, would need to produce the prohibitively strained *trans* oxides (three-membered ring fused *trans* to a five- or six-membered ring). Thus, the *cis*-chlorohydrins react more slowly with alkali, and the reaction, when it does occur, produces carbonyl compounds.

With carbohydrate toluenesulfonates, it is generally recognized that the ethylene oxide ring is formed if an hydroxyl group is *trans* to

61 Winstein and Lucas, *J. Am. Chem. Soc.*, **61**, 2845 (1939).
62 Bartlett and Rosenwald, *J. Am. Chem. Soc.*, **56**, 1990 (1934).
63 Suter and Lutz, *J. Am. Chem. Soc.*, **60**, 1360 (1938).
64 Böeseken, *Ber.*, **58**, 1470 (1925).

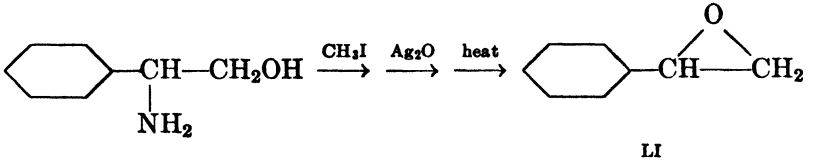
the sulfonyl group.[65] The inversion has already been illustrated with the example of 3-*p*-toluenesulfonyl-α-methylglucoside (XXXV) (p. 9).

Naturally, the group X in the intermediate XXX for oxide production may be other than halogen or toluenesulfonate. It may be $^{+}N(CH_3)_3$ from exhaustive methylation of an amino group. Thus, if an aminoethanol is exhaustively methylated and the product is treated with silver oxide, there is produced the quaternary ammonium base (XLIX) which, when heated, gives rise to oxide by way of the inter-



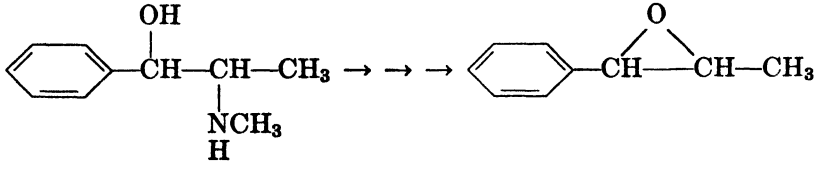
XLIX L

mediate (L) which discards trimethylamine. For example, 2-cyclohexyl-2-aminoethanol [66,67] yields the oxide (LI). Also, ephedrine [68–70]

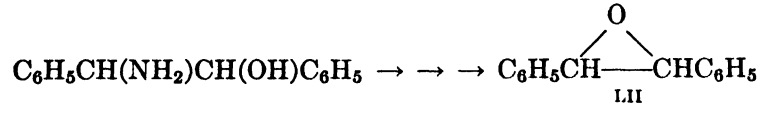


LI

yields the oxide (VI), and 1,2-diphenyl-2-aminoethanol [71] yields stilbene oxide (LII).



VI

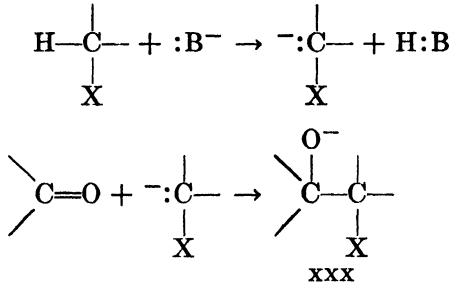


LII

65 Ohle and Schultz, *Ber.*, **71**, 2302 (1938).
66 v. Braun and Teuffert, *Ber.*, **58**, 2210 (1925).
67 v. Braun, *Ber.*, **56**, 2178 (1923).
68 Fourneau and Benoit, *Bull. soc. chim. France*, [5] **12**, 985 (1945).
69 Rabe, *Ber.*, **44**, 824 (1911).
70 Emde and Rumme, *Ber.*, **43**, 1727 (1910).
71 Read and Campbell, *J. Chem. Soc.*, 2377 (1930).

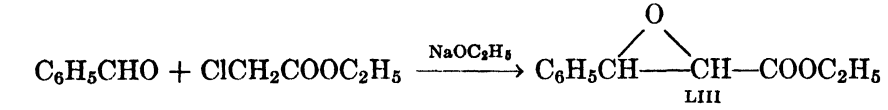
The steric aspects of the ring closure are identical with those discussed with halohydrins. Optically active amino alcohols give rise to optically active oxides [68–71] unless the oxide product is an internally compensated one, such as *cis*-stilbene oxide.

Condensation Reactions. Several methods by which ethylene oxides are produced are those in which intermediate XXX is derived by base-promoted condensation of a carbonyl compound with a halo ester or something similar. The halide has an acidic hydrogen which is removed by strong base, the resulting anion adding to the carbonyl compound, according to the equations



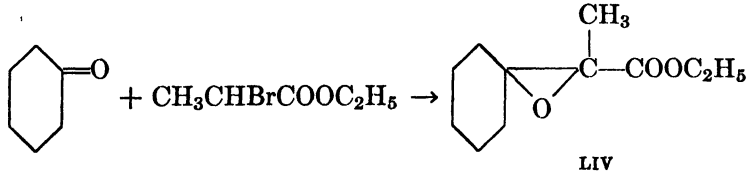
XXX

In the Darzens reaction, the halide component is an α-halo ester. Thus, Erlenmeyer [72] prepared the oxide of cinnamic ester (LIII) from



LIII

benzaldehyde, chloroacetic ester, and sodium ethoxide. Claisen [73] and Darzens [74] showed that the reaction was quite general with sodamide and sodium ethoxide as bases. In this way, cyclohexanone and ethyl



LIV

α-bromopropionate yield the glycidic ester [75] (LIV), 2-dimethylaminomethylcyclohexanone and chloroacetic ester yield the glycidic

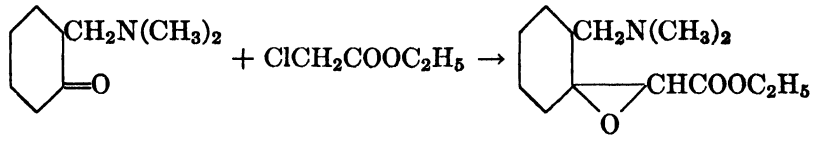
72 Erlenmeyer, *Ann.*, **271**, 137 (1892).

73 Claisen, *Ber.*, **38**, 693 (1905).

74 Darzens, *Compt. rend.*, **139**, 1214 (1904); **204**, 272 (1937); and intervening papers.

75 Yarnall and Wallis, *J. Org. Chem.*, **4**, 270 (1939).

ester[76] (LV), and β-ionone with chloroacetic ester yields a glycidic ester.[9] The glycidic esters may be hydrolyzed and rearranged to

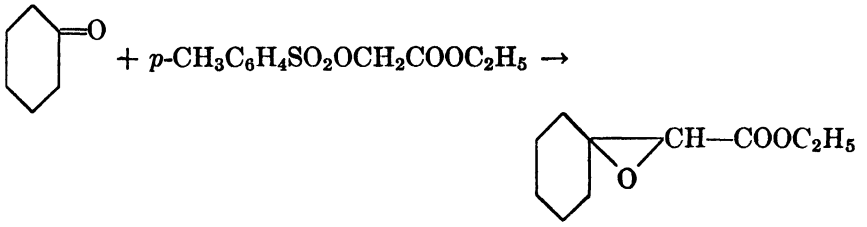


LV

produce an aldehyde or a ketone as discussed later, and therefore the Darzens reaction is of considerable utility in organic chemistry.

The Darzens reaction appears to be general in application, although aromatic and semiaromatic aldehydes and ketones seem to give poorer yields than alicyclic or aliphatic[73,74] ones. Ethyl α-chloropropionate gives better yields of the glycidic ester than does ethyl α-chloroacetate[73,74] or ethyl α-bromopropionate.[75]

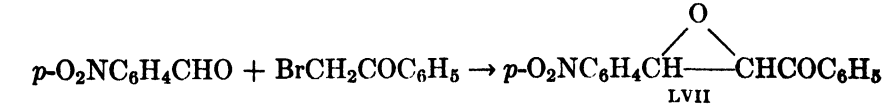
The substance with the acidic hydrogen atom may naturally be varied. One recent variation is the substitution of *p*-toluenesulfonylacetic ester for chloroacetic ester in the condensation with cyclohexanone to produce the glycidic ester[77] (LVI). X in formula XXX then



LVI

becomes *p*-toluenesulfonate instead of halide. Another variation utilizes halo ketones.

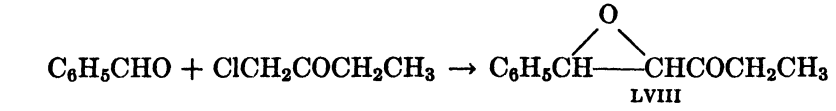
Reaction at room temperature of haloacetophenones with aromatic aldehydes with sodium ethoxide as a catalyst leads to good yields of the aroylarylethylene oxides.[78–80] For example, *p*-nitrobenzaldehyde and ω-bromoacetophenone yield the oxido ketone[80] (LVII). Substi-



LVII

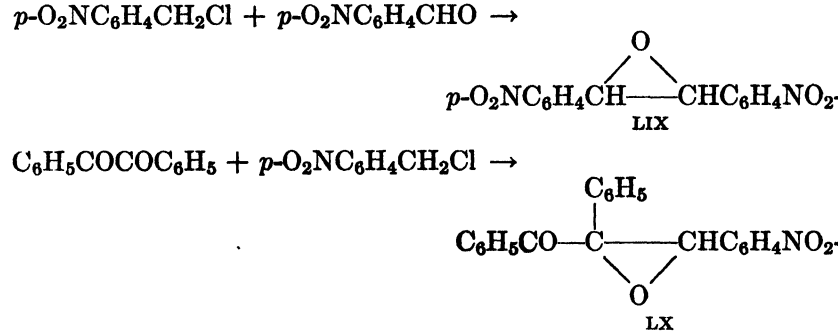
[76] Howton, *J. Org. Chem.*, **12**, 379 (1947).
[77] Newman and Magerlein, *J. Am. Chem. Soc*, **69**, 469 (1947).
[78] Widman, *Ber.*, **49**, 477 (1916).
[79] Jörlander, *Ber.*, **49**, 2782 (1916); **50**, 1457 (1917).
[80] Bodforss, *Ber.*, **49**, 2795 (1916); **51**, 192 (1918).

tution of nitro groups or halogen in the nucleus of the aromatic aldehyde favors the reaction greatly, but the yield is lowered when such groups are in the haloacetyl moiety.[80] Aliphatic halo ketones may be used in the Darzens reaction to produce oxido ketones, as illustrated by the formation of α-propionyl-β-phenylethylene oxide (LVIII) from benzaldehyde and 1-chloro-2-butanone.[81]



LVIII

The material with the acid hydrogen for condensation with a carbonyl compound may be *p*-nitrobenzyl chloride and analogous halides,[82–85] in which the acidic character of the hydrogen atoms on the methyl group in *p*-nitrotoluene is enhanced in *p*-nitrobenzyl chloride and its analogs. Diarylethylene oxides are formed to a certain extent in many reactions of such halides with aromatic aldehydes under basic conditions. Thus, for example, *p*-nitrobenzyl chloride gives, with *p*-nitrobenzaldehyde, *p,p'*-dinitrostilbene oxide[82,84] (LIX), and with benzil it gives the keto oxide[87] (LX), identical with the product ob-



LIX

LX

tained by condensing *p*-nitrobenzaldehyde with desoxybenzoin to the *p*-nitrobenzaldesoxybenzoin and treatment of the latter with alkaline hydrogen peroxide.

Similar to the above condensation methods for producing ethylene oxides is the reaction in which the intermediate is LXI and is produced

[81] Temnikova and Martynov, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 499 (1945) [*C. A.*, **40**, 4694 (1946)].

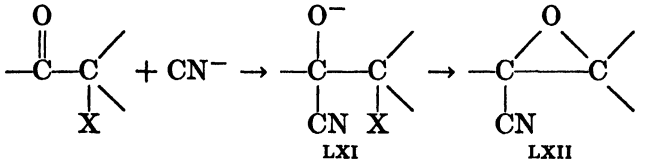
[82] Bergmann and Hervey, *Ber.*, **62**, 893 (1929).

[83] Kleucker, *Ber.*, **62**, 2587 (1929).

[84] Hahn, *Ber.*, **62**, 2485 (1929).

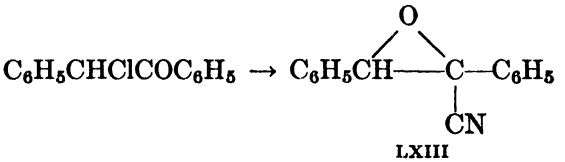
[85] Kleucker, *Ber.*, **55**, 1634 (1922).

by reaction of an α-halo ketone with cyanide ion. Thus, some halo ketones will produce an oxide cleanly by treatment in aqueous or alcoholic solution with an alkali or alkaline earth cyanide.[86-88] The product is a glycidic nitrile (LXII) or sometimes the related imino ether

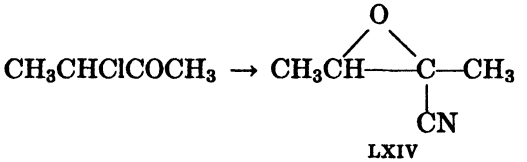


LXI LXII

from alcoholic solution.[86] In this way, ω-phenyl-ω-chloroacetophenone yields [86] LXIII, and 3-chlorobutanone-2 yields [88] LXIV. The product can be hydrolyzed or alcoholyzed carefully to a glycidic acid or ester.

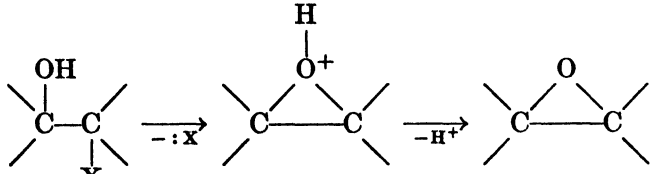


LXIII



LXIV

Miscellaneous Methods. Just as oxides may be obtained by loss of a group from a species (formula XXX) with a neighboring O^- group, so they are sometimes produced by loss of a group from a species bearing a neighboring OH group, as shown in formula XXXI. Loss or re-



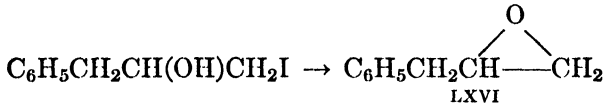
XXXI LXV

moval of :X from XXXI with participation of the neighboring hydroxyl group [89] produces the conjugate acid of the oxide (LXV), which

[86] Kohler and Brown, *J. Am. Chem. Soc.*, **55**, 4299 (1933).
[87] Richard, *Compt. rend.*, **199**, 71 (1934).
[88] Justoni, *Gazz. chim. ital.*, **69**, 378 (1939) [*C. A.*, **33**, 8574 (1939)].
[89] Winstein and Buckles, *J. Am. Chem. Soc.*, **64**, 2780 (1942).

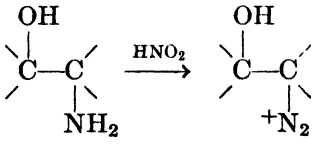
can lead to an oxide by loss of a proton. In general, other processes, such as group migrations leading to rearrangements, may compete with participation of the hydroxyl group. This competition is not yet fully understood. Also, many oxides will not survive the reaction conditions employed. Therefore, oxides are only rarely obtained from loss of :X from species XXXI.

Actually, some oxide (LXVI) is claimed in the product of the action of silver nitrate on the iodohydrin of allylbenzene.[90] Similarly, oxides

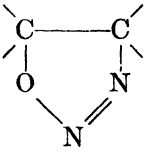


LXVI

are sometimes produced, at least to some extent, by the action of nitrous acid on amino alcohols. This deamination is often employed to induce pinacol-type rearrangement. Species XXXI takes the form LXVII, but it remains a question what part the possible furodiazole (LXVIII) may play in this connection. In this way, the ethylene

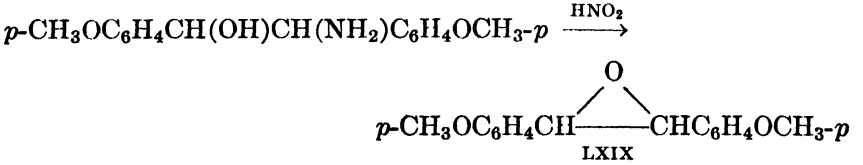


LXVII

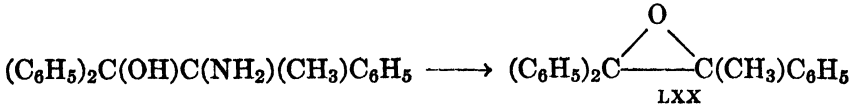


LXVIII

oxide (LXIX) [91] is obtained from treatment of 1,2-dianisyl-2-aminoethanol with nitrous acid. Also, α,α,β-triphenyl-β-aminopropyl alcohol yields a small amount of the ethylene oxide (LXX) along with a rearrangement product.[92]



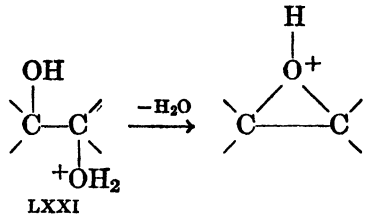
LXIX



LXX

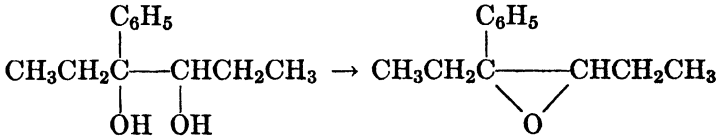
90 Porcher, *Bull. soc. chim. France,* [4] **31,** 334 (1922).
91 Read and Campbell, *J. Chem. Soc.,* 2674 (1930).
92 McKenzie and Myles, *Ber.,* **65,** 209 (1932).

Occasionally, treatment of a glycol with acidic reagents gives rise to an oxide, although the pinacol rearrangement alone is observed in the great majority of cases. Intermediate XXXI then takes the form LXXI, the loss of water giving rise to an oxide-conjugate acid. For



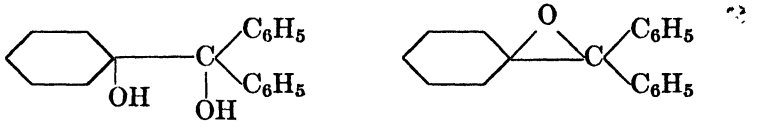
LXXI

example, formic acid or phosphorus pentoxide converts 3-phenyl-3,4-hexanediol to the corresponding oxide [93] (LXXII). Also, Meerwein [94]



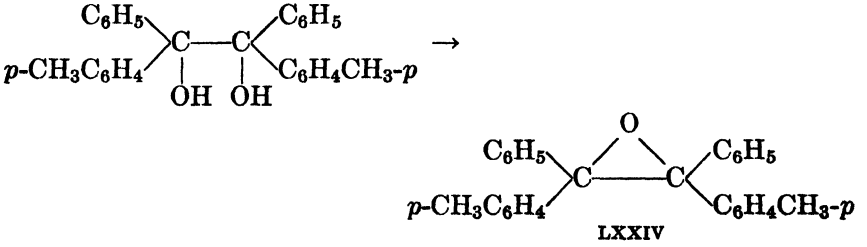
LXXII

converted α,α-diphenyl-β,β-pentamethyleneethylene glycol to the oxide (LXXIII) with sulfuric acid. Thörner [95,96] allowed α,β-diphenyl-α,β-



LXXIII

di-*p*-tolylethylene glycol to stand with hydrochloric acid and was able to isolate the ethylene oxide (LXXIV). More vigorous treatment with



LXXIV

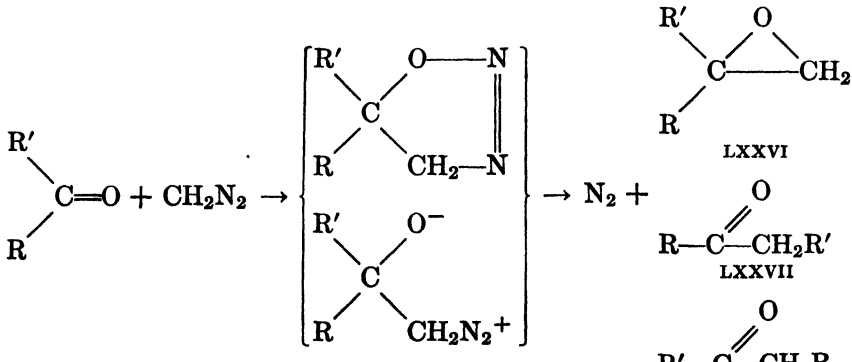
93 Tiffeneau and Levy, *Bull. soc. chim. France*, [4] **33**, 735, 759 (1923).
94 Meerwein, *Ann.*, **396**, 200 (1913).
95 Thörner, *Ann.*, **189**, 104 (1877).
96 Thörner and Zincke, *Ber.*, **10**, 1473 (1877); **11**, 65, 1396 (1878).

hot dilute sulfuric acid produces some oxide but also the pinacolone and other materials.

The conversion of glycol to oxide probably is the cause of the occasional formation of oxide from bimolecular reductions of a ketone containing two aryl groups and, rarely, from a semiaromatic ketone.[97] Benzophenone, when treated with zinc and dilute sulfuric acid [96] or with zinc and acetyl chloride,[98] or when boiled in ether with magnesium and silicon tetrachloride and then treated with water,[99] gives some tetraphenylethylene oxide. Treatment of *p*-methylbenzophenone with zinc and acid [95,96] under the proper conditions produces predominantly oxide.

Hydrolysis of tetraphenylethylene dichloride with hot water produces tetraphenylethylene oxide,[100] which arises either from the glycol or chlorohydrin. The behavior of tetra-*p*-chlorophenylethylene dichloride is similar.[101]

Diazomethane reacts with many aldehydes and ketones to produce ethylene oxides,[102] probably by way of the intermediate furodiazole or its open modification (LXXV). The reaction appears to be catalyzed by polar substances such as water, alcohols, salts, formamide, etc.[103,104] The evolution of nitrogen may result in not only the oxide (LXXVI) but also the carbonyl compound (LXXVII) with migration of R′ and the carbonyl compound (LXXVIII) with migration of R. These higher carbonyl compounds may themselves react with diazomethane

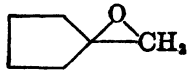


LXXV LXXVI LXXVII LXXVIII

97 Tendick, U. S. pat. 2,393,129 [*C. A.*, **40**, 2471 (1946)].
98 Paal, *Ber.*, **17**, 911 (1884).
99 Kipping and Abrams, *J. Chem. Soc.*, 81 (1944).
100 Schmidlin and v. Escher, *Ber.*, **43**, 1153 (1910).
101 Norris, Thomas, and Brown, *Ber.*, **43**, 2940 (1910).
102 Arndt, Eistert, and Partale, *Ber.*, **61**, 1107 (1928).
103 Meerwein and Burneleit, *Ber.*, **61**, 1840 (1928).
104 Meerwein, Bersin, and Burneleit, *Ber.*, **62**, 999 (1929).

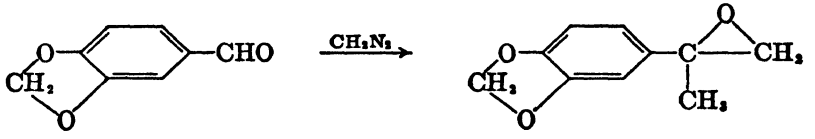
so that, almost invariably, a mixture of oxide, higher ketones or aldehydes, and oxides thereof are produced. Separation in good yield of the desired oxide may be difficult.

The simple aliphatic aldehydes usually fail to produce significant amounts of oxide, and aliphatic ketones give yields that are not entirely satisfactory. Thus, acetone is converted to isobutylene oxide;[103,104] cyclopentanone,[105] cyclohexanone [105,106] cycloheptanone,[106] and various alkyl-substituted cyclohexanones [106] produce low yields of the expected oxides, for example, LXXIX from cyclopentanone.[105]



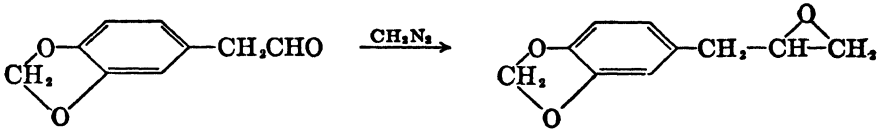
LXXIX

Aromatic aldehydes have a tendency to produce oxides derived from the next higher ketones. For example, the oxide from piperonal is mainly [107] LXXX. On the other hand, piperonylacetaldehyde gives

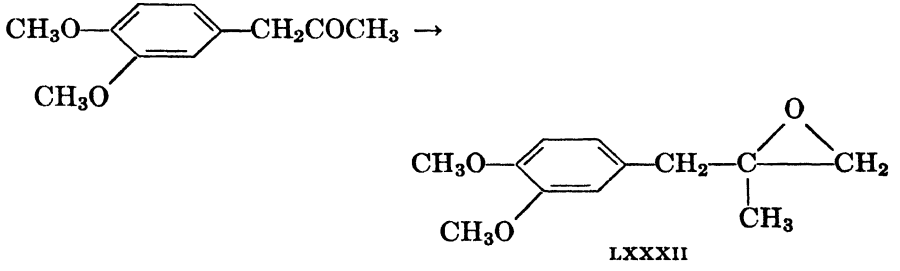


LXXX

3-piperonyl-1,2-epoxypropane [108] (LXXXI). Veratrylacetone gives rise to [109] LXXXII.



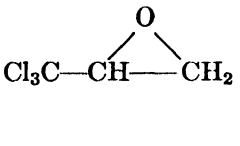
LXXXI



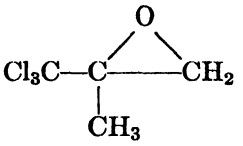
LXXXII

[105] Mosettig and Burger, *J. Am. Chem. Soc.*, **52**, 3456 (1930).
[106] Adamson and Kenner, *J. Chem. Soc.*, 181 (1939).
[107] Mosettig, *Ber.*, **61**, 1391 (1928).
[108] Mosettig and Czadek, *Monatsh.*, **57**, 291 (1931).
[109] Mosettig and Jovanovic, *Monatsh.*, **53**, 427 (1929).

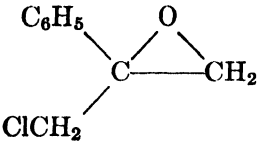
Substituents exert a powerful influence on the yields. Acetaldehyde and chloroacetaldehyde [110] give little, if any, oxide, but chloral [104,111] can be converted in high yield to trichloromethylethylene oxide (LXXXIII). Similarly, trichloroacetone [110] gives a high yield of LXXXIV. Although acetophenone [109] is largely unattacked by diazomethane in 3 days at 20°, chloroacetophenone is 90% converted in a few hours at 0° to α-phenyl-α-chloromethylethylene oxide (LXXXV).



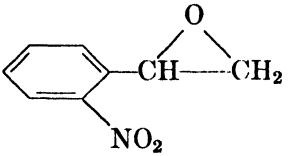
LXXXIII



LXXXIV

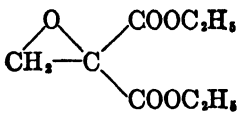


LXXXV

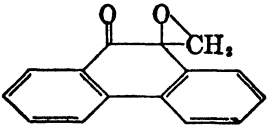


LXXXVI

The presence of a nitro group in an aromatic aldehyde favors the formation of the corresponding oxide; thus, *o*-nitropiperonal [108] gives a high yield of the expected oxide, and *o*-nitrobenzaldehyde [102] yields *o*-nitrostyrene oxide (LXXXVI) satisfactorily. The influence of the nitro group is most pronounced in the *o* position and least in the *m* position. Good conversion of diethyl oxomalonate [112] and 9,10-phenanthraquinone [110] to the corresponding oxides (LXXXVII and LXXXVIII) can be realized.



LXXXVII



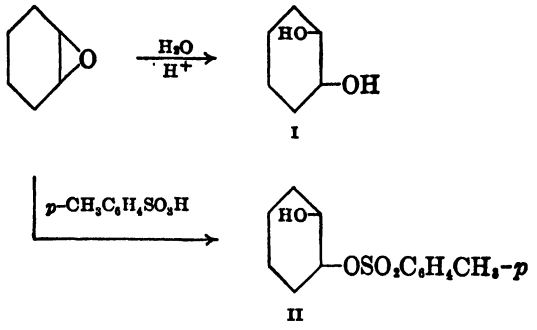
LXXXVIII

Metathetical Opening of the Oxide

General. The ethylene oxide ring may be opened with a very large variety of reagents so that these substances lead simply to many classes of compounds. Water easily opens the oxide ring to give a glycol, for

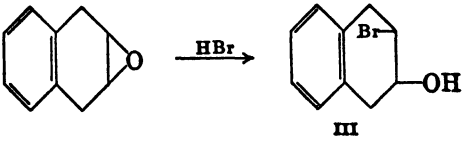
110 Arndt, Amende, and Ender, *Monatsh.*, **59**, 202 (1932).
111 Arndt and Eistert, *Ber.*, **61**, 1118 (1928).
112 Arndt, Eistert, and Ender, *Ber.*, **62**, 44 (1929).

example in the conversion of cyclohexene oxide to 1,2-cyclohexanediol [113] (I). Similarly, alcohol opens the oxide ring, as in the conversion of ethylene oxide to the commercially important ethylene glycol monoalkyl ethers. Phenols may be used instead of alcohols in opening the oxide ring.



$$CH_2{-}CH_2 \xrightarrow[H^+]{ROH} ROCH_2CH_2OH$$

Hydrogen halides, in general, quickly convert an oxide to a halohydrin. Ethylene oxide reacts with hydrogen bromide to give ethylene bromohydrin, even at −78°.[114] Similarly 1,4-dihydronaphthalene oxide [115] gives the corresponding bromohydrin (III). Hydrogen chloride has been very widely employed to open the oxide ring, leading to the corresponding chlorohydrin. Actually, the reaction has been made the basis for estimation of ethylene oxides.[116] These are treated with excess standard hydrogen chloride solution, and the excess hydrogen chloride is determined by back-titration.

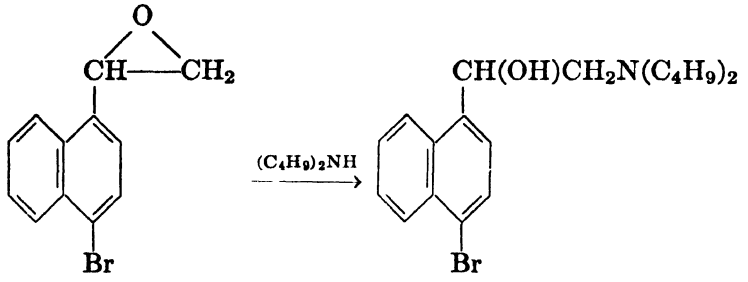


Hydrogen iodide opens ordinary epoxides, but this reagent also reduces glycidic materials, as discussed later in this chapter. Hydrogen fluoride in ether converts ethylene, propylene, and isobutylene oxides

113 Rothstein, *Ann. chim.*, [10] **14**, 461 (1930).
114 Maass and Boomer, *J. Am. Chem. Soc.*, **44**, 1709 (1922).
115 Bamberger and Lodter, *Ber.*, **26**, 1836 (1893).
116 Swern et al., *Anal. Chem.*, **19**, 414 (1947).

to fluorohydrins.[55] Quite analogous to the opening with a hydrogen halide is the opening with toluenesulfonic acid, for example the conversion of cyclohexene oxide to the cyclohexanediol monotoluenesulfonate (II).[117]

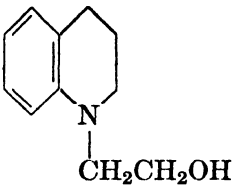
Ammonia and amines may be employed in the opening of ethylene oxides. Aqueous ammonia reacts vigorously with ethylene oxide to produce a mixture of mono-, di-, and tri-ethanolamines. The conversion of oxides to amino alcohols is extremely general. For example, 4-bromo-1-naphthylethylene oxide is converted by dibutyl amine to the amino alcohol (IV).[118] Similarly, ethylene oxide may be converted



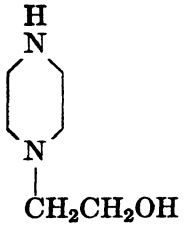
IV

to V with ethylene diamine,[119] to VI with tetrahydroquinoline,[120] and to VII or VIII with piperazine.[121] Other substances that may enter

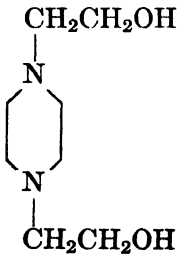
V



VI



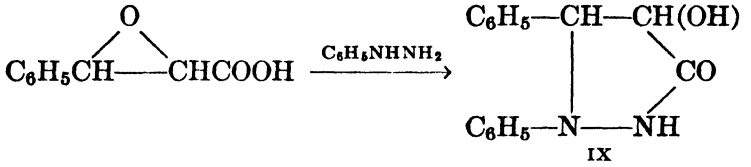
VII



VIII

117 Criegee and Stanger, *Ber.*, **69**, 2753 (1936).
118 Winstein et al., *J. Org. Chem.*, **11**, 157 (1946).
119 Kitchen and Pollard, *J. Org. Chem.*, **8**, 342 (1943).
120 Koroleva, *J. Gen. Chem.* (*U.S.S.R.*) **9**, 2200 (1939) [*C. A.*, **34**, 4069 (1940)].
121 Kitchen and Pollard, *J. Org. Chem.*, **8**, 338 (1943).

into similar reactions are thiourea,[122] *p*-toluenesulfonanilide,[123] phthalimide,[124] and hydrazine.[125,126] When a hydrazine enters into reaction with a substance such as a glycidic acid, an additional ring closure may take place. For example, β-phenylglycidic acid, when treated with phenylhydrazine, gives rise to IX.[127]



IX

Carboxylic acids will open the oxide ring,[46] since it is possible to convert an epoxide to the glycol monoacetate with acetic acid or to a monovalerate with valeric acid.[128] Thioacetic acid has been used in this way; with ethylene oxide it gives rise to X.[129]

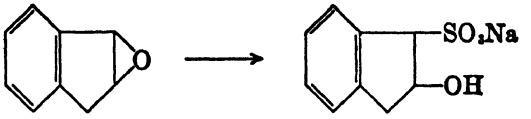
$$HOCH_2CH_2SCOCH_3$$

X

Bisulfite and hydrocyanic acid will open the ethylene oxide, although rearrangements are sometimes encountered (p. 51). Epichlorohydrin

XI XII

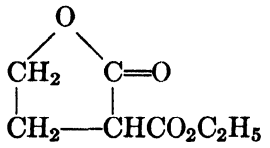
is converted to XI with hydrocyanic acid [130] and to XII with potassium cyanide,[131] and sodium sulfite converts indene oxide to XIII.[132]



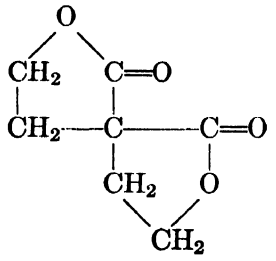
XIII

122 Olin and Dains, *J. Am. Chem. Soc.*, **52**, 3322 (1930).
123 Ohle and Haeseler, *Ber.*, **69**, 2324 (1936).
124 Gabriel and Ohle, *Ber.*, **50**, 819 (1917).
125 Gabriel, *Ber.*, **47**, 3028 (1914).
126 Benoit, *Bull. soc. chim. France*, [5] **6**, 708 (1939).
127 Japp and Maitland, *J. Chem. Soc*, **85**, 1490 (1904).
128 Fraenkel-Conrat and Olcott, *J. Am. Chem. Soc.*, **66**, 1420 (1944).
129 Nylén and Olsen, *Svensk Kem. Tid.*, **53**, 274 (1941) [*C. A.*, **36**, 753 (1942)].
130 Hörmann, *Ber.*, **12**, 23 (1879).
131 Hartenstein, *J. prakt. Chem.*, [2] **7**, 295 (1873).
132 Suter and Milne, *J. Am. Chem. Soc.*, **65**, 582 (1943).

Malonic ester [133–135] and similar substances such as acetoacetic ester [136, 137] and cyanoacetic ester [138] open the oxide ring. Thus, ethylene oxide is converted to α-carbethoxy-γ-butyrolactone (XIV) with sodiomalonic ester,[133] and it may be made to yield the dilactone (XV)

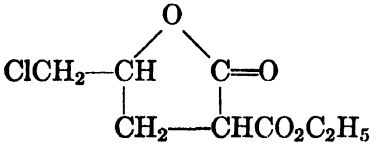


XIV

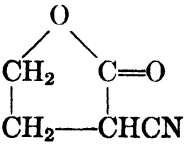


XV

with malonic ester and piperidine.[134] Similarly, sodiomalonic ester converts epichlorohydrin to α-carbethoxy-δ-chloro-γ-valerolactone [135] (XVI), and ethylene oxide gives α-cyano-γ-butyrolactone (XVII) on treatment with sodiocyanoacetic ester.[138]



XVI



XVII

Epichlorohydrin is interesting in its reactions. When it is allowed to react with an amine, the first molecule of amine opens the oxide ring. Then, if an excess of amine is present, a second molecule acts as a base to remove hydrogen chloride, regenerating an oxide ring, and producing a 3-amino-1,2-epoxypropane which can then react with a third molecule of the amine.[139–141] The sequence is:

133 McRae et al., *Can. J. Research*, **21B**, 186 (1943).

134 Pakendorf, *Compt. rend. acad. sci. U.R.S.S.*, **25**, 387 (1939); **27**, 956 (1940) [*C. A.*, **34**, 4381 (1940); **35**, 1382 (1941)].

135 Traube and Lehmann, *Ber.*, **32**, 720 (1899).

136 Haller and Blanc, *Compt. rend.*, **137**, 1203 (1903).

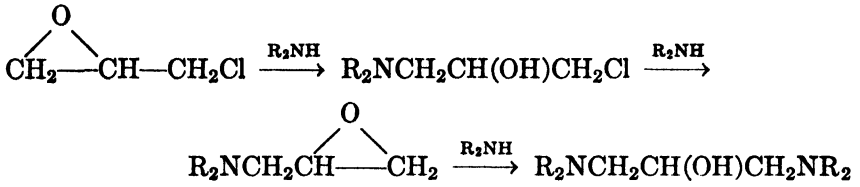
137 Chelintsev and Osetrova, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 2373 (1937) [*C. A.*, **32**, 2099 (1938)].

138 Glickman and Cope, *J. Am. Chem. Soc.*, **67**, 1012 (1945).

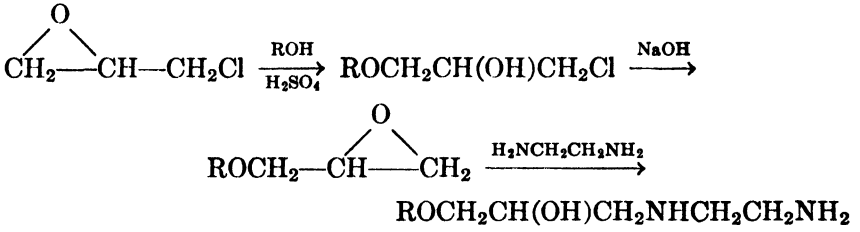
139 Cohn and Friedlaender, *Ber.*, **37**, 3034 (1904).

140 Eisleb, U. S. pat. 1,790,042 [*C. A.*, **25**, 1259 (1931)]. Cf. Gilman et al., *J. Am Chem. Soc.*, **68**, 1291 (1946).

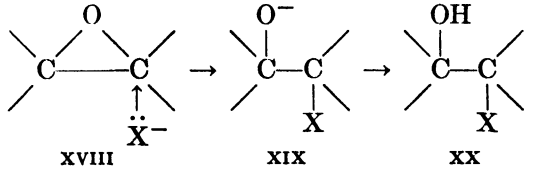
141 Fukagawa, *Ber.*, **68**, 1344 (1935).



In general, the presence of the halogen atom in epichlorohydrin makes possible the preparation of molecules with a variety of functional groups. For example,[142]

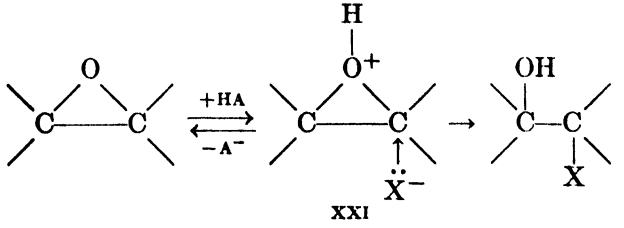


Mechanism and Stereochemistry. The opening of the oxide rings in the reactions of the type outlined represents a nucleophilic displacement on carbon,[51] the displaced group being the ring oxygen atom. The displacements may differ with respect to the form of the reactive oxide species. This may be the oxide itself, as symbolized in formula XVIII, or it may be the conjugate acid of the oxide, as symbolized in



XVIII XIX XX

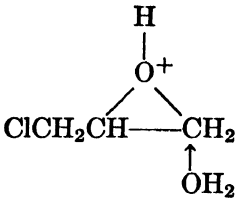
formula XXI. If the displacement is on the oxide itself, there is produced intermediate XIX which, by acquiring a proton, gives the open product (XX). The conjugate acid of the oxide is much more reactive than the oxide itself, acid catalysis being very common.



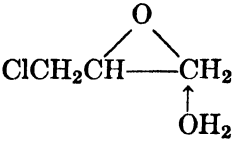
XXI

142 Flores-Gallardo and Pollard, *J. Org. Chem.*, **12**, 831 (1947).

Kinetic data of Brønsted and co-workers,[143] who investigated the reactions of several oxides with water and several anions, show that, at substantial acid concentrations, reaction by way of the conjugate acid of the oxide (XXI) is much faster than by attack on the oxide itself. Thus, with epichlorohydrin at 20°, correcting to 1 *M* hydronium-ion concentration, the reaction symbolized by XXII is over 400 times as fast as that symbolized by XXIII, and the reaction sym-

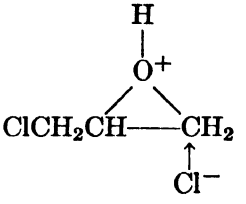


XXII

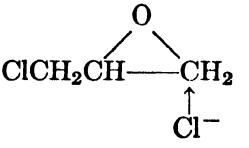


XXIII

bolized by XXIV is similarly approximately 400 times as fast as that symbolized by XXV.



XXIV



XXV

Often there is a possibility of variation in the form of the attacking nucleophilic species in the opening of an oxide. Thus, if the nucleophilic agent is symbolized by YH, the addition of base B^- may convert YH, at least partly, to a superior nucleophilic agent Y^-, according to the equation

$$YH + B^- = BH + Y^-$$

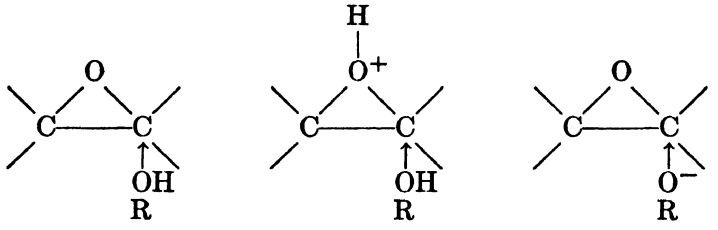
Consequently, basic catalysis can be observed in a number of oxide openings.

In the opening of several oxides with phenols, Boyd and Marle [144] have demonstrated kinetically the great reactivity of phenolate ion (base-catalyzed reaction [144]) over phenol. The rate of reaction with oxide diminishes as the basicity of the phenolate ion decreases,[144] and

[143] Brønsted, Kilpatrick, and Kilpatrick, *J. Am. Chem. Soc.*, **51**, 428 (1929).
[144] Boyd and Marle, *J. Chem. Soc.*, **93**, 838 (1908); **105**, 2117 (1914).

it can be correlated by Hammett's rho-sigma [145] treatment in both the ethylene and propylene oxide series.

When the oxide ring is opened by a reagent such as an alcohol, three kinds of rate-determining steps become possible, as symbolized below for the reaction under neutral, acid-catalyzed, and base-catalzyed



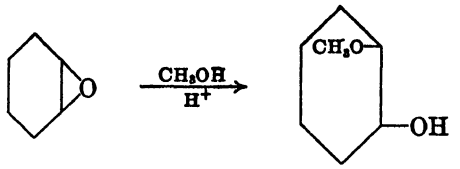
conditions. Other reagents exhibiting this versatility are water, hydrogen sulfide, mercaptans, thiophenols, hydrogen cyanide, and carboxylic acids. With water and alcohols, the acid-catalyzed reaction is most often employed.

In the addition of hydrogen halides as ordinarily carried out, the reaction is by way of the oxide conjugate acid (XXI). With phenols and thiols, the base-catalyzed reaction is more common. With malonic ester (and similar reagents), it is the malonic ester anion which attacks the oxide (XVIII).

Since the ring-opening reactions are nucleophilic displacements on carbon, it is logical that inversion of configuration is very generally observed as the steric result of oxide opening. In other words, the opening is *trans*. This is very clear in a number of alicyclic openings. Thus, cyclohexene oxide gives the *trans*-chlorohydrin [146] and similarly the *trans*-bromohydrin [147] with hydrogen halide. The cyclohexanediol mono-*p*-toluenesulfonate (II) from the opening of cyclohexene oxide with *p*-toluenesulfonic acid has the *trans* configuration.[148] The cyclohexanediol (I) from the opening of cyclohexene oxide with water also has the *trans* configuration; [147] this is typical [149] of the behavior of oxides of alicyclic olefins. Thus, the *trans*-glycol is produced from opening the oxide ring in the oxides from cyclopentene, indene, 1-methylcyclohexene, 1-cyclohexylcyclohexene,[150] and cycloheptene.[151]

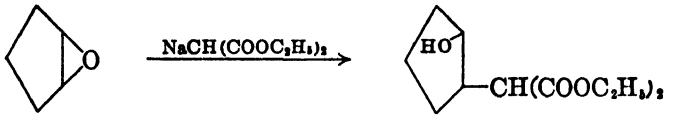
145 Ref. 51, Chapter VII.
146 Bartlett, *J. Am. Chem. Soc.*, **57**, 224 (1935).
147 Winstein, *J. Am. Chem. Soc.*, **64**, 2792 (1942).
148 Winstein, Hess, and Buckles, *J. Am. Chem. Soc.*, **64**, 2796 (1942).
149 Böeseken and van Giffen, *Rec. trav. chim.*, **39**, 184 (1920).
150 Böeseken and Maan, *Ber.*, **56**, 2409 (1923).
151 Godchot and Mousseron, *Compt. rend.*, **198**, 837 (1934).

Similarly the 1,2-cyclohexanediol monomethyl ether (XXVI) from cyclohexene oxide and methanol is *trans*.[152] In the reaction of cyclopentene oxide with sodiomalonic ester, it is clear that Walden inversion



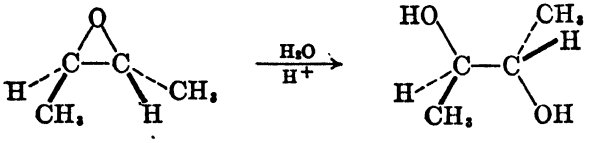
XXVI

occurs, for there is produced the *trans*-cyclopentane-1-ol-2-malonic ester (XXVII).[153] In this case, the product cannot be a lactone as are the products from oxides of open-chain olefins.

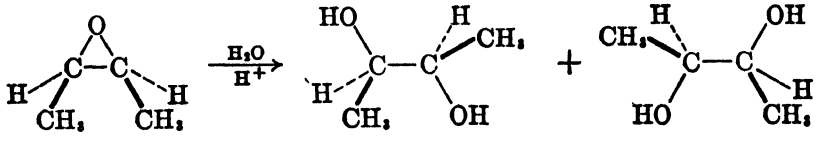


XXVII

The opening of a variety of oxides of open-chain olefins has been shown to proceed with Walden inversion. Thus, optically active *trans*-2,3-epoxybutane gives internally compensated and therefore optically inactive *meso*-2,3-butanediol [154] (XXVIII). On the other hand, the *cis*-2,3-epoxybutane gives rise to *dl*-2,3 butanediol [154] (XXIX), which



XXVIII



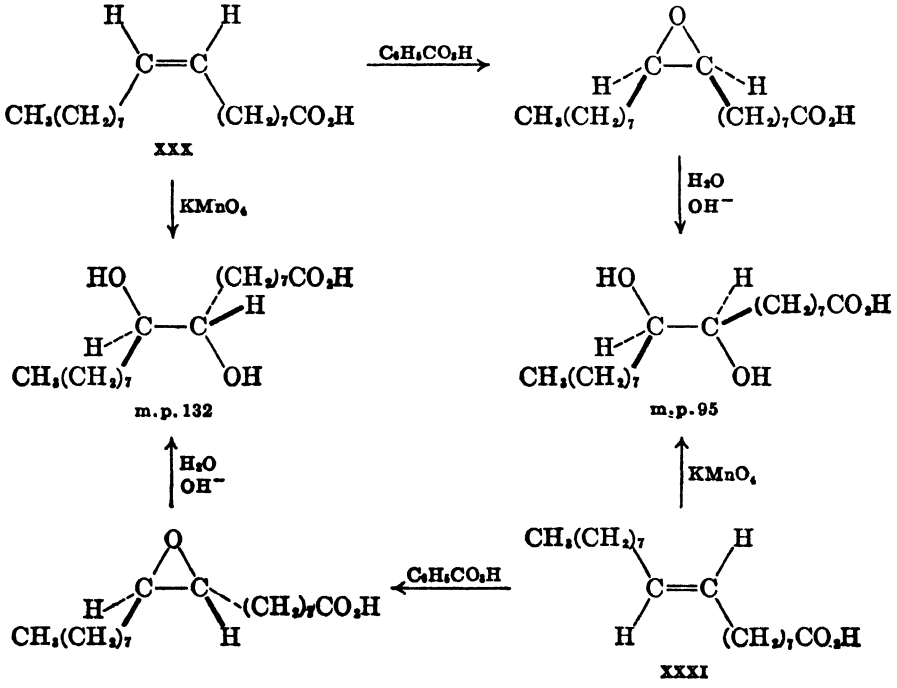
XXIX

can be resolved. The epoxysuccinic acids, one of which, the *trans*, can be resolved into active forms, are similar. This oxide, when treated with hydrogen bromide or chloride, gives the corresponding *erythro* halo-

152 Winstein and Henderson, *J. Am. Chem. Soc.*, **65**, 2196 (1943).
153 Grigsby et al., *J. Am. Chem. Soc.*, **64**, 2606 (1942).
154 Wilson and Lucas, *J. Am. Chem. Soc.*, **58**, 2396 (1936).

hydrin (XLV on p. 11). Conversely, the inactive *cis* oxide gives the other halohydrin.[59] The stilbene oxides also exist in two forms: *trans*, which can be resolved, and *cis*, which is internally compensated.[71] The *cis*- or iso-stilbene oxide produces the *threo* halohydrin when treated with hydrogen chloride, bromide, or iodide,[60] and the *trans* oxide yields the *erythro* halohydrin (XLVI on p. 12).

It is apparent that an oxide is opened with hydrogen halide to produce the original halohydrin from which the oxide can be derived. Also, the conversion of an olefin to a glycol by way of the oxide (with the aid of perbenzoic acid) gives a glycol isomeric with that prepared by treatment of the olefin with such reagents as potassium permanganate which gives *cis* addition.[155] A further example of this stereo specificity is to be found in the derivatives of oleic and elaidic acids. Thus, oleic acid (XXX) (*cis*) [156] gives rise directly to the glycol acid,

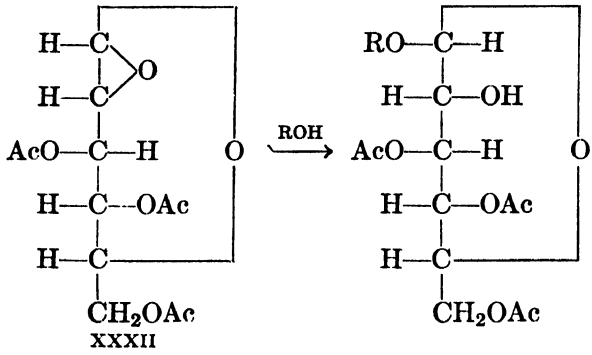


m.p. 132°, on treatment with permanganate, but to the glycol acid, m.p. 95°, by way of the oxide. Elaidic acid (XXXI) (*trans*) gives the glycol acid, m.p. 95°, on treatment with permanganate.

155 Böeseken, *Rec. trav. chim.*, **47**, 683 (1928).

156 E.g., Atherton and Hilditch, *J. Chem. Soc.*, 204 (1943).

The phenomenon of Walden inversion in the opening of ethylene oxides is general for anhydro sugars. For example, Brigl's anhydride,[157] 1,2-anhydro-3,4,6-triacetylglucose (XXXII), gives β-methyl glucosides on treatment with alcohols.[158]



XXXII

Direction of Opening of Unsymmetrical Oxides. When an oxide is not symmetrical, the opening can conceivably give rise to either of two structural isomers or to a mixture of the two. Very often, one direction of opening is very predominant, although mixtures are sometimes obtained. Actually, it is possible to understand the direction of opening to a considerable degree and to make predictions with confidence.

For ordinary bimolecular nucleophilic displacements on carbon, the rate sequence, primary > secondary > tertiary, is general, and analogy with these accounts in general for the direction of opening observed in reactions of the neutral oxide (formula XVIII).

With propylene oxide, where the competition is between reactions at primary and secondary carbon atoms, reactivity is considerably higher at the primary carbon atom, leading very predominantly to the one mode of opening as shown in formula XXXIII. Thus, propylene oxide opens in this way predominantly with amines [119,120,159–162] to give a 1-amino-2-propanol derivative (XXXIV). The opening with phenoxide [144] or alkoxide [163,164] ion is similar, the secondary alcohol (XXXV) being obtained. This mode of opening of propylene oxide is observed with sodiomalonic ester [133] and cyanoacetic ester.[138]

157 Brigl, *Z. physiol. Chem.*, **122**, 245 (1922).

158 Hickinbottom, *J. Chem. Soc.*, 3140 (1928).

159 Krasuskii and Pilyugin, *Ukrain. Khem. Zhur.*, **5**, Sci. Pt., 135 (1930) [*C. A.*, **25**, 2690 (1931)].

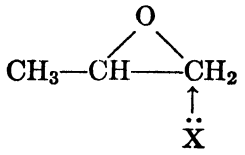
160 Krasuskii, *J. chim. Ukraine*, **1**, 65, 398 (1923) [*C. A.*, **20**, 2820 (1926)].

161 Matskevich, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 1241 (1941) [*C. A.*, **39**, 4076 (1945)].

162 Wickert, U. S. pat. 1,988,225 [*C. A.*, **29**, 1489 (1935)].

163 Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **14**, 1038 (1944) [*C. A.*, **40**, 7153 (1946)].

164 Chitwood and Freure, *J. Am. Chem. Soc.*, **68**, 680 (1946).



XXXIII

$CH_3CH(OH)CH_2NR_2$

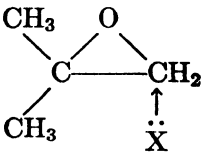
XXXIV

$CH_3CH(OH)CH_2OR$

XXXV

Many analogs of propylene oxide open in the same direction. Examples of this are the reactions with amines of glycidol,[165,166] epichlorohydrin,[139–141,167–172] epihydrinaldehyde dimethyl acetal,[173] 1,2-epoxybutane,[174] isopropylethylene oxide,[175,176] 1,2-epoxyhexanol-6,[177] benzylethylene oxide,[178] *p*-nitrobenzylethylene oxide,[179] 3-(α-naphthyl)-1,2-epoxypropane,[180] and 3-phenoxy-1,2-epoxypropane.[181] The opening of epichlorohydrin with phenolate ion [144] or sodiomalonic ester [185] is analogous (formula XVI).

The operation of the rate sequence, primary> secondary> tertiary, is seen in the reactions of isobutylene oxide which opens in the sense of formula XXXVI with amines [119,182–184] and with cyanoacetic ester.[138]



XXXVI

165 Knorr and Knorr, *Ber.*, **32**, 750 (1899).

166 Rider and Hill, *J. Am. Chem. Soc.*, **52**, 1528 (1930).

167 Drozdov and Cherntzov, *J. Gen. Chem.* (*U.S.S.R.*), **4**, 969 (1934) [*C. A.*, **29**, 2148 (1935)].

168 Fauconnier, *Compt. rend.*, **107**, 115 (1888).

169 Gerhard, *Ber.*, **24**, 352 (1891).

170 Gilman et al., *J. Am. Chem. Soc.*, **68**, 1291 (1946).

171 Knunyantz, *Ber.*, **68**, 397 (1935).

172 Strukov, *Khim. Farm. Prom.*, No. 2, 11 (1934) [*C. A.*, **28**, 5421 (1934)].

173 Wohl and Momber, *Ber.*, **47**, 3346 (1914).

174 deMontmollin and Matile, *Helv. Chim. Acta*, **7**, 106 (1924).

175 Krivonos, *Ukrain. Khem. Zhur.*, **5**, Sci. Pt., 141 (1930) [*C. A.*, **25**, 2690 (1931)].

176 Krasuskii and Krivonos, *Ukrain. Khem. Zhur.*, **4**, Sci. Pt., 211 (1929) [*C. A.*, **24**, 3218 (1930)].

177 Niemann, Benson, and Mead, *J. Org. Chem.*, **8**, 397 (1943).

178 Castro and Noller, *J. Am. Chem. Soc.*, **68**, 203 (1946).

179 Fourneau and Brydowna, *Bull. soc. chim. France*, [4] **47**, 626 (1930).

180 Fourneau, Trefouel, and Trefouel, *Bull. soc. chim. France*, [4] **43**, 454 (1928).

181 Boyd, *J. Chem. Soc.*, **97**, 1791 (1910).

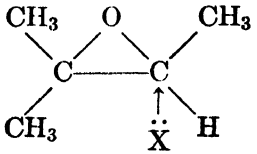
182 Riedel, Ger. pat. 199,148; *Chem. Zentr.*, **1908**, II, 121.

183 Krasuskii and Kutzenos, *Ukrain. Khem. Zhur.*, **4**, Sci. Pt., 75 (1929) [*C. A.*, **24**, 1083 (1930)].

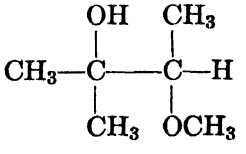
184 Kiprianov and Krasinskaya, *Ukrain. Khem. Zhur.*, **5**, Sci. Pt., 353 (1930) [*C. A.*, **25**, 5143 (1931)]; *Ukrain. Khem. Zhur.*, **4**, Sci. Pt., 215 (1929) [*C. A.*, **24**, 1083 (1930)].

Analogs of isobutylene oxide open in the same sense, as illustrated by the reaction of amines with 2-methyl-1,2-epoxybutane,[126,182] 2,5-dimethyl-1,2-epoxyhexane,[182,185] 2-phenyl-1,2-epoxypropane,[109,126,185] and α-methylglycidic acid.[186]

The operation of the same rate sequence is observed in the reactions of trimethylethylene oxide, which opens in the sense of formula XXXVII with amines.[160,187,188] Similarly the mono ether (XXXVIII)



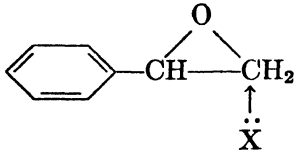
XXXVII



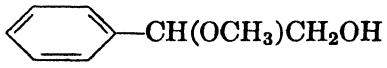
XXXVIII

is obtained in the methoxide ion-catalyzed opening with methanol.[189]

Styrene oxide opens chiefly in the sense of formula XXXIX with

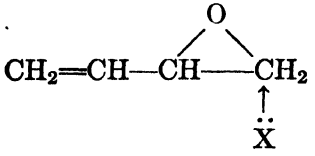


XXXIX



XL

amines [119,190] and sodiomalonic ester.[191] This same direction of opening predominates in the methoxide ion-catalyzed opening with methanol, but some of the isomeric material (XL) is obtained.[189] Similarly, butadiene monoxide opens in the sense of formula XLI with sodiomalonic



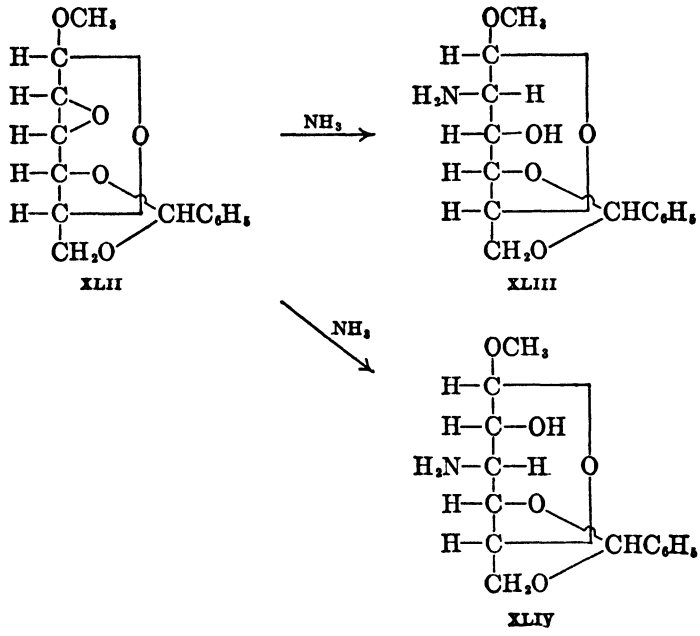
XLI

ester,[191] and in the base-catalyzed opening with methanol it gives rise to a mixture of products corresponding to each of the two modes of

185 Ger. pat. 203,082; *Chem. Zentr.*, **1908**, II, 1706.
186 Fourneau and Maréchal, *Bull. soc. chim. France*, [5] **12**, 990 (1945).
187 Plisov, *Ukrain. Khem. Zhur.*, **3**, No. 1, 125 (1928) [*C. A.*, **22**, 3392 (1928)].
188 Gabel, *Ukrain. Khem. Zhur.*, **2**, Sci. Pt., 382 (1926) [*C. A.*, **23**, 3908 (1929)].
189 Winstein and Ingraham, unpublished work.
190 Tiffeneau and Fourneau, *Compt. rend.*, **146**, 697 (1908).
191 Russell and VanderWerf, *J. Am. Chem. Soc.*, **69**, 11 (1947).

attack.[192] There are indications that, with 3,4-dimethoxystyrene oxide, even amines give rise to a mixture of isomeric amino alcohols.[193]

When the ethylene oxide is similarly enough substituted on the two carbon atoms involved, nucleophilic agents will, in general, give rise to a mixture of products. Thus, for example, 1-phenyl-1,2-epoxypropane with methyl amine leads to ephedrine, pseudoephedrine, isoephedrine, and pseudoisoephedrine.[68] Similarly, 4,6-benzylidene-2,3-anhydro-α-methylalloside (XLII) with ammonia gives rise to a mixture of 4,6-benzylidene-2-amino-α-methylaltroside (XLIII) and 4,6-benzylidene-3-amino-α-methylglucoside (XLIV), the former predominating.[48] Also,



4,6-benzylidene-2,3-anhydro-β-methyltaloside (XLV) gives, in the base-catalyzed cleavage with methanol, a mixture of 4,6-benzylidene-3-methyl-β-methylidoside (XLVI) and 4,6-benzylidene-2-methyl-β-methylgalactoside (XLVII), with the former in excess.[194]

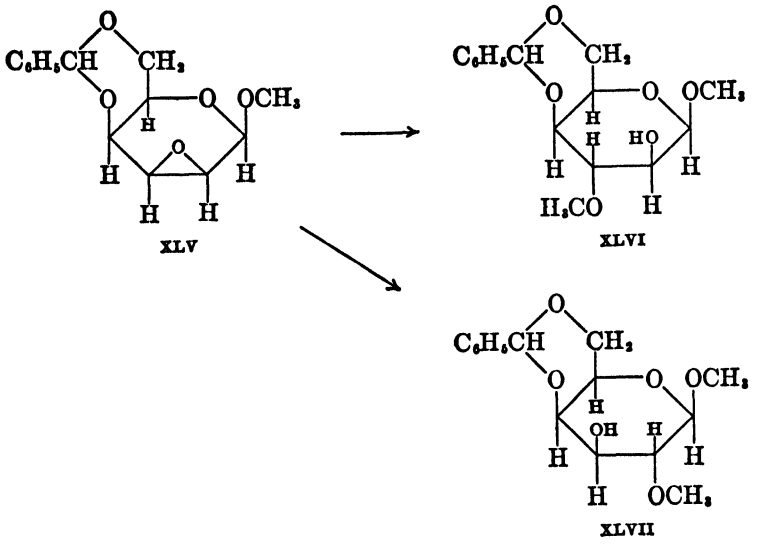
The glycidic esters and amides furnish a somewhat more complicated situation. Some of the patent literature[195] states that all glycidic

192 P. D. Bartlett, private communication.

193 Mannich, Neumann, and Jacobsohn, *Arch. Pharm.*, **248**, 127 (1910); *Chem. Zentr.*, **1910**, I, 2115.

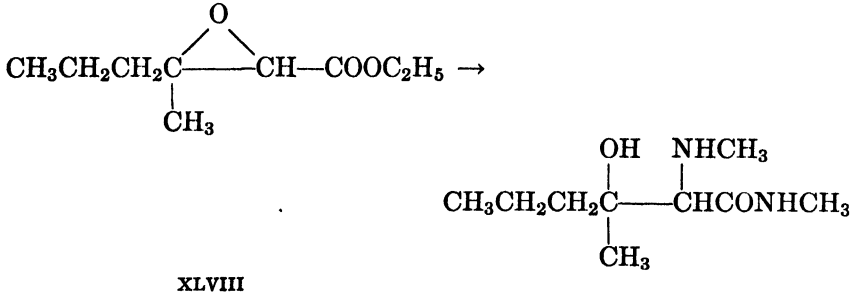
194 Wiggins, *J. Chem. Soc.*, 522 (1944).

195 Ger. pat. 583,243 [*C. A.*, **28**, 260 (1934)]; Ger. pat. 588,045 [*C. A.*, **28**, 1360 (1934)]; Brit. pat. 389,310 [*C. A.*, **27**, 4543 (1933)].



XLV XLVI XLVII

esters or amides, regardless of the presence of alkyl or aryl substituents, react with amines to give β-amino-α-hydroxy esters or amides. However, Fourneau and Billeter [196] report that ethyl β-methyl-α,β-epoxycaproate (XLVIII) and methyl amine produce N-methyl-α-methyl-

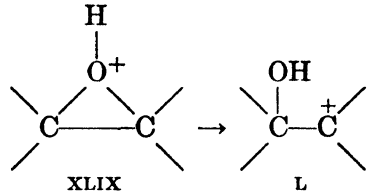


XLVIII

amino-β-methyl-β-hydroxycaproamide, which is to be expected on the basis of other reactions discussed earlier. Also, the same authors report that β-phenylglycidic esters or acids with ammonia or aliphatic amines give the β-amino isomer but that with aromatic amines they yield the α-amino acid or ester.[197] Ethyl β-phenylglycidate and β,β-dimethylglycidate have been reported to open at the α-carbon atom in the reaction with sodioacetoacetic ester.[187]

[196] Fourneau and Billeter, *Bull. soc. chim. France*, [5] **6**, 1616 (1939).
[197] Fourneau and Billeter, *Bull. soc. chim. France*, [5] **7**, 593 (1940).

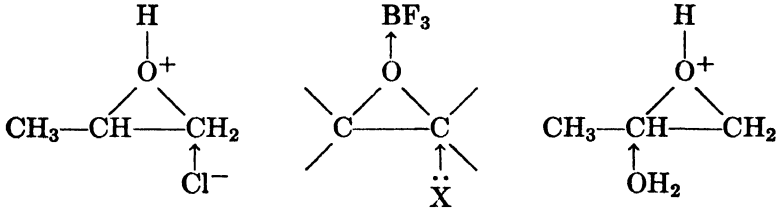
In the acid-catalyzed opening of ethylene oxides, there are wide deviations from the primary > secondary > tertiary rule. A new mechanism needs to be considered here, involving the unimolecular ring opening of the oxide-conjugate acid (XLIX), followed by rapid reaction



XLIX L

of the open carbonium ion (L).[198,199] For this mechanism, the rate sequence would be tertiary > secondary > primary. Thus, the direction of opening may be affected by the incursion of this new mechanism. Actually, there is no kinetic evidence on this matter, so it is not clear to what extent the direction of opening is still due to the mechanism symbolized by formula XXI, the rule primary > secondary > tertiary not being general enough to enable predictions with such reactions.

With propylene oxide, hydrogen chloride opens the oxide ring largely in the sense of formula LI, but roughly a tenth to a sixth of the other



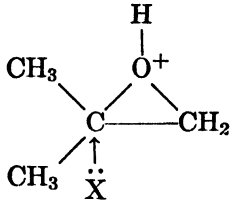
LI LII LIII

isomer is produced.[52,200] In the acid-catalyzed opening with alcohols, propylene oxide gives mixtures containing large amounts of both isomers,[163,164] in contrast to the base-catalyzed opening. The acid catalyst may be an ordinary acid such as sulfuric acid or some other electrophilic substance as boron trifluoride, the reaction taking the form symbolized by formula LII. In the acid-catalyzed hydration of propylene oxide, reaction by the path symbolized by formula LIII predominates. This is indicated by the production of *d*-propylene glycol from *d*-propylene oxide, whereas the base-catalyzed hydration gives *l*-propylene glycol.[201]

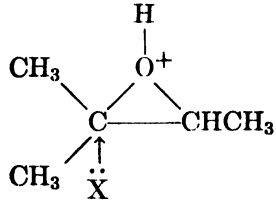
198 Ref. 89, footnote 25.
199 Kadesch, *J. Am. Chem. Soc.*, **68**, 41 (1946).
200 Smith, *Z. physik. Chem.*, **93**, 59 (1918).
201 Levene and Walti, *J. Biol. Chem.*, **75**, 325 (1927).

Like propylene oxide, β-ethoxyethylethylene oxide [202] opens with hydrogen chloride to give chiefly the secondary alcohol, and β-methoxyethylethylene oxide [203] gives 91% of the secondary alcohol and 9% of the primary. With epichlorohydrin, the acid-catalyzed addition of alcohols [204,205] and phenols [206,207] does not show so much tendency as does propylene oxide to give mixtures, the product being mainly secondary alcohol.

With isobutylene oxide, the direction of opening shifts considerably from that observed with propylene oxide. Thus, hydrogen chloride gives a product of which 50–65% arises from reaction in the sense of formula LIV,[52,208] and the acid-catalyzed addition of alcohols takes



LIV

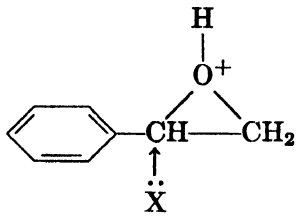


LV

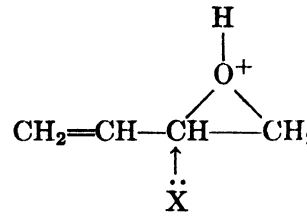
a similar course.[209,210] Trimethylethylene oxide with hydrogen chloride gives a product of which 67–85% is derived from reaction in the sense of formula LV,[52,208] whereas the acid-catalyzed opening with methanol gives essentially entirely the secondary alcohol.[189]

With styrene oxide [189,211,212] and butadiene monoöxide,[192,199,213] the shift in direction of addition is quite complete. The addition of hydrogen iodide or chloride or the acid-catalyzed addition of methanol goes quite completely in the sense of formulas LVI and LVII. Analogous to butadiene monoöxide are the halogen-substituted derivatives, 2-bromo-3,4-epoxybutene-1 [214] and 1-bromo-3,4-epoxybutene-1.[215] It

202 Pariselle, *Compt. rend.*, **150**, 1056 (1910); *Ann. chim.*, [8] **24**, 382 (1911).
203 Paul, *Ann. chim.*, [10] **18**, 303 (1932).
204 Fairbourne, Gibson, and Stephens, *J. Chem. Soc.*, 1965 (1932).
205 Blanchard, *Bull. soc. chim. France*, [4] **39**, 1263 (1926).
206 Levas and Lefebvre, *Compt. rend.*, **222**, 555 (1946).
207 Lefebvre, Levas, and Levas, *Compt. rend.*, **222**, 1439 (1946).
208 Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 690 (1945) [*C. A.*, **40**, 5698 (1946)].
209 Sparks and Nelson, *J. Am. Chem. Soc.*, **58**, 671 (1936).
210 Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 981 (1940) [*C. A.*, **35**, 3603 (1941)].
211 Tiffeneau, *Ann. chim.*, [8] **10**, 322 (1907).
212 Golumbic and Cottle, *J. Am. Chem. Soc.*, **61**, 996 (1939).
213 Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 991 (1941) [*C. A.*, **37**, 1699 (1943)].
214 Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 819 (1940) [*C. A.*, **35**, 2112 (1941)].
215 Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1887 (1940) [*C. A.*, **35**, 4347 (1941)].



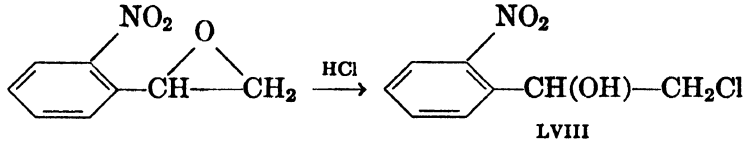
LVI



LVII

is interesting that very little, if any, of the allylic isomer of the predominant halohydrin is obtained from butadiene monoöxide and hydrogen chloride.[199] This fact is not in good accord with a reaction path by way of the ion (L) and agrees better with a concerted displacement symbolized by formula XXI.

Substitutients may exert a profound effect on the direction of opening of the oxide ring, an example apparently being found in the reaction of *o*-nitrostyrene oxide with hydrogen chloride, which yields the halohydrin (LVIII).[102] The direction of opening is opposite to that observed with styrene oxide, which does not carry the electron-removing nitro group.



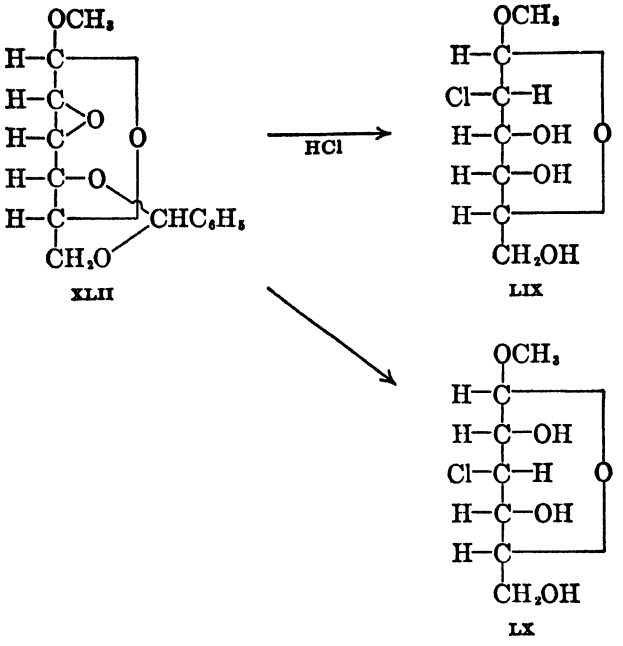
LVIII

The tendency for reversal of the direction of opening of the oxide ring on going from basic reagents to acidic ones has been observed also in the carbohydrate field. Thus, 4,6-benzylidene-2,3-anhydro-α-methylalloside (XLII, p. 40) with hydrogen chloride yields a mixture of 2-chloro-α-methylaltroside (LIX) and 3-chloro-α-methylglucoside (LX), the latter predominating, whereas ammonia gives a predominance of opening in the other direction (XLIII).[216]

Miscellaneous. It is a fact worthy of emphasis that reactions involving halohydrins under basic conditions may proceed by way of the epoxide. This will naturally affect the stereochemical result and the structure of the product. For example, in the conversion of a halohydrin to an amino alcohol, an oxide is sometimes definitely an intermediate [217] and possibly is quite generally so. Thus, indene bromohy-

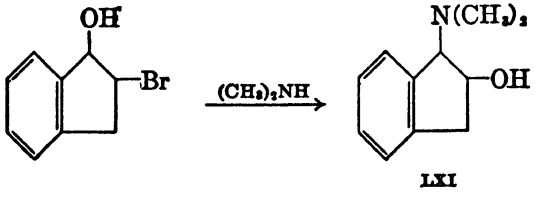
216 Newth, Overend, and Wiggins, *J. Chem. Soc.*, 10 (1947).

217 Smith and Nilsson, *J. prakt. Chem.*, [2] **162**, 63 (1943).



XLII LIX LX

drin and dimethylamine yield the 2-hydroxy-1-aminohydrindene (LXI).[218]



LXI

The base-catalyzed opening of ethylene oxide in the presence of limited amounts of water or alcohol favors a reaction of the type

$$HO(CH_2CH_2O)_nCH_2CH_2O^- + \underset{\diagdown\,O\,\diagup}{CH_2—CH_2} \rightarrow HO(CH_2CH_2O)_{n+1}CH_2CH_2O^-$$

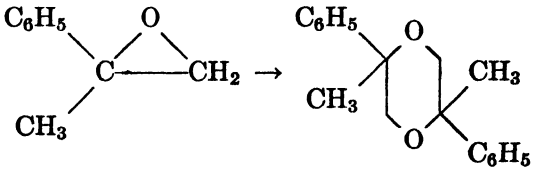
Thus, base-catalyzed polymerization produces linear polymers of various average molecular weights, depending on conditions.[219,220]

218 v. Braun and Weissbach, *Ber.*, **63**, 3052 (1930).

219 Perry and Hibbert, *J. Am. Chem. Soc.*, **62**, 2599 (1940); *Can. J. Research*, **8**, 102 (1933).

220 Brit. pat. 406,443 [*C. A.*, **28**, 4743 (1934)]; Fr. pat. 750,520 [*C. A.*, **28**, 782 (1934)]; Brit. pat. 346,550 [*C. A.*, **26**, 1941 (1932)].

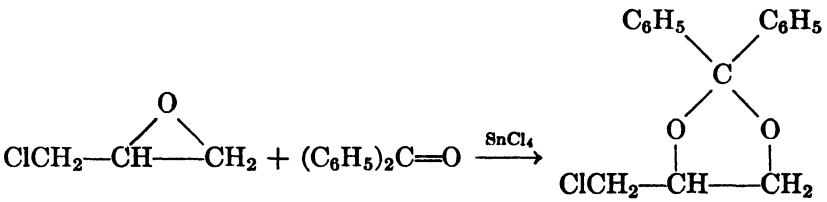
Treatment of oxides under acidic conditions can give rise to dioxanes. For example, ethylene oxide can be converted to dioxane by treatment with concentrated sulfuric acid or zinc chloride.[221] Similarly, α-methylstyrene oxide can be converted to the corresponding dioxane (LXII).[222] The corresponding glycols yield the dioxanes[223]



LXII

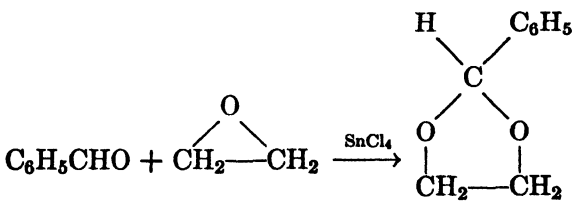
also, but the formation of dioxane from the oxide may be formulated without proceeding through the glycol.

Treatment of oxides with aldehydes or ketones with the help of acidic catalysts such as stannic chloride or boron trifluoride produces cyclic acetals or ketals. The yields are sometimes poor because simultaneous polymerization is a competing reaction. Benzophenone and epichlorohydrin yield the ketal (LXIII),[224] benzaldehyde and ethylene oxide



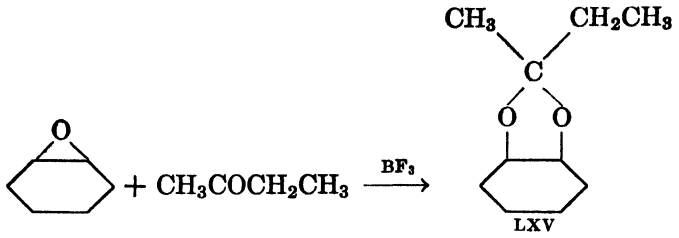
LXIII

yield 2-phenyl-1,3-dioxolane (LXIV),[225] and cyclohexene oxide and methyl ethyl ketone give the ketal (LXV).[210]



LXIV

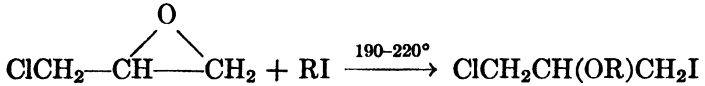
221 Favorsky, *J. Russ. Phys. Chem. Soc.*, **38**, 741 (1906); *Chem. Zentr.*, **1907**, I, 15.
222 Cohen, Marshall, and Woodman, *J. Chem. Soc.*, **107**, 898 (1915).
223 Stoermer, *Ber.*, **39**, 2288 (1906).
224 Willfang, *Ber.*, **74**, 145 (1941).
225 Bogert and Roblin, *J. Am. Chem. Soc.*, **55**, 3741 (1933).



LXV

Ethylene oxide serves as an alkylating agent in the Friedel-Crafts reaction. Benzene, toluene, anisole, etc., are converted to the β-arylethyl alcohols,[226] more vigorous conditions leading to the diarylethanes.[226,227] Ethylene and ethylene oxide, with aluminum chloride on bauxite, produce butadiene.[228]

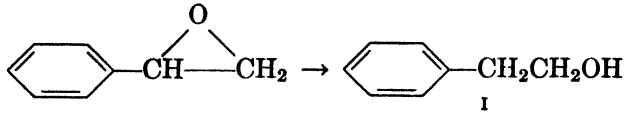
Several further miscellaneous addition reactions deserve mention. Ethylene oxide reacts rapidly with acetyl iodide, even at low temperature, to give β-iodoethyl acetate.[229] Acetyl chloride reacts much more slowly, however. Epichlorohydrin reacts with several alkyl iodides to give materials of the type of LXVI.[230] Also, ethylene oxide has been opened with arsenous chloride [231] and silicon tetrachloride.[232]



LXVI

Reduction of Ethylene Oxides

Ethylene oxides may be reduced to alcohols, either by chemical reducing agents or catalytically with hydrogen. Examples are the formation of ethyl alcohol from ethylene oxide [233] with the aid of hydrogen over a nickel or a palladium catalyst, the conversion of styrene oxide to β-phenylethyl alcohol [234] (I) with the aid of sodium and water,



I

226 Cologne and Rochas, *Compt. rend.*, **223**, 403 (1946).

227 Schaarschmitt, Hermann, and Szemzo, *Ber.*, **58**, 1914 (1925).

228 Schulze, U. S. pat. 2,371,848 [*C. A.*, **39**, 3552 (1945)].

229 Gustus and Stevens, *J. Am. Chem. Soc.*, **55**, 378 (1933).

230 Paal, *Ber.*, **21**, 2971 (1888).

231 Malinovskii, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1918 (1940) [*C. A.*, **35**, 4736 (1941)].

232 Patnode and Sauer, U. S. pat. 2,381,137 [*C. A.*, **39**, 4888 (1945)].

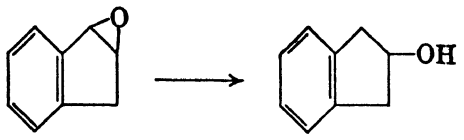
233 Ushakov and Mikhailov, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 249 (1937) [*C. A.*, **31**, 4645 (1937)].

234 Tiffeneau and Fourneau, *Compt. rend.*, **146**, 697 (1908).

and the conversion of cyclohexene oxide to cyclohexanol with hydrogen over a nickel catalyst.[235]

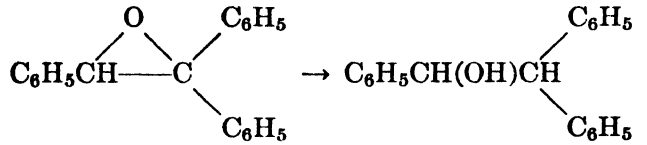
The generalization made by Stavely [236] that the hydroxyl group will be found on the carbon atom bearing the smaller number of hydrogen atoms seems to apply to aliphatic oxides. Thus, propylene oxide produces isopropyl alcohol when reduced with sodium amalgam in water.[237] The 5,6-sterol oxides appear to open with a variety of reducing agents to give the tertiary alcohol, 5-hydroxysterol.[236, 238, 239] Similarly, the 14,15-epoxysteroids open to give the tertiary rather than the secondary alcohol.[240] There may be exceptions to this rule, as indicated by the reported hydrogenation of propene and 1-butene oxides to *n*-propyl and *n*-butyl alcohol.[241]

For aryl-substituted ethylene oxides, there is a tendency for reduction to rupture the bond to the carbon atom bearing the most aryl groups. Thus, styrene oxide gives β-phenylethyl alcohol (I) on catalytic reduction [241] as well as chemical reduction, and other aryl-substituted ethylene oxides behave similarly.[242–244] Indene oxide gives 2-indanol [245] (II) on catalytic hydrogenation or on treatment with



II

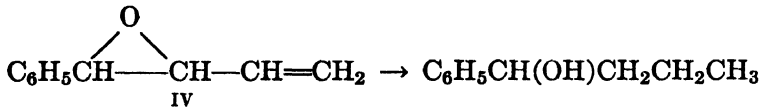
sodium in liquid ammonia, and triphenylethylene oxide yields α,β,β-triphenylethyl alcohol [243] (III) on hydrogenation over a nickel catalyst.



III

235 Brunel, *Ann. chim.*, [8] **6**, 237 (1905).
236 Stavely, *J. Am. Chem. Soc.*, **64**, 2723 (1942).
237 Linnemann, *Ann.*, **140**, 178 (1866).
238 Fernholz, *Ann.*, **508**, 215 (1933).
239 Swiss pat. 214,540 [*C. A.*, **36**, 4977 (1942)].
240 Plattner et al., *Helv. Chim. Acta*, **29**, 2023 (1946).
241 Brit. pat. 320,424 [*C. A.*, **24**, 2468 (1930)].
242 Billon-Bardon, *Compt. rend.*, **188**, 1412 (1929).
243 Weill and Kayser, *Bull. soc. chim. France*, [5] **3**, 841 (1936).
244 Kohler and Tishler, *J. Am. Chem. Soc.*, **57**, 217 (1935).
245 Whitmore and Gebhart, *J. Am. Chem. Soc.*, **64**, 912 (1942).

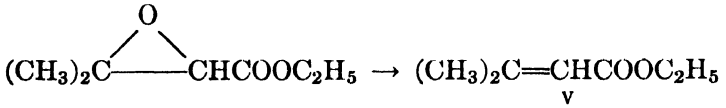
Apparent exceptions to this generalization for aryl-substituted oxides are to be found with vinyl-substituted arylethylene oxides,[246,247] in which the bond to the carbon with the vinyl substituent is reported to be broken on reduction. Thus, α-phenyl-β-vinylethylene oxide (IV) is



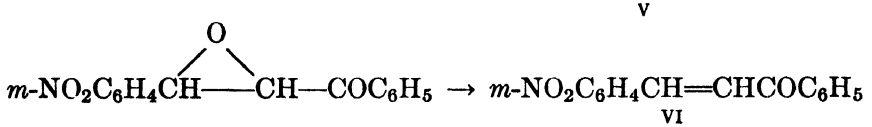
IV

reported to yield α-phenylbutyl alcohol [246] on hydrogenation over Raney nickel.

Treatment of glycidic acids or esters or oxido ketones with hydrogen iodide normally reduces these materials to olefinic substances. For example, β,β-dimethylglycidic ester is reduced to β-methylcrotonic ester (V),[248] and *m*-nitrobenzalacetophenone oxide is converted to *m*-nitrobenzalacetophenone (VI).[80]

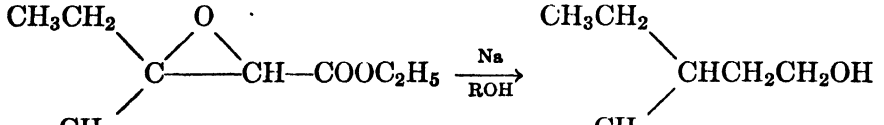


V



VI

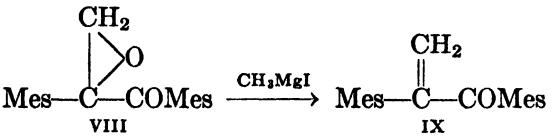
Several glycidic esters have been reduced to saturated alcohols with sodium and alcohol, as in the conversion of β-methyl-β-ethylglycidic ester (VII) to 3-methyl-1-pentanol.[249]



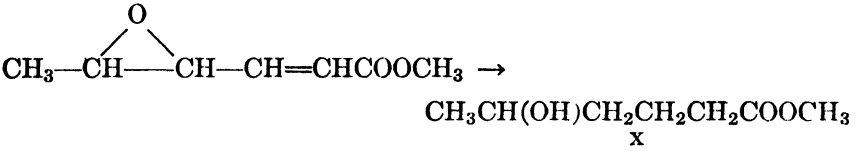
VII

An interesting reduction has been discovered by Fuson and co-workers [87] to take place when 1-mesityl-1-mesitoylethylene oxide (VIII) and similar hindered α-oxido ketones are treated with methylmagnesium iodide, VIII giving rise to the unsaturated ketone (IX).

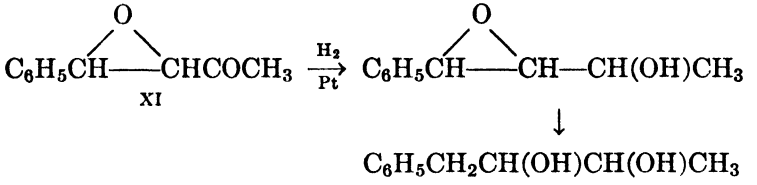
246 Abragam and Deux, *Compt. rend.*, **205**, 285 (1937).
247 Deux, *Compt. rend.*, **213**, 209 (1941).
248 Darzens, *Compt. rend.*, **150**, 1243 (1910).
249 Verley, *Bull. soc. chim. France*, [4] **35**, 487 (1924).



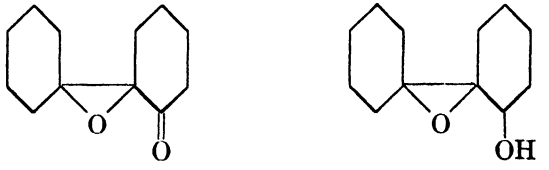
In substances containing unsaturated centers in addition to the ethylene oxide ring, it is interesting to observe the relative rates of reduction of the different groupings. With methyl 4,5-epoxy-2-hexenoate, the oxide ring is reduced more rapidly than the double bond by hydrogen over a platinum catalyst.[250] The final product is methyl hydroxycaproate (X), corresponding to the opening of the oxide ring at the vinyl-substituted carbon atom.



Oxido ketones of the type of (XI) are reduced catalytically at the ketone function more rapidly than at the oxide ring.[81] Thus, XI may



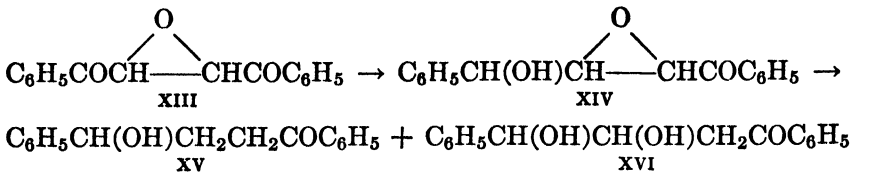
be reduced to 1-phenyl-1,2-epoxy-3-butanol, further reduction yielding a glycol. Similarly, the oxide of cyclohexylidenecyclohexanone is hydrogenated to the glycidol (XII).[36]



XII

Reduction of oxido ketones such as XIII with chemical agents (potassium iodide in acetic acid, iodine and phosphorus, zinc and ammonium chloride in ethanol, sodium dithionate, or zinc in acetic acid)

250 Heinänen, *Suomen Kemistilehti*, **16B**, 14 (1942) [*C. A.*, **39**, 4051 (1945)].



proceeds first at the oxide ring. Sodium in alcohol leads to the 1,4-glycol. Hydrogenation with Raney nickel reduces the oxide ring to an alcohol or saturated hydrocarbon before the carbonyls are altered, but platinum in ethanol causes reduction of a carbonyl group first (XIII–XIV). The compound XIV, containing an hydroxyl group, an oxide ring, and a carbonyl group, is reduced by Raney nickel to a mixture containing mostly XV and some XVI.[251,252]

Oxidation of Ethylene Oxides

The oxidation of an ethylene oxide sometimes yields an hydroxy acid. Thus, ethylene oxide oxidized over platinum black with oxygen gives glycolic acid,[253] and epichlorohydrin with nitric acid produces β-chlorolactic acid.[254] Oxidation of some ethylene oxides results in ring opening and cleavage of the carbon-to-carbon bond. Thus, propylene oxide, on oxidation with oxygen over silver oxide, yields acetic acid,[255] stilbene oxide with chromic acid gives benzoic acid,[256] and treatment of tetraarylethylene oxides with chromic acid yields the corresponding benzophenones.[95,96,257]

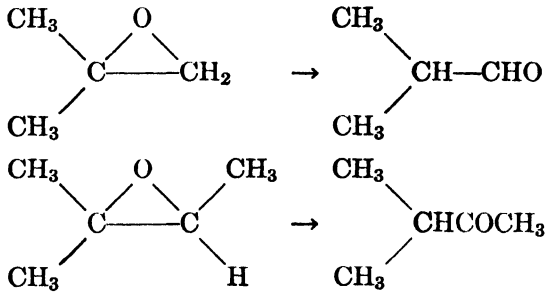
A few oxidations have been carried out on ethylene oxides containing other functional groups, and these groups have been oxidized preferentially.[254]

When treated with chlorine, epichlorohydrin in diffuse light yields 3,3-dichloro-1,2-epoxypropane,[258] whereas propylene oxide [259] under anhydrous conditions yields chloroacetone and propylene chlorohydrin.

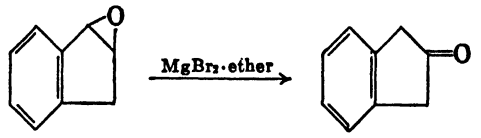
251 Lutz and Wood, *J. Am. Chem. Soc.*, **60**, 229 (1938).
252 Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 2065 (1934).
253 Wurtz, *Ann. chim.*, [3] **69**, 317 (1863).
254 v. Richter, *J. prakt. Chem.*, [2] **20**, 193 (1879).
255 Linnemann, *Monatsh.*, **6**, 369 (1885).
256 Rabe and Hallensleben, *Ber.*, **43**, 884 (1910).
257 Thörner, *Ber.*, **11**, 65 (1878).
258 Cloetz, *Ann. chim.*, [6] **9**, 145 (1886).
259 Dobryanskii, Davydova, and Papkina, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 291 (1937) [*C. A.*, **31**, 4645 (1937)].

Rearrangements and Cleavage Reactions

Formation of Carbonyl Compounds. Ring Enlargements. Ethylene oxides may be rearranged to carbonyl compounds on being heated alone or with catalysts. Thus, ethylene oxide gives acetaldehyde at 500° or at 200–300° over aluminum oxide.[260] Similarly, but more easily, isobutylene oxide yields isobutyraldehyde, and trimethyleth-

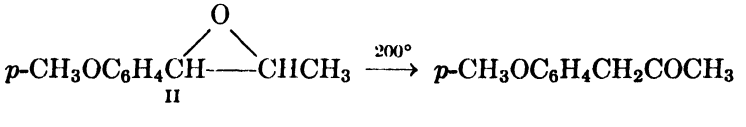


ylene oxide yields methyl isopropyl ketone. Also, indene oxide (I) is isomerized by magnesium bromide etherate to 2-indanone,[261] anethole

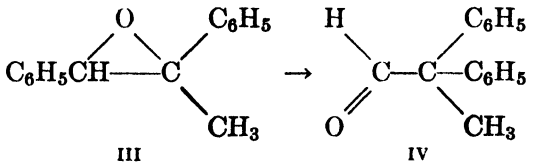


I

oxide (II) is isomerized by heat to *p*-methoxyphenylacetone,[46] and α-methyl-α,β-diphenylethylene oxide (III) may be isomerized to the substituted acetaldehyde (IV).[262]



II



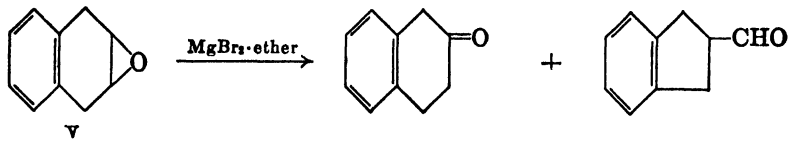
III IV

260 Ipatieff and Leontowitsch, *Ber.*, **36**, 2016 (1903).

261 Tchoubar, *Compt. rend.*, **214**, 117 (1942).

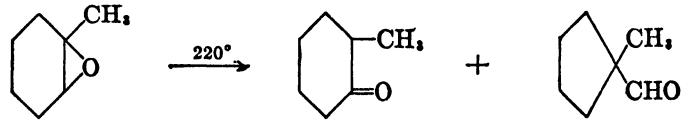
262 Tiffeneau and Levy, *Bull. soc. chim. France*, [4] **49**, 1806 (1931).

The group that migrates in the rearrangement of an ethylene oxide may be involved in a ring, with consequent change in ring size. For example, 1,4-dihydronaphthalene oxide (V), when rearranged with the



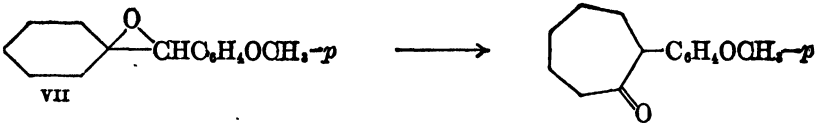
V

aid of magnesium bromide etherate, yields, besides β-tetralone, some 2-indanaldehyde.[261] Similarly, 1-methylcyclohexene oxide (VI)



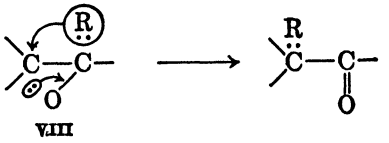
VI

yields some 1-methylcyclopentylformaldehyde, along with 2-methylcyclohexanone.[18] Ring enlargement has been reported in the rearrangement of the oxide of anisalcyclohexane (VII) to anisylcycloheptanone.[18]



VII

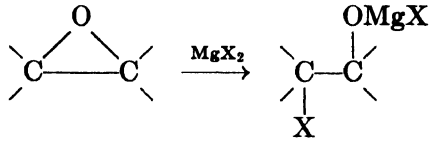
Mechanism and Prediction of Course of Openings Involving Rearrangement. Electronically, the rearrangement of an oxide may be symbolized by formula VIII. In the over-all process, one of the carbon-



VIII

oxygen bonds has ionized, the shared pair of electrons has gone to make the carbonyl double bond, and a group, R, together with a shared pair of electrons has migrated to the carbon atom from which the carbon-oxygen bond ionized. The catalysis by acids is due to the greater reactivity of species, such as the conjugate acid of the oxide.

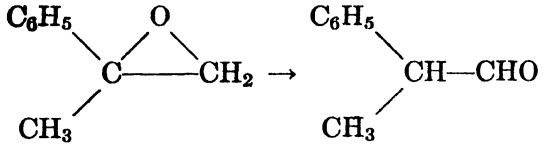
The rearrangement is closely related to the pinacol rearrangement, and some of the intimate details are not yet clear. It often is not clear whether the oxide rearranges or whether something produced from it under the conditions of the reaction actually rearranges. With magnesium bromide, the halomagnesium salt of the halohydrin (IX) is formed, and this species may do the rearranging.



IX

The direction of opening of oxides in rearrangements may in general be predicted simply on the basis of the relative ease of ionization of the two carbon-oxygen bonds in question. By analogy with other situations in organic chemistry, the sequence is expected to be tertiary > secondary > primary for the aliphatic series. The rearrangements of isobutylene oxide and trimethylethylene oxide illustrate this rule. Similarly, propylene oxide gives largely propionaldehyde.[260] The rearrangement of 1-methylcyclohexene oxide (VI) is another example.

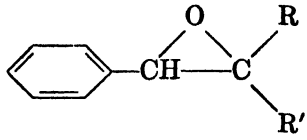
Aryl groups are superior to alkyl groups in increasing the ease of ionization of the carbon-oxygen bond. The above rule may be generalized to state that, in rearrangements, the carbon-oxygen bond that tends to be broken is the one to the carbon atom substituted to the greatest extent with groups promoting ionization, namely alkyl and aryl. The rule is illustrated by the reactions of indene oxide (I), α-methyl-α,β-diphenylethylene oxide (III), and anethole oxide (II), quoted above. Similarly, styrene oxide yields phenylacetaldehyde,[263] and α-methylstyrene oxide (X) yields α-methylphenylacetaldehyde.[211]



X

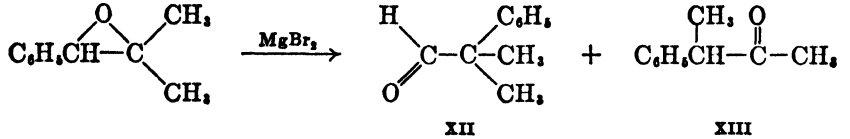
A phenyl group is roughly the equivalent of two alkyl groups in promoting ionization, and thus the nature of the products in the rearrangement of oxides of the type of XI may vary, depending on sub-

263 Breuer and Zinke, *Ber.*, **11**, 1399 (1878).

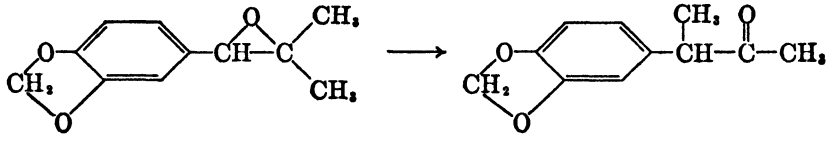


XI

stitution in the benzene ring and the nature of R and R′. Thus, β,β-dimethylstyrene oxide gives rise to a mixture consisting very largely of α,α-dimethylphenylacetaldehyde (XII), together with a little α-phenyl-α-methylacetone (XIII).[264,265] On the other hand, the 3,4-methylenedioxy derivative (XIV) gives largely the reversed mode of opening with the ketone (XV) as the product.[266] This shift in the



XII XIII



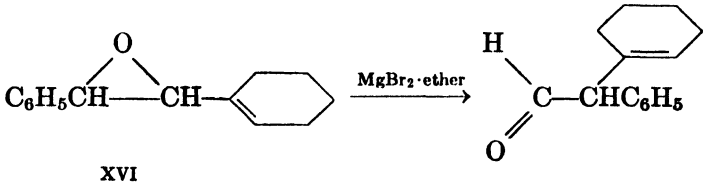
XIV XV

nature of the product is in line with the electron-supplying nature of the methylenedioxy group. When R and R′ in formula XI are both ethyl, or methyl and ethyl, or methyl and propyl, a mixture of products results, corresponding to cleavage at either carbon-oxygen bond.[265] When R is benzyl and R′ is methyl, ethyl, propyl, or benzyl, the rupture occurs mainly at the phenyl-substituted carbon atom with migration of the benzyl group.[265]

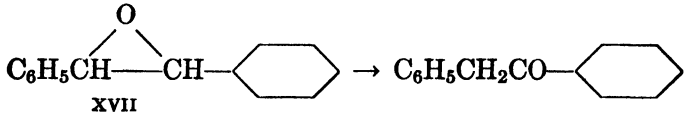
Vinyl substitution, like phenyl substitution, weakens a carbon-oxygen bond with respect to ionization, and there are a number of reports of rearrangements of ethylene oxides involving breakage of the bond to a vinyl-substituted rather than a phenyl-substituted carbon atom.[246,267] For example, the phenyl cyclohexenyl ethylene oxide

264 Poctivas and Tchoubar, *Compt. rend.*, **205**, 287 (1937).
265 Levy and Tabart, *Compt. rend.*, **188**, 402 (1929).
266 Tiffeneau and Levy, *Compt. rend.*, **190**, 1510 (1930).
267 Deux, *Compt. rend.*, **211**, 441 (1940); **208**, 1090, 2002 (1939); **212**, 795 (1941).

(XVI) is rearranged to phenyl cyclohexenyl acetaldehyde [268] in contrast to the cyclohexyl analog (XVII), which rearranges with cleavage of the other carbon-oxygen bond to give benzyl cyclohexyl ketone.



XVI

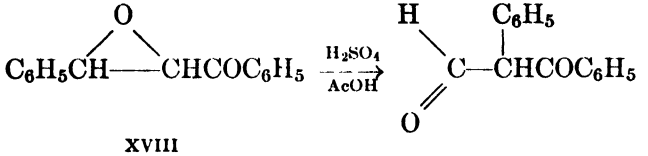


XVII

There has been a vast amount of work on the question of relative migration aptitudes of different groups in the rearrangements of the type illustrated, and it is not within the scope of the present discussion to deal at length with this subject. In general, phenyl or benzyl will migrate before hydrogen, and hydrogen will migrate before methyl.

Attempted addition reactions sometimes give the addition compound of the rearranged carbonyl compound. Thus, α-methylstyrene oxide, when treated with bisulfite, yields partly the hydrogen sulfite compound of the rearranged aldehyde.[269] Similarly, styrene oxide and hydrogen cyanide yield the cyanohydrin of phenylacetaldehyde.[270]

The α-oxido ketones may be transformed to dicarbonyl compounds, but these reactions have not been studied in detail. By treatment with sulfuric acid in glacial acetic acid, Weitz and Scheffer [271] transformed benzalacetophenone oxide (XVIII) to formyldesoxybenzoin.



XVIII

Similarly, benzalacetone oxide is converted to α-phenylacetoacetic aldehyde. Several substituted benzalacetophenone oxides have also been similarly rearranged under acidic conditions.[272]

268 Tiffeneau and Kuriaki, *Compt. rend.*, **209**, 465 (1939).

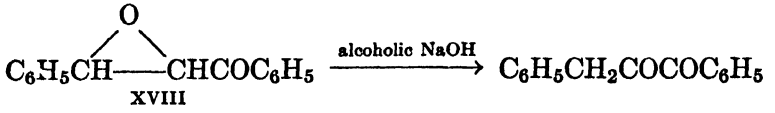
269 Klages, *Ber.*, **38**, 1969 (1905).

270 Fourneau and Tiffeneau, *Compt. rend.*, **146**, 697 (1908).

271 Weitz and Scheffer, *Ber.*, **54**, 2344 (1921).

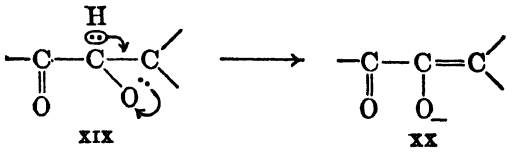
272 Algar and McKenna, *Proc. Roy. Irish Acad.*, **49**, 225 (1944) [*C. A.*, **38**, 5502 (1944)].

Oxides such as benzalacetophenone oxide (XVIII) may also be converted to 1,2 diketones. Thus, alcoholic sodium hydroxide converts XVIII to benzoyl benzyl ketone.[273] This rearrangement may be the

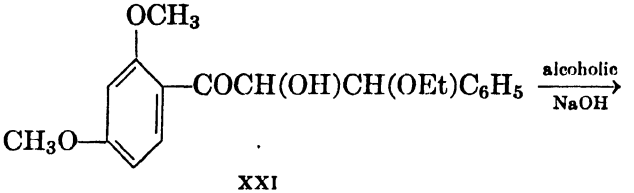


XVIII

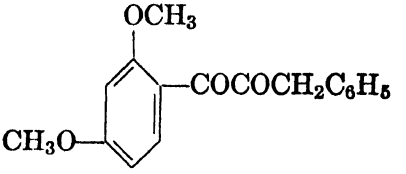
result of an elimination reaction symbolized in formulas XIX and XX. An attack on a relatively acidic hydrogen atom *alpha* to the



carbonyl group can break the oxide ring with the formation of the enol ion (XX). This type of elimination is analogous to some other reactions of oxides. On the other hand, another conceivable rearrangement path involves opening the oxide ring by addition, followed by formation of an α,β-olefinic linkage by elimination. In fact, compound XXI yields a 1,2 diketone on treatment with alcoholic sodium hydroxide.[274]



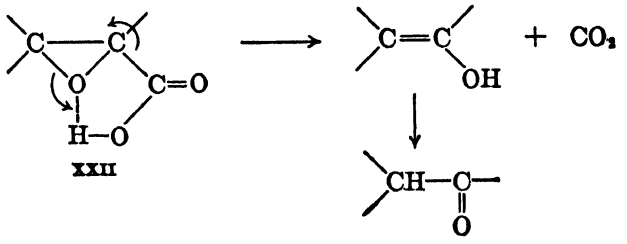
XXI



Decarboxylation of Glycidic Acids. Decarboxylation of glycidic acids produces aldehydes or ketones and is part of the Darzens method for preparing these materials. The reaction is analogous to the decarboxylation of β-keto acids, and Arnold has suggested a cyclic mecha-

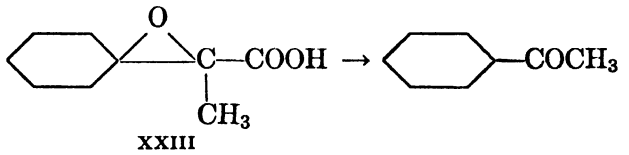
273 Jörlander, *Ber.*, **50**, 406 (1917).
274 Baker and Robinson, *J. Chem. Soc.*, 1798 (1932).

nism as a possibility here.[275] The chelated molecule (XXII) is thought to cleave directly to carbon dioxide and the enol modification of the



XXII

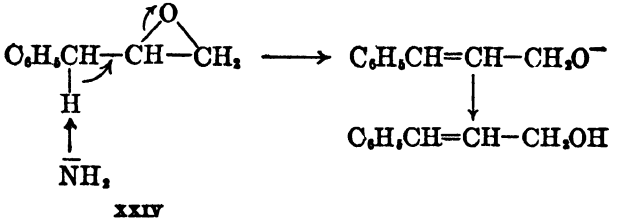
final product. The decarboxylation may be illustrated by the formation of cyclohexyl methyl ketone from the glycidic acid (XXIII).[75]



XXIII

Usually a glycidic acid is heated to cause decarboxylation, but sometimes better yields are obtained when the glycidic acid is treated with hydrogen chloride to produce the chlorohydroxy acid which is then heated in pyridine.[75]

There are several examples of other cleavage reactions of ethylene oxides. Benzylethylene oxide is transformed by sodamide into cinnamyl alcohol.[276] Apparently, as indicated in formula XXIV, the attack of



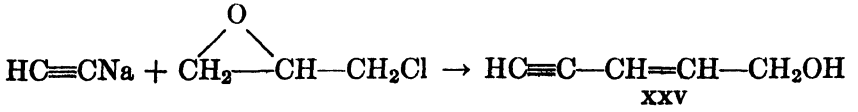
XXIV

amide ion is on a hydrogen atom, and an olefinic linkage is created and the oxide ring is broken to produce the cinnamyl alcoholate ion. Similarly, the action of sodium acetylide on epichlorohydrin gives rise to

275 Arnold, abstract of paper, *The Stereochemistry of Five- and Six-Membered Rings*, delivered at the Tenth National Organic Symposium of the American Chemical Society, Boston, June 1947.

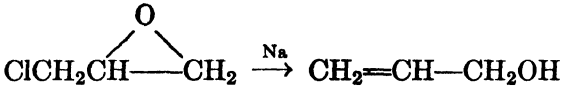
276 Haynes et al., *J. Chem. Soc.*, 1583 (1947).

the alcohol (XXV); the elimination-cleavage reaction occurs after the usual sequence of reactions typical for epichlorohydrin. Epichloro-

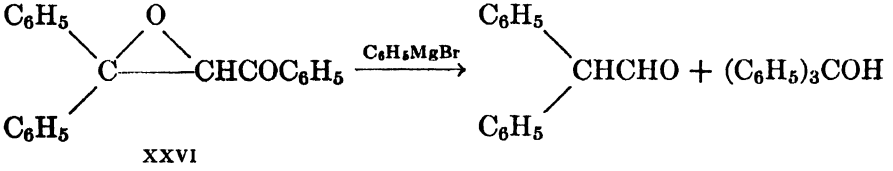


XXV

hydrin yields allyl alcohol on treatment with sodium,[277,278] a reaction which is analogous to the formation of an olefin by the treatment of a 1,2-dihalide or a β-halo ether with sodium, zinc, or magnesium.

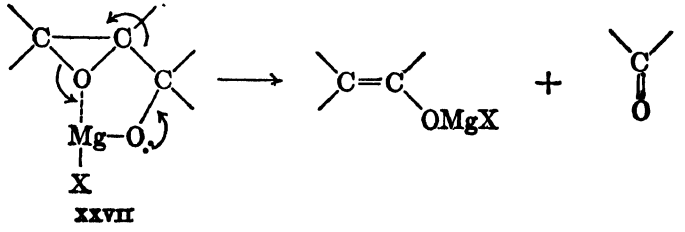


Closely analogous to the decarboxylation of glycidic acids is the cleavage shown by the halomagnesium salts of glycidols. Thus, treatment of α-oxido ketones such as XXVI with a Grignard reagent results



XXVI

in a cleavage reaction, with diphenylacetaldehyde and triphenylcarbinol the specific products in the example chosen.[279] A possible formulation of this cleavage may be symbolized as follows:



XXVII

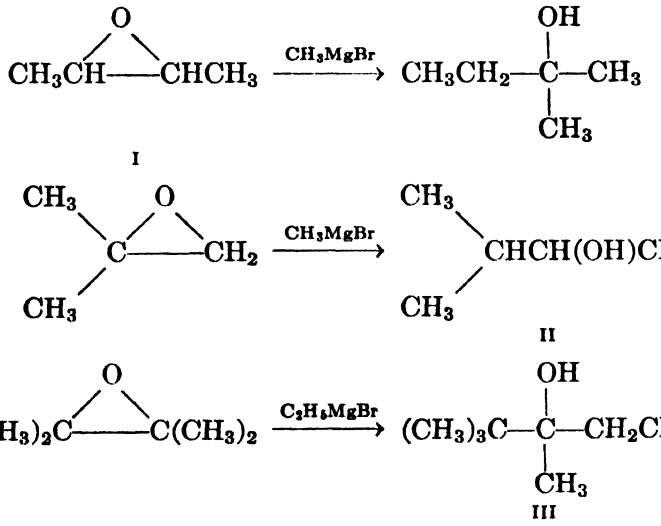
The adduct (XXVII) cleaves to the enolate and the carbonyl compound, and further reaction is possible to give products such as the triphenylcarbinol from XXVI.

277 Claus, *Ber.*, **10**, 556 (1877).
278 Tornöe, *Ber.*, **21**, 1290 (1888).
279 Kohler, Richtmyer, and Hester, *J. Am. Chem. Soc.*, **53**, 205 (1931).

Reaction with Grignard Reagents

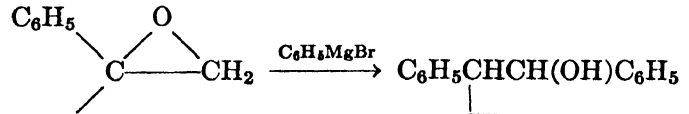
Occurrence of Rearrangements. Grignard reagents react less readily with ethylene oxides than with carbonyl compounds.[280,281] Ethylene oxide may be used for the preparation of primary alcohols, for example, *n*-hexyl alcohol from butylmagnesium bromide.[282] Although the product of treatment of an oxide with a Grignard reagent corresponds simply to an opening of the ring in some cases, rearrangements are very commonly observed.

Even in the reaction of ethylene oxide with *n*-butylmagnesium bromide, some 2-hexanol is produced.[283] Propylene oxide and ethylmagnesium bromide yield 3-pentanol along with 2-pentanol,[284] and the more alkyl-substituted ethylene oxides yield, on treatment with Grignard reagents, carbinols related to the rearrangement products. Thus, either *cis*- or *trans*-2,3-epoxybutane (cf. p. 30) (I) yields *t*-amyl alcohol [285] on treatment with methylmagnesium bromide, isobutylene oxide yields 3-methyl-2-butanol (II),[286] and tetramethylethylene oxide, with ethylmagnesium bromide, is converted [284] to 2,2,3-trimethylpentanol-3 (III). Similarly, the reaction of α-methylstyrene oxide



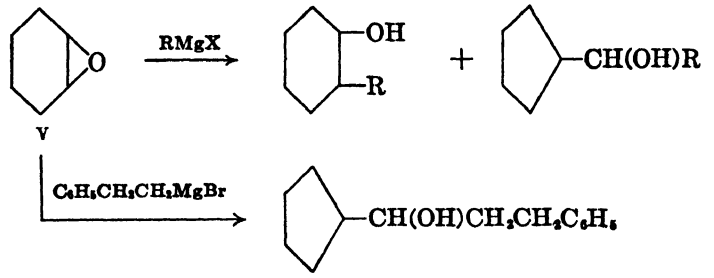
280 Grignard, *Compt. rend.*, **136**, 1260 (1903).
281 Fourneau and Tiffeneau, *Bull. soc. chim. France*, [4] **33**, 741 (1905).
282 Dreger, *Org. Syntheses Coll. Vol.* **1**, 306 (1941).
283 Cottle and Hollyday, *J. Org. Chem.*, **12**, 510 (1947).
284 Norton and Hass, *J. Am. Chem. Soc.*, **58**, 2147 (1936).
285 Henry, *Compt. rend.*, **145**, 458 (1907).
286 Henry, *Compt. rend.*, **145**, 21 (1907).

(IV) with phenylmagnesium bromide gives rise to 2-methyl-1,2-diphenylethanol.[287] When a cycloalkene oxide is treated with a Grignard



IV

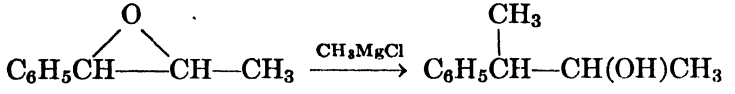
reagent, the rearrangement may give rise to ring contraction. Thus, from cyclohexene oxide V one obtains, with some of the expected alcohol, a cyclopentyl alkylcarbinol.[288, 289] In this way, with the β-phenyl-



V

ethyl Grignard reagent, cyclopentyl β-phenylethylcarbinol is obtained.[290, 291]

It is interesting that cyclohexene oxide gives the normal product with benzylmagnesium chloride.[292] Similarly, rearrangement is not observed in the reaction of propenylbenzene oxide with the methyl Grignard reagent, 3-phenylbutanol-2 being obtained.[29]



It is quite clear that the rearrangements are due to the halide component of the Grignard reagent. Often the product of reaction between an ethylene oxide and a Grignard reagent at room temperature or below is a halohydrin after hydrolysis.[293] For example, cyclohexene oxide and methylmagnesium iodide give rise to the iodohydrin

287 Tiffeneau, *Compt. rend.*, **140**, 1458 (1905).

288 Godchot and Bedos, *Bull. soc. chim. France*, [4] **43**, 521 (1928); *Compt. rend.*, **174**, 461 (1922).

289 Vavon and Mitchovitch, *Compt. rend.*, **186**, 702 (1928).

290 Robinson, *J. Chem. Soc.*, 80 (1936).

291 Fulton and Robinson, *J. Chem. Soc.*, 1463 (1933).

292 Cook, Hewett, and Lawrence, *J. Chem. Soc.*, 71 (1936).

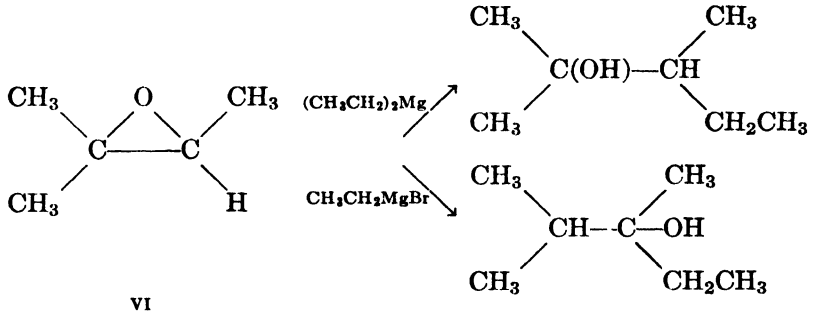
293 Meisenheimer et al., *Ann.*, **442**, 180 (1925).

when the unheated mixture is hydrolyzed.[288] The reaction with oxide appears to shift the equilibrium, $2RMgX = R_2Mg + MgX_2$, the insoluble product from the reaction of 1 mole of ethylene oxide with 1 mole of Grignard reagent being the same as the one obtained from passing the oxide into an ethereal solution of magnesium bromide.[294] Although the addition of more oxide will give the desired reaction, presumably by the action of the dialkylmagnesium, the usual procedure is to distil off the solvent ether and to heat the reaction mixture. The halohydrin magnesium salt must be able to rearrange to aldehyde or ketone; magnesium bromide is often used to rearrange oxides.

With cyclohexene oxide itself, magnesium bromide etherate produces cyclopentylformaldehyde.[295,296]

Use of Dialkylmagnesium to Avoid Rearrangements. The use of dialkylmagnesium instead of the conventional Grignard reagent eliminates halohydrin formation and rearrangement. Thus, cyclohexene oxide and dimethylmagnesium or diethylmagnesium produces only the normal *trans*-2-alkylcyclohexanol[297] to be expected from a nucleophilic displacement which opens the oxide ring. The action of an aryllithium is similar, cyclohexene oxide being converted by phenyllithium to *trans*-2-phenylcyclohexanol.[292]

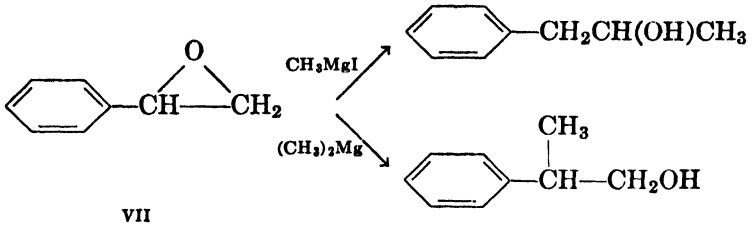
The action of diethylmagnesium on the methyl-substituted ethylene oxides from propylene oxide to tetramethylethylene oxide yields unrearranged alcohols derived from nucleophilic attack on the least substituted carbon atom.[284] For example, trimethylethylene oxide (VI)



VI

yields 2,3-dimethyl-2-pentanol, in contrast to the 2,3-dimethyl-3-pentanol which is obtained with ethylmagnesium bromide. Styrene oxide (VII) with methylmagnesium iodide gives 1-phenylpropanol-2, but, with dimethylmagnesium, 2-phenylpropanol-1 is obtained.[212]

294 Huston and Agett, *J. Org. Chem.*, **6**, 123 (1941).
295 Bedos, *Compt. rend.*, **189**, 255 (1929).
296 Clemo and Ormston, *J. Chem. Soc.*, 362 (1933).
297 Bartlett and Berry, *J. Am. Chem. Soc.*, **56**, 2683 (1934).

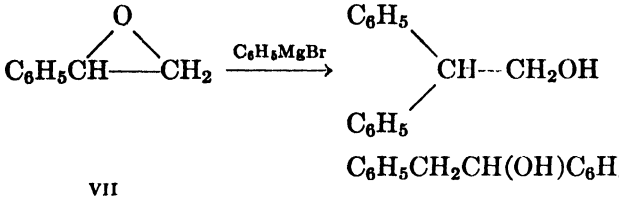


VII

Epichlorohydrin with magnesium bromide or ethylmagnesium bromide yields only ethane, ethylene, tar, and a low-boiling alcohol believed to be cyclopropanol. With diethylmagnesium, epichlorohydrin is converted to 1-chloropentanol-2 in good yield.[298]

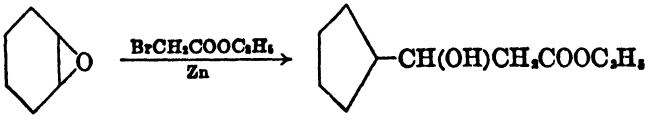
An interesting effect of configuration of the oxide is the much higher yield of 3-methylpentanol-2 obtained from the *cis*-2,3-epoxybutane (II of p. 2) than from the *trans* isomer (III of p. 2) with diethylmagnesium.

An unusual effect of the order of addition of the Grignard reagent has been reported by Kharasch and Clapp.[299] When styrene oxide (VII) was added to phenylmagnesium bromide, the product was β,β-diphenylethyl alcohol, but addition in the reverse order gave α,β-diphenylethyl alcohol. Similar results were obtained with styrene oxide and *p*-methoxyphenylmagnesium bromide.



VII

Analogous to the rearrangements observed in the reactions of Grignard reagents with ethylene oxides are the Reformatsky reactions of cyclohexene and cyclopentene oxides with ethyl bromoacetate.[296] Cyclohexene oxide yields the product (VIII) derived from cyclopentylformaldehyde, and cyclopentene oxide yields the product derived from cyclopentanone.



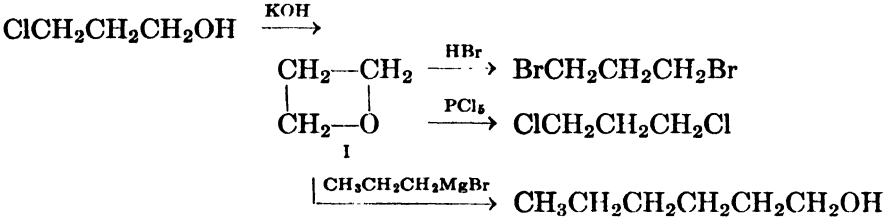
VIII

298 Magrane and Cottle, *J. Am Chem. Soc.*, **64**, 484 (1942).
299 Kharasch and Clapp, *J. Org. Chem.*, **3**, 355 (1938).

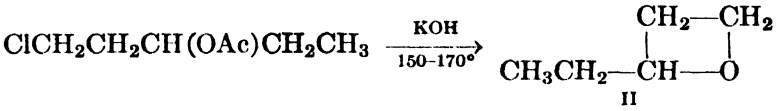
TRIMETHYLENE OXIDES

Trimethylene oxides, or 1,3 oxides, have been very little investigated and are quite rare. In general, they are much less reactive than the ethylene oxides.

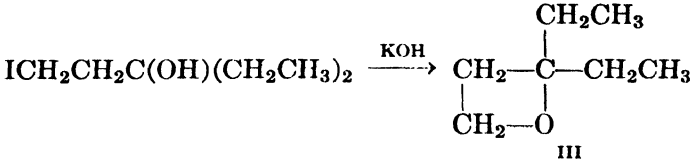
The only method of any generality for preparing trimethylene oxides is the dehydrohalogenation of the corresponding halohydrin. In this way, trimethylene oxide (I) (oxetane, oxacyclobutane) may be pre-



pared from trimethylene chlorohydrin[300] or, preferably, its acetate. Similarly, α-ethyltrimethylene oxide[301] (II) may be prepared from



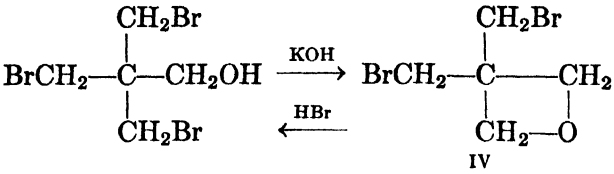
1-chloro-3-pentanol acetate, and 2,2-diethyloxacyclobutane (III) is formed from 1-iodo-3-ethyl-3-pentanol.[302]



The rate of the reaction for formation of the 1,3 oxides is quite slow, and there are competing reactions such as ordinary substitution and elimination processes. Therefore, the yields of trimethylene oxides are generally low. However, the yields are high when elimination and ordinary substitution are virtually prevented as they are with pentaerythritol derivatives such as pentaerythritol tribromohydrin.

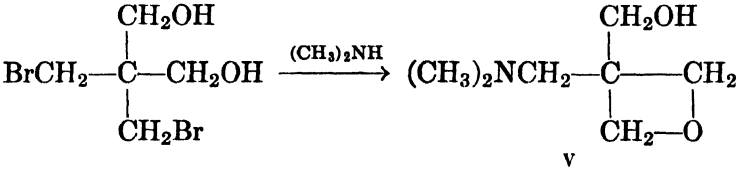
300 Derick and Bissell, *J. Am. Chem. Soc.*, **38**, 2483 (1916).
301 Lespieau, *Bull. soc. chim. France*, [5] **7**, 254 (1940).
302 Dalebroux and Wuyts, *Bull. soc. chim. Belg.*, **20**, 156 (1906).

This substance, with no β-hydrogen atoms and with ordinary substitution opposed by steric hindrance, gives a high yield of 3,3-dibromomethyloxacyclobutane [303] (IV). In the reaction of pentaerythritol di-



IV

bromohydrin with dimethylamine, considerable 3-hydroxymethyl-3-dimethylaminomethyloxacyclobutane [304] (V) is found in the product.



V

There are a few examples of reactions of 1,3 oxides which are analogous to those of the 1,2 oxides. Thus, trimethylene oxide is converted by hydrobromic acid to trimethylene bromide,[300] by phosphorus pentachloride to trimethylene chloride,[300] and by the propyl Grignard reagent to 1-hexanol.[300] Similarly, the 3,3-dibromomethyloxacyclobutane (IV) is converted by hydrogen halides to the pentaerythritol trihalohydrins.[303]

303 Govaert and Beyaert, *Natuurw. Tijdschr.*, **22**, 73 (1940); *Chem. Zentr.*, **1941**, I, 1810 [*C. A.*, **37**, 3045 (1943)].

304 Fourneau, Matti, and Dunant, *Bull soc. chim. France*, [5] **4**, 1155 (1937).

CHAPTER 2

ETHYLENIMINE

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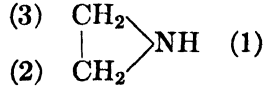
CONTENTS

Among the saturated heterocyclic compounds containing nitrogen, ethylenimine (I) (otherwise termed aziridine, azacyclopropane, or dimethylenimine [1]) represents the simplest member of the homologous series which also includes propylenimine, pyrrolidine, and piperidine.



I

Synthesis of Ethylenimine. As a result of the active interest, during the latter part of the nineteenth century, in the chemistry of the heterocyclic compounds, a number of efforts were made at that time to prepare ethylenimine. Ladenburg and Abel [2] heated ethylene diamine hydrochloride but, in place of the expected ethylenimine, obtained piperazine as the principal product. This method, which is suitable

1 Patterson and Capell, *The Ring Index*, Reinhold Publishing Corp., New York, 1940.
2 Ladenburg and Abel, *Ber.*, **21**, 758 (1888).

for the synthesis of pyrrolidine and piperidine from tetra- and pentamethylenediamine, respectively, is therefore not applicable to the preparation of ethylenimine.

The first successful preparation of ethylenimine was described by Gabriel,[3,4] who showed that, on treatment of β-bromoethylamine hydrobromide with silver oxide or, preferably, with concentrated potassium hydroxide, there is formed a reactive base which he formulated as vinylamine $CH_2{=}CHNH_2$. Subsequent work of Marckwald,[5,6] however, showed that the product of the reaction is ethylenimine.

$$\begin{matrix} CH_2Br \\ | \\ CH_2NH_2 \end{matrix} \rightarrow \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>\!NH + HBr$$

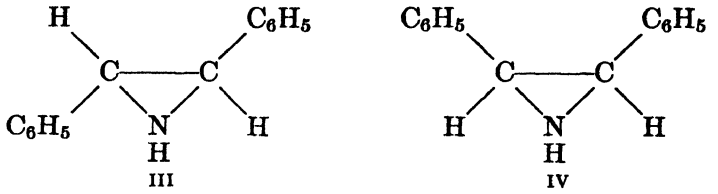
Wenker[7] has described a convenient method for the preparation of ethylenimine from ethanolamine which, if heated with sulfuric acid, yields the inner salt (II). Distillation of II with alkali gives ethylenimine.

$$\begin{matrix} CH_2OSO_3^- \\ | \\ CH_2NH_3^+ \end{matrix}$$

II

Preparation of Substitution Derivatives of Ethylenimine. The application of the Gabriel method to a variety of halogenated alkylamines has led to the successful synthesis of numerous derivatives of ethylenimine. Thus, 2-methylethylenimine was prepared from β-bromoisopropylamine[8] by treatment with alkali, and 2-phenylethylenimine (styrenimine) was made in a similar manner from β-phenyl-β-chloroethylamine.[9] 2,3-Diphenylethylenimine was made by the action of alkali on α-amino-β-chlorodibenzyl.[10] Since two isomeric forms of this β-halogenated amine are possible, each of these may be expected to yield different isomers of 2,3-diphenylethylenimine. Weissberger and Bach showed that optically active *trans*-diphenylethylenimine (III) is formed upon treatment of *l*-iso-α-amino-β-chlorodibenzyl with alkali, and the optically inactive *cis* isomer (IV) arises from

3 Gabriel, *Ber.*, **21**, 1049 (1888).
4 Gabriel and Stelzner, *Ber.*, **28**, 2929 (1895).
5 Howard and Marckwald, *Ber.*, **32**, 2036 (1899).
6 Marckwald, *Ber.*, **33**, 764 (1900).
7 Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935).
8 Gabriel and Hirsch, *Ber.*, **29**, 2747 (1896).
9 Wolfheim, *Ber.*, **47**, 1450 (1914).
10 Weissberger and Bach, *Ber.*, **64**, 1095 (1931).

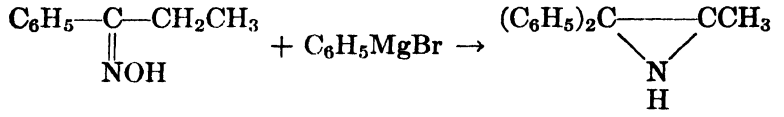


III IV

l-α-amino-β-chlorodibenzyl. 2,3-Diphenylethylenimine has also been prepared by the reaction of α-amino-β-chlorodibenzyl with hydrazine.[11]

It may be noted that the Wenker method is not applicable to the preparation of aryl-substituted ethylenimines from the corresponding amino alcohols. Treatment of such amino alcohols with sulfuric acid leads to the formation of vinylamines and other products.[12] On the other hand, difficulties were encountered in attempts to prepare 2,2-dialkylethylenimines by the Gabriel method [13] but substances of this type may be made by the Wenker method. Thus, Cairns [14] has synthesized 2,2-dimethylethylenimine from 2-methyl-2-amino-1-propanol by successive treatment with sulfuric acid and alkali.

Of considerable interest is the method introduced by Hoch [15] and developed by Campbell.[16] This involves the reaction of a ketoxime with Grignard reagent, followed by hydrolysis of the Grignard complex. In this manner, it is possible to prepare 2-methyl-3,3-diphenylethylenimine by the reaction of propiophenone oxime with phenylmag-

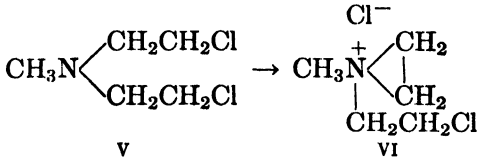


nesium bromide. In an analogous manner, 2-ethyl-3,3-diphenylethylenimine has been made from butyrophenone oxime and phenylmagnesium bromide, 2-ethyl-2-phenylethylenimine from acetophenone oxime and ethylmagnesium bromide, and 2-ethyl-2-phenyl-3-methylethylenimine from propiophenone oxime and ethylmagnesium bromide.[16]

All the ethylenimine derivatives mentioned above involve substitution at the carbon atoms of the ring. Some of the methods for the

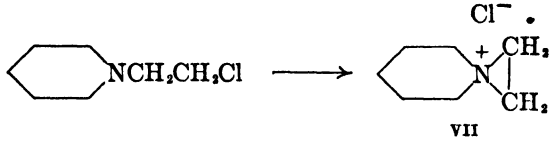
11 Darapsky and Spannagel, *J. prakt. Chem.*, [2] **92**, 272 (1915).
12 Krabbe and Schmidt, *Ber.*, **72**, 381 (1939).
13 Meisenheimer and Chou, *Ann.*, **539**, 70 (1939).
14 Cairns, *J. Am. Chem. Soc.*, **63**, 871 (1941).
15 Hoch, *Compt. rend.*, **198**, 1865 (1934).
16 Campbell et al., *J. Org. Chem.*, **8**, 103 (1943); **9**, 184 (1944).

preparation of these compounds may also be applied to the synthesis of N-substituted ethylenimines. Thus, Marckwald and Frobenius [17] made 1-methylethylenimine from N-methyl-β-chloroethylamine by the Gabriel method. This procedure was also applied in the synthesis of 1,2,3-triphenylethylenimine.[18] Furthermore, by treatment with alkali, tertiary chloroalkylamines are converted to ethylenimmonium derivatives. For example, N-methyl-bis(β-chloroethyl)amine (V) readily yields 1-methyl-1-(β-chloroethyl)ethylenimmonium chloride (VI).[19]



V VI

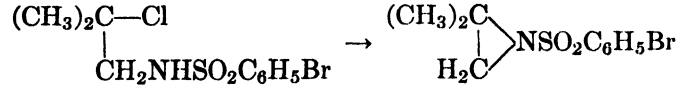
Related ethylenimmonium derivatives may be prepared from other chloroalkylamines described by Ford-Moore et al.[20] and by Hanby and Rydon.[21] Similarly, N-β-chloroethylpiperidine is readily converted to the bicyclic compound (VII).[17]



VII

It may be added that 1-ethylethylenimine has been obtained as a product in the reaction of bis(β-chloroethyl)amine with sodium,[22] and the assumption was made that 1-vinylethylenimine is an intermediate.

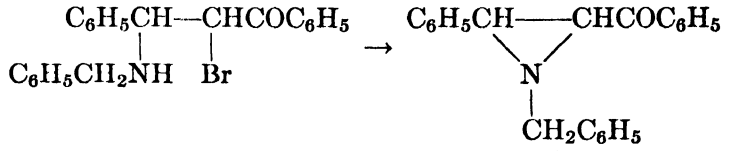
Not only halogenated secondary and tertiary amines but also sulfonamides may be converted to N-substituted ethylenimine derivatives by treatment with alkali. Adams and Cairns [23] made the *p*-bromophenylsulfonyl derivative of 2,2-dimethylethylenimine as follows.



17 Marckwald and Frobenius, *Ber.*, **34**, 3544 (1901).
18 Taylor, Owen, and Whittaker, *J. Chem. Soc.*, 206 (1938).
19 Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, **11**, 518 (1946).
20 Ford-Moore, Lidstone, and Waters, *J. Chem. Soc.*, 819 (1946).
21 Hanby and Rydon, *J. Chem. Soc.*, 513 (1947).
22 Lasselle and Sundet, *J. Am. Chem. Soc.*, **63**, 2374 (1941).
23 Adams and Cairns, *J. Am. Chem. Soc.*, **61**, 2464 (1939).

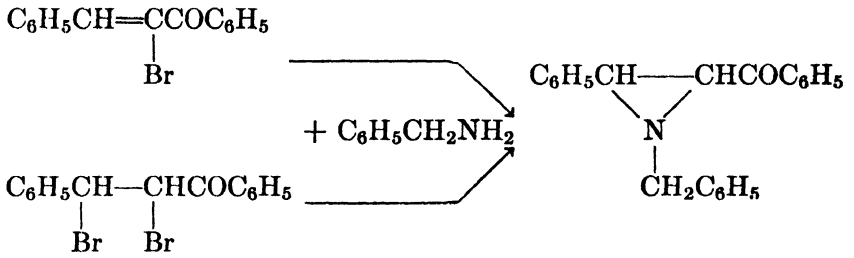
There is an analogous procedure for the synthesis of 1-*p*-toluenesulfonyl-2-phenylethylenimine.[24]

Cyclization of substituted β-halogenated alkylamines also occurs if one of the substituents is a benzoyl group. Thus, Cromwell and Caughlan [25] showed that α-bromo-β-benzylamino-β-phenylpropiophenone (VIII), on treatment with excess benzylamine in alcohol, yields 1-benzyl-2-phenyl-3-benzoylethylenimine (IX). This representative



VIII IX

of the interesting group of ethylenimine ketones may also be obtained by the reaction of benzylamine with α-bromobenzalacetophenone or with α,β-dibromo-β-phenylpropiophenone.[26] The use of methylamine

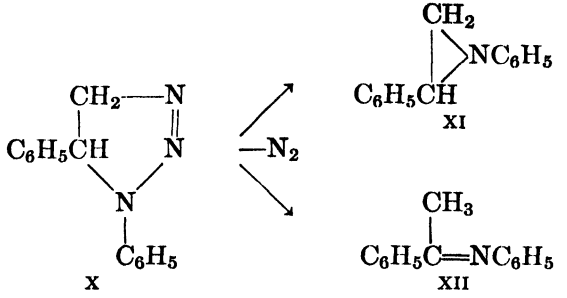


or of cyclohexylamine in place of benzylamine leads to the corresponding 1-methyl or 1-cyclohexylethylenimine ketones.

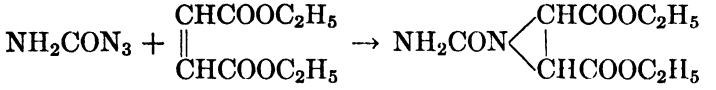
Another method for the synthesis of N-substituted ethylenimines has been provided by Wolff [27] and Alder and Stein,[28] who showed that the addition product formed from styrene and phenylazide, 1,5-diphenyl-4,5-dihydro-1,2,3-triazole (X), gives, when heated, 1,2-diphenylethylenimine (XI). This procedure may also be applied to complex unsaturated compounds, especially where the double bond is in a six-membered ring with a 1,4-bridge methylene group. With the triazole derived from such a bicyclic olefin, heating yields only the ethylenimine derivative; with the triazole derived from styrene, however, there is formed a mixture of (XI) and the anil of acetophenone

24 Kharasch and Priestley, *J. Am. Chem. Soc.*, **61**, 3425 (1939).
25 Cromwell and Caughlan, *J. Am. Chem. Soc.*, **67**, 2235 (1945).
26 Campbell, Babson, and Harris, *J. Am. Chem. Soc.*, **65**, 312 (1943).
27 Wolff, *Ann.*, **394**, 68 (1912).
28 Alder and Stein, *Ann.*, **501**, 1 (1933).

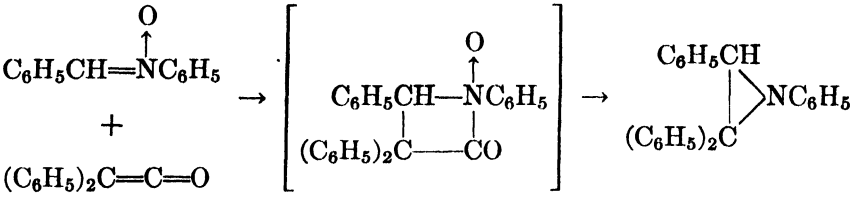
(XII). With simple aliphatic unsaturated compounds, the product is predominantly the corresponding anil.



A related method is that of Curtius and Dörr,[29] who found that carbamic acid azide and diethyl fumarate react to give an ethylenimine derivative.



In addition, Taylor et al.[18] have demonstrated that the product obtained on treatment of a ketene with the N ether of an oxime is not a "nitrene," as assumed by Staudinger and Miescher,[30] but is rather an ethylenimine derivative (cf. p. 106). For example, the reaction of diphenylketene with the N-phenyl ether of benzaldoxime yields 1,2,2,3-tetraphenylethylenimine, via the substance given in brackets as a hypothetical intermediate:

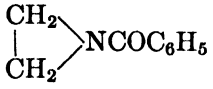


Substitution of the Nitrogen of Ethylenimine and Its Derivatives. One of the decisive data brought forward by Marckwald for the cyclic nature of ethylenimine was the fact that, on treatment with benzenesulfonyl chloride, there is formed a sulfonamide which is insoluble in alkali.[5] This supported the view that ethylenimine is a secondary amine and, together with the demonstration [6] that ethylenimine does

[29] Curtius and Dörr, *J. prakt. Chem.*, [2] **125**, 425 (1930).
[30] Staudinger and Miescher, *Helv. Chim. Acta*, **2**, 554 (1919).

not react with permanganate, disproved Gabriel's formulation of the substance as vinylamine.

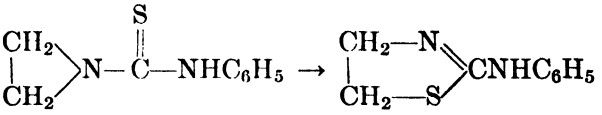
In addition to benzenesulfonyl chloride, benzoyl chloride and phenyl isocyanate effect substitution at the nitrogen atom of ethylenimine, yielding products related to (XIII) [4] and (XIV).[4,14]



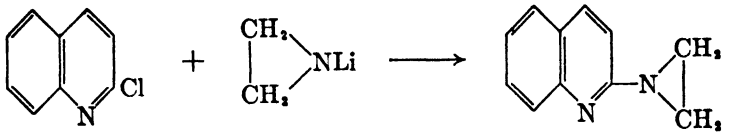
XIII

XIV

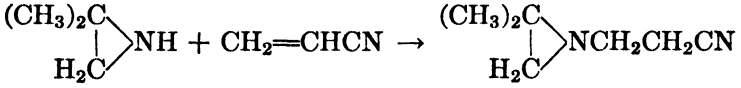
With phenyl isothiocyanate, ethylenimine gives a thiourethane, which may be converted to 2-anilino-4,5-thiazoline.[4]



For the preparation of N-substituted ethylenimines, advantage may also be taken of the relative stability of the ring to treatment with organolithium compounds. Thus, 1-lithiumethylenimine (prepared by the reaction of methyllithium with ethylenimine) may be treated with 2-chloroquinoline to give 2-ethylenimminoquinoline.[31]



Substitution at the nitrogen atom of the ethylenimine ring may also be effected by treatment with acrylonitrile [32] to give a 1-β-cyanoethyl



derivative. Reduction of the nitrile gives 1-(γ-aminopropyl)-2,2-dimethylethylenimine.

It may be added that, as with other secondary amines, the action of nitrous acid on ethylenimine gives a nitroso compound.[33] Further

31 Gilman et al., *J. Am. Chem. Soc.*, **67**, 2106 (1945).

32 Tarbell and Fukushima, *J. Am. Chem. Soc.*, **68**, 2499 (1946).

33 Euler, *Chem. Zentr.*, **1903**, II, 1165.

reaction with nitrous acid results in ring cleavage followed by deamination.

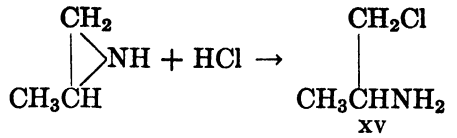
Reaction of Ethylenimine and Its Derivatives with Halogen Acids. It was noted previously that the classical method for the synthesis of ethylenimine and its derivatives involves the treatment of a β-halogenated alkylamine with alkali. As shown by Gabriel,[3] this reaction may readily be reversed by the treatment of ethylenimine with the appropriate halogen acid. Thus, ethylenimine adds HCl to give β-chloroethylamine hydrochloride, or HBr to give β-bromoethylamine hydrobromide, or HI to give β-iodoethylamine hydroiodide. The kinetics of the ring formation and its reversal have been the subject of close study by Freundlich and his collaborators.[34,35] They showed that, in alkaline solution, ring closure proceeds quantitatively with the kinetics of a first-order reaction, whereas, in acid solution (containing a halogen acid), the conversion of ethylenimine to a β-halogenated alkylamine approximately follows the kinetics of a second-order reaction. In neutral solution, an equilibrium is attained which may be described as follows.

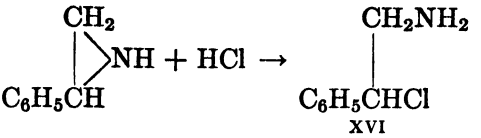
$$\beta\text{-chloroethylamine} \underset{K_2}{\overset{K_1}{\rightleftharpoons}} \text{ethylenimine} + Cl^-$$

A similar equilibrium reaction has been found to occur with substituted ethylenimines, the rates of the forward and back reactions depending on the nature of the substituent groups. For example, the rate constant for cyclization (K_1) of β-phenyl-β-chloroethylamine is about 1000 times greater than that of β-chloroethylamine.[36] Similarly, the rate constant for the opening of the ethylenimine ring (K_2) is profoundly influenced by substitution. In the course of their studies, Freundlich and his collaborators[37,38] also noted that the halogenated alkylamines are adsorbed more strongly on blood charcoal than is ethylenimine, and, consequently, if charcoal is added to an equilibrium mixture of the two components, the reaction is markedly shifted to the left ($K_2 \gg K_1$).

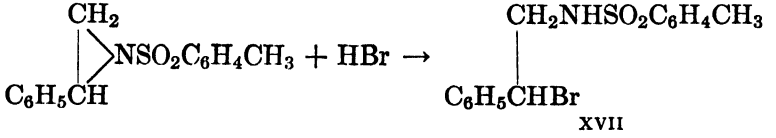
It is of interest that, although 2-methylethylenimine reacts with HCl to yield largely β-chloroisopropylamine (XV),[39] 2-phenylethylenimine

[34] Freundlich and Neumann, *Z. physik. Chem.*, **87A**, 69 (1914).
[35] Freundlich and Kroepelin, *Z. physik. Chem.*, **122A**, 39 (1926).
[36] Freundlich and Salomon, *Z. physik. Chem.*, **166A**, 161 (1933).
[37] Freundlich and Juliusberger, *Z. physik. Chem.*, **146A**, 321 (1930).
[38] Freundlich and Salomon, *Z. physik. Chem.*, **166A**, 179 (1933).
[39] Gabriel and Ohle, *Ber.*, **50**, 804 (1917).



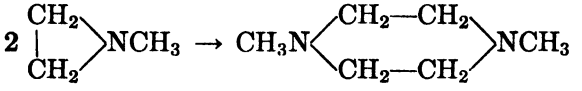


gives β-phenyl-β-chloroethylamine (XVI).[9] In analogy with the latter example, 1-*p*-toluenesulfonyl-2-phenylethylenimine adds the halogen atom to the carbon bearing the phenyl group as in XVII.[24]



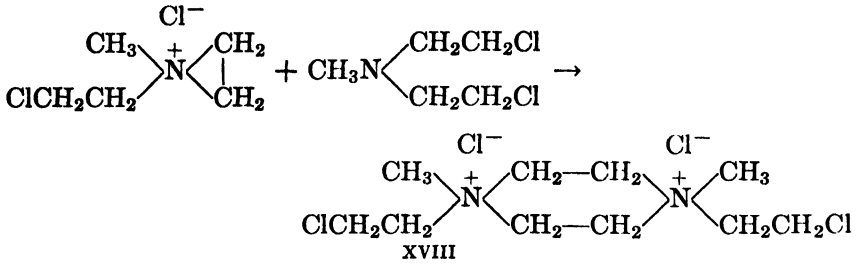
In the addition of HCl to either *cis*- or *trans*-2,3-diphenylethylenimine, there is formed a mixture of the two isomeric α-amino-β-chlorodibenzyls, thus indicating that both *cis* and *trans* addition take place during the opening of the ethylenimine ring.[40]

An important side reaction which occurs during the reaction of many ethylenimine derivatives with halogen acids is dimerization to piperazine derivatives. Under suitable conditions of concentration and *p*H, piperazine formation may, in fact, be the predominant reaction. Thus, 1-methylethylenimine is readily converted to N,N-dimethylpiperazine.[41] Numerous other instances of such dimerization may be found



in the literature. The conversion of 1-alkyl-1-(β-chloroethyl)ethylenimmonium compounds to piperazinium derivatives [19,21,42] is of interest. One such example is the dimerization of 1-methyl-1-(β-chloroethyl)-ethylenimmonium chloride to give N,N′-bis(β-chloroethyl)piperazinium dichloride (XVIII). There is good reason to believe that such reactions involve the combination of the ethylenimmonium compound with the β-halogenated alkylamine from which it is derived. As may

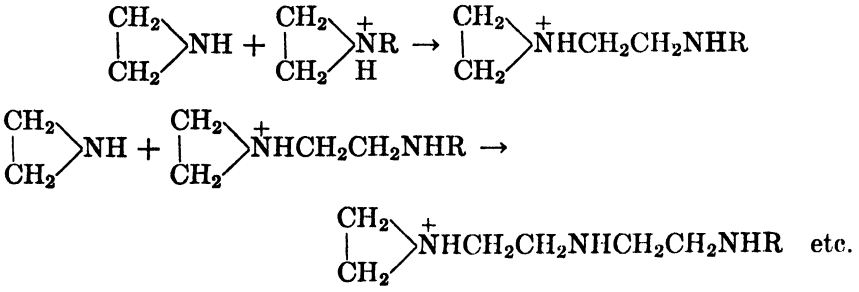
40 Weissberger and Bach, *Ber.*, **65**, 631 (1932).
41 Knorr, *Ber.*, **37**, 3507 (1904).
42 Golumbic, Stahmann, and Bergmann, *J. Org. Chem.*, **11**, 550 (1946).



XVIII

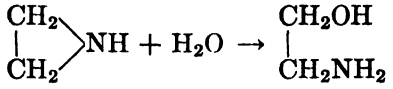
be expected, compounds such as XVIII exhibit geometrical isomerism, and it has been possible to obtain both the *cis* and *trans* forms of this piperazine derivative.[43] This appears to be the first recorded case of stereoisomerism due to the arrangement of groups about two nitrogen atoms forming part of a ring.

The reaction of ethylenimine with halogen acids is of interest in connection with its polymerization, a process which has attracted some attention.[44,45] Although ethylenimine, if stored in the absence of carbon dioxide, is quite stable at room temperature and polymerizes only slightly at higher temperatures, the presence of small amounts of HCl will induce a violent polymerization reaction, even at 25°. Jones et al.[46] have called attention to the fact that those reagents that catalyze the polymerization of ethylenimine are those that cause the formation of quaternary nitrogen compounds. Among these catalysts are acids, alkylating agents (e.g., β-chloroethylamine), oxidizing agents (peroxides, etc.), and acceptors such as copper salts and boron trifluoride. The polymerization is interpreted therefore as a chain reaction between ethylenimine and quaternary ethylenimine derivatives as follows.

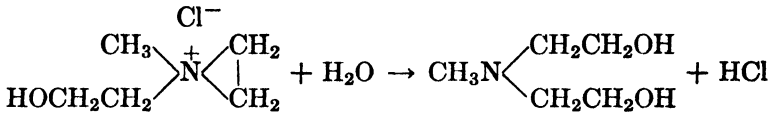


43 Hanby and Rydon, *J. Chem. Soc.*, 833 (1945).
44 Lautsch, *Die Chemie*, **57**, 149 (1944).
45 Gardner, *J. Polymer Sci.*, **1**, 289 (1946).
46 Jones et al., *J. Org Chem*, **9**, 125, 500 (1944).

Hydrolysis of Ethylenimine and Its Derivatives. The ethylenimine ring is readily opened in aqueous solution to yield a β-hydroxyethyla-

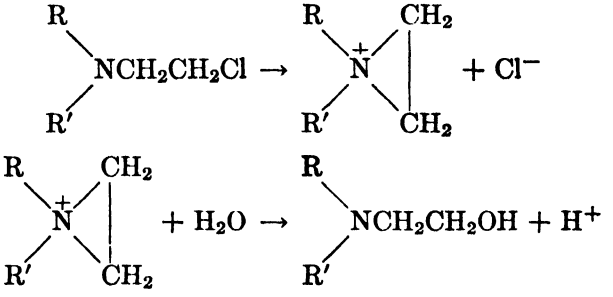


mine. This conversion occurs in acid solution in the presence of nitric acid or sulfuric acid [4] and is especially rapid at neutral or alkaline *p*H. For example, 1-methyl-1-(β-hydroxyethyl)ethylenimmonium chloride is hydrolyzed at *p*H 8 to give N-methyldiethanolamine.[19] The rate and



manner of hydrolysis of ethylenimine compounds of this type vary with the nature of the substituents on the ring.[42,47] Hydrolysis of 2-phenylethylenimine yields β-phenyl-β-hydroxyethylamine.

It should be added that studies on the mode of hydrolysis of the nitrogen mustard gases [e.g., N-methyl-bis(β-chloroethyl)amine] to derivatives of ethanolamine have shown that the elimination of the halogen atom proceeds more rapidly than the appearance of hydrogen ions.[19,48] This is to be expected if cyclization of the β-halogenated amine occurs before the hydroxyl group is introduced, as follows.



Ethylenimine and Its Derivatives as Alkylating Agents. Considerable similarity is observed between the reactivity of ethylenimine compounds and the β-halogenated alkylamines from which they may be derived. Studies of the kinetics of alkylations by means of reactive β-halogenalkylamines strongly support the view that, in aqueous solu-

[47] Fruton and Bergmann, *J. Org Chem.*, **11**, 543 (1946).
[48] Hanby et al., *J. Chem. Soc.*, 519 (1947).

tion, cyclization to an ethylenimine precedes the alkylation.[19,48] Consequently, many of the reactions observed with β-halogenalkylamines actually represent the action of the ethylenimine derivatives which are in equilibrium with these amines. It has been pointed out [48] that the ethylenimmonium cation may be regarded as a stabilized form of the carbonium ion postulated by Hughes and Ingold [49] as an intermediate in S_N1 aliphatic substitution reactions.

A particularly interesting example apparently involving the action of an ethylenimmonium compound as an alkylating agent is found in the synthesis of the German analgesic drug, Amidone.[50] As originally described, the drug was prepared by the condensation of diphenylacetonitrile with 1-dimethyl-2-chloropropane in the presence of sodamide or potassium *t*-butoxide followed by reaction of XIX with ethylmagnesium bromide to yield XX.

$$(C_6H_5)_2CH{-}CN + ClCH(CH_3){-}CH_2N(CH_3)_2 \rightarrow$$

$$(C_6H_5)_2C(CN){-}CH(CH_3){-}CH_2N(CH_3)_2 \quad \text{(XIX)} \xrightarrow{C_2H_5MgBr} C_6H_5C(CO{-}C_2H_5){-}CH(CH_3){-}CH_2N(C_2H_5)_2 \quad \text{(XX)}$$

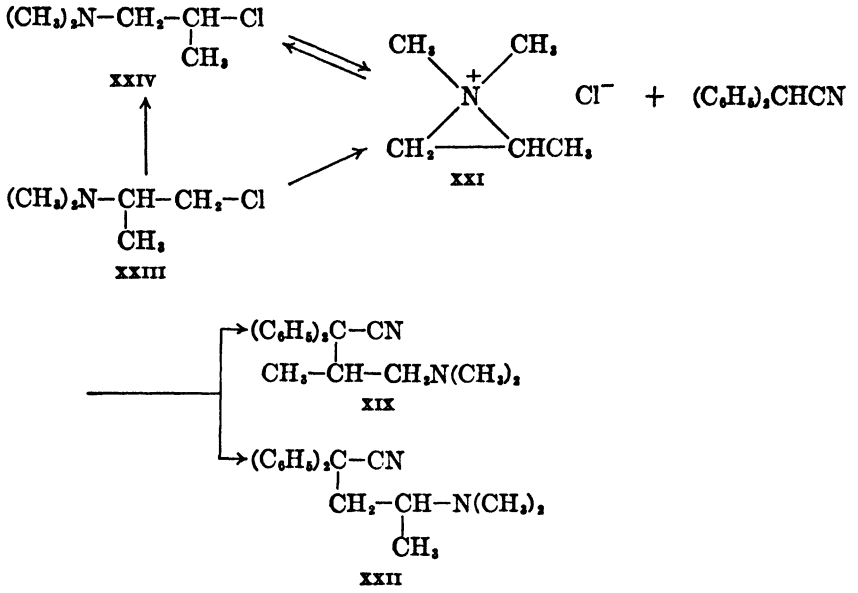
Subsequent investigations, principally by Sprague and co-workers,[51] showed that such an interpretation of the structure of the drug was conceivably open to serious criticism. Corroborative evidence as to the uncertainty of the structure assigned to Amidone was furnished by other investigators.[52] As pointed out by Schultz, Robb, and Sprague, interaction of diphenylacetonitrile with 1-dimethylamino-2-chloropropane can involve intermediate cyclization of the chloroamine with formation of an ethylenimmonium compound (XXI) which in turn can act as an alkylating agent in two modes to yield XIX or XXII. By a rigorous structural proof, Schultz et al. demonstrated conclusively that the structure of Amidone was correctly represented by XX but that the reaction of diphenylacetonitrile with 1-dimethylamino-2-chloropropane leads to the formation of the two isomers (XIX and XXII).

[49] Hughes and Ingold, *J. Chem. Soc.*, 244 (1935).

[50] *U. S. Dept. Commerce, Office Pub. Board Rept.* PB-981, p. 96-A.

[51] Schultz, Robb, and Sprague, *J. Am. Chem. Soc.*, **69**, 2454, 3155 (1947).

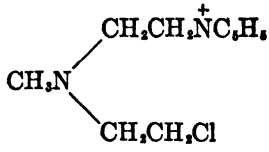
[52] Scott and Chen, *J. Pharmacol. Exptl. Therap.*, **87**, 63 (1946); Scott, Robbins, and Chen, *Science*, **104**, 587 (1946); Scott et al., *Anesthesia & Analgesia*, **26**, 12, 18 (1947).



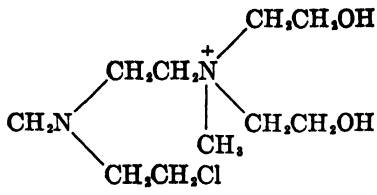
In a subsequent paper, Schultz and Sprague [53] showed that 2-dimethylamino-1-chloropropane (XXIII) rearranges when heated either as the free base or as the hydrochloride into 1-dimethylamino-2-chloropropane (XXIV) which is thermally stable. However, both chlorodimethylaminopropanes on reaction with diphenylacetonitrile gave the same mixture of isomeric aminonitriles. The conclusion appears to be inescapable that an intermediate ethylenimmonium compound is the reactive intermediate. Interpretation of similar alkylations with amino halides should be made with these facts in mind.

Attention has already been drawn to the tendency of ethylenimine compounds to react with the nitrogen atom of β-chloroalkylamines to give piperazine derivatives. Numerous additional examples of the capacity to alkylate nitrogen compounds may be cited. Thus, 1-methyl-1-(β-chloroethyl)ethylenimmonium chloride readily reacts with pyridine, methyldiethanolamine, and hexamethylentetramine to give XXV, XXVI, and XXVII, respectively.[54] In addition, ethylenimmonium compounds react with the nitrogen of aliphatic amines, amino acids, and the ring nitrogen of imidazole.[55]

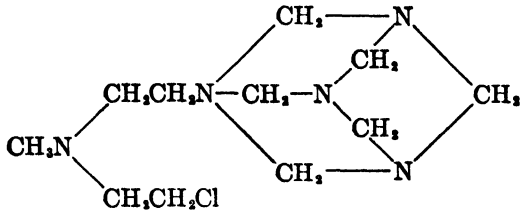
[53] Schultz and Sprague, *J. Am. Chem. Soc.*, **70**, 48 (1948).
[54] Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, **11**, 581 (1946).
[55] Fruton et al., *J. Org. Chem.*, **11**, 559, 571 (1946).



XXV

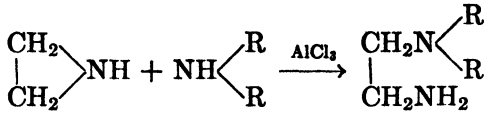


XXVI

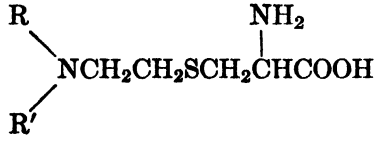


XXVII

The reaction of ethylenimine with amines has led to the development of a one-step method for the preparation of mono- and unsymmetrically di-substituted ethylenediamines.[56] In this procedure, the addition of primary or secondary amines (e.g., benzylamine, diethylamine, dibutylamine) to ethylenimine is effected under anhydrous conditions at high temperatures in the presence of aluminum chloride as a catalyst.



Of the known alkylation reactions of ethylenimine compounds, the most rapid appears to be that with the sulfhydryl group. Thus, with cysteine,[57] there is formed a thio ether having the general structure XXVIII. Extremely rapid reaction is also noted with thiosulfate,



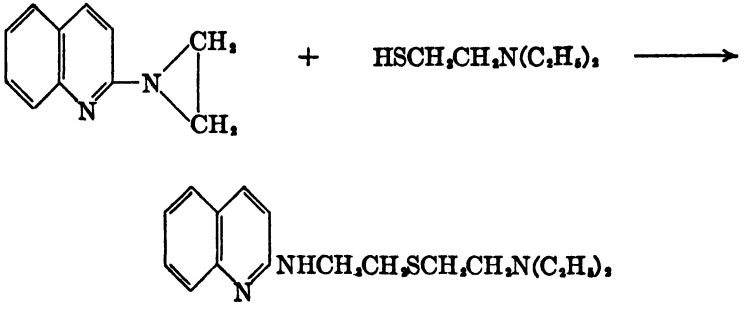
XXVIII

which furnishes a convenient means for the titrimetric determination of reactive ethylenimmonium groups present in a solution.[19]

56 Coleman and Callen, *J. Am. Chem. Soc.*, **68**, 2006 (1946).

57 Hellerman, personal communication.

A further example of the reaction of ethylenimine compounds with thiols is that shown by 2-ethylenimminoquinoline with β-diethylaminoethylmercaptan to give XXIX.[31]

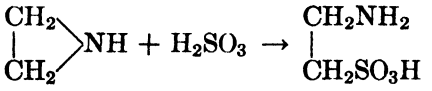


XXIX

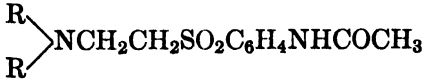
Ethylenimine reacts with hydrogen sulfide to give bis(β-aminoethyl)sulfide.[58]

In analogy with the alkylation of nitrogen compounds to give quaternary bases, cited above, there may be mentioned the ability of ethylenimine derivatives to react with several thio ethers to form sulfonium compounds. Examples are the reaction of 1-methyl-1-(β-chloroethyl)ethylenimmonium chloride with thiodiglycol,[54] and the reaction of several ethylenimmonium compounds with the sulfur of methionine.[55]

Other Addition Reactions of Ethylenimine and Its Derivatives. Gabriel [4] showed that ethylenimine reacts with sulfurous acid to give taurine. With 2-methylethylenimine, 2-aminopropane-1-sulfonic acid



is formed;[30] the reaction of 2-phenylethylenimine with sulfurous acid, however, does not appear to proceed to an appreciable extent.[9] Goldberg [59] has noted that ethylenimine, when treated with *p*-acetaminobenzenesulfinic acid, does not give the expected sulfone. On the other hand, β-halogenated derivatives of tertiary amines, in the presence of excess base, react to give the desired product (XXX). Prior cycliza-



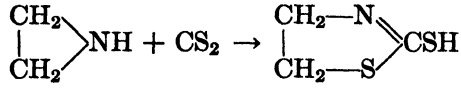
XXX

58 Gabriel and Eschenbach, *Ber.*, **30**, 2497 (1897).

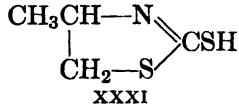
59 Goldberg, *J. Chem. Soc.*, 826 (1945).

tion to an ethylenimmonium derivative may be assumed to occur in the reaction with the sulfinic acid.

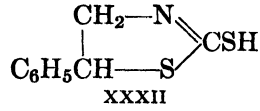
Ethylenimine and its derivatives react very rapidly with carbon disulfide to give 2-mercaptothiazolines.[4] It is of interest that, with



2-methylethylenimine, carbon disulfide forms 4-methyl-2-mercaptothiazoline (XXXI),[39] whereas 2-phenylethylenimine reacts to form the 5-phenyl derivative (XXXII).[60]

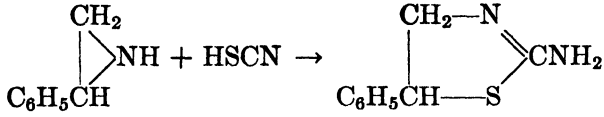


XXXI



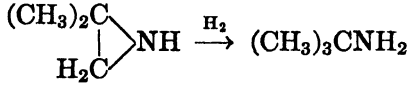
XXXII

With thiocyanate, ethylenimine derivatives give 2-aminothiazolines. Thus, 2-phenylethylenimine reacts with thiocyanate to form 2-amino-5-phenylthiazoline.[60]



Treatment of ethylenimine with methyliodide opens the ring and yields $[ICH_2CH_2N(CH_3)_3]I$. This reaction is also given by substituted ethylenimines.[22]

Reduction of Ethylenimine Derivatives. The reduction of substituted ethylenimines may be effected by catalytic hydrogenation, either in the presence of nickel at high pressure [61] or in the presence of Raney nickel at low temperature and pressure.[62] In this manner, 2,2-dimethylethylenimine may readily be converted to tertiary butylamine. Re-



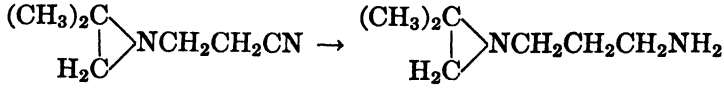
duction of N-substituted ethylenimines has been achieved by means of aluminum amalgam [18] and palladium.[24] It may be noted that the ring is not cleaved by treatment with sodium in an alcohol-toluene

60 Gabriel and Colman, *Ber.*, **47**, 1866 (1914).

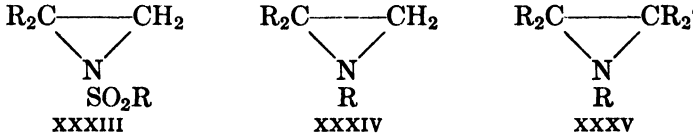
61 Karabinos and Serijan, *J. Am. Chem. Soc.*, **67**, 1856 (1945).

62 Campbell, Somers, and Campbell, *J. Am. Chem. Soc.*, **68**, 140 (1946).

mixture.[82] This has permitted the conversion of 2,2-dimethyl-1-(β-cyanoethyl)ethylenimine to the corresponding γ-aminopropyl derivative.



Stereochemistry of N-Substituted Ethylenimine Derivatives. There has been considerable interest in the possibility that ethylenimine derivatives of the type indicated in XXXIII, XXXIV, and XXXV may be subject to resolution to give two optically active enantiomorphs.[63] This might be expected from the calculation,[64] from spectroscopic data,[65,66] of the activation energy of ethylenimine. The value obtained, 38 kcal. per mole, is appreciably greater than the activation energy required for the nitrogen atom to pass through the plane formed by the two carbon atoms and the substituent group on the nitrogen. Despite a number of attempts to effect the resolution of ethylenimine derivatives,[13,14,28,67] success in this direction has not been achieved as yet.



XXXIII XXXIV XXXV

Biological Action of Ethylenimine and Its Derivatives. As may be expected from their chemical reactivity toward substances of biological importance (amino acids, sulfhydryl compounds, etc.), ethylenimine and its derivatives are potent pharmacological agents. The toxic effects of ethylenimine itself involve vesication of the skin, irritation of the eyes, reduction of the white cell count, and internal inflammation.[46,68,69] In addition, the fact that, in neutral solution β-halogenated alkylamines give rise to ethylenimine compounds, has served to explain in part the powerful biological action of the N-alkyl-bis-(β-chloroethyl)amines, the nitrogen mustard gases.[19,70]

63 Shriner, Adams, and Marvel, in Gilman, *Organic Chemistry*, 2nd ed., John Wiley & Sons, New York, 1943, p. 412.

64 Kincaid and Henriques, *J. Am. Chem. Soc.*, **62**, 1474 (1940).

65 Eyster, *J. Chem. Phys.*, **6**, 576 (1938).

66 Thompson and Harris, *J. Chem. Soc.*, 301 (1944).

67 Mole and Turner, *Chemistry & Industry*, **58**, 582 (1939).

68 Duden and Macintyre, *Ann.*, **313**, 59 (1900).

69 Danehy and Pflaum, *Ind. Eng. Chem.*, **30**, 778 (1938).

70 Gilman and Philips, *Science*, **103**, 490 (1946).

CHAPTER 3

DERIVATIVES OF AZETE

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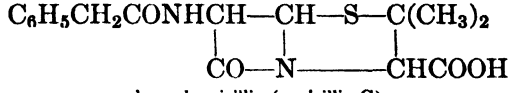
CONTENTS

INTRODUCTION

The chemistry of derivatives of azete, the four-membered nitrogen-containing heterocycle, has received relatively little attention, and prior to 1940 the subject was of minor interest. This is in contrast to the great volume of work in the field of the five- and six-membered nitrogen heterocycles, pyrrole and pyridine, and their derivatives.

The neglect of these compounds was due to their difficulty of preparation and to the fact that the four-membered nitrogen-containing ring was not found in any naturally occurring compounds, except as part of bicyclic or tricyclic systems in some alkaloids. Even now, the synthesis of azetidines (trimethylenimines) and their quaternary derivatives is of interest primarily as a basis for comparison of their ease of formation with that of other cyclic imines of smaller or larger ring size. Among their reactions, ring cleavage is of chief interest since it provides a measure of relative ring stability.

The azetidinones or β-lactams have been known as products of the reaction of certain ketenes with anils. With the discovery, during World War II, that the important antibiotics known as the penicillins



benzylpenicillin (penicillin G)

contained a fused ring system of which one part was a β-lactam ring, the chemistry of azetidines and of β-lactams in particular acquired new theoretical and practical significance. The penicillins and other compounds containing azetidine rings as part of a fused ring system are not within the scope of this chapter; however, the preparation and reactions of the monocyclic azetidinones discussed herein are closely related to the study of the β-lactam ring in the penicillins.

Derivatives of 2,4-azetidinedione (malonimide) are known, including some that were prepared as potential hypnotic drugs but were found to be inactive.

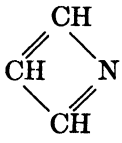
No authentic examples of compounds having the unhydrogenated azete ring are known. A brief discussion of the literature on the subject is presented in the concluding section of this chapter because of the theoretical interest in azete as a lower homolog of pyrrole and pyridine.

No simple azetines have been described in the literature. Certain compounds [1] which have been tentatively formulated as azetinone de-

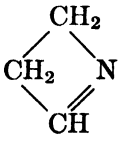
1 Kipping and Perkin, *J. Chem. Soc.*, **55**, 339 (1889); Diels and Stein, *Ber.*, **40**, 1655 (1907); Bruylants, *Bull. acad. roy. méd. Belg.*, [5] **7**, 252 (1921).

rivatives are not discussed herein because of their questionable structure.

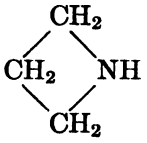
Nomenclature. The systematic name assigned to the conjugated doubly unsaturated ring made up of three carbon atoms and one nitrogen atom is azete.[2] Accordingly, the dihydro derivative is named azetine, and the saturated ring system is named azetidine.



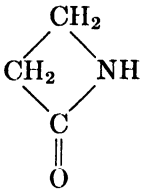
azete
(azacyclobutadiene)
(pyriculine)



1-azetine



azetidine
(trimethylenimine)



2-azetidinone
(2-ketotrimethylenimine)

The azete ring has also been given the descriptive name azacyclobutadiene and, in the older literature, the trivial name pyriculine. The azetidines have been almost exclusively referred to in the literature as trimethylenimines, but, for indexing purposes and for naming complex derivatives like the quaternary salts (azetidinium compounds), the azetidine nomenclature is clearer and more convenient.

The 2-azetidinones are lactams of β-amino acids and have usually been named as such: that is, by giving the general name "β-lactam" followed by the name of the specific amino acid from which the cyclic compound is hypothetically derived. This system is used in the present chapter along with the system of naming β-lactams as derivatives of 2-azetidinone.[3] Similarly, the malonimides are derivatives of 2,4-azetidinedione.

AZETIDINES (TRIMETHYLENIMINES)

Trimethylenimine, the simplest azetidine, was first described in 1888 but was not isolated in pure form until 1899. In later years a number of substituted azetidines, quaternary azetidinium salts (p. 91), and functional derivatives like the 2-azetidinones (β-lactams) (p. 98) have been synthesized and investigated.

The preparation of azetidines by ring-closure reactions and the rupture of the ring by cleavage reactions are of particular interest.

[2] Patterson and Capell, *The Ring Index*, Reinhold Publishing Corp., New York, 1940, p. 4.

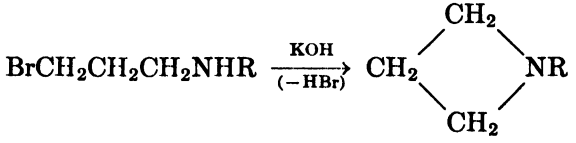
[3] Precedent for the name "azetidinone" has been established by its use in the index of *Chemical Abstracts* [*C. A.*, **38**, 7061 (1944)].

The formation of azetidine by dehydrohalogenation of γ-bromopropylamine proceeds more slowly even than the analogous formation of ethylenimine from β-bromoethylamine. Cleavage of the azetidine ring takes place readily.

The N-unsubstituted azetidines, which are secondary amines, are referred to in the ensuing discussion as "secondary azetidines." Similarly, the N-substituted azetidines are referred to as "tertiary azetidines."

Preparation of Azetidines

Dehydrohalogenation of γ-Haloalkylamines. Azetidine and its alkyl derivatives have been commonly prepared by intramolecular dehydrohalogenation of γ-haloalkylamines in which the amine is primary or secondary.



R is H or an alkyl group

The first application of this method was described in 1888 by Gabriel and Weiner,[4] who obtained a small amount of impure azetidine by the action of alkali on γ-bromopropylamine. Azetidine was prepared by this method in 1937 by Ruzicka and collaborators;[5] after careful purification, the imine was obtained in very pure form but in unspecified yield.

In general, the dehydrohalogenation of γ-chloro- or γ-bromo-alkylamines in which the amine is primary gives poor yields of the four-membered ring compound. Much of the secondary azetidine formed initially probably undergoes decomposition or polymerization reactions.

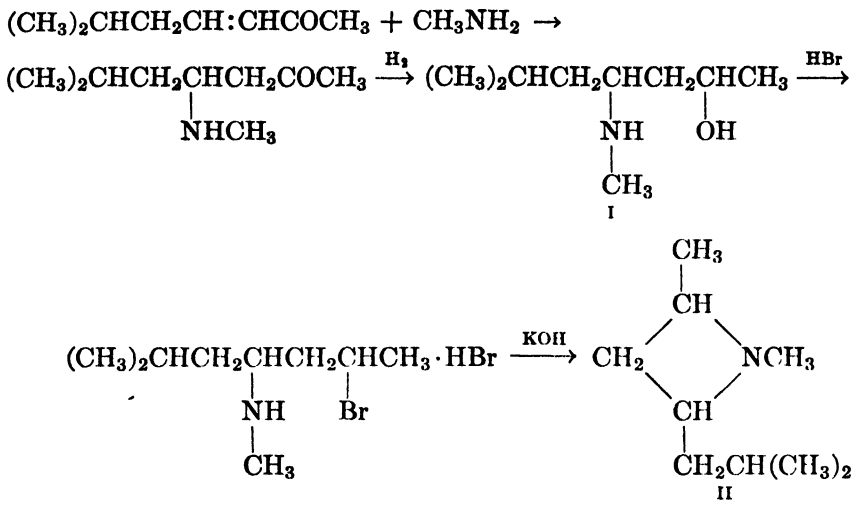
Azetidines containing three and four alkyl substituents have been prepared by Kohn and co-workers[6] by cyclization of γ-bromoalkylamines derived from readily available alkamines, such as a diacetonealkamine, which can be prepared from mesityl oxide and its homologs. In all these compounds, the bromine atom was in secondary union; the amines were primary or secondary. Cyclization was effected by subjecting a mixture of the bromoamine and 33–50% potassium hydroxide to distillation. The yields of substituted azetidines were rela-

4 Gabriel and Weiner, *Ber.*, **21**, 2676 (1888).

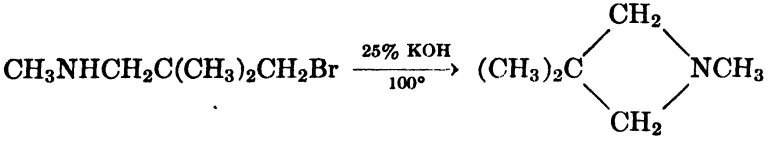
5 Ruzicka, Salomon, and Meyer, *Helv. Chim. Acta*, **20**, 109 (1937).

6 (*a*) Kohn, *Ann.*, **351**, 134 (1907); (*b*) *Monatsh.*, **28**, 423 (1907); Kohn and Giaconi, *ibid.*, **28**, 461 (1907); (*c*) Kohn and Morgenstern, *ibid.*, **28**, 479, 529 (1907)

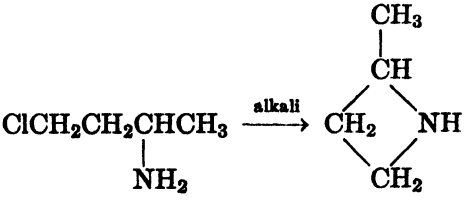
tively high; for example, 1,2-dimethyl-4-isobutylazetidine (II) was obtained, as shown below, in 79% yield from the amino alcohol (I).



Mannich and Baumgarten [7] have reported that cyclization does not take place readily with γ-bromoalkylamines in which the bromine is secondary. However, if the bromine is primary and the amine is secondary, cyclization takes place rapidly and smoothly. 1,3,3-Trimethylazetidine was formed in 80% yield by the reaction shown in the equation,



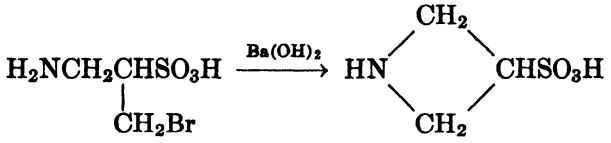
A German patent [8] issued in 1912 describes the preparation of 2-methylazetidine by dehydrochlorination of γ-aminobutyl chloride, in which both the chlorine atom and the amino group are primary.



[7] Mannich and Baumgarten, *Ber.*, **70**, 210 (1937).

[8] Bayer and Company, Ger. pat. 247,144 (*Chem. Zentr.*, **1912**, II, 159).

The only recorded sulfonic acid in the azetidine series of compounds is 3-azetidinesulfonic acid,[9] formed by dehydrobromination of α-(bromomethyl)taurine.



Freundlich and co-workers have made an extensive investigation into the kinetics of the formation of cyclic imines by ring closure of haloalkylamines. In the first paper of the series, Freundlich and Krestovnikoff [10] reported experimentally determined values of the rate constants for the cyclization of δ-chlorobutylamine to pyrrolidine and ε-chloroamylamine to piperidine. They were unable to determine the constant for the cyclization of γ-chloropropylamine to azetidine because of predominating side reactions, and their estimated value for this rate constant ($k_{25°}$ about 0.003) was later shown to be too high.

Experimentally determined values of the first-order rate constants for the cyclization of the ω-bromoalkylamines from ethyl to hexyl as indicated by rate of formation of bromide ion, reported by Freundlich and Kroepelin,[11] are given in the accompanying table.

FIRST-ORDER RATE CONSTANTS FOR THE CYCLIZATION OF BROMOALKYLAMINES

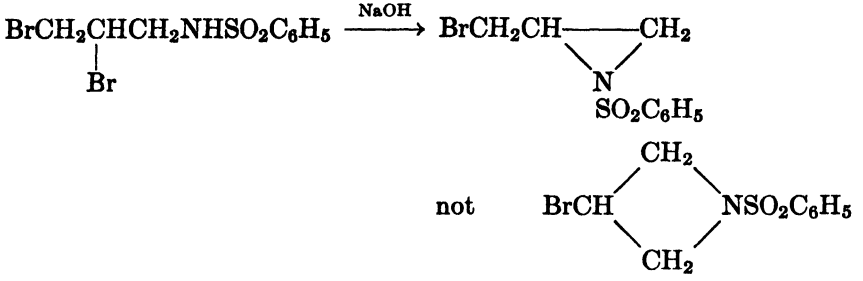
Amine	$k_{25°}$
β-Bromoethyl	0.036
γ-Bromopropyl	0.0005
δ-Bromobutyl	About 30
ε-Bromoamyl	0.5
ζ-Bromohexyl	0.001

It is apparent that the cyclization of γ-bromopropylamine proceeds the most slowly. The extremely great difference between the rates of cyclization of δ-bromobutylamine and γ-bromopropylamine is surprising, as is the fact that β-bromoethylamine cyclizes more readily than the bromopropylamine.

In agreement with the latter observation is the finding of Gensler [12] that 1-benzenesulfonamido-2,3-dibromopropane cyclizes in the presence of free alkali to an ethylenimine derivative and not to the four-

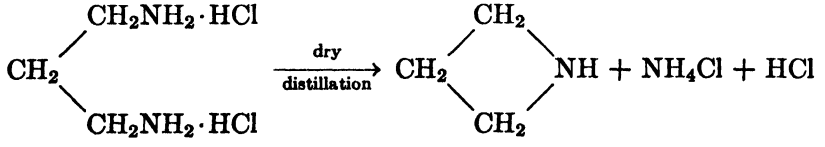
9 Gabriel and Colman, *Ber.*, **39**, 2889 (1906).
10 Freundlich and Krestovnikoff, *Z. physik. Chem.*, **76A**, 79 (1911).
11 Freundlich and Kroepelin, *Z. physik. Chem.*, **122**, 39 (1926).
12 Gensler, *J. Am. Chem. Soc.*, **70**, 1843 (1948).

membered ring compound. The ethylenimine derivative is formed as a result of preferential elimination of secondary bromine in the β position over primary bromine in the γ position.



Theories have been advanced [13] which consider ease of cyclization as the resultant of two factors. One is the statistical frequency of mutual approach of the reacting groups at the ends of the chains, which diminishes and thereby makes ring closure more difficult with increasing chain length. The second factor, the bond-angle deviation necessary to form the ring, decreases and therefore facilitates ring closure with increasing ring size up to the strainless six-membered ring. Presumably, with the cyclic imines as with the lower cycloparaffin derivatives,[14] the resultant of these factors leads to a minimum in the rate of cyclization to the four-membered ring. However, the rate of cyclization of γ-bromopropylamine is even lower than might be expected from consideration of the above factors alone.

Pyrolysis of Diamines and Related Compounds. The preparation of azetidine in low yield and impure form by dry distillation of trimethylenediamine dihydrochloride was described by Ladenburg and Sieber [15] in 1890. β-Picoline was also formed in the reaction. 3,3-Di-



methylazetidine [16] has been similarly prepared by pyrolysis of 2,2-dimethyl-1,3-diaminopropane dihydrochloride, but the heterocyclic compound was isolated as the picrate in only 6% yield.

[13] Freundlich and Salomon, *Ber.*, **66**, 355 (1933); Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933); *Trans. Faraday Soc.*, **32**, 153 (1936).

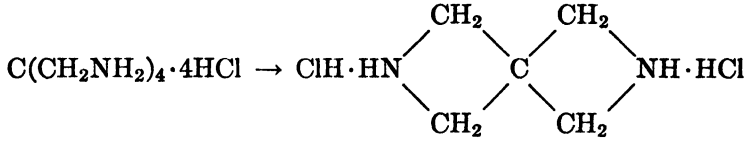
[14] Ruzicka et al., *Helv. Chim. Acta*, **9**, 499 (1926).

[15] Ladenburg and Sieber, *Ber.*, **23**, 2727 (1890).

[16] Komppa and Sévon, *Ann. Acad. Sci. Fennicae*, **37A**, No. 7, 1–8 (1933) [*C. A.*, **27**, 3914 (1933)].

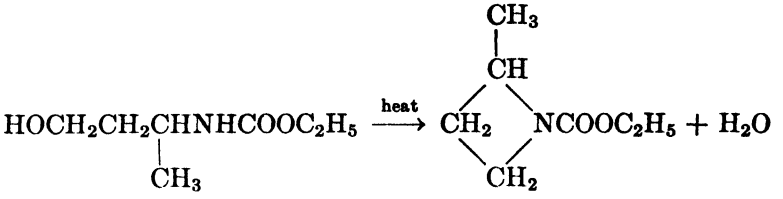
In 1888, the same year in which azetidine was first described, Balbiano [17] reported the preparation of N-phenylazetidine by heating N-phenyltrimethylenediamine dihydrochloride. The free base was not isolated but was precipitated as the chloroplatinate.

The tetramine derived from pentaerythritol has been reported by Govaert [18] to be unstable; when attempts were made to isolate it as the tetrahydrochloride, a spirobisazetidine (2,6-diazaspiro[3.3]heptane) was obtained.

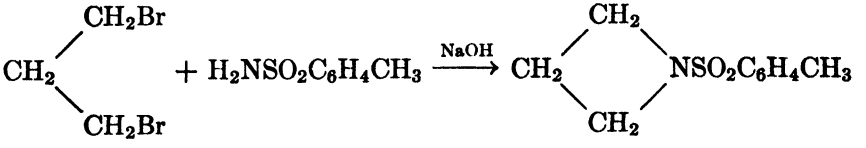


Subsequently, two British workers, Litherland and Mann,[19] prepared tetrakis(aminomethyl)methane, $C(CH_2NH_2)_4$, and found it to be stable under conditions the same as or more drastic than those under which Govaert obtained cyclization. The British workers also prepared the spirobisazetidine but by a different procedure (see p. 86).

Pyrolysis of ethyl N-(1-methyl-3-hydroxypropyl)carbamate is reported in the patent literature [20] to give ethyl 2-methyl-1-azetidine carboxylate.

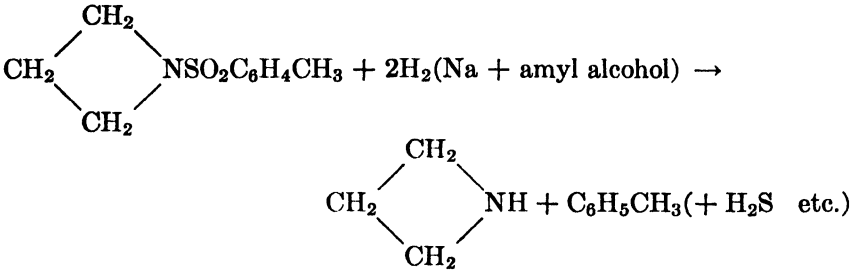


Reaction of a Dihalide with an Amide or Amine. The *p*-toluenesulfonyl derivative of azetidine (*p*-toluenesulfonazetidide) is formed as one of the products of the reaction of trimethylene dibromide with *p*-toluenesulfonamide in the presence of alkali.[21]



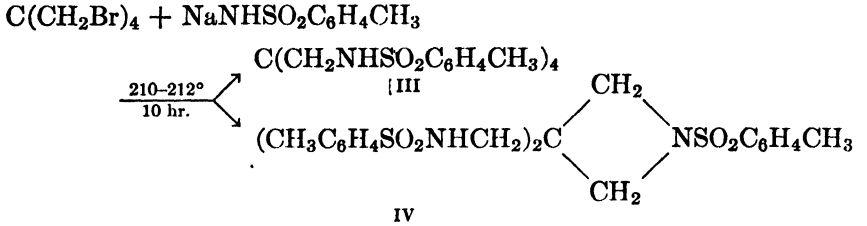
17 Balbiano, *Atti accad. nazl. Lincei*, [4] 4, 44 (1888) (*Chem. Zentr.*, 1888, II, 1356).
18 Govaert, *Proc. Acad. Sci. Amsterdam*, 37, 156 (1934) [*C. A.*, 28, 4038 (1934)].
19 Litherland and Mann, *J. Chem. Soc.*, 1588 (1938).
20 Paquin, Ger. pat. 713,467 [*C. A.*, 38, 1533 (1944)].
21 Howard and van Droste-Huelshoff, *Ber.*, 31, 3264 (1898).

The free azetidine was so readily decomposed that it could not be isolated as an hydrolysis product of the sulfonazetidide. However, reduction of the sulfonazetidide with sodium and an alcohol, as carried out by Howard and Marckwald,[22] led to the free cyclic imine, and this still remains one of the best methods of preparing azetidine. Subsequent workers [23] have reported yields of 14% and 36% of azetidine

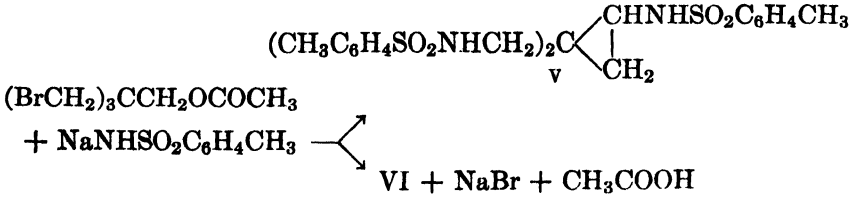


from the *p*-toluenesulfonyl compound; Yanbikov and Dem'yanov, who obtained the higher yields, isolated by-products which they identified as γ-hydroxypropylamine and di-(γ-hydroxypropyl)amine.

Litherland and Mann [19] synthesized a substituted azetidine (IV) in low yield by the reaction of pentaerythrityl tetrabromide with the sodium derivative of *p*-toluenesulfonamide in an anhydrous medium; the chief product of the reaction was the acyclic tetramine derivative (III).



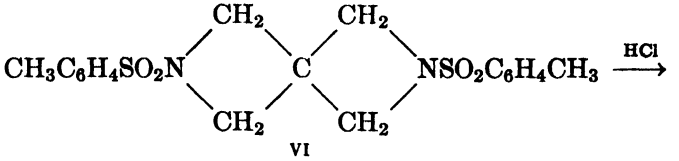
A similar reaction starting with pentaerythrityl tribromide monoacetate resulted in the formation of the bis-(*p*-toluenesulfonyl) derivative (VI) of the spiran described by Govaert (see p. 85), along with



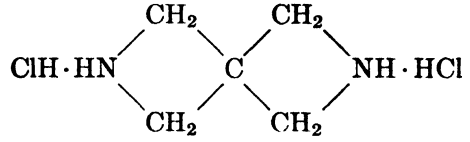
22 Howard and Marckwald, *Ber.*, **32**, 2032 (1899).

23 Yanbikov and Dem'yanov, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 1545 (1938); Jones, *J. Org. Chem.*, **9**, 484 (1944).

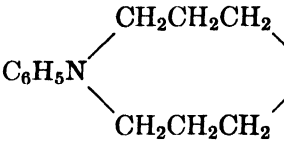
a cyclopropylamine derivative (V). The disulfonamide (VI), upon hydrolysis with concentrated hydrochloric acid at 140°, was converted to the dihydrochloride of the spiran.



VI



There is only one recorded instance of the preparation of an azetidine from a dihalide and an amine. This is the formation of 1-phenylazetidine [24] by the reaction of trimethylene dibromide and aniline. However, the chief product of this reaction was N,N′-diphenyltrimethylenediamine. A small amount of the eight-membered ring compound,



was also formed. No cyclic compounds were formed by the reaction of trimethylene dibromide and *o*-toluidine; the only product was N,N′-di-*o*-tolyltrimethylenediamine.

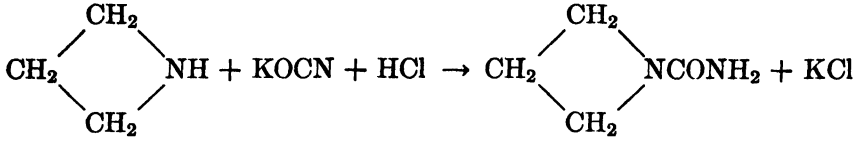
Properties and Reactions of Azetidines

The azetidines, including their N-alkyl derivatives, are in many respects typical secondary or tertiary aliphatic amines. They are liquids, are soluble in organic solvents, and have strong ammoniacal or amine-like odors. The lower members fume in the air and are soluble in water. The azetidines are basic and are frequently isolated or characterized as their halogen acid salts, chloroplatinates, and picrates. The N-alkyl derivatives readily form methiodides.

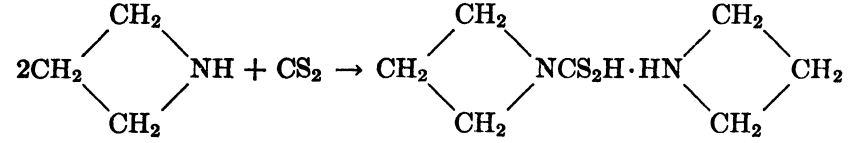
In general, the individual compounds have been prepared only in small amounts and have not been thoroughly investigated. For example, no determinations of the basic strengths of azetidines have been reported.

[24] Scholtz, *Ber.*, **32**, 2251 (1899).

Substitution Reactions. Typical secondary amine reactions have been carried out with a few N-unsubstituted azetidines and particularly with azetidine itself. These reactions include formation of the substituted urea, the N-phenylurea, and the N-phenylthiourea by reaction with potassium cyanate,[22] phenyl isocyanate,[25] and phenyl isothiocyanate,[22] respectively. With potassium cyanate the reaction is as follows.



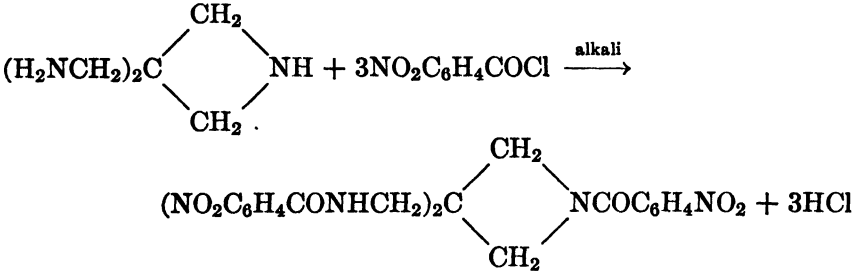
Reaction with carbon disulfide [6a, 22] produces the imine salt of the dithiocarbamic acid. Compounds for treating or impregnating textile



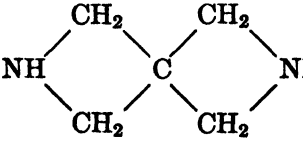
fibers can be prepared by reaction of azetidine with carbon disulfide.[26]

The expected benzenesulfonazetidide is formed by the reaction of azetidine with benzenesulfonyl chloride in the presence of alkali.[22]

No N-acyl derivatives of simple azetidines have been described, but it seems probable that acetylation and benzoylation could be effected if desired. 3,3-Bis(aminomethyl)azetidine has been converted to



the tris(*o*-nitrobenzoyl) derivative.[19] Also, the spirobisazetidine,



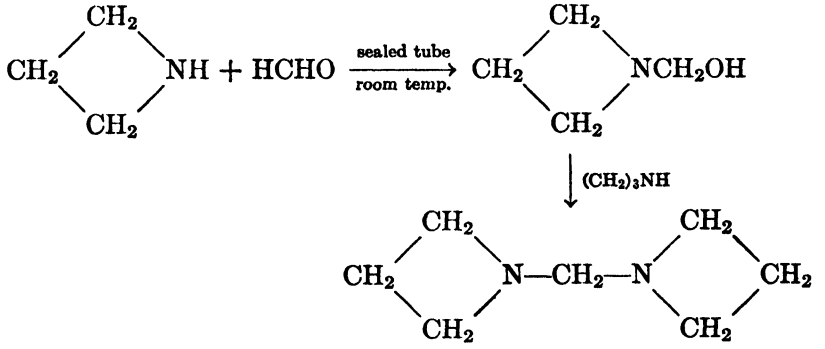
has been converted to the bis(*o*-nitrobenzoyl) derivative.[19]

[25] Yanbikov, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 1470 (1938).
[26] Brit. pat. 491,565 [*C. A.*, **33**, 1062 (1939)].

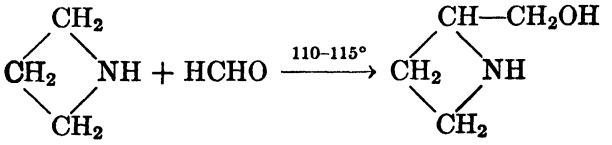
Oily N-nitroso compounds [6a,22] are formed by the action of nitrous acid on secondary azetidines.

The alkylation of secondary azetidines has been studied but little and appears to require further investigation. It was reported by Yanbikov [25] that a compound having the correct analysis for N-methylazetidine hydriodide was formed by treatment of azetidine with methyl iodide in ether. More recently, Gibson et al.,[27] who may have been unaware of Yanbikov's work, stated that they were unable to prepare the N-methyl compound from azetidine and methyl iodide. When the reactants were mixed in cold ether, the product was azetidine hydriodide, whereas reaction in alcoholic base resulted in complete methylation to the quaternary iodide. Other examples of complete methylation are known (see p. 94).

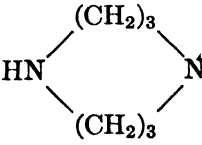
The hydroxymethylation of azetidine by reaction with paraformaldehyde has been described.[25] Under mild conditions, the product appeared to be 1-azetidinemethanol, which could not be isolated in pure form, and was converted to 1,1′-methylenebisazetidine by reac-



tion with excess imine. At higher temperatures, an isomeric alcohol,



believed to be 2-azetidinemethanol, was formed. An eight-membered

ring compound,  , and carbon dioxide had been re-

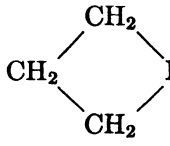
[27] Gibson et al., *J. Chem. Soc.*, 163 (1942).

ported [28] as the products of reaction of azetidine with formaldehyde at 120°.

Tertiary azetidines, lacking a reactive functional group, exhibit the typical unreactivity of tertiary amines. Their reactions with methyl and ethyl halides, forming the quaternary salts, are described below in connection with the preparation of 1,1-dialkylazetidinium halides (see p. 94).

Cleavage Reactions. The most important and characteristic reactions of azetidines are those involving cleavage of the relatively unstable four-membered ring. Low yields are obtained in many of the substitution reactions described above because of the formation of by-products having open-chained structures.

Concentrated inorganic acids open the ring by direct addition, forming substituted *n*-propylamines in which the acidic group is in the γ position. In dilute acid solution the cleavage follows the same course,



$$+ 2HCl \rightarrow ClCH_2CH_2CH_2NH_2 \cdot HCl \qquad (1)$$

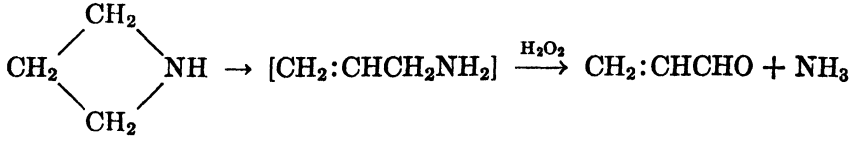
but the acidic group may be further hydrolyzed with the formation of a γ-hydroxypropylamine. Reaction 1 may be reversed in alkaline solution, especially if the γ-substituted amine is subjected to steam

$$ClCH_2CH_2CH_2NH_2 + H_2O \xrightarrow{\text{dil. acid}} HOCH_2CH_2CH_2NH_2 \qquad (2)$$

distillation, and the ring compound is thus regenerated. However, the γ-hydroxypropylamines formed as in reaction 2 do not readily undergo ring closure.[19]

Azetidine is for the most part unaffected by passage over alumina at 360–365°, but there is qualitative evidence for the presence of a primary amine, possibly allylamine, in the products.[25]

Rupture of the ring in azetidine takes place upon treatment with dilute hydrogen peroxide at reflux.[25] Acrolein and ammonia are formed; allylamine has been postulated as the intermediate.

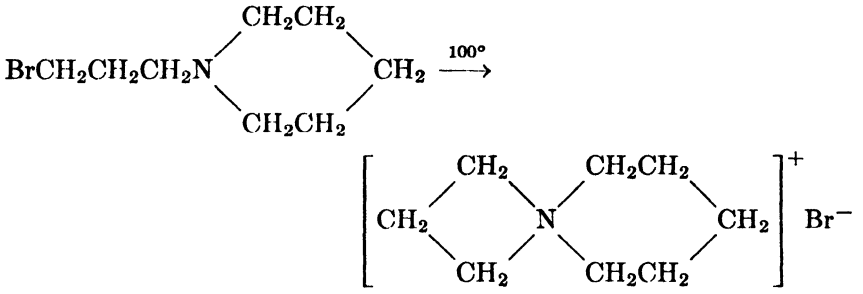


28 Potokhin, *J. Russ. Phys. Chem. Soc.*, **59**, 761 (1927).

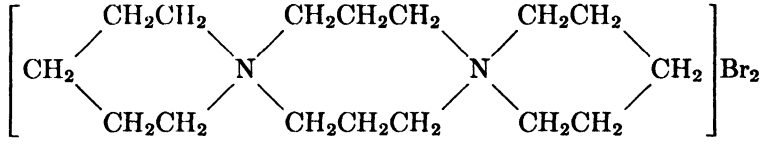
QUATERNARY AZETIDINIUM COMPOUNDS

Preparation

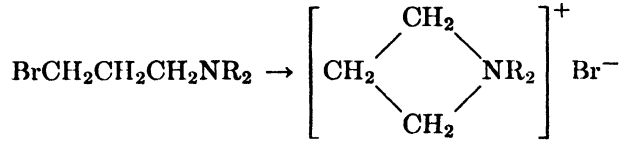
Cyclization of γ-Dialkylaminopropyl Halides. The first azetidinium halide was described by Gabriel and Stelzner,[29] who reported that N-γ-bromopropylpiperidine was converted when heated on the water bath to the spirocyclic salt, 1,1-pentamethyleneazetidinium bromide (1,1-



trimethylenepiperidinium bromide). A dimeric formula, having a spirocyclic system made up of a hexamethylenediimine (or 1,5-diazacycloöctane) ring and two piperidine rings has also been proposed[30] for this salt.



It has been shown by Gibbs and Marvel[31] that γ-dialkylaminopropyl bromides spontaneously undergo intramolecular cyclization, with conversion of covalent halogen to ionic halogen. The products are crystalline 1,1-dialkylazetidinium bromides. The cyclization takes



29 Gabriel and Stelzner, *Ber.*, **29**, 2381 (1896); see also Gabriel and Colman, *Ber.* **39**, 2875 (1906); **40**, 424 (1907); Dunlop, *J. Chem. Soc.*, **101**, 1998 (1912).

30 Horlein and Knelsel, *Ber.*, **39**, 1429 (1906); see also v. Braun, *Ann.*, **386**, 297 (1912); v. Braun and Goll, *Ber.*, **60**, 339 (1927).

31 Gibbs and Marvel, *J. Am. Chem. Soc.*, **56**, 725 (1934); **57**, 1137 (1935).

place when the liquid bromo amines, in which R is ethyl, *n*-propyl, *n*-butyl, or isoamyl, are allowed to stand at any temperature between 0 and 100°. With γ-dimethylaminopropyl bromide, the greater tendency under ordinary conditions is to undergo intermolecular condensation, leading to the formation of a linear polymeric quaternary am-

$$Br(CH_2)_3N(CH_3)_2 \rightarrow$$

$$\{Br[(CH_2)_3\overset{+}{N}(CH_3)_2]_{n-1}(CH_2)_3N(CH_3)_2\} \quad (n-1)Br^-$$

monium salt. In very dilute solution, however, the dimethyl compound cyclizes to the four-membered ring compound.

$$Br(CH_2)_3N(CH_3)_2 \xrightarrow[\text{(abs. EtOH)}]{\text{dil. soln.}} \left[\begin{array}{c} CH_2 \\ CH_2 \quad N(CH_3)_2 \\ CH_2 \end{array}\right]^+ Br^-$$

Soon after the appearance of the work described above, Mannich and Baumgarten,[7] in connection with a study of the reactions of derivatives of ketoamines, published experimental data on which they based the following generalizations.

1. γ-Chloropropyldialkylamines in which the chlorine atom is primary are converted to the cyclic quaternary chlorides by being warmed at 50° for about 10 days. The following specific examples were given.

$$ClCH_2C(CH_3)_2CH_2NR_2 \rightarrow \left[\begin{array}{c} CH_2 \\ (CH_3)_2C \quad NR_2 \\ CH_2 \end{array}\right]^+ Cl^-$$

R is methyl or ethyl, or NR_2 is piperidyl

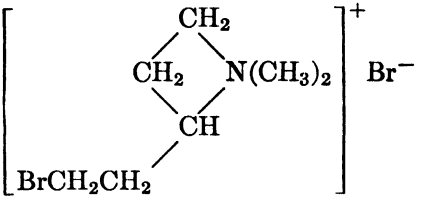
$$ClCH_2CH_2CH(CH_3)N(CH_3)_2 \rightarrow \left[\begin{array}{c} CH_2 \\ CH_2 \quad N(CH_3)_2 \\ CH \\ | \\ CH_3 \end{array}\right]^+ Cl^-$$

2. The above chloro amines are most easily cyclized by treatment with sodium iodide in acetone. The sodium iodide converts the aminoalkyl chlorides to the iodides, and the latter undergo rapid spontaneous cyclization to the quaternary iodides.

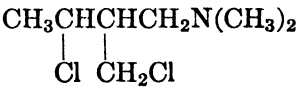
3. γ-Chloroalkyldialkylamines in which the chlorine atom is secondary, as in $CH_3CHClCH_2CH_2N(CH_3)_2$, show no tendency toward intramolecular alkylation with formation of the azetidine ring. However, the cyclization of a secondary bromide, $CH_3CHBrCH(CH_3)CH_2N(CH_3)_2$, in the presence of potassium hydroxide has been described in a patent.[8] Some of the dehydrohalogenation product, $CH_2{:}CHCH(CH_3)CH_2N(CH_3)_2$, was formed in addition to the cyclic compound, 1,1,2,3-tetramethylazetidinium bromide.

The cyclization of some primary and secondary amines containing secondary bromine in the γ position has already been mentioned in connection with the preparation of azetidines (p. 82); strong heating with concentrated caustic was required in order to effect the dehydrobromination.[6] On the other hand the compound $BrCH_2C(CH_3)_2CH_2NHCH_3$, a secondary amine containing primary bromine, changes rapidly on the water bath in the presence of less concentrated caustic to 1,3,3-trimethylazetidine.[7]

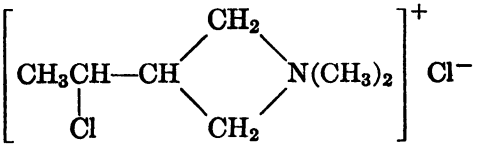
An attempt to isolate the free base, $(CH_3)_2NCH(CH_2CH_2Br)_2$, from its hydrobromide resulted in formation of the quaternary bromide,[32]



The two diastereoisomeric forms of the compound,



have been converted to the same quaternary chloride,[33]

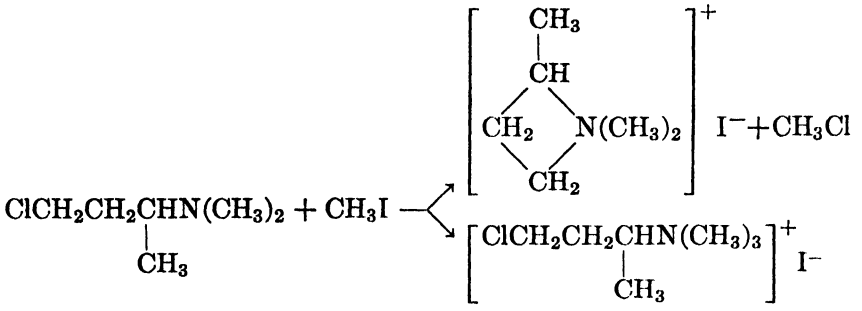


32 Cerkovnikov and Prelog, *Ber.*, **74**, 1648 (1941).
33 Mannich and Salzmann, *Ber.*, **72**, 499 (1939).

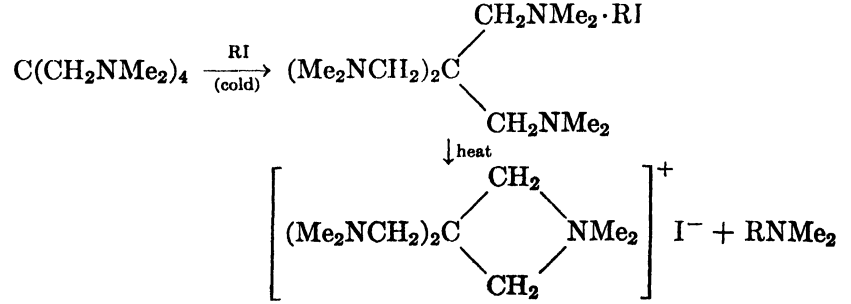
Reaction of Azetidines with Alkyl Halides. N-Alkylazetidines are tertiary amines and undergo the normal methiodide (quaternary iodide) formation on treatment with methyl iodide.

The reaction of secondary azetidines with methyl iodide also results in formation of the quaternary salts,[6,8,27] presumably through the intermediate N-methyl compounds. However, in only one somewhat equivocal case has such an N-methyl compound been isolated from this type of reaction [25] (p. 89).

An instance of the formation of an azetidinium iodide by treatment of a γ-chloroalkyldimethylamine with methyl iodide has been reported;[7] however, the tertiary amine was in part converted to the acyclic quaternary ammonium iodide.



A rather unusual synthesis of an azetidinium iodide has been described by Gibson and Mann,[34] who found that a tertiary amine is eliminated by pyrolysis from the monoquaternary iodides of the tetratertiary amine, $C(CH_2NMe_2)_4$, with formation of a cyclic quaternary salt.



R is ethyl, allyl, or benzyl

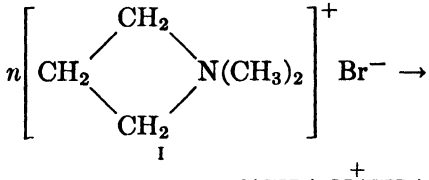
[34] Gibson and Mann, *J. Chem. Soc.*, 175 (1942).

Properties and Reactions of Azetidinium Compounds

The quaternary azetidinium salts are crystalline solids, soluble in water and insoluble in most organic solvents. Their aqueous solutions are neutral. The presence of the inorganic ion can be demonstrated in these solutions, and the molecular weights, as determined by lowering of the freezing point in aqueous solution, are half the values calculated for the undissociated molecules.

The azetidinium halides in which R is a small alkyl group, such as methyl or ethyl, melt at rather high temperatures with decomposition; the higher members have lower and sharper melting points. Many of the salts are very hygroscopic and deliquescent. They do not add bromine from a solution of the halogen in carbon tetrachloride.

Polymerization of Azetidinium Bromides. 1,1-Dimethylazetidinium bromide is unstable and is transformed slowly when it stands at room temperature, or rapidly when it is heated at 200°, into a linear polymeric quaternary salt.[31]



I

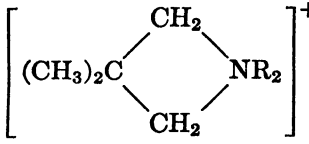
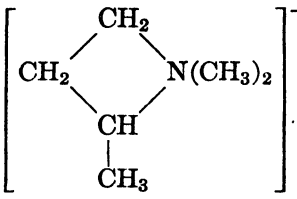
$$\{Br[(CH_2)_3\overset{+}{N}(CH_3)_2]_{n-1}(CH_2)_3N(CH_3)_2\}\ (n-1)Br^-$$

II

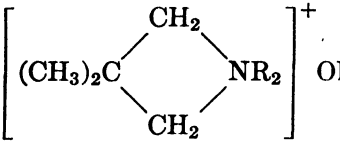
Since γ-bromopropyldimethylamine, which is converted to the azetidinium bromide (I) only in very dilute solution, changes very readily to a linear polymeric salt, it is evident that the cyclic salt (I) is under sufficient strain so that it is transformed by reversal of the ring closure to the free bromo amine. The bromo amine then polymerizes to form the linear salt (II).

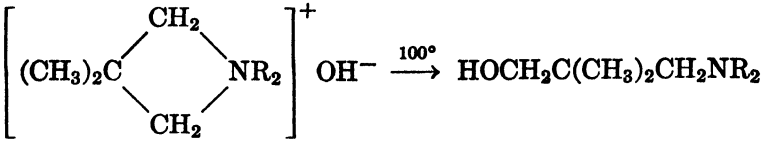
Impure 1,1-diethylazetidinium bromide also changes, after a long period, to a linear polymeric salt. The pure diethyl compound, however, is stable under ordinary conditions; when heated above its melting point, it decomposes but without the formation of polymer.

The cyclic salts with groups higher than ethyl show no tendency to form polymeric materials under the conditions which affect the methyl and ethyl derivatives.[31]

Pyrolysis of Azetidinium Salts and Hydroxides. The azetidinium chlorides prepared by Mannich and Baumgarten (see p. 92), of the type  Cl^- (R is methyl or ethyl or NR_2 is piperidyl) and  Cl^-, volatilize above their melting points and yield liquid distillates consisting of the original acyclic bases from which the cyclic compounds had been made.[7] In effect, the ring opens and the ionic chlorine of the salt is converted to covalent chlorine. This change is like that assumed to be the first step in the conversion of 1,1-dimethylazetidinium bromide to a linear polymeric salt (see above). However, the open-chained chloro amines of Mannich and Baumgarten apparently do not undergo polymerization even when both groups attached to the nitrogen are methyl groups.

The cleavage of the ring in the azetidinium chlorides upon pyrolysis is indicative of the greater instability of the four-membered ring compared with the six-membered (piperidine) ring. When dialkylpiperidinium chlorides are pyrolyzed, the ring is not cleaved; instead the products are alkylpiperidine and alkyl chloride.

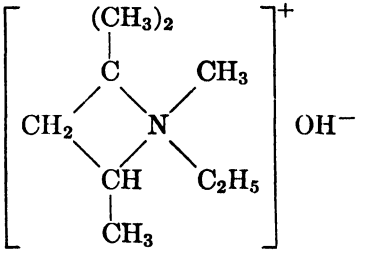
The azetidinium hydroxides,  OH^-, prepared by shaking the iodides with silver oxide in water, decompose like the chlorides but at a lower temperature (about 100°). The products are γ-hydroxypropylamines.[7]



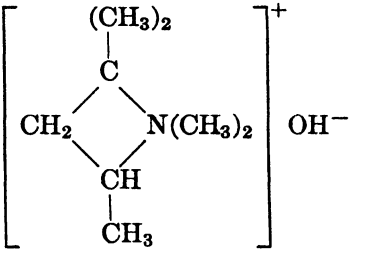
The iodides, when subjected to dry distillation, decompose quite differently. Gaseous hydrocarbons, chiefly ethylene, are evolved, and a residue consisting of the hydriodide of a secondary amine (dimethylamine, diethylamine, or piperidine) remains.

There are only two references in the literature to the pyrolytic cleavage of dialkylazetidinium hydroxides under the conditions of exhaustive methylation. The products formed upon distillation from solid potassium hydroxide have not been fully characterized. They are dialkylaminoalkenes,[6c,8] formed by cleavage of a C—N bond in the azetidine ring and elimination of water.

Kohn and Morgenstern[6c] have presented evidence indicating that 1-ethyl-1,2,2,4-tetramethylazetidinium hydroxide (III) and the 1,1,2,2,4-pentamethyl compound (IV) decompose differently, the former cleaving between N and $>CH(CH_3)$ to give $\begin{matrix} C_2H_5 \\ \diagdown \\ \quad NC(CH_3)_2CH_2CH{:}CH_2 \\ \diagup \\ CH_3 \end{matrix}$, the latter between N and $>C(CH_3)_2$ to give $(CH_3)_2NCH(CH_3)CH{:}C(CH_3)_2$.



III

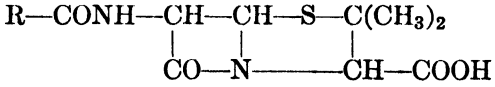


IV

Both unsaturated amines on exhaustive methylation gave the same diene, which the authors believed to be 4-methyl-1,3-pentadiene, but which may have been 2-methyl-1,3-pentadiene. In a patent[8] describing the preparation of butadiene and isoprene from 2-methyl- and 2,3-dimethyl-azetidine, respectively, by two successive exhaustive methylations, it is postulated that in both compounds the bond between N and $>CH_2$ is broken rather than the bond between N and $>CH(CH_3)$. The 1,1,2-trimethyl- and 1,1,2,3-tetramethyl-azetidinium iodides could be converted to the hydroxides and pyrolyzed as such, or the halides themselves could simply be heated with caustic. The products, described without experimental proof of structure as 3-dimethylamino-1-butene and 3-dimethylamino-2-methyl-1-butene, were cleaved by exhaustive methylation to trimethylamine and butadiene or isoprene, respectively.

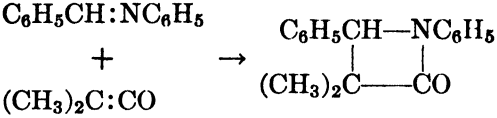
2-AZETIDINONES (β-LACTAMS)

The development of the chemistry of the β-lactams was initiated by Staudinger and his collaborators during his classical studies of ketenes.[35] For several years these researches stood as the only important contribution to this field of heterocyclic chemistry. However, since 1940 a tremendous impetus has been given to the study of the reactivity of these compounds because of their relation to the structure of the naturally occurring penicillins.



Methods of Preparation

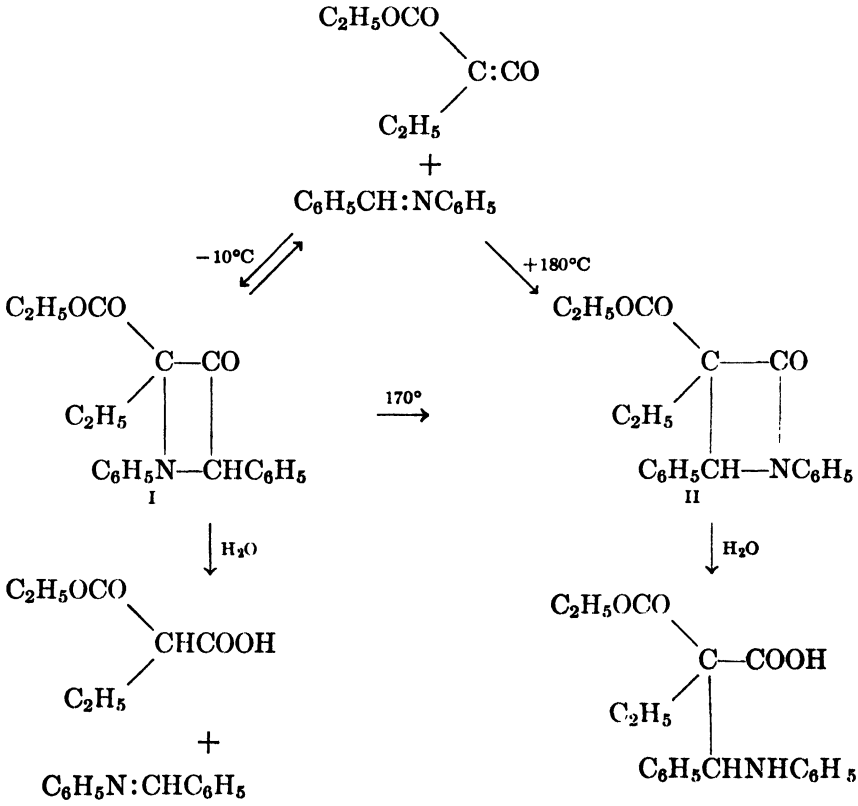
Reaction of Ketenes with Imines. The direct combination of ketene itself or substituted ketenes with anils or other imines has been the most commonly employed method of synthesis. For example, the reaction of dimethylketene with benzylideneaniline [36] goes to completion at room temperature in a few hours, and the β-lactam can be easily isolated as a stable crystalline compound.



This reaction is by no means general and, in regard to the ketenes employed, is limited largely to disubstituted members, the so-called "ketoketenes." In particular, diphenyl- and dimethyl-ketene have given a number of β-lactams by this reaction. Diethylketene and *o,o'*-biphenyleneketene have also yielded the desired product in at least one instance.[37] Although a more exhaustive study may demonstrate that monosubstituted ketenes would in many instances react to form β-lactams, the inherent tendency of these "aldoketenes" to polymerize, coupled with evidence that these compounds are less reactive with double bonds than are the disubstituted ketenes, has been a practical limitation to further research in this direction. Ketene itself, the simplest aldoketene, reacts with benzylideneaniline at high temperatures to give the β-lactam.[38]

[35] Staudinger, *Die Ketene*, Enke, Stuttgart, 1912.
[36] Staudinger and Klever, *Ber.*, **40**, 1149 (1907).
[37] Staudinger and Maier, *Ann.*, **401**, 292 (1913).
[38] Staudinger, *Ber.*, **50**, 1040 (1917).

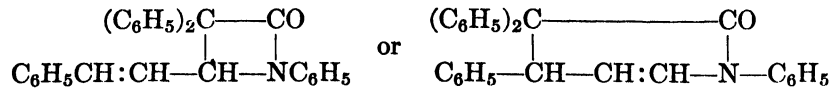
Ethylcarbethoxyketene, although in fact a disubstituted ketene, displays many of the properties of aldoketenes. Staudinger was able to condense it with benzylideneaniline only at high temperatures (180°) to give the β-lactam which could be hydrolyzed to the corresponding β-amino acid. At low temperatures (−10°), the product of the reaction was postulated to be the 3-azetidinone (I) formed by the reverse addition of the two components, although satisfactory proof of structure has not been obtained. If it stood at room temperature, the 3-azetidinone dissociated to give benzylidenecaniline and the ketene. The ketene then polymerized unless the dissociation occurred in the presence of water, alcohols, or amines, whereupon the usual products of reaction of these reagents with the ketene were isolated. However, when the 3-azetidinone was heated at high temperatures, it was converted to the β-lactam (II), presumably through an intermediate dissociation to its original components.



In the case of phenylcarbomethoxyketene, Staudinger [38] could not isolate the corresponding 3-azetidinone and obtained the β-lactam di-

rectly. When dicarbethoxyketene was treated with benzophenoneaniline, an impure product was obtained which appeared to be the 3-azetidinone derivative.[38] Phenylmethylketene combined with benzylideneaniline to give what was thought to be a mixture of 2- and 3-azetidinones.[39]

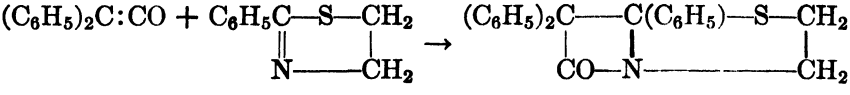
The reaction of cinnamylideneaniline with diphenylketene gave a product which could be either a 1,2 or a 1,4 addition product.



Staudinger [40] was unable to establish the structure by studying the decomposition products or by an independent synthesis via dibromocinnamylideneaniline. However, a study of the infrared spectrum of this compound during the penicillin synthesis program [41] demonstrated that it was a true β-lactam.

In regard to the reactivity of the various types of aldimines and ketimines towards β-lactam formation, it is apparent that the type of substitution around the carbon-nitrogen double bond is quite critical. So far, only imines derived from aromatic aldehydes and ketones such as benzaldehyde, benzophenone, acetophenone, and cinnamaldehyde have given β-lactams. A greater variety of amines can be used to produce reactive imines. Among those already successfully employed are aniline, *p*-dimethylaminoaniline, benzohydrylamine, benzylamine, and methylamine; however, the last two give low yields.

It is interesting to note that Staudinger [35] studied the reaction of ketenes with cyclic compounds, such as quinoline,[40] but was unable to isolate any true β-lactams. The only authentic case where a "cyclic imine" combined with a ketene to give a β-lactam is the reaction of diphenylketene with 2-phenylthiazoline to yield a fused ring compound.[41]



This product was the first known compound containing the basic heterocyclic system of penicillin and a study of its infrared spectrum

[39] Staudinger and Ruzicka, *Ann.*, **380**, 301 (1911).

[40] Staudinger, *Ann.*, **356**, 100 (1907).

[41] *The Chemistry of Penicillin*, Princeton University Press, 1948, Ballard, Melstrom, and Smith, Chapter XXVI.

furnished important evidence for establishing the β-lactam formula for penicillin.[41]

Reaction of Ketenes with Aromatic Nitroso Compounds. Nitroso compounds, such as nitrosobenzene and *p*-nitrosodimethylaniline, react with ketenes [42] in the following manner.

$$(C_6H_5)_2C{:}CO + ONC_6H_5 \rightarrow \left[\begin{array}{c}(C_6H_5)_2C\text{—}CO \\ \quad\quad\quad | \quad\quad | \\ \quad C_6H_5N\text{—}O\end{array}\right] \downarrow$$

$$(C_6H_5)_2C \\ \quad\quad \| \\ \quad C_6H_5N + CO_2$$

Apparently, a four-membered ring may form which is, however, very unstable and splits to give the Schiff base and carbon dioxide. The Schiff base can then react with another molecule of diphenylketene to give the β-lactam.

Another reaction which yields the β-lactam, presumably via the nitroso compound and the Schiff base, was also discovered by Staudinger.[42]

$$(C_6H_5)_2\underset{\displaystyle Cl}{\underset{|}{C}}COCl + C_6H_5NHOH \rightarrow (C_6H_5)_2C{:}CO + C_6H_5NO + 2HCl$$

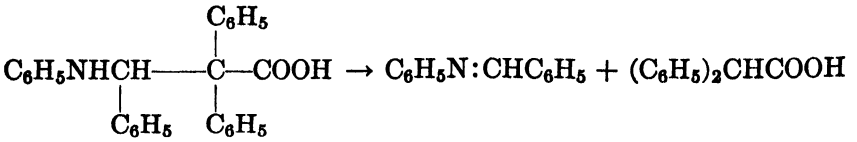
The diphenylketene and the nitrosobenzene then react as described above.

Cyclization of β-Amino Acids. No authenticated examples are known of the formation of β-lactams by the thermal elimination of water from the corresponding β-amino acid; and, in view of the fact that this is obviously one of the simplest and most direct possible methods of synthesis, it is worthy of discussion. Cleavage, rather than cyclization, of the β-amino acid invariably occurs in one of two directions. Typical of the first mode of decomposition is the rupture of β-anilinopropionic acid to give aniline and acrylic acid.

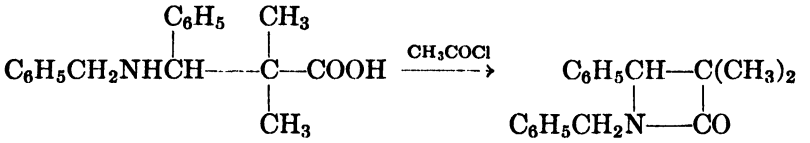
$$C_6H_5NHCH_2CH_2COOH \rightarrow C_6H_5NH_2 + CH_2{:}CHCOOH$$

The second mode of decomposition of β-amino acids can be illustrated by the cleavage of α,α,β-triphenyl-β-anilinopropionic acid which has no α-hydrogen atoms and, therefore, cannot undergo the first type of decomposition. The reaction proceeds to give benzylideneaniline and diphenylacetic acid.

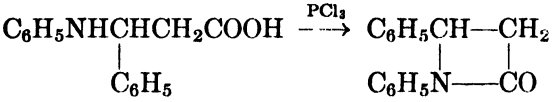
[42] Staudinger and Jelagin, *Ber.*, **44**, 365 (1911).



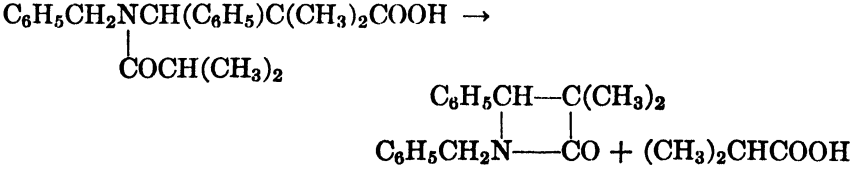
Although the thermal elimination of water from β-amino acids to form β-lactams has not yet been accomplished, there are at least two examples wherein the chemical elimination of water has accomplished the same objective. Staudinger was able to convert β-benzylamino-β-phenyl-α,α-dimethylpropionic acid to the β-lactam by treatment with acetyl chloride.[43]



β-Phenyl-β-anilinopropionic acid is converted to the corresponding lactam when refluxed with phosphorus trichloride.[41] It is of particular interest that cyclization occurred in spite of the opportunity for cleavage of aniline from the amino acid.



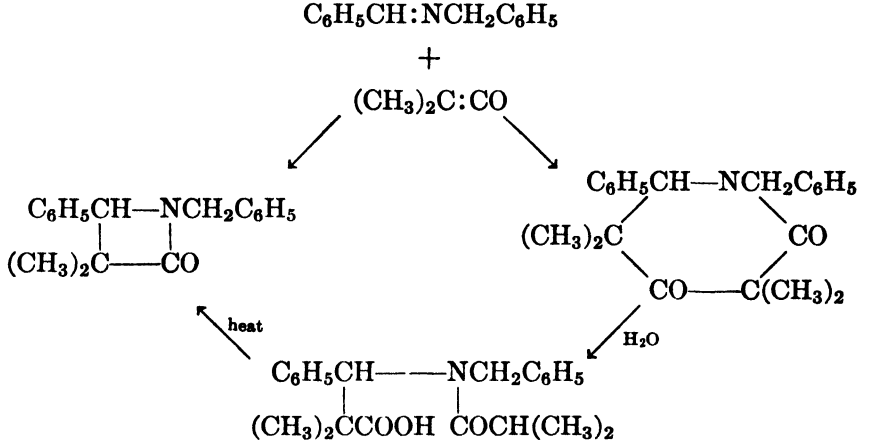
Cyclization of β-Acylamino Acids. A limited but simple and direct method for closing the β-lactam ring was discovered by Staudinger.[43] When certain β-acylamino acids are heated at their melting points, ring closure is effected with the loss of the carboxylic acid which was originally present as the acyl group in the β-acylamino acid. Thus, N-isobutyryl-β-benzylamino-β-phenyl-α,α-dimethylpropionic acid can be converted to the corresponding lactam in high yields by elimination of isobutyric acid.



The discovery of this reaction by Staudinger was the result of an interesting corollary to his study of the preparation of β-lactams by

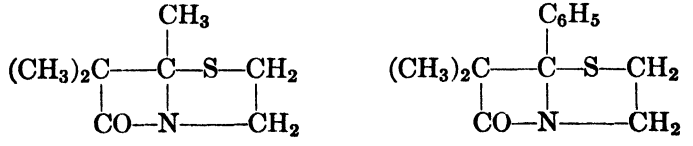
[43] Staudinger, Klever, and Kober, *Ann.*, **374**, 1 (1910).

the direct combination of ketenes with imines. He had observed that the products of the reaction of dimethylketene with benzylidenebenzylamine and benzylidenemethylamine contained only small amounts of the β-lactams. The bulk of the reaction mixtures consisted of compounds derived from 2 moles of the ketene with 1 mole of the imine. These compounds were very unstable to hydrolysis and produced, on treatment with water, β-acylamino acids, the structure of which Staudinger was able to establish by independent synthesis. The parent compounds were thereby shown to be piperidinedione derivatives. Thus, an indirect route to the β-lactams from ketenes and Schiff bases via piperidinediones was established.



This series of reactions has also been carried out with benzylideneethylamine.[41]

These reactions were of particular interest in the study of the structure of penicillin and provided a method for preparing two additional compounds (see p. 98) which served as models for the β-lactam formula of penicillin.[41]



Cyclization of β-Amino Esters with Organometallic Compounds. This synthetic method was discovered by Breckpot [44] and is of special

[44] Breckpot, *Bull. soc. chim. Belg.*, **32**, 412 (1923).

interest inasmuch as it leads to the only β-lactam of certain structure reported in the literature which contains purely aliphatic substituents. This compound, 1-ethyl-4-methyl-2-azetidinone, was synthesized by the reaction of ethyl β-ethylaminobutyrate with ethylmagnesium bromide.

$$C_2H_5NHCH(CH_3)CH_2COOC_2H_5 + C_2H_5MgBr \rightarrow$$

$$\left[\begin{array}{c} CH_3 \\ | \\ C_2H_5N{-}CH{-}CH_2COOC_2H_5 \\ | \\ MgBr \end{array}\right] + C_2H_6$$

$$\downarrow$$

$$C_2H_5N{-}\underset{\displaystyle CO}{\overset{\displaystyle |}{\underset{|}{}}}{-}\overset{\displaystyle |}{\underset{\displaystyle CH_2}{\underset{|}{}}}{-}CH{-}CH_3 + [C_2H_5OMgBr]$$

The reaction apparently proceeds through reaction of the Grignard reagent with the active hydrogen attached to the nitrogen of the amino ester with the formation of ethane as a by-product. The intermediate complex then cyclizes by reaction with the ester grouping. The azetidinone was found to hydrolyze easily with aqueous hydrochloric acid to give the hydrochloride of the original amino acid in contrast to Staudinger's more stable compounds prepared by reaction of diphenylketene with anils.

This synthetic method was further developed during the penicillin synthesis program [41] and was successfully applied to the synthesis of several β-lactams. Some of these were particularly interesting because of their structural similarity to penicillin inasmuch as they contained an acylamino group in the 3 position of the azetidine ring.

$$C_6H_5CH_2CONHCH{-}CH_2NHC_6H_5 \xrightarrow{CH_3MgI}$$

$$\underset{\displaystyle COOC_2H_5}{\overset{\displaystyle |}{\underset{|}{}}}$$

III

$$C_6H_5CH_2CONHCH{-}\underset{\displaystyle CO}{\overset{\displaystyle |}{\underset{|}{}}}{-}\overset{\displaystyle |}{\underset{\displaystyle NC_6H_5}{\underset{|}{}}}{-}CH_2$$

A study of various Grignard reagents was carried out,[41] and it was indicated that methylmagnesium iodide was one of the best for reaction with the ester (III). Phenyllithium and di-*n*-propylmagnesium have given the β-lactams in poorer yield.

Some of the other compounds prepared by this general procedure were 1-phenyl-, 1,4-diphenyl-, 1,4-diphenyl-3-methyl-, and 3-benza-

mido-1-phenyl-2-azetidinone.[41] The 3-acylamino azetidinones described above can be hydrogenated with saturation of the benzene rings and without affecting the heterocycle.

Reaction of Anils with Halogenated Esters. Gilman and Speeter [45] demonstrated that benzylideneaniline reacts with either ethyl bromoacetate or ethyl bromopropionate in the presence of zinc to give the corresponding β-lactam.

$$C_6H_5N{:}CHC_6H_5 + BrCH_2COOEt + Zn \rightarrow C_6H_5N(CO)-CHC_6H_5(CH_2) + [EtOZnBr]$$

The reaction can be considered as a modified Reformatsky reaction wherein the anil reacts similarly to a carbonyl compound prior to cyclization.

Reaction of an Isocyanate with Diazomethane. 1-Phenylazetidone has been prepared in 20% yield by the reaction of phenyl isocyanate with two molecules of diazomethane.[46] This convenient synthesis is

$$C_6H_5N{:}CO + 2CH_2N_2 \rightarrow C_6H_5N(CH_2)-CO(CH_2) + 2N_2$$

analogous to that by which cyclobutanone is formed from ketene with two molecules of diazomethane.[47]

1-Phenylazetidone, which is the only known monosubstituted β-lactam, had been prepared earlier by Grignard cyclization of ethyl β-anilinopropionate (see p. 104), but this work, carried out during the penicillin synthesis program,[41] had not been revealed at the time of publication of the preparation from phenyl isocyanate and diazomethane.

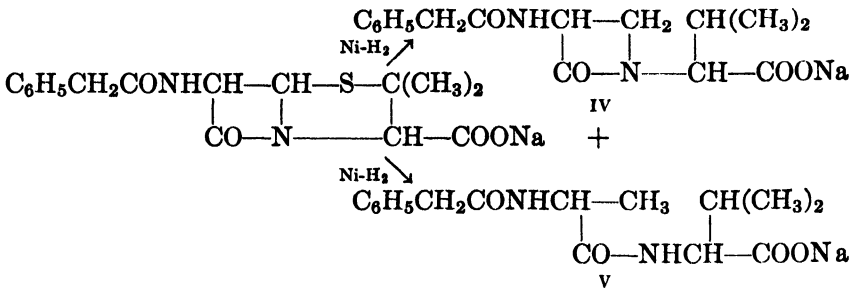
Miscellaneous β-Lactams. During a study of the degradation of penicillin [48] it was demonstrated that the molecule would undergo hydrogenolysis in the presence of Raney nickel to give a compound (IV) containing a β-lactam ring. Compound V was obtained as a coproduct and was not formed when IV was hydrogenolyzed. The hydrogenolysis product (IV) was not independently synthesized; the chemical and physical properties of the compound furnished strong evi-

[45] Gilman and Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).

[46] Sheehan and Izzo, *J. Am. Chem. Soc.*, **70**, 1985 (1948).

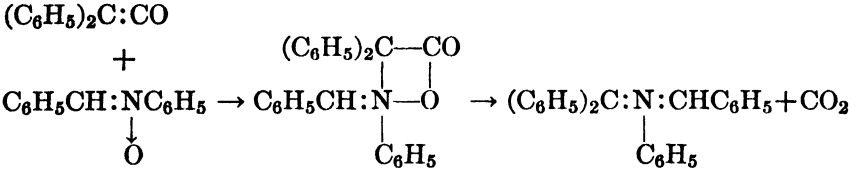
[47] Lipp and Köster, *Ber.*, **64**, 2823 (1931).

[48] *The Chemistry of Penicillin*, Princeton University Press, 1948, Kaczka and Folkers, Chapter IX.

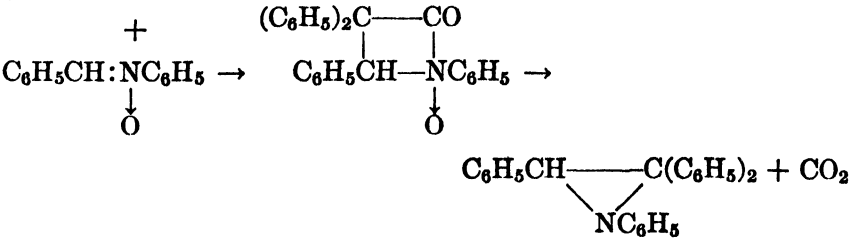


dence for its structure, and the conclusions drawn from this research were an important contribution towards the study of the structure of penicillin.

During a study of compounds previously postulated as containing pentacovalent nitrogen, Taylor, Owen, and Whittaker [49] reexamined the experiments of Staudinger [50] on the reaction of diphenylketene with the N-phenyl ether of benzaldoxime. Staudinger had believed that the reaction proceeded first to form a compound involving addition of the ketene across the semipolar bond of the oxime ether (nitrone), which then lost carbon dioxide at a higher temperature to give a compound containing pentacovalent nitrogen (named a "nitrene" by Staudinger and Miescher).



Staudinger's evidence for the structure of the nitrene was invalidated by Taylor, Owen, and Whittaker, who postulated that the reaction proceeded through a β-lactam oxide and obtained evidence that the final decomposition product was in reality an ethylenimine derivative.



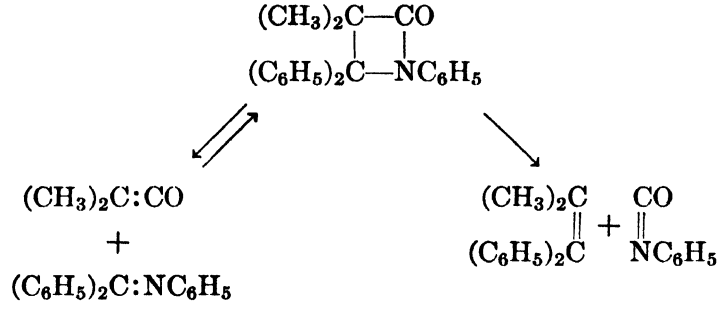
49 Taylor, Owen, and Whittaker, *J. Chem. Soc.*, 206 (1938).
50 Staudinger and Miescher, *Helv. Chim. Acta*, **2**, 554 (1919).

During the penicillin synthesis program, a large number of unsuccessful experiments were carried out in an attempt to develop new methods for synthesizing β-lactams.[41]

Reactions of β-Lactams

Most of the β-lactams prepared by Staudinger and his collaborators are crystalline solids and are unexpectedly stable. The carbonyl group in the β-lactam ring shows a characteristic absorption in the infrared region and can be readily distinguished from the corresponding group in acyclic amides and in lactams consisting of five- and six-membered rings.[51] By means of this analytical tool, it should be possible to shed light on the structure of many compounds postulated but not established as β-lactams.

At high temperatures the β-lactams can undergo thermal fission of the four-membered ring in two directions; the first to give an olefin and an isocyanate, the second to regenerate the original components.



A study of the relative ease of decomposition of a number of β-lactams showed wide differences in thermal stability, depending on the type of substituents on the β-lactam ring. In general, it was apparent that those β-lactams which were more difficult to prepare in the sense of slow reaction rates were in turn more stable towards pyrolysis.

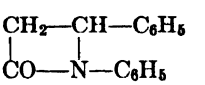
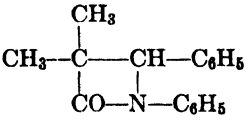
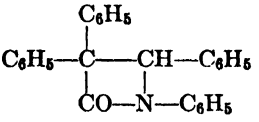
Hydrolysis. The highly substituted aryl β-lactams are particularly stable towards hydrolysis. In fact, until the later stages of the penicillin research had been reached, no β-lactams had been prepared which even approached penicillin in regard to ease of hydrolysis. This fact was to a large degree responsible for the initial poor reception of the β-lactam formula.

51 *The Chemistry of Penicillin*, Princeton University Press, 1948, Thompson, Brattain, Randall, and Rasmussen, Chapter XIII.

To some extent, the effect of structure on the ease of hydrolysis can be determined, although the data are at best qualitative because of the lack of comparable conditions. The alkaline hydrolysis of a series of β-lactams is presented in Table 1 where the structural differences consist of variations of groups in the 3 position of the azetidinone nucleus.[41]

TABLE 1

ALKALINE HYDROLYSIS OF β-LACTAMS

Compound	Conditions of Hydrolysis	Degree of Hydrolysis
	5% KOH in methanol—reflux 1 hour	At least 85%
	0.5 *N* methanolic KOH—25 hours at 78°	34%
	0.5 *N* methanolic KOH—25 hours at 78°	Very slight

It is apparent that increasing the size and number of substituents in the 3 position favors resistance to hydrolysis. A possible explanation of this phenomenon is the steric effect of these substituents on the attack on the carbonyl group during hydrolysis. For example, it has been demonstrated that substitution of phenyl groups in the α position of ethyl esters of aliphatic acids greatly lowers the rate of saponification.[52] These authors postulated that the rate differences were caused by a powerful steric effect which more than balances any polarization effect of the phenyl groups (except in the esters of phenylacetic acid).

The effect of substituents in the 4 and 1 positions was studied by Staudinger [35] and is shown in Table 2.

It was demonstrated [41] that 1-benzyl-3-methyl-4-phenyl-2-azetidinone was much more susceptible to hydrolysis under alkaline conditions than its saturated derivative, 1-cyclohexylmethyl-3-methyl-4-cyclohexyl-2-azetidinone. One factor which explains this effect is the relative acid strengths of the acids from which the β-lactams are de-

[52] Levenson and Smith, *J. Am. Chem. Soc.*, **62**, 2324 (1940).

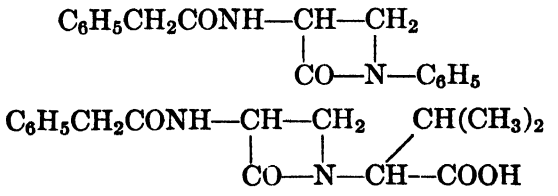
TABLE 2

HYDROLYSIS OF SOME β-LACTAMS DERIVED FROM DIMETHYLKETENE (AT 78° FOR 25 HR. WITH 0.5 *N* METHANOLIC KOH)

Compound	Degree of Hydrolysis
$(CH_3)_2C—CO$ $(C_6H_5)_2C—NC_6H_5$	2%
$(CH_3)_2C—CO$ $(CH_3)_2NC_6H_4CH—NC_6H_5$	7%
$(CH_3)_2C—CO$ $C_6H_5CH—NC_6H_5$	34%
$(CH_3)_2C—CO$ $C_6H_5CH—NC_6H_4NO_2$	95%

rived. For example, it was demonstrated by Calvet [58] that the rates of hydrolysis of amides increase with higher acid strengths of the parent acids. Inasmuch as phenylacetic acid is a stronger acid ($K_a = 5.56 \times 10^{-5}$) than cyclohexaneacetic acid ($K_a = 2.36 \times 10^{-5}$), it would be expected that 1-benzyl-3-methyl-4-phenyl-2-azetidinone would hydrolyze more rapidly than its saturated derivatives, as it does. In order that this argument may remain valid, it must be assumed that the differences in base strength of the amine portion of the molecule would not obscure the issue.

The effect of acid strengths on the ease of hydrolysis of amides explains, at least in part, the ease of hydrolysis of β-lactams containing an acylamino group in the 3 position of the azetidinone nucleus. Several of these compounds have been synthesized [41] as models for the β-lactam formula of penicillin, which also has an acylamino group in the same relative position. Typical examples of these compounds are:

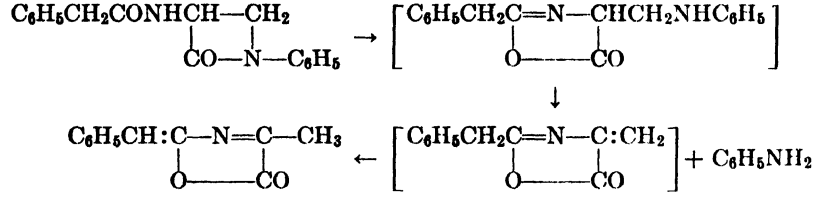


58 Calvet, *J. chim. phys.*, **30**, 140 (1933); see also *Compt. rend.*, **192**, 1569 (1931).

Inasmuch as it is known that α-acylamino acids are stronger than the corresponding aliphatic acids,[54] it is not surprising that the β-lactams in question are readily hydrolyzed.

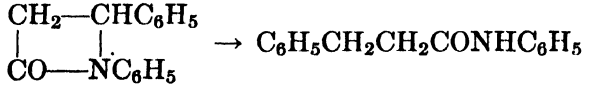
The acid hydrolysis of β-lactams apparently does not occur as readily as alkaline hydrolysis. Here again, however, it is indicated that the acylamino- and alkyl-substituted β-lactams hydrolyze more readily than those compounds containing aromatic substituents.[41,44]

Miscellaneous Reactions. Conversion of some acylamino β-lactams to 5(2)-oxazolones by heating them in a solvent has also been accomplished.[41] For example, 1-phenyl-3-phenylacetamido-2-azetidinone gives 2-benzylidene-4-methyl-5(2)-oxazolone when heated in anisole, presumably through the indicated intermediates. Desthiobenzylpeni-



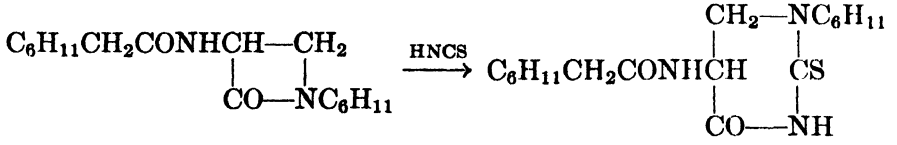
cillin also decomposes to give the same 5(2)-oxazolone when treated in the same manner.[48]

In some instances, hydrogenolysis of β-lactams proceeds with the fission of the azetidinone ring between the nitrogen atom and the 4-carbon atom. Thus, 1,4-diphenyl-2-azetidinone on treatment with Raney nickel gives β-phenylpropionanilide.[41] Other β-lactams such as 1-phenyl-3-phenylacetamido-2-azetidinone and desthiobenzylpeni-



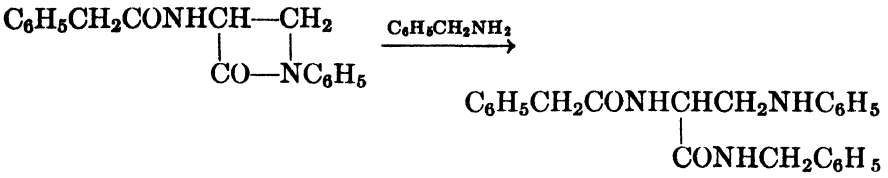
cillin were unaffected by this treatment.

Thiocyanic acid has been shown to react with 1-cyclohexyl-3-cyclohexaneacetamido-2-azetidinone to give a thiodihydrouracil.[41]

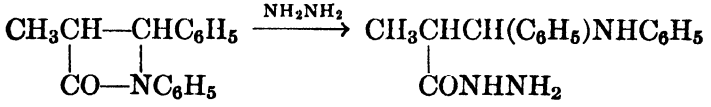


Amines in some cases will cleave β-lactams to give the β-amino acid amides. When 1-phenyl-3-phenylacetamido-2-azetidinone is heated with benzylamine at 160°, the corresponding amide is produced.

[54] Zief and Edsall, *J. Am. Chem. Soc.*, **59**, 2047 (1937).

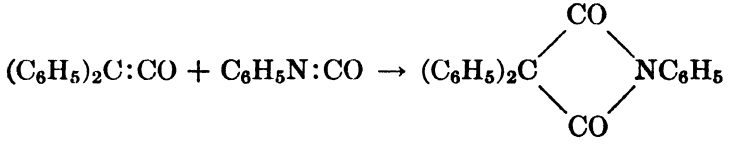


1,4-Diphenyl-3-methyl-2-azetidinone has been treated with hydrazine to yield the hydrazide of the β-amino acid.[41]

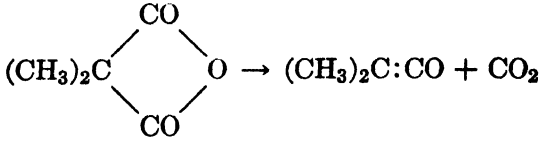


2,4-AZETIDINEDIONES (MALONIMIDES)

Staudinger [55] was able to synthesize 1,3,3-triphenyl-2,4-azetidinedione by heating phenyl isocyanate with diphenylketene at 220° for 5 hr. At lower temperatures, only polymerization of diphenylketene occurred.

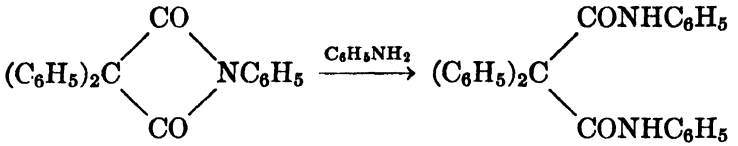


The azetidinedione is exceptionally stable to pyrolysis in contrast to the substituted malonic acid anhydrides, just as β-lactams are more resistant to cleavage than the β-lactones. Only after a long period of heating at 300° will the compound break down, apparently to its original components, phenyl isocyanate and diphenylketene. This cleavage of four-membered rings to give two unsaturated residues is characteristic, and the type of fission is quite analogous to that of the malonic acid anhydrides; for example, dimethylmalonic acid anhydride yields dimethylketene and carbon dioxide.

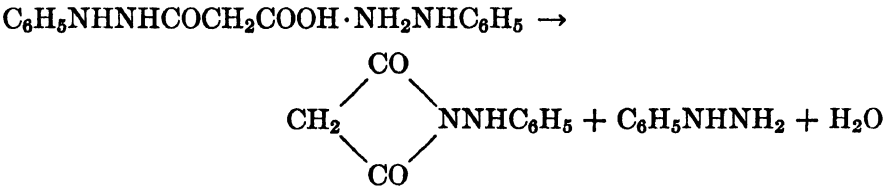


[55] Staudinger, Göring, and Schöller, *Ber.*, **47**, 41, 46 (1914).

The azetidinedione also reacts with aniline at 200° to give the dianilide of diphenylmalonic acid, confirming the structure of the compound in question.

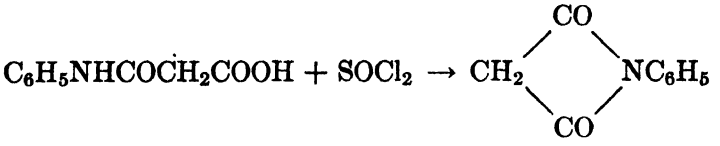


According to Fischer and Passmore,[56] who studied the formation of phenylhydrazides by the reaction of phenylhydrazine with aqueous solutions of a variety of organic acids, 1-anilino-2,4-azetidinedione (malonylphenylhydrazine) is formed when the phenylhydrazine salt of malonic acid monophenylhydrazide is heated at 200°. The product



does not decompose at its melting point, 128°.

During an investigation of the effect of thionyl chloride on the monoanilides of a series of dibasic acids, Warren and Briggs [57] demonstrated that the monoanilide of malonic acid, on reaction with thionyl chloride, was readily converted to 1-phenyl-2,4-azetidinedione (N-phenylmalonimide). The exceptional stability of the 2,4-azetidinedione ring



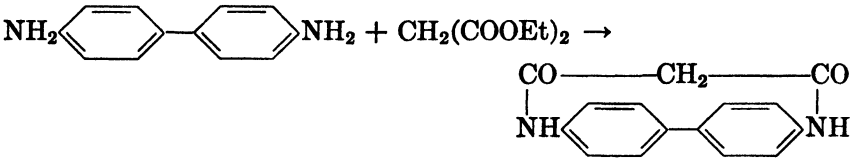
was also demonstrated with this compound, inasmuch as it was unaffected by concentrated nitric or hydrochloric acids. With hot concentrated sulfuric acid, decomposition to aniline, acetic acid, and carbon dioxide was effected. Caustic alkali hydrolyzed the malonimide to sodium malonate and aniline; ammonia at high temperatures converted the compound to malonamide and malonanilide.

The reaction of malonic ester and its substituted derivatives with aromatic amines has given products which apparently have the malon-

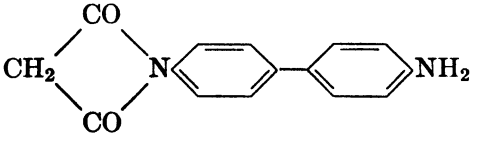
[56] Fischer and Passmore, *Ber.*, **22**, 2735 (1889).

[57] Warren and Briggs, *Ber.*, **64**, 26 (1931).

imide ring system. Remfry [58] condensed benzidine with diethyl malonate and some of its C-substituted derivatives but postulated that the structures of the compounds were as follows.

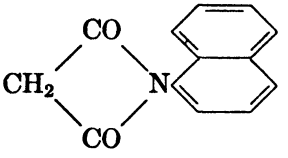


In repeating the synthesis using diethyl malonate, Le Fèvre [59] obtained evidence of a free amino group in Remfry's compound by forming a sulfate salt and a salicylidene derivative and, consequently, it is more likely that the original compound should be represented by the 2,4-azetidinedione structure (I). These compounds are apparently quite stable to heat and show no decomposition below 250° as evidenced by melting points.



I

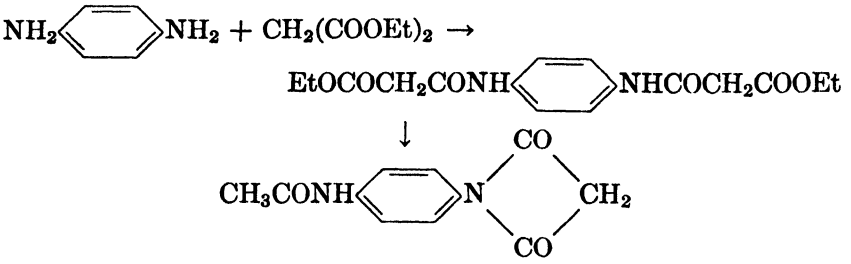
Apparently the combination of malonic ester with aromatic amines to give the malonimides is by no means a general reaction. Meyer [60] was unable to prepare the imides from aniline, β-naphthylamine, *m*- and *p*-phenylenediamine, and *m*-toluylenediamine. However, he was successful with α-naphthylamine, and the compound was high melting.



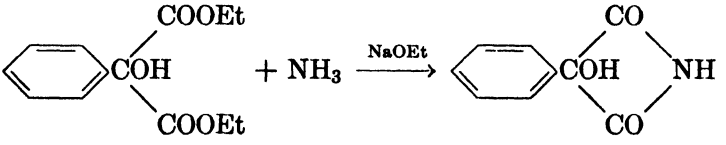
The product exhibited acid characteristics, dissolving in dilute caustic from which it could be precipitated with acids. Further studies by Mehta and Thosar [61] on the reaction of *p*-phenylenediamine with ma-

[58] Remfry, *J. Chem. Soc.*, **99**, 610 (1911).
[59] Le Fèvre, *J. Chem. Soc.*, 733 (1929).
[60] Meyer, *Ann.*, **347**, 23 (1906).
[61] Mehta and Thosar, *J. Indian Chem. Soc.*, **15**, 629 (1938).

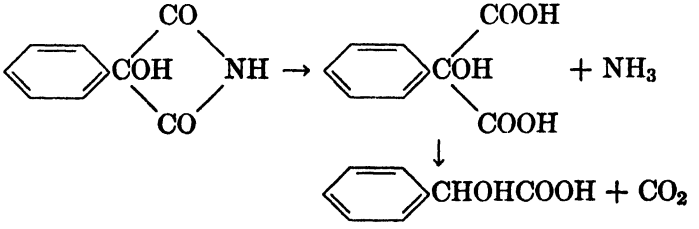
lonic ester did prove successful in the preparation of 1-(*p*-acetamidophenyl)-2,4-azetidinedione. The reaction proceeded first to give diethyl *p*-phenylenedimalonamate which was isolated and heated further to give, among other products, the 2,4-azetidinedione.



There is only one case reported in the literature where the direct reaction of ammonia with a substituted malonic ester has given the malonimide. Riebsomer et al.[62] treated diethyl phenylhydroxymalonate (phenyltartronate) with ammonia in the presence of sodium ethoxide to give the 2,4-azetidinedione. Although the reaction gave very

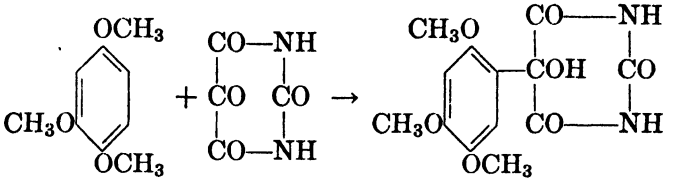


poor yields (about 3%), the authors were able to obtain products from the *p*-tolyl and *p*-ethylphenyl homologs. Better yields were obtained when urea replaced the ammonia, whereas aromatic amines did not react in this sense.[63] Hydrolysis of the azetidinediones with caustic gave the corresponding mandelic acids, presumably through the intermediate dicarboxylic acid which decarboxylated under the conditions of hydrolysis.

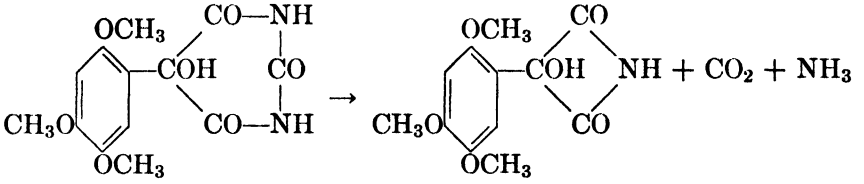


62 Riebsomer et al., *J. Am. Chem. Soc.*, **61**, 3491 (1939).
63 Riebsomer et al., *Proc. Indiana Acad. Sci.*, **50**, 118 (1940).

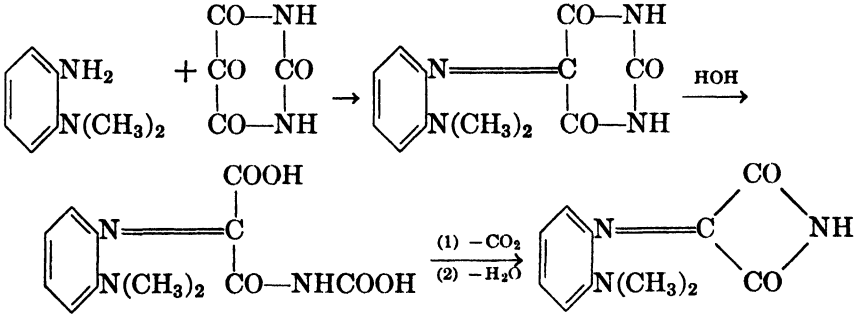
A series of reactions which may involve similar intermediates at some stage was discovered by Széki.[64] 1,3,4-Trimethoxybenzene was condensed with alloxan in the presence of hydrogen chloride to give 2,4,5-trimethoxyphenyldialuric acid. The product was hydrolyzed



with dilute caustic and then acidified with dilute hydrochloric acid to give the 2,4-azetidinedione. The compound dissolves in concentrated sulfuric acid with evolution of gas.



The decomposition of substituted alloxans to give malonimides has also been postulated by Rudy and Cramer[65] in their studies on the condensation products of aromatic amines with alloxan. For example, the product of reaction of N,N-dimethyl-*o*-phenylenediamine and alloxan is an anil which hydrolyzes stepwise to give the malonimide.



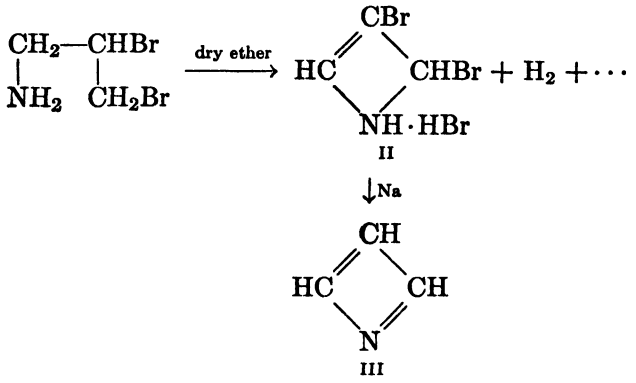
The compound is soluble in alkali and can be regenerated with acid, indicating the acidity of the imide hydrogen. It can be methylated with diazomethane on the imide nitrogen to give a compound which no longer has acidic properties.

64 Széki, *Ber.*, **56**, 2464 (1923).

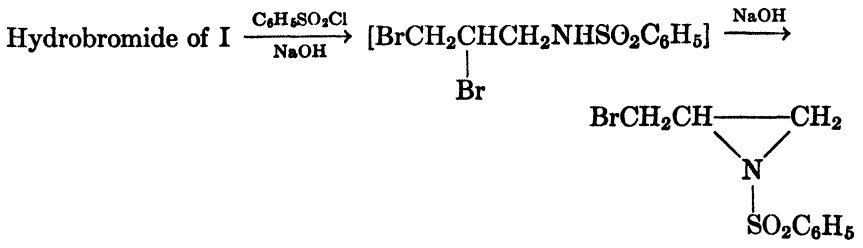
65 Rudy and Cramer, *Ber.*, **71**, 1234 (1938); **72**, 227 (1939).

AZETES (AZACYCLOBUTADIENES OR "PYRICULINES")

There are no reported compounds in which the presence of an azete ring has been established. In 1920, Abderhalden and Paquin [66] reported the preparation of what they believed to be azete itself (C_3H_3N) from 2,3-dibromopropylamine (I). The latter decomposed with the formation of a compound which appeared to be a secondary amine hydrobromide, 3,4-dibromo-2-azetine hydrobromide (II); this was debrominated by treatment with sodium with the formation of the

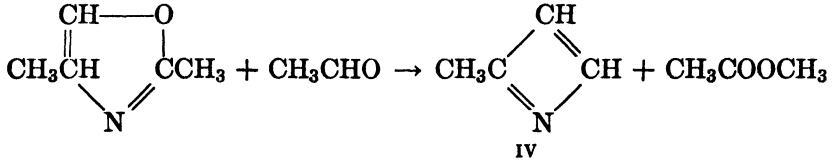


supposed azete (III). However, it has been shown by Gensler [67] that the supposed dibromoazetine hydrobromide (II) was in reality simply the hydrobromide of the original 2,3-dibromopropylamine and that the supposed azete was in all probability allylamine, (C_3H_5N). Gensler found that the original authors had made a consistent error in the calculation of percentage compositions and that all but one of their observations could be readily reconciled with the simpler formulation. The formation of a base-insoluble N-benzenesulfonyl derivative of the supposed dibromoazetine, indicating a secondary amine, has been interpreted as follows (cf. p. 64).



[66] Abderhalden and Paquin, *Ber.*, **53**, 1125 (1920).
[67] Gensler, *J. Am. Chem. Soc.*, **69**, 1966 (1947).

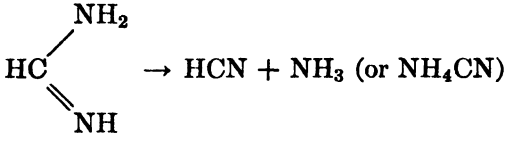
An oil boiling at 156–157° and having an odor of pyridine was obtained by Oesterreich [68] from the reaction of 2,4-dimethylisoxazole with acetaldehyde. It was called "methylpyriculine" by the author and assigned the structure of 2-methylazete (IV) on the basis of analyses in agreement with C_4H_5N and because ethyl or methyl acetate, identified by the odor, was also formed in the reaction.



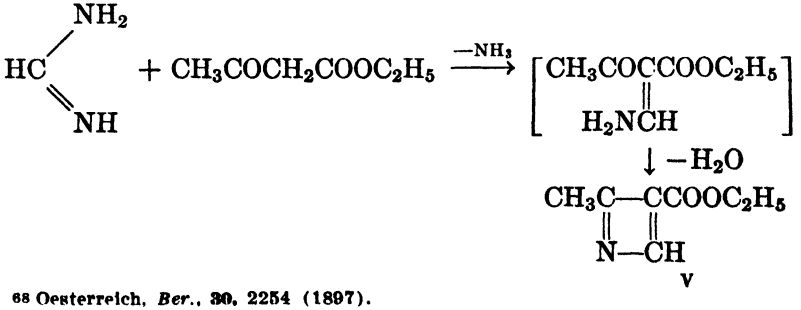
IV

The above formulation was only very tentatively offered, since ethyl acetate could have been formed from two molecules of acetaldehyde. Furthermore, it seems unlikely that a compound C_4H_5N would boil as high as 156–157°.

From the reaction of ethyl acetoacetate and formamidine, Pinner [69] obtained a neutral product which he reported to be ethyl β-cyanocrotonate, formed as follows.



However, Shestakov and Kazakov [70] later reported work indicating that Pinner's product was more probably ethyl 2-methyl-3-azetecarboxylate (V). Although compound V would be expected to be weakly



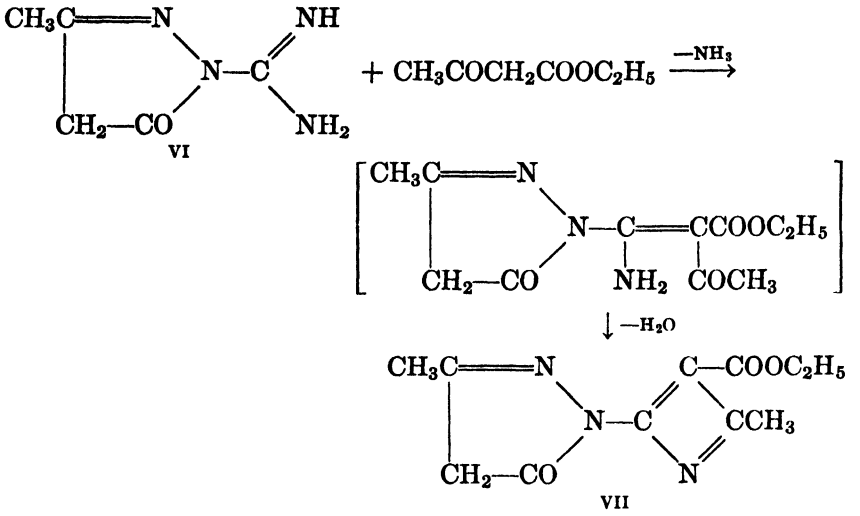
V

[68] Oesterreich, *Ber.*, **30**, 2254 (1897).

[69] Pinner, *Ber.*, **18**, 2845 (1885).

[70] Shestakov and Kazakov, *J. Russ. Phys Chem. Soc.*, **44**, 1312 (1912).

basic, Pinner described his product as being neutral. The later authors made their assignment of the azete structure because of the fact that ethyl β-cyanocrotonate cannot be prepared from ethyl acetoacetate and hydrogen cyanide and because of the results of their study of the reaction of amidines in general with ethyl acetoacetate. According to Shestakov and Kazakov, the reaction of 3-methyl-5-pyrazolone-1-carbamidine (VI) with ethyl acetoacetate resulted in the formation



VI

VII

of a product (VII) believed to be a derivative of azete. The authors postulated that amidines in which the amidine carbon atom is linked to H (as in formamidine) or to N (as in compound VI) in general react with β-keto esters by loss of ammonia and water and form compounds containing the azete or azacyclobutadiene ring, whereas amidines in which the amidine carbon atom is linked to carbon react by loss of water only and form pyrimidine derivatives.

CHAPTER 4

FURAN

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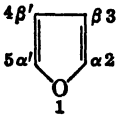
Department of Chemistry, Columbia University

CONTENTS

INTRODUCTION

Nomenclature. Furan represents the parent doubly unsaturated heterocycle containing four carbon atoms and one oxygen atom from which a large and increasingly important group of organic compounds is derived. Although in the early literature the compound is referred to as furfurane, the name furan has become firmly implanted in later publications. Two conventions are commonly used in denoting the positions in the furan cycle, one embodying Greek notations and the second following rigidly the conventional rules for numbering positions in any heterocycle (I). Further, common practice over the years has resulted in the general acceptance of certain terms representing radicals derived from furan, such as α- (or 2-) furyl (II), α- (or 2-) furfuryl (III), and α- (or 2-) furoyl (IV), to give a few representative exam-



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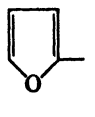

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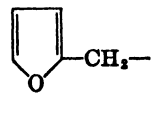

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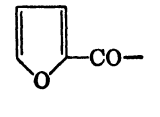


IV

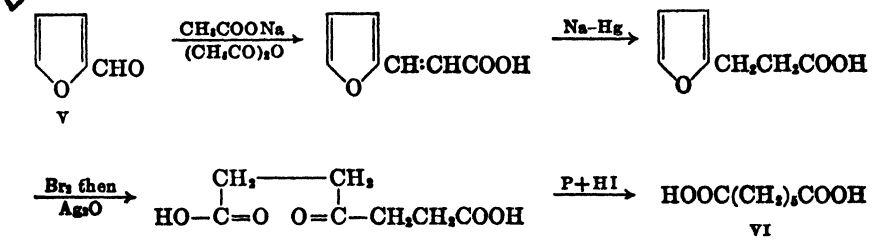
ples. Obviously, a similar series of β (or 3) radicals is possible, and the analogy of the radicals represented by II, III, and IV with the phenyl, benzyl, and benzoyl radicals is at once apparent.

In addition to the above conventions, trivial names have become associated with certain furan derivatives. Thus, furan-2-aldehyde is commonly known as furfural; furan-2,5-dicarboxylic acid, which was first obtained from mucic acid by intramolecular loss of water, is frequently called dehydromucic acid; furan-2-carboxylic acid, obtained by pyrolytic decarboxylation of dehydromucic acid, is referred to as pyromucic acid; and 2-methylfuran is known as sylvan.

The arrangement of the atoms in furan can be clearly shown by the classical conversion of furfural to pimelic acid[1] (V–VI), which also serves to demonstrate that furfural is furan-2-aldehyde.

There are several general reviews of various phases of furan chemistry. The early development of the subject has been summarized by

1 Baeyer, *Ber.*, **10**, 355, 695, 1358 (1877).



Marquis.[2] Two reviews of the substitution reactions of furan and the preparation of substituted furans are also available.[3,4] An exhaustive compilation of furan derivatives is found in Grignard's treatise,[5] and the more recent developments are admirably reviewed by Owen.[6] There are also reviews of the industrial applications of furan.[7]

Many furan compounds may be recognized by the characteristic color imparted by their vapors to a pine splinter soaked in hydrochloric acid. Although the color usually ascribed to furan in this test is green, this is by no means always so. Reichstein [8] found that, although many furan compounds give the green color, many others give a red color indistinguishable from that given by pyrrole. No definitive rule can be formulated to cover such tests. All monoalkyl furans give the green color, and a free α position plays a certain but minor role in determining the color developed in the test. Since the *p*-dimethylaminobenzaldehyde (Ehrlich) test, usually regarded as characteristic of pyrroles, is also given by some furans, it is obvious that caution must be exercised in interpreting the results of such color tests.

FURAN DERIVATIVES FROM CARBOHYDRATES

The early chemistry of furan and its simple derivatives has been largely associated with their production from natural sources. In particular, the development of the chemistry of furfural owes its impetus largely to the ready accessibility of this substance from a wide variety of natural products. Although the importance of furfural will be dealt with more in detail at later stages of this discussion, it may not be

2 Marquis, *Ann. chim. phys.*, [8] **4**, 200 (1905).

3 Gilman and Wright, *Chem. Revs.*, **11**, 323 (1932).

4 Gilman and Wright, *Chem. Eng. News*, **40**, 1517 (1948).

5 Grignard, *Traité de chimie organique*, Masson et Cie., Paris, 1945, Vol. 18, pp. 49 ff.

6 Owen, *Ann. Repts. Progress Chem. (Chem. Soc. London)*, **42**, 157 (1945).

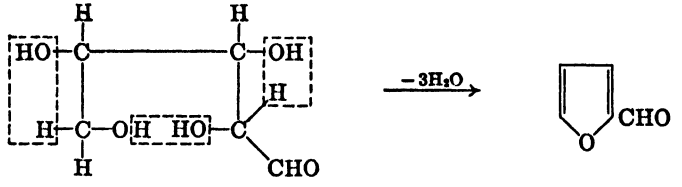
7 (*a*) Natta, Rigamonti, and Beati, *Chimica e industria Milan*, **23**, 117 (1941); (*b*) Peters, *Ind. Eng. Chem.*, **28**, 755 (1936); **31**, 178 (1939); (*c*) Wacek, *Angew. Chem.*, **54**, 453 (1941).

8 Reichstein, *Helv. Chim. Acta*, **15**, 1112 (1932).

amiss to review briefly the early history of this most important of the furan derivatives.

Since the earliest days in which furfural was recognized as a chemical individual, the source of the substance has been recognized as intimately connected with the decomposition of various naturally occurring carbohydrate products. Thus, the fortuitous discovery of furfural,[9] somewhat over one hundred years ago, rested on an investigation of the products formed by the action of sulfuric acid on sugar or starch in an attempt to prepare formic acid by this method. Later investigations [10–12] showed that the production of furfural from carbohydrate material was undoubtedly due to the action of sulfuric or other mineral acid on pentoses, either occurring as such or arising from hydrolysis of pentosans originally present in the carbohydrate material.

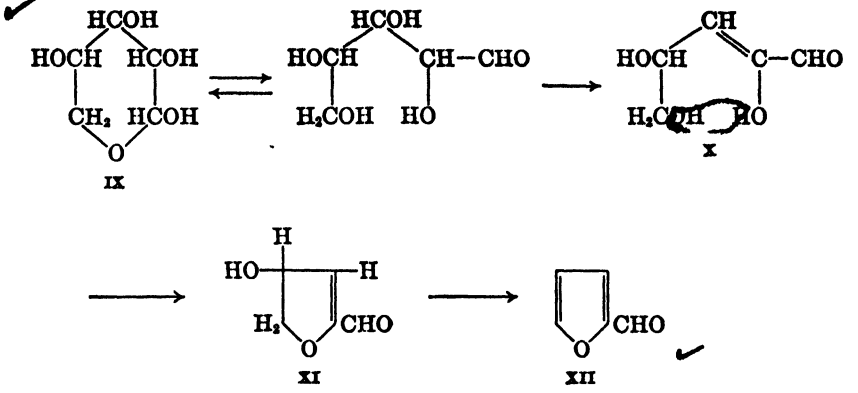
A mechanism for the conversion of pentoses to furfural has been proposed by Hurd and Isenhour.[13] This mechanism is based largely on a study of the conversion of xylose to furfural in which the effect of concentrations of acid, time, and temperature were studied. Although it is convenient to picture the conversion in terms of a simple dehydration (VII–VIII), such simplicity apparently does not repre-



VII VIII

sent the true state of affairs, and the mechanism suggested is represented by IX–XII. That the reaction is not a simple dehydration (VII–VIII) is indicated by the failure to obtain any furfural from the action of the usual dehydrating reagents such as phosphorus pentoxide, zinc chloride, or 4 *M* phosphoric acid on xylose. Rather, dilute mineral acid is required. Since similar treatment of erythritol yields no furan, it is concluded that the presence of a β-hydroxyaldehyde is a necessary condition for the reaction. Similarly, hexoses yield exclusively 5-hydroxymethylfurfural (XIII), with none of its isomer (XIV) being

9 Döbereiner, *Ann.*, **3**, 141 (1832).
10 Stenhouse, *Ann.*, **35**, 301 (1840).
11 Fownes, *Ann.*, **54**, 66 (1845).
12 Stone and Tollens, *Ann.*, **249**, 227 (1888).
13 Hurd and Isenhour, *J. Am. Chem. Soc.*, **54**, 317 (1932).



found in the products of the reaction. This is interpreted to indicate that ring formation is probably preceded by dehydration. Otherwise, both XIII and XIV should be formed. Methyl pentoses, for example

rhamnose, similarly yield 5-methylfurfural. Under comparable conditions, arabinose gives a lower yield of furfural than does xylose, indicating that some relationship, not well understood at present, exists between configuration of the sugar and the amount of furfural formed.

Commercial practice for the manufacture of furfural in this country has been discussed by Miner, Trickey, and Brownlee,[14] and by Killefer.[15]

It is not necessary, provided conditions are properly chosen, to start with an aldose as a source of furan derivatives. Haworth and Jones,[16] in a careful study of the formation of 5-hydroxymethylfurfural (XIII) from sucrose, a reaction earlier noted by several workers,[17] obtained 54% of XIII (based on the fructose present) by treatment of sucrose with aqueous oxalic acid at temperatures of 125–145°. That only the fructose underwent conversion to XIII was shown by oxidation of the residual solution to saccharic acid in yield equal to that obtainable from glucose alone. Such conversion of fructose to a furan requires

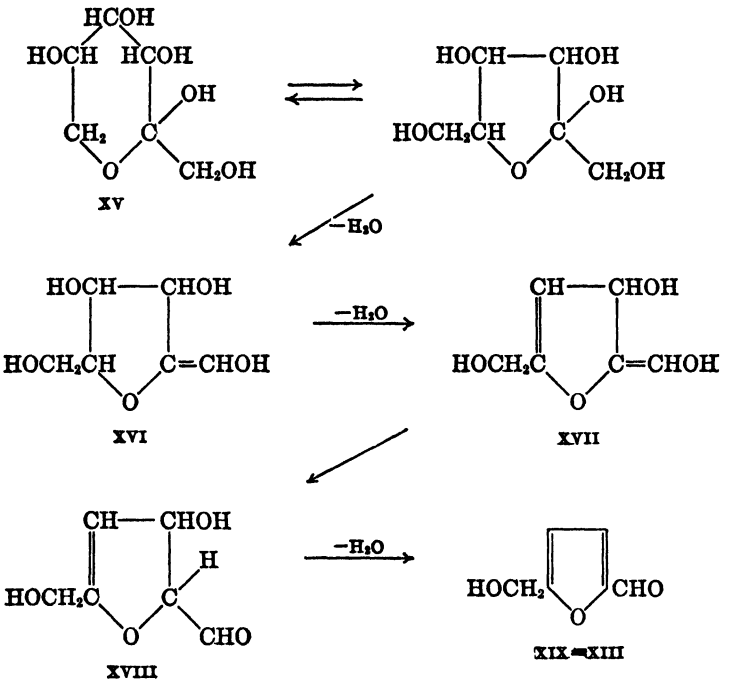
14 Miner, Trickey, and Brownlee, *Chem. Met. Eng.*, **27**, 299, 362 (1922).

15 Killefer, *Ind. Eng. Chem.*, **18**, 1217 (1926).

16 Haworth and Jones, *J. Chem. Soc.*, 667 (1944).

17 Düll, *Chem. Ztg*, 216 (1895); Kiermayer, *ibid.*, 1003; Middendorp, *Rec. trav. chim.*, **38**, 1 (1919).

a different explanation from that of Hurd and Isenhour [18] as applied to the aldoses, and the steps represented by XV–XIX are suggested. It follows, in accordance with this mechanism, that, if glucose could



be converted to the ene-diol form, formation of XIX should ensue under the action of oxalic acid. This has been accomplished by pretreating glucose with sodium or calcium hydroxide [18] and then proceeding with the oxalic acid reaction. The maximum yield of XIX was 28%. Finally, Haworth and Jones [16] have extended the original observation of Fenton [19] and have obtained yields of 21% of 5-chloromethylfurfural by saturating a concentrated aqueous suspension of sucrose with hydrogen chloride. From this, 5-methylfurfural is readily obtained by reductive removal of the chlorine with stannous chloride.[20]

By treatment of tetramethylglucoseen-1,2 with 3 *N* hydrochloric acid, Wolfrom, Wallace, and Metcalf [21] obtained 5-methoxymethylfurfural by the interesting series of transformations outlined. Support

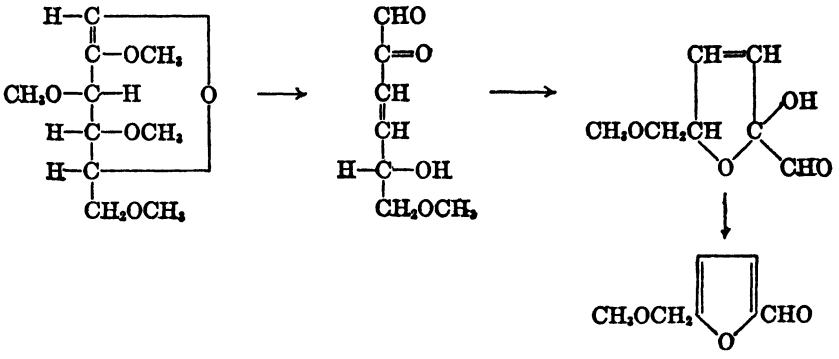
18 Evans, *J. Am. Chem. Soc.*, **48**, 2665 (1926); Wolfrom and Lewis, *ibid.*, **50**, 842 (1928).

19 Fenton, *J. Chem. Soc.*, **79**, 808 (1901); **95**, 1334 (1909).

20 Rinkes, *Org. Syntheses Coll. Vol.* **2**, 393 (1943).

21 Wolfrom, Wallace, and Metcalf, *J. Am. Chem. Soc.*, **64**, 265 (1942).

for such a formulation is found in the observations of Bergmann and Zervas [22] on the very sensitive glucoseens, the behavior of which may



be represented by intramolecular dismutation reactions involving elimination of methanol. A similar conversion of trimethylpentoses

$$C_6H_8O_2(OCH_3)_4 \xrightarrow{-HOH} C_6H_6O(OCH_3)_4 \xrightarrow[+2H_2O]{-3CH_3OH}$$

tetramethylgluco-pyranose

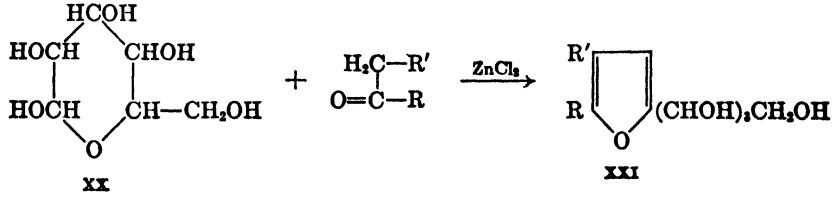
$$C_6H_7O_3(OCH_3) \xrightarrow{-H_2O} C_6H_5O_2(OCH_3)$$

to furfural on treatment first with alkali and then with acid has been noted by Weber and Lewis.[23]

An interpretation of many of the above reactions based on the concept of consecutive electron displacement has been suggested by Isbell.[24]

Furan derivatives may also be obtained from aldoses by a reaction first noted by West,[25] which involves condensation of the sugar with a β-dicarbonyl compound under the influence of zinc chloride.

The mechanism of this reaction is not at once apparent, but the over-all result is represented by XX–XXI and proceeds readily with

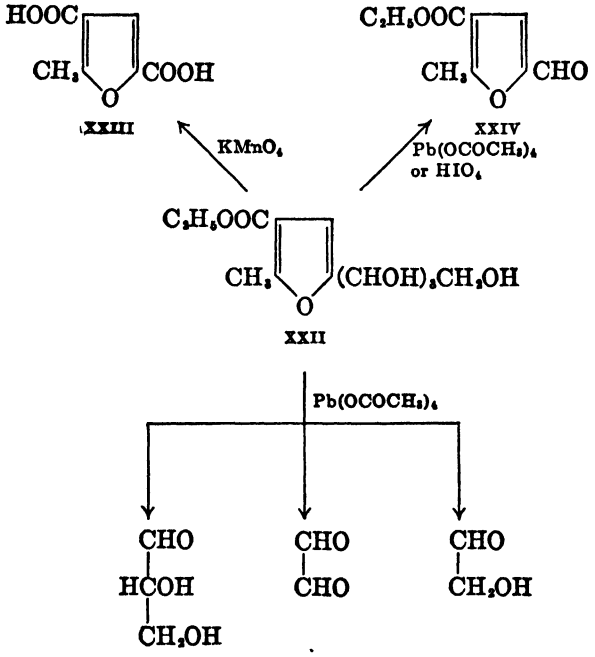


XX XXI

22 Bergmann and Zervas, *Ber.*, **64**, 1434 (1922).
23 Weber and Lewis, *J. Am. Chem. Soc*, **53**, 4411 (1931).
24 Isbell, *Bur. Standards J. Research*, **32**, 45 (1944).
25 West, *J. Biol. Chem.*, **74**, 561 (1927).

acetoacetic ester, benzoylacetic ester, acetonedicarboxylic ester,[26] and acetylacetone.[27]

The structures of the products have been established by the investigations of Gonzalez,[28] Müller and Varga,[29] Széki and László,[26] and Jones.[27] From the product from glucose and acetoacetic ester (XXII), a monoacetone derivative is formed under the influence of copper sulfate, and a diacetone derivative with sulfuric acid.[28] Oxidation with permanganate yields 2-methylfuran-3,5-dicarboxylic acid (XXIII).[15]



On oxidation with periodic acid [27] or with lead tetraacetate,[26,27] a variety of products has been isolated—4-carbethoxy-5-methylfurfural (XXIV), glyceric aldehyde, glyoxal, and glycolic aldehyde. From this, the structure of XXII may readily be deduced.

SYNTHESES OF FURANS

By Ring Closure of 1,4-Glycols. 1,4-Glycols readily lose water intramolecularly to yield furans. Phosphoric acid is a useful reagent

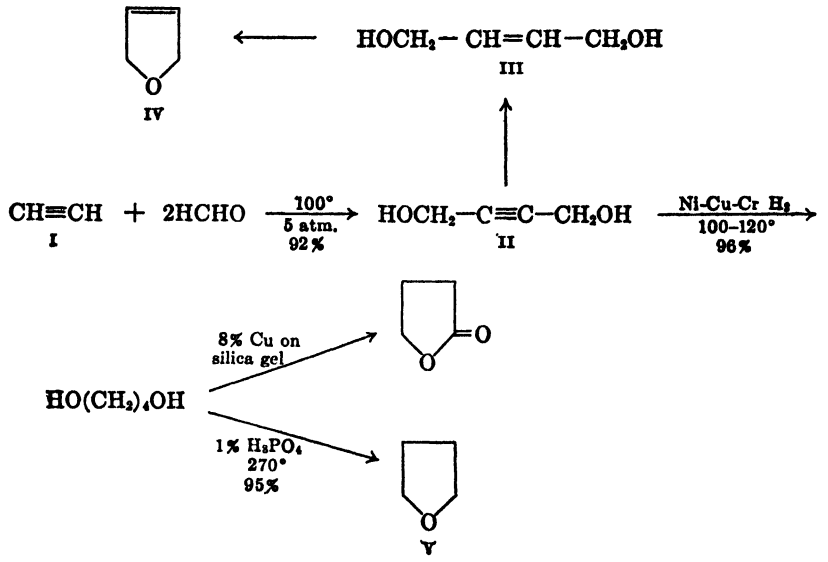
[26] Széki and László, *Ber.*, **73**, 924 (1940).

[27] Jones, *J. Chem. Soc.*, 116 (1945).

[28] Gonzalez, *Anales soc. españ. fis. y quím.*, **32**, 815 (1934); *Chem. Zentr.*, 1935, I, 2810.

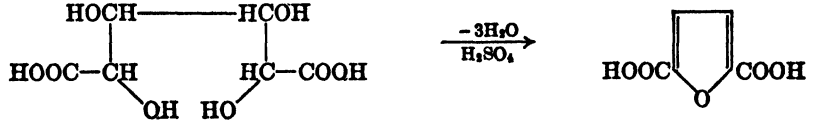
[29] Müller and Varga, *Ber.*, **72**, 1993 (1939).

for this purpose. In this way, the production of tetrahydrofuran (V), an important intermediate for many commercial products, has been developed to a full manufacturing scale in Germany. The process proceeds from acetylene by a remarkable series of reactions (I–V).[30] The



catalyst for the first step is composed of 12% copper and 3% bismuth supported on silica gel. By partial reduction of the butyne diol (II) to butene-2-diol-1,4 and ring closure, $\Delta^{3,4}$-dihydrofuran may be obtained. From this, maleic anhydride results on oxidative ring cleavage.[31]

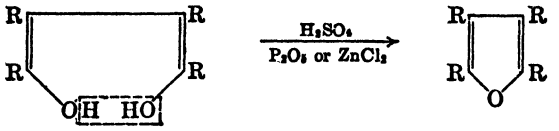
Furan-2,5-dicarboxylic acid, dehydromucic acid, is one of the oldest of the furan derivatives and is prepared by ring closure and dehydration of mucic acid.[32]



By Ring Closure of 1,4-Dicarbonyl Compounds. Ring closure involving elimination of water between the dienolic forms of 1,4-dicarbonyl compounds represents one of the oldest and most convenient

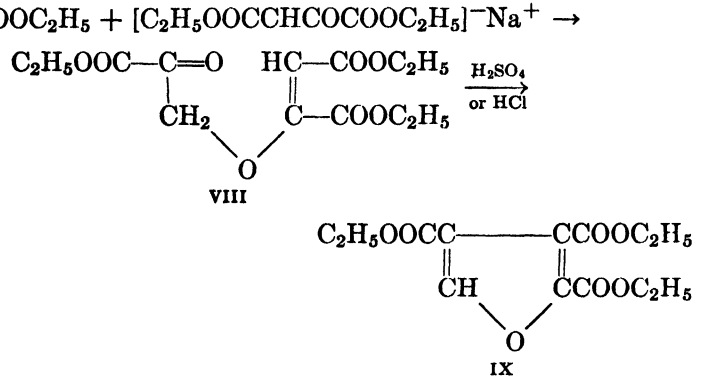
30 *U. S. Dept. Commerce, Office of Technical Services, Rept.* PB 1661, 1812.
31 *U. S. Dept. Commerce, Office of Technical Services, Rept.* PB 672.
32 Yoder and Tollens, *Ber.*, 34, 3446 (1901).

methods for the preparation of furan derivatives (VI–VII).[33,34] The method is capable of the widest application and appears to be limited



VI VII

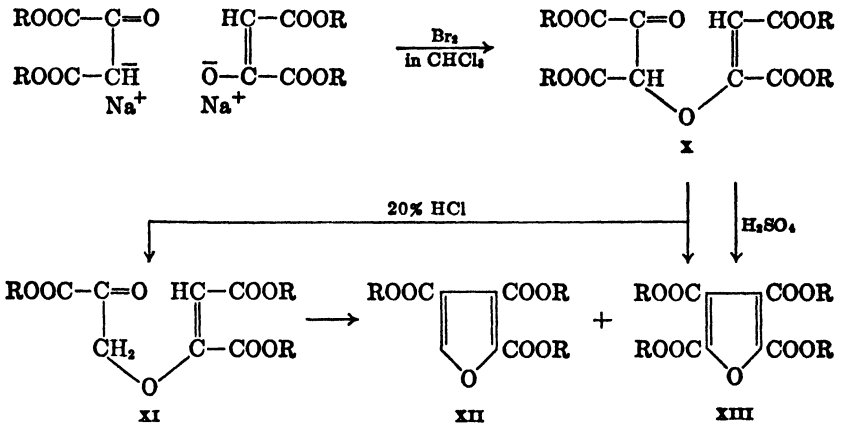
only by the availability of the requisite dicarbonyl compounds. In this connection, caution is sometimes required in assigning structures to these intermediates. Thus, Reichstein et al.[35] showed that, in the reaction of sodiodiethyloxaloacetate with ethyl bromopyruvate, alkylation on the oxygen atom of the β-keto ester occurs and not C alkylation as originally supposed by Sutter.[36] The course of the formation of the furan then is represented by VIII–IX, the product being 2,3,4-



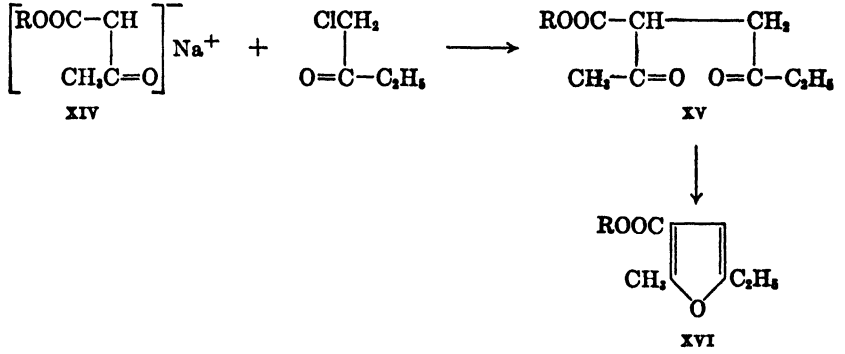
tricarbethoxyfuran (IX) rather than 2,3,5-tricarbethoxyfuran as would be expected on the basis of Sutter's interpretation. Similar O alkylation has been noted in the reaction of ethyl bromopyruvate with ethyl sodioacetonedicarboxylate or with ethyl sodio-β-ketosuberate, leading to ethyl 3,4-dicarbethoxyfuran-2-acetate and 2-valerate, respectively.[37] Condensation of two molecules of ethyl sodioöxaloacetate with bromine appears to take a similar course.[35] In this instance, partial cleavage of the β-ketonic ester occurs when hydrochloric acid is

33 Paal, *Ber.*, **17**, 2765 (1884); **18**, 58, 367, 2251 (1885).
34 Knorr, *Ber.*, **17**, 2756 (1884).
35 Reichstein et al., *Helv. Chim. Acta*, **16**, 276 (1933).
36 Sutter, *Ann.*, **490**, 54 (1932).
37 Archer and Pratt, *J. Am. Chem. Soc.*, **66**, 1656 (1944).

the furanizing reagent (X–XII) but does not take place when sulfuric acid is used (X–XIII).



That O alkylation does not always take place is shown by the observation of Reichstein [38] that ethyl sodioacetoacetate condenses with 1-chlorobutanone-2,[39] according to XIV–XVI. Condensation in a simi-



lar fashion takes place with the isomeric 2-chlorobutanone-3.[40] The factors that determine the mode of the alkylation reaction do not appear to be clear at present.

A reaction, originally noted by Fittig [41] and subsequently studied by Reichstein and Grüssner, deserves comment, if for no other reason

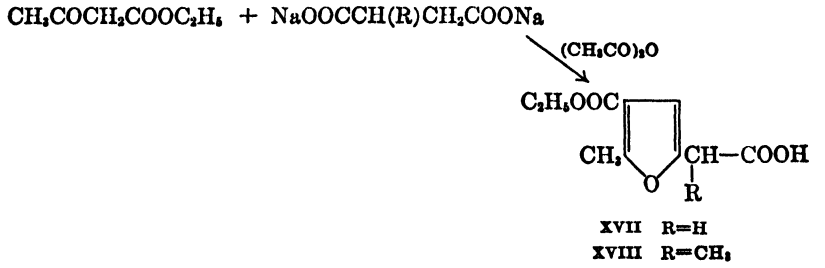
38 Reichstein and Grüssner, *Helv. Chim. Acta*, **16**, 6 (1933); cf. Hurd and Wilkinson, *J. Am. Chem. Soc.*, **70**, 739 (1948).

39 Cf. Harrow, *Ann.*, **201**, 147, 158 (1880); Paal, *Ber.*, **17**, 2765 (1884).

40 Reichstein, Zschokke, and Sys, *Helv. Chim. Acta*, **15**, 1112 (1932).

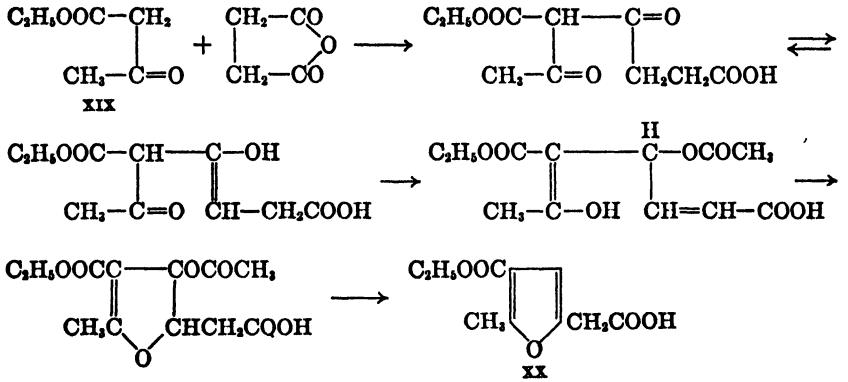
41 Fittig, *Ber.*, **18**, 2526 (1885); *Ann.*, **250**, 166 (1888).

than because of the obscurity surrounding its course. If ethyl acetoacetate and sodium succinate are heated with acetic anhydride, the monoethyl ester of methronic acid (XVII), 4-carboxy-5-methylfuran-2-acetic acid results. With sodium α-methylsuccinate in the same reaction, the product is XVIII. Apparently the second carboxyl group



XVII R=H
XVIII R=CH₃

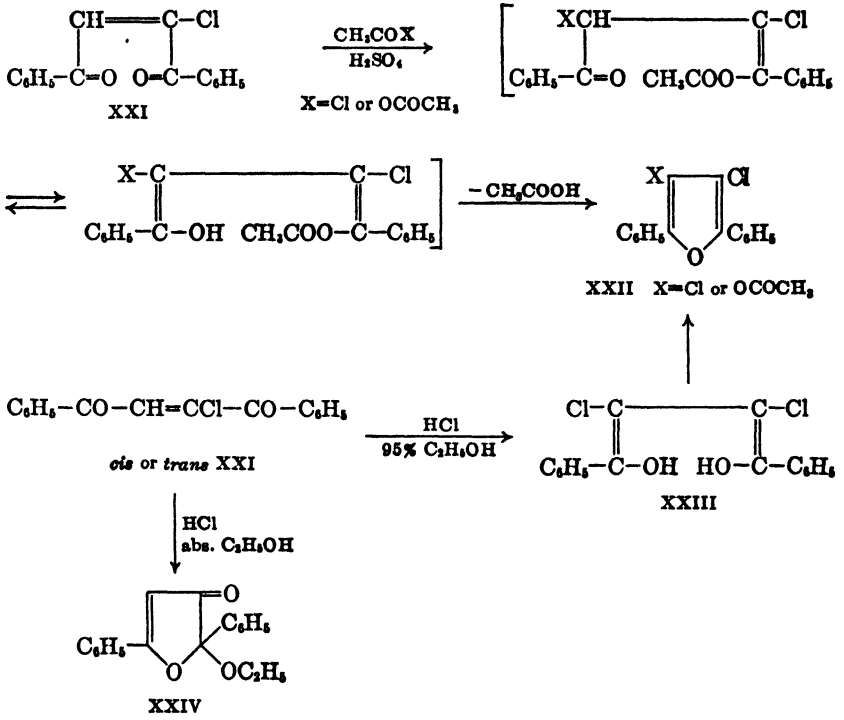
of succinic acid is vital because the reaction fails with sodium acetate. Although no experimental evidence for the course of the reaction is available, it can be tentatively formulated as shown in XIX–XX.



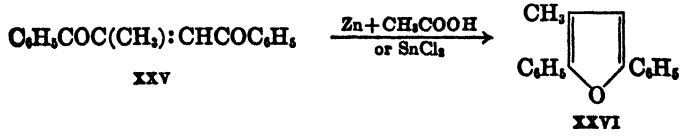
The preparation of furan derivatives from unsaturated 1,4 diketones represents another example of ring closure of such dicarbonyl compounds to furans. However, the actual ring closure in this case is probably preceded by 1,4 addition of the elements of the reagent employed to promote the cyclization. Lutz and McGinn [42] studied the conversion of certain dibenzoylethylenes to furans. The stereo arrangement of the unsaturated diketone plays a role in determining the ease of ring closure. Whereas, for example, only *cis*-dibenzoylchloroethylene (XXI) reacts with acetyl chloride or acetic anhydride (in the presence of sulfuric acid as catalyst) to yield the corresponding chloro-

42 Lutz and McGinn, *J. Am. Chem. Soc.*, **64**, 2585 (1942).

or acetoxy-furans (XXII), both the *cis* and *trans* isomers react with hydrogen chloride in 95% ethanol to yield the chlorofuran (XXII). The reactions are most easily understood if one postulates intermediate addition of the acetyl chloride or acetic anhydride to the unsaturated ketone. On the other hand, either *cis* or *trans* XXI with absolute alcoholic hydrogen chloride yields the ethoxyfuranone (XXIV), a reaction discussed more fully on p. 179. With 95% alcoholic hydrogen chloride ring closure follows the course XXI–XXIII–XXII.

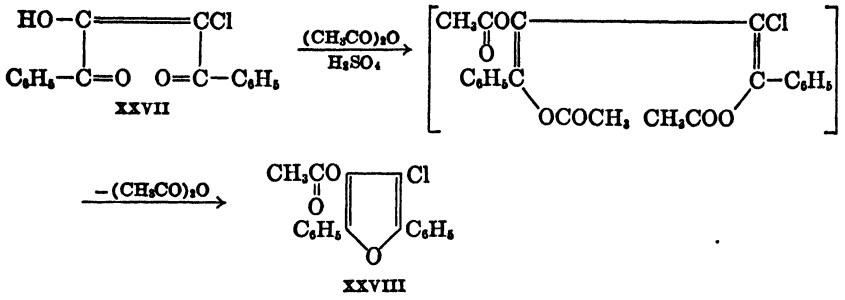


If the ring closure is carried out in a reducing medium such as zinc and acetic acid or stannous chloride, a furan also results, the unsaturated ketone being reduced to the saturated one from which furan



formation proceeds normally (XXV–XXVI). Similarly, 1,2,4 triketones can be considered to combine the properties of α, β, and γ di-

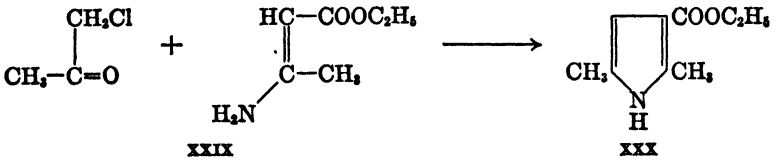
ketones and in the enol form to act as unsaturated 1,4 diketones from which furans can be formed, e.g., reactions (XXVII–XXVIII) in which



XXVII XXVIII

1,6 addition of acetic anhydride is suggested. Many reactions of this type have been studied by Lutz and co-workers. The interpretation of earlier observations [43] has been corrected [44] by reinvestigation in the light of the observations of Kohler and co-workers.[45,46] The conditions leading to hydroxyfurans rather than to simple furan derivatives have been investigated more in detail by Lutz and Stuart (p. 180).[47]

The Feist-Benary Synthesis. The classical Hantzsch pyrrole synthesis [48] proceeds from an α-chloroketone, ethyl acetoacetate, and ammonia (p. 290). In an attempt to apply the reaction substituting acetonedicarboxylic ester for ethyl acetoacetate, Feist [49] found that a furan derivative rather than the expected pyrrole was formed. For the formation of the pyrrole derivatives, Hantzsch suggested the sequence of reactions XXIX–XXX, which has been confirmed by Kor-



XXIX XXX

schun [50] and differs somewhat from Feist's idea on the mode of formation of pyrroles. Feist explains the formation of the furan as in XXXI–XXXIII.

[43] Lutz, Wilder, and Parrish, *J. Am. Chem. Soc.*, **56**, 1980 (1934); Lutz and Wilder, *ibid.*, **56**, 1987, 2065, 2145 (1934); Lutz and Stuart, *ibid.*, **58**, 1933 (1936).

[44] Lutz, Stuart, Wilder, and Connor, *J. Am. Chem. Soc.*, **59**, 2314 (1937).

[45] Kohler, Westheimer, and Tishler, *J. Am. Chem. Soc.*, **58**, 264 (1936).

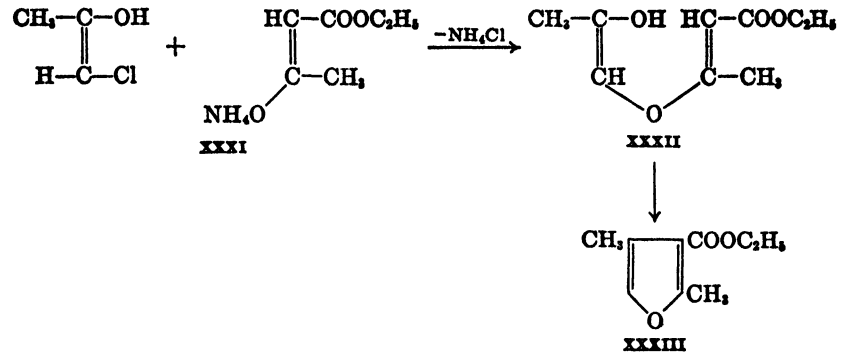
[46] Kohler and Woodward, *J. Am. Chem. Soc.*, **58**, 1933 (1936).

[47] Lutz and Stuart, *J. Am. Chem. Soc.*, **59**, 2316. 2322 (1937).

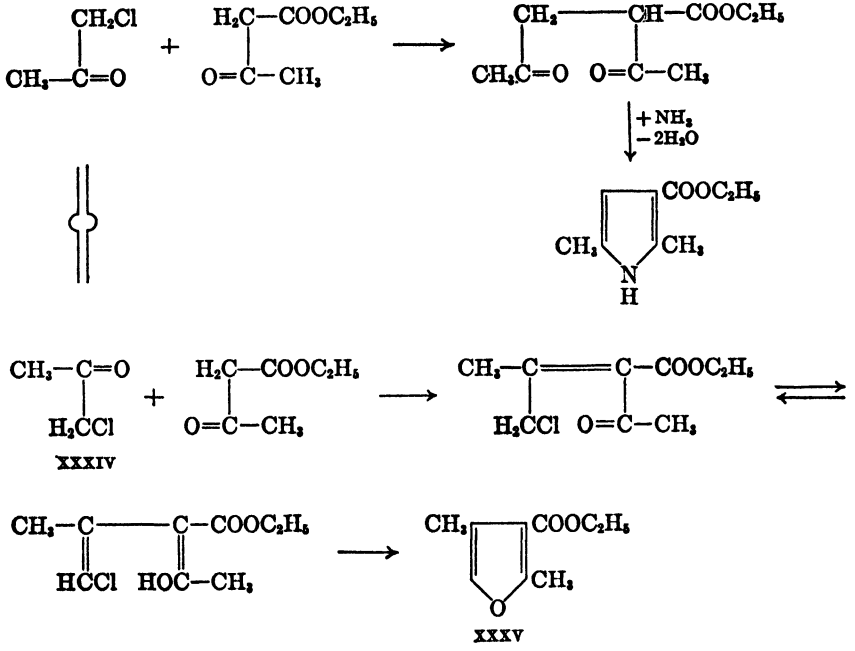
[48] Hantzsch, *Ber.*, **23**, 1474 (1890).

[49] Feist, *Ber.*, **35**, 1539, 1545 (1902).

[50] Korschun, *Ber.*, **38**, 1125 (1905).



Another scheme for reconciling the observed experimental facts has been put forward by Plancher and Albini,[51,52] as represented by XXXIV–XXXV.



It should be noted that pyrrole is formed only on heating the reactants and that, as far as is known, the action of ammonia on acetoacetic ester, either in the presence or absence of a chloroketone, yields

51 Plancher and Albini, *Atti reale accad. Lincei*, [5] 13, I, 39 (1904).
52 Benary, *Ber.*, 44, 489, 493 (1911).

β-aminocrotonic ester. Feist postulates an intermediate ammonium salt of the enol XXXI, via which the formation of the furan proceeds. Further, the furan obviously cannot come from the pyrrole, or vice versa, which can only mean that a different intermediate must be involved in the two reactions. In a reinvestigation of the original Hantzsch synthesis, Feist was able to isolate a small quantity of furan derivative. However, with acetonedicarboxylic ester, the yields of furan compound are considerably improved as a result of the more recent work of Reichstein and Zschokke.[53] The use of pyridine rather than ammonia has been recommended as resulting in more satisfactory yields in this synthesis.[54]

The yields of furan derivative obtained by the Feist method are closely dependent on the β-keto ester employed. With acetoacetic ester the product consists predominantly of pyrrole, whereas with acetonedicarboxylic ester satisfactory yields of the furan can be obtained. On the other hand, oxaloacetic ester yields no furan and but a small amount of pyrrole. Rather, the main product is 2,3-dihydroxy-5- (or 6-) methylisonicotinic ethyl ester.[55]

Closely related to the Feist synthesis is that of Benary [52] which involves the interaction of a 1,2-dichloroether with ammonia and a β-dicarbonyl compound. Since the dichloroethers decompose in the presence of ammonia to a monochloroketone or aldehyde,[56] the subsequent steps of the Benary synthesis can be considered the same as those involved in the Feist procedure, and an easily separable mixture of furan and pyrrole derivatives results.

From Pyrone Derivatives. In a study of the bromination of simple derivatives of α-pyrone, Feist noted a number of interesting reactions, some of which serve as useful syntheses for furan compounds. Isodehydracetic acid (dimethylcoumalic acid) (XXXVI), prepared by the action of sulfuric acid on ethyl acetoacetate or by condensation of ethyl sodioacetoacetate with ethyl β-chlorocrotonate, on bromination in aqueous solution yields a monobromo derivative (XXXVII) which when heated with water yields 2,4-dimethylfuran-3-carboxylic acid, presumably by way of the intermediate XXXVIII.[57] However, when the bromo derivative (XXXIX) of the ethyl ester of XXXVI is subjected to alkaline hydrolysis, a different reaction path is followed,

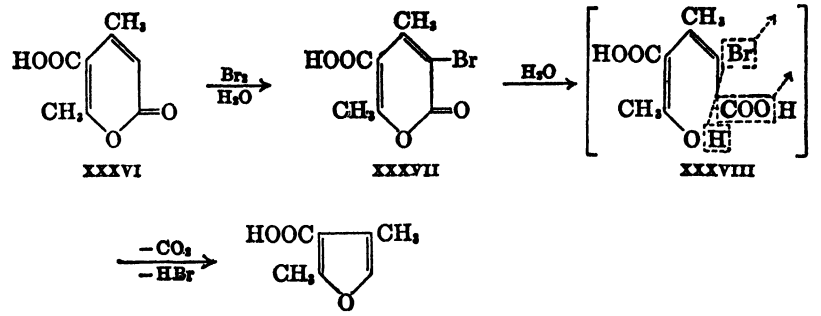
53 Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931); **15**, 268, 1105, 1112 (1932).

54 Scott and Johnson, *J. Am. Chem. Soc.*, **54**, 2549 (1932).

55 Feist, Widmer, and Dubosc, *Ber.*, **35**, 1552 (1902).

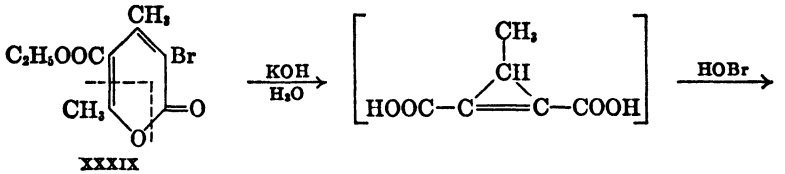
56 Natterer, *Monatsh.*, **5**, 491 (1884).

57 Feist, *Ber.*, **26**, 747 (1893).

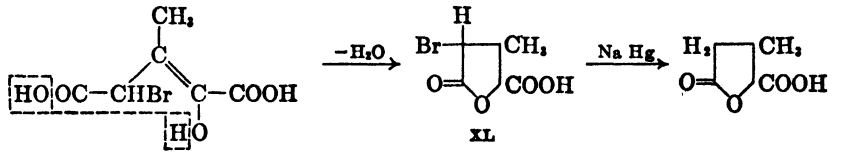


XXXVI XXXVII XXXVIII

leading eventually to the lactone acid (XL). The series of reactions XXXIX–XL is postulated (cf. p. 357).

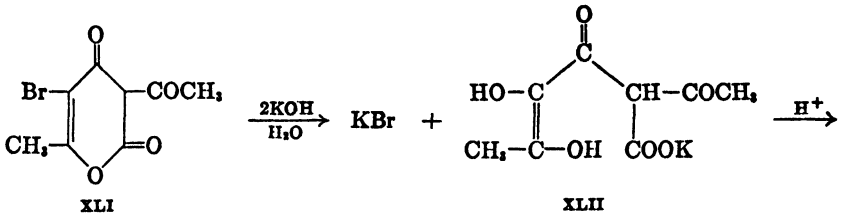


XXXIX

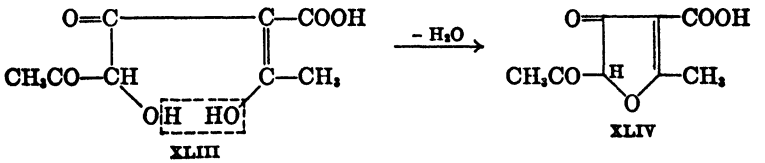


XL

From the bromo derivative of dehydracetic acid (XLI) by the action of alkali, Feist[58] obtained a substance assigned the structure XLIV,



XLI XLII

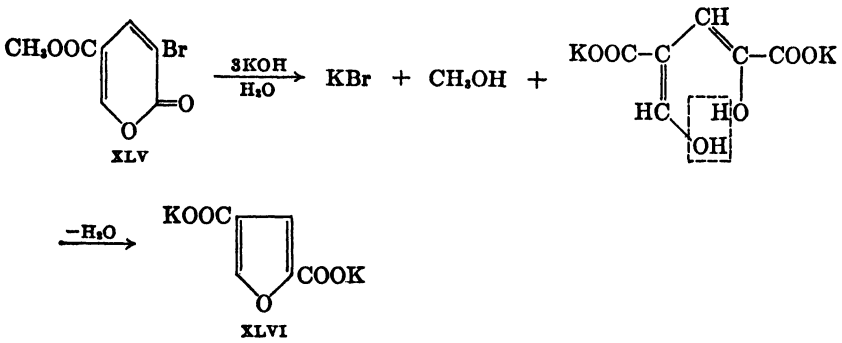


XLIII XLIV

[58] Feist, *Ber.*, **25**, 315 (1892).

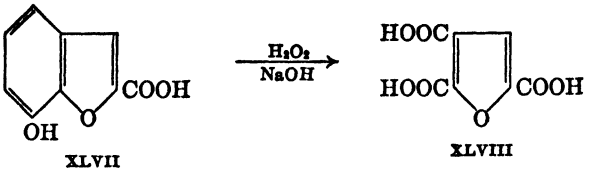
although no definite proof was offered to support this. It should be noted that XLIII represents merely a rewriting of the acid derived from XLII and that XLIV is one of the rare derivatives of β-hydroxyfuran.

Finally, in an attempt to parallel one or the other of the above reactions with methyl coumalate, Feist [59] found that the bromo derivative (XLV) of this comparatively simple pyrone derivative followed an entirely different course of decomposition under the influence of alkali, as represented by XLV–XLVI, the final product being furan-



2,4-dicarboxylic acid. If the bromination of coumalic acid had occurred elsewhere in the molecule, formation of a furan derivative would obviously have been impossible.

Furan-2,3-dicarboxylic acids can also be conveniently made by oxidation of coumarins in which the benzene ring is rendered susceptible to oxidation by the presence of hydroxyl groups. Thus, Reichstein and Grüssner [60] obtained furan-2,3,5-tricarboxylic acid, as shown by XLVII–XLVIII. Success by this method depends on the stability of the furan acids to alkaline hydrogen peroxide.[61]



59 (*a*) Feist, *Ber.*, **34**, 1992 (1901); (*b*) Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

60 Reichstein and Grüssner, *Helv. Chim. Acta*, **16**, 555 (1933).

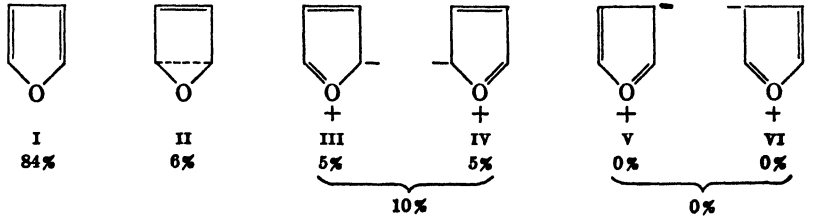
61 Wessely et al., *Monatsh.*, **59**, 161 (1932); **60**, 141 (1932).

ADDITION AND DIRECT SUBSTITUTION REACTIONS OF FURANS

Resonance of Furan

Furan displays many of the characteristics of a 1,4-diene system, a vinyl ether and a typical aromatic substance. Frequently, the behavior of furan and its derivatives in simple substitution and addition reactions cannot be ascribed to any one of these characteristics. It is therefore necessary to take into account in some detail the resonance of furan and to consider the contributions of the various resonance forms. By proceeding in this fashion, it is possible to arrive at a reasonably rational explanation for the reactions undergone by the substance. The work of Gilman and co-workers [8] has served as a basis for later developments in this phase of furan chemistry.

Six resonance forms may be written for furan,[62] of which structure II has a formal bond.[63] By means of Pauling's formula [64] the "per cent



double-bond character" (VIII) may be calculated from interatomic distances in furan (VII) which have been measured by Beach [65] by the electron diffraction method. If one assumes that the six forms (I–VI) contribute to the resonance in the proportions shown below (I–VI), the "per cent double-bond character" may be calculated by simple addition. For example, the C—C bond in VIII with 18% double-bond character receives the following C=C contributions from forms I–VI.

I	0%	IV	5%
II	6%	V	0%
III	5%	VI	0%

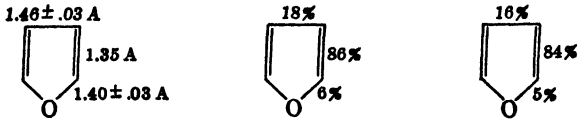
62 Wheland, *The Theory of Resonance*, John Wiley & Sons, New York, 1944, p. 62.

63 Wheland, *The Theory of Resonance*, John Wiley & Sons, New York, 1944, p. 14.

64 Pauling, Brockway, and Beach, *J. Am. Chem. Soc.*, **57**, 2705 (1935); Pauling and Brockway, *ibid.*, **59**, 1223 (1937).

65 Beach, *J. Chem. Phys.*, **9**, 54 (1941).

The sum of these is 16%. In a similar fashion, the "per cent double-bond character" shown in IX may be arrived at. The agreement with the figures based on electron diffraction data (VIII) is good.



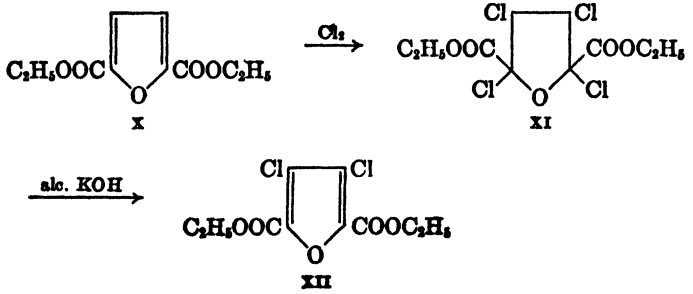
VII VIII IX

Thus, furan may be considered to consist chiefly of form I with contributions from III and IV favoring substitution in the α positions and from form II favoring 1,4 addition. The contributions from forms V and VI, which would favor substitution in the β positions, play but a minor part in the resonance. With this picture clearly in mind, many of the reactions of furan become more logical.

Addition Reactions of Furans

Furan undergoes a wide variety of addition reactions. The addition of hydrogen leading to the production of reduced furans is frequently complicated by cleavage of the ring, and therefore the question of the reduction of furan derivatives will be considered separately in its entirety (p. 161).

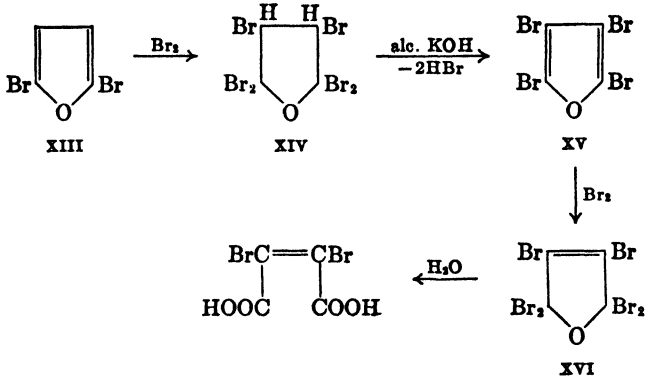
In reactions with halogens, the tendency is for substitution to predominate with furan itself.[3,4] Many reactions of furan derivatives which at first glance appear to be substitution reactions actually take place through addition across the diene system of the nucleus, followed by a subsequent elimination reaction. For example, diethyl furan-2,5-dicarboxylate (X) on chlorination in the molten state yields the 3,4-dichloro ester as the final product. However, available evidence



X XI XII

indicates that the initial reaction involves intermediate formation of a tetrachloro compound (XI) from which XII is formed by elimination

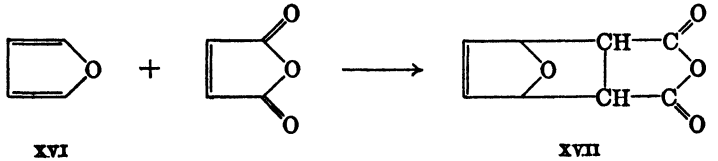
of hydrogen chloride on treatment with alcoholic alkali.[66] In this connection it is interesting to compare the behavior of X in other substitution reactions such as sulfonation and the Friedel-Crafts reaction. In such reactions which may not involve an intermediate addition, no further substitution takes place.[67] Similarly, 2,5-dibromofuran (XIII) on further bromination yields 2,2,3,4,5,5-hexabromotetrahydrofuran (XIV).[68] From the hexabromo compound (XIV), 2,3,4,5-tetrabromofuran (XV) may be prepared by elimination of hydrogen bromide. XV, in turn, undergoes 1,4 addition of bromine to yield



XIII XIV XV XVI

XVI, the structure of which may be shown by hydrolysis to dibromomaleic acid. It is thus apparent that the unsaturation of the furan nucleus frequently manifests itself as a diene, or possibly as a reactive vinyl ether, rather than as a true aromatic system typified by benzene.

Furan, itself, behaves as a typical diene in the Diels-Alder reaction. Thus, it undergoes normal 1,4 addition with maleic anhydride (XVI–XVII),[69] as do α- and β-methylfuran.[70] Proof of the 1,4 addition rests



XVI XVII

66 Gilman and Vanderwal, *Rec. trav. chim.*, **52**, 267 (1933).

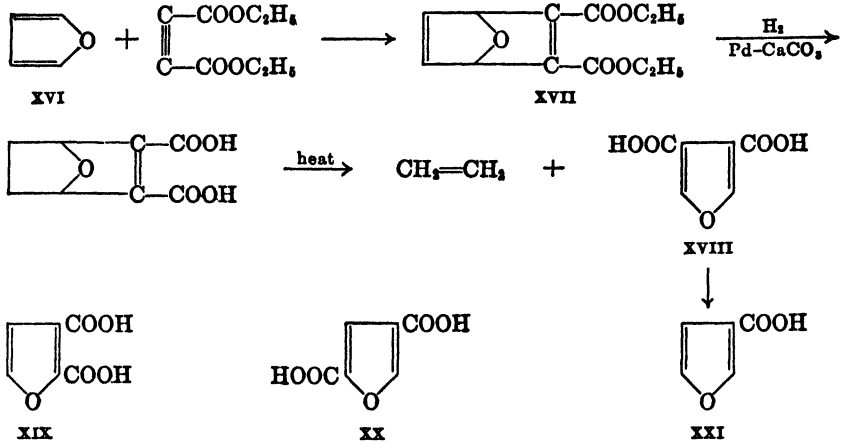
67 Gilman and Young, *Rec. trav. chim.*, **51**, 761 (1932).

68 Hill and Hartshorn, *Ber.*, **18**, 448 (1885).

69 Diels, *Ber.*, **62**, 554 (1929). In a very recent paper [Woodward and Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948)], the stereochemistry of the reaction has been studied and the stereochemical course of the reaction has been found to be a function of the solvent in which it is carried out. From furan and maleic acid in water an *endo-cis* product is formed, whereas with furan and maleic anhydride in ether an *exo-cis* adduct is obtained.

70 Rinkes, *Rec. trav. chim.*, **50**, 1127 (1931).

on analogy to the addition of acetylenedicarboxylic ester to furan.[71] The initial adduct (XVII), after partial reduction and hydrolysis of the esters, if heated yields furan-3,4-dicarboxylic acid (XVIII), the structure of which has been established by elimination of the other



possibilities (XIX and XX). On decarboxylation of XVIII, β-furoic acid (XXI) is formed, since it is not identical with the α acid, pyromucic acid. Thus, one carboxyl group in XVIII must be in a β position. The 2,4 acid (XX) has been synthesized by known methods (p. 136), as has the 2,3 acid (XIX) (p. 134). Neither of these is identical with XVIII which establishes the structure of XVIII.

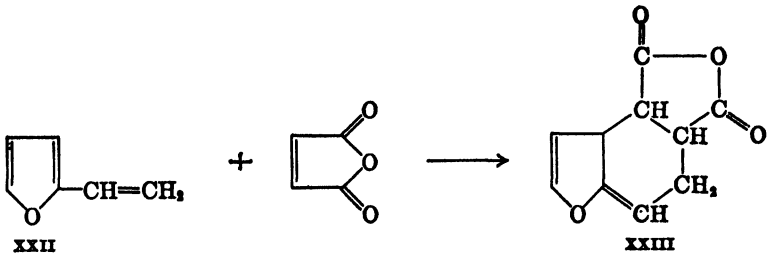
Whereas furan and its alkyl derivatives behave as typical 1,4-dienes in the Diels-Alder reaction, a different state of affairs obtains when an ethylenic grouping is attached to the nucleus in the α position.[72–74] α-Furylethylene (XXII), on reaction with maleic anhydride, adds the latter across the 1,4 system comprised of the β-carbon atom of the nucleus and the β-carbon atom of the side chain (XXII–XXIII). On the other hand, α-furylacrolein (XXIV), α-furylacrylic acid, and 1-(α-furyl)-2-nitroethylene fail to undergo addition of maleic anhydride, although ethyl β-(α-furyl)propionate reacts normally through the 1,4 system of the nucleus. It is suggested that the strongly electrophilic groups attached to the β-carbon atom of the side chain of those substances which do not add maleic anhydride deactivate this atom and,

71 Alder and Rickert, *Ber.*, **70**, 1354 (1937); Hofmann, *J. Am. Chem. Soc.*, **66**, 51 (1944).

72 Herz, *J. Am. Chem. Soc.*, **68**, 2782 (1946).

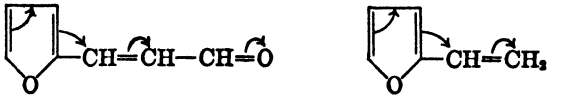
73 Paul, *Bull. soc. chim. France*, [5] **10**, 163 (1943).

74 Van Campen and Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).



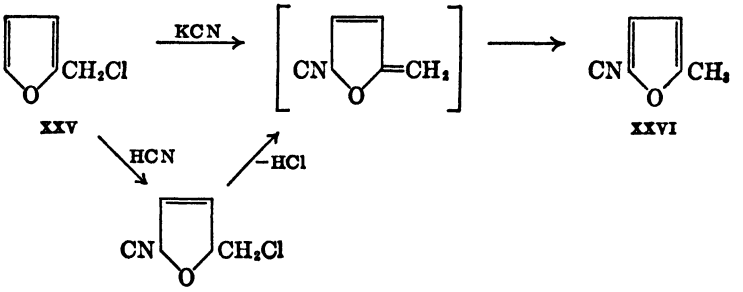
XXII XXIII

through conjugation, the nucleus, to such an extent as to prevent addition (e.g., in α-furylethylene, the extended conjugation favors attack of the dienophile on the β-carbon atom of the side chain).[75]



XXIV XXII

The furan nucleus under certain conditions undergoes 1,4 addition of hydrogen cyanide. When α-furfuryl chloride (XXV) is treated with potassium cyanide, the expected α-furylacetonitrile is not formed.[76-78]



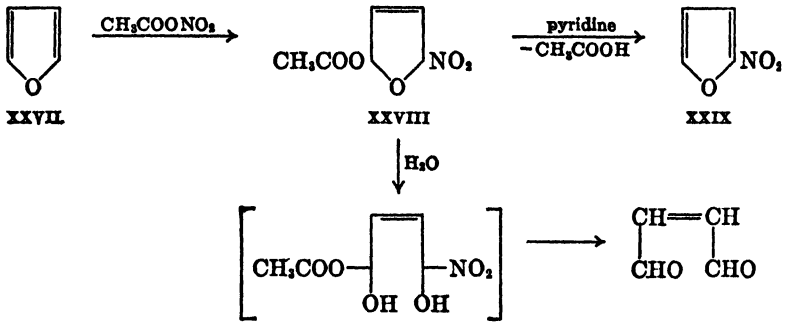
XXV XXVI

Rather the major product is 2-methyl-5-cyanofuran (XXVI). It is possible to isolate a small amount of the expected α-furylacetic acid from the products of hydrolysis of the crude nitrile, but 5-methyl-2-furoic acid is obtained as the preponderating product. Although the formation of XXVI can be explained on the basis of an allylic shift through the double bond in conjugation with the allyl group,[77] the reaction can also be readily explained by a sequence of reactions in-

75 Herz, *J. Am. Chem. Soc.*, **67**, 1854 (1945).
76 Runde, Scott, and Johnson, *J. Am. Chem. Soc.*, **52**, 1284 (1930).
77 Reichstein, *Ber.*, **63**, 749 (1930).
78 Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 1124 (1932).

volving 1,4 addition of hydrogen cyanide, loss of hydrogen chloride, and tautomerism.

Furan is unusually susceptible to oxidizing agents. For this reason, direct nitration of furan with nitric acid results in destruction of the nucleus through the oxidizing action of the nitric acid. However, by taking advantage of the diene character of furan, it is possible to secure 2-nitrofuran by the action of nitric acid and acetic anhydride.[2] The actual reactant is probably acetyl nitrate which adds across the 1,4 system (XXVII–XXIX). The intermediate acetoxynitrodihydro-



furan (XXVIII) is readily decomposed to maleic dialdehyde, acetic acid, and nitrous acid by warm water.[79]

Monosubstituted Furans

Furan undergoes substitution as well as addition reactions. Since the nucleus is readily destroyed by strong acids unless stabilizing negative substituents are present, experimental conditions must be relatively mild. Under such circumstances, furan substitutes quite readily,[67] indeed more readily than does benzene. This fact, taken together with other properties, has led to application of the term "superaromatic" to furan.[80] Such a descriptive term seems hardly warranted, and the behavior of furan appears to be better explained on the basis of resonance. Since furan does possess a strongly electronegative carbon atom (at the α position), it is only natural that it should undergo substitution more readily than benzene in which all the carbon atoms are identical.

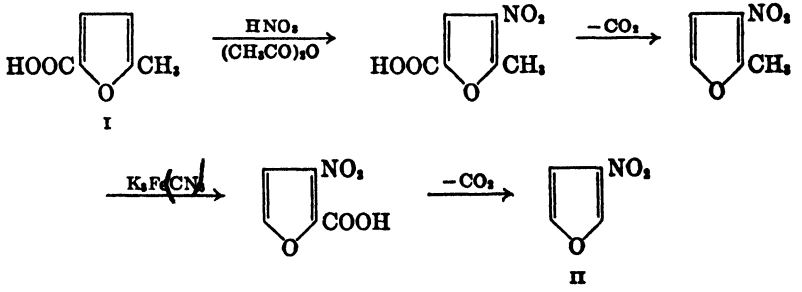
The position of furan relative to other so-called "aromatic" compounds as far as reactivity in certain substitution reactions is con-

[79] Freure and Johnson, *J. Am. Chem. Soc.*, **53**, 1142 (1931).
[80] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933), and earlier papers.

cerned has been established by Reichstein.[81] With the Friedel-Crafts reaction as a criterion, he established the order: benzene, thiophene, furan, and pyrrole, in increasing order of reactivity. Thus, furan undergoes such substitution under milder conditions than does benzene but less easily than does pyrrole.

Since the resonance forms III and IV (p. 137) contribute far more to the structure of furan than do forms V and VI, the usual electrophilic reagents attack the more electronegative α-carbon atoms. Indeed, direct β substitution in the simple unsubstituted furan molecule has not been established definitely.

As already indicated, α-nitrofuran may be prepared by the action of acetyl nitrate on furan. Conclusive proof of the position taken by the nitro group in α-nitrofuran was not forthcoming until Rinkes' synthesis of β-nitrofuran[82] by the series of reactions I–II. β-Nitrofuran (II),



I II

the structure of which is proved by the above synthesis, is different from the product of the direct nitration of furan. Since both α positions and both β positions are equivalent, the structure of the compound in question is proved. Frequently, decarboxylation accompanies nitration of furoic acids. Thus, nitration of pyromucic acid leads to the formation of α-nitrofuran.[83]

Owing to the electronegativity of its α-carbon atoms, furan undergoes acylation reactions of the Friedel-Crafts type even more easily than does benzene; the reactions, indeed, are best carried out in benzene solution.[81] Because of the susceptibility of the furan ring to acids, aluminum chloride is useless as a catalyst for this purpose, but stannic chloride serves well. Either acid chlorides or anhydrides may be used as acylating agents Excellent yields of 2-acetylfuran have been reported from the reaction of equimolar amounts of furan and acetic an-

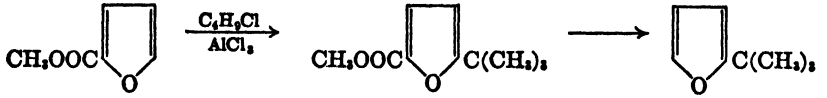
81 Reichstein, *Helv. Chim. Acta*, **13**, 356 (1930).
82 Rinkes, *Rec. trav. chim.*, **57**, 390 (1938).
83 Rinkes, *Rec. trav. chim.*, **49**, 1167 (1930).

hydride by the use of 4×10^{-4} mole of iodine or 1×10^{-2} mole of hydriodic acid per mole of furan as catalysts, as well as with zinc chloride, silica-metal oxide gels and strong inorganic oxy acids of fluorine, phosphorus, and sulfur having an ionization constant greater than 1×10^{-2} for the first hydrogen. *o*-Phosphoric acid is particularly valuable because of its slight effect on the ring.[84] The position of the entering acyl group may be easily shown by synthesis from pyromucic acid.[85]

If the α positions in furan are occupied, an acyl group can be introduced into one of the β positions. Thus, Lutz and Rowlett [86] prepared 2,5-diphenyl-3-acetylfuran from 2,5-diphenylfuran and acetic anhydride with stannic chloride. Here, also, aluminum chloride was useless. It is interesting that, in this instance, substitution even in the β position of furan apparently proceeds with greater facility than does substitution in the phenyl groups. Acylation with bromoacetyl chloride failed.

Furan undergoes the Gattermann reaction with hydrogen cyanide and hydrogen chloride much more easily than does benzene. No catalyst is required, and the product is furfural.[87]

Direct alkylation of furan itself does not proceed, probably because aluminum chloride is required as a catalyst and the ring is ruptured. However, if the ring is stabilized by the presence of electronegative groups, alkylation may be carried out by the Friedel-Crafts method. Thus, alkylation of methyl pyromucate with any of the butyl chlorides results in the remarkable introduction of a *t*-butyl group. From the acid thus obtained, α-(*t*-butyl)furan may be obtained by decarboxylation,[80] e.g., III–V.



III IV V

The chloromethylation reaction of Blanc may also be carried out on suitably substituted furans containing stabilizing electronegative groups. Thus, Lutz and Bailey [88] succeeded in introducing not one but

[84] Hartough and Kosak, *J. Am. Chem. Soc.*, **68**, 2639 (1946); **69**, 1012, 1014, 3093, 3098 (1947).

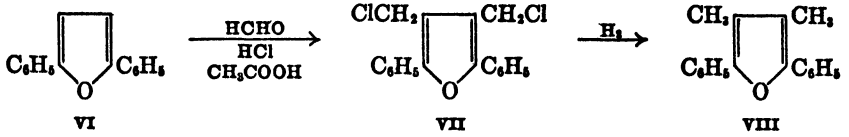
[85] Sandelin, *Ber.*, **33**, 492 (1900).

[86] Lutz and Rowlett, *J. Am. Chem. Soc.*, **70**, 1359 (1948).

[87] Reichstein, *Helv. Chim. Acta*, **13**, 345 (1930).

[88] Lutz and Bailey, *J. Am. Chem. Soc.*, **68**, 2002 (1946).

two chloromethyl groups in the β positions of 2,5-diphenylfuran, from which the methyl derivatives may be obtained on reduction (VI–VIII).



VI VII VIII

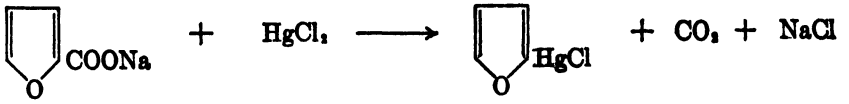
Metalation. The α-hydrogen of furan may be replaced by sodium or potassium on treatment with the metal alkyls, and, as usual, the resulting metal derivative may in turn be carbonated to yield furoic acid, thereby establishing the position taken by the metal.[89,90]

Mercuration of furan proceeds readily and is of particular advantage since it may be carried out in a basic medium, thereby avoiding acidic reagents to which furan is very susceptible.[91] Again, the α position is the one involved, which may easily be demonstrated by reaction of the mercurichloride derivative with acetyl chloride to yield α-acetylfuran (IX–XI). The mercuration reaction is accompanied by the

IX X XI

formation of small amounts of polysubstitution products. Such mercurichloro derivatives are of particular importance in the furan series because of their great reactivity which resembles that of Grignard reagents. Since the Grignard reagents can be made only from the difficultly accessible halogen furan derivatives, the advantage of the mercurials is obvious for the synthesis of furan derivatives.

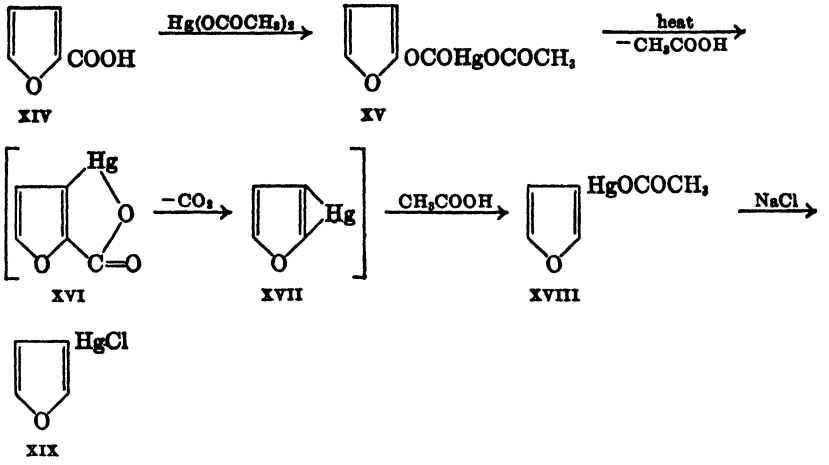
The behavior of the furoic acids on mercuration deserves special comment. The sodium salts of α-furoic acids on treatment with mercuric chloride easily undergo decarboxylation to yield mercurials (XII–XIII).[91] The salts of β-furoic acids do not undergo this reaction. On



XII XIII

89 Morton and Patterson, *J. Am. Chem. Soc.*, **65**, 1346 (1943).
90 Gilman and Breuer, *J. Am. Chem. Soc.*, **56**, 1123 (1934).
91 Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).

the contrary, free α-furoic acids (XIV) on treatment with mercuric acetate give a mixed acetoxymercury furoate (XV). When heated, this loses the elements of acetic acid and passes into a β-mercurial (XVIII), presumably by way of the intermediates XVI and XVII.[91]



The presence of an Hg—O rather than an Hg—C bond in the acetoxymercury furoate has been definitely proved by x-ray diffraction studies.[92] A large series of β-substituted furans from the β-mercurials is thus opened up. The acetoxymercury group in XVIII is readily converted to a chloromercury group by treatment with sodium chloride yielding XIX.

Not all substituted furans readily give mercurials. 2,5-Diiodofuran and 2-nitrofuran are resistant to the usual mild mercurating reaction but may yield to harsher experimental conditions. Most other furan derivatives will mercurate, and the orientation rules discussed later on are obeyed.

The furan mercurials undergo some of the reactions characteristic of Grignard compounds, thus opening up a wide variety of derivatives. They react with acyl halides, but not with aroyl halides, to yield ketones. With very active halides, e.g., furyl chloride, they give hydrocarbon derivatives by elimination of mercuric chloride. In contrast to the Grignard compounds, treatment of the mercurials with bromine or iodine yields the corresponding halogen-substituted furans. Ketene gives acetylfuran.[93]

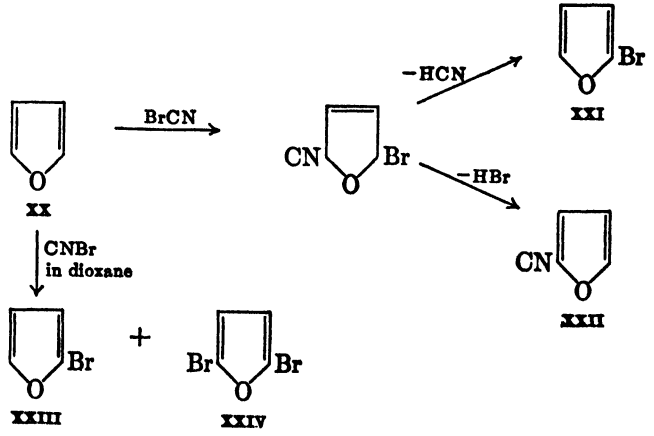
92 Baroni and Marini-Bettolo, *Gazz. chim. ital.*, **70**, 670 (1940).

93 Gilman, Wright, and Wooley, *J. Am. Chem. Soc.*, **55**, 2906 (1933); Chute, Orchard, and Wright, *J. Org. Chem.*, **6**, 157 (1941).

Furan itself cannot be sulfonated directly with sulfuric acid because of the lability of the ring, but a good yield of furan-2-sulfonic acid, isolated as the barium salt, is reported to result from the action of Baumgarten's pyridine-sulfur trioxide complex (cf. p. 481) on furan.[94] However, the presence of electronegative substituents in the furan nucleus stabilizes the ring sufficiently to permit the direct introduction of the sulfonic acid group. For example 2-furoic acid may be sulfonated to yield 2-furoic-5-sulfonic acid.[95]

Halogenation. In general, furan decomposes, sometimes violently, when direct halogenation is attempted, although Henninger[96] has brominated furan directly in carbon tetrachloride solution. The 2,5-dibromo derivative was the major product along with a small amount of 2-bromofuran. Again, as in the reaction with other acidic reagents, the presence of negative substituents stabilizes the ring, and the monochloro- and monobromo-furans may be prepared by halogenation of a furoic acid followed by decarboxylation.[97] The halogen-substituted furans are less stable than the corresponding benzene derivatives.

Furan reacts with cyanogen bromide to yield a mixture of 2-bromo- and 2-cyano-furan.[98] The yield is very low. When the reaction is carried out in dioxane, only 2-bromo- and 2,5-dibromo-furan are formed, and the yield is considerably better. The formation of these products is explained by XX–XXII and XX–XXIV.



[94] Terentieo and Kazitzyna, *Compt. rend. acad. sci. U.R.S.S.*, **51**, 603 (1946).
[95] Hill and Palmer, *Am. Chem. J.*, **10**, 373 (1888).
[96] Henninger, *Ann. chim.*, [6] **7**, 222 (1886).
[97] Shepard, Winslow, and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).
[98] Klopp and Wright, *J. Org. Chem.*, **4**, 142 (1939).

A report [99] of direct chlorination of tetrahydrofuran to 2,3-dichlorotetrahydrofuran in excellent yield by the action of chlorine in carbon tetrachloride in the presence of a catalytic amount of phosphorus trichloride, or in the vapor phase, is of interest and is reminiscent of the chlorination of dioxane.

Disubstituted Furans

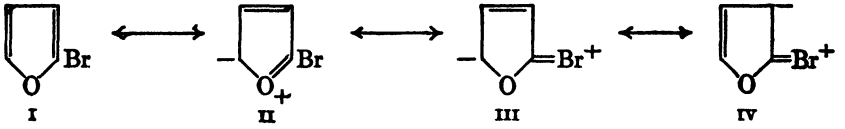
In considering the question of orientation as applied to the introduction of a second substituent into a furan nucleus already carrying a substituent, it must be pointed out that the over-all problem is not so simple as with the disubstituted benzenes. In the benzene series, the position taken by a second substituent is conditioned largely by the relative positive or negative characteristics of the group already present. The resonance effects of the benzene ring, in so far as they are independent of influences due to the presence of the first group, are comparatively simple by virtue of the symmetry of benzene and the equivalence of the resonance forms of benzene. In the furan series, the resonance forms are not equivalent and, in general, the influence of the various resonance forms of furan outweighs the orienting effects which are ascribed to the positive or negative character of initial substituents in the benzene series. Although certain exceptions to this generalization have been noted, in a broad over-all sense, the statement appears to be warranted.

In general, a simple monosubstituted furan tends to receive a second substituent in a free α position, regardless of whether the original substituent is positive or negative in character or whether the original substituent occupies the α or β position. When an original substituent is in the β position, two α positions are open for occupancy by the new substituent, one *ortho* to the position already occupied and the other *meta* to this position. In general, the α position taken by the new substituent depends on whether the original β substituent is of the class generally known as *o,p*-orienting groups or *m*-orienting groups in the benzene series. A reasonably close analogy to the effects of such groups in the benzene series is followed in the furan series. It will thus be apparent that, in the sequel, considerable attention must be paid to rigorous structural proof for furan derivatives resulting from introduction of a second substituent into a monosubstituted furan. The exceptions to the above general rules compel such critical exami-

[99] *U. S. Dept. Commerce, Office of Technical Services, Rept.* PB 675.

nation of the disubstituted furans. In the light of these comments, several reactions will be considered. The examples chosen do not represent a complete presentation of all such reactions possible but will serve to bring out the essential principles involved.

Introduction of a Second Substituent into an α-Substituted Furan. *Type I. The furan nucleus already carries an electropositive α substituent.* If 2-bromofuran is taken as typical, introduction of a second substituent is conditioned by several factors. The resonance of the nucleus itself (I–IV) will tend to attract the usual electrophilic reagents



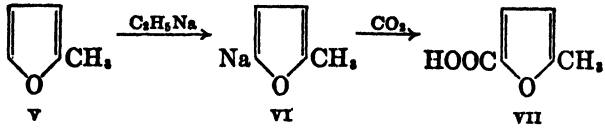
to the other α position. Furthermore, the electron-donating α substituent tends to direct the entering group to the free α position. Resonance form IV probably contributes to the over-all picture, but its effect is negligible compared to the two α-orienting forms, II and III. No instance is recorded in which a furan already carrying an electropositive α substituent furnishes a significant yield of a disubstituted furan in which the new group assumes a β position.

With the above limitation in mind, one can consider the cases in which the second substituent is positive or negative in character. Few examples of the former category can be found in the literature. Since the furan nucleus itself is easily destroyed, a positively substituted furan would tend to be still more unstable, and the introduction of a second positive substituent would tend to decrease the stability of the ring even more, especially in the acidic media usually employed for the introduction of such a substituent (e.g., alkylation and halogenation reactions). A possible exception is the bromination of furan in carbon tetrachloride (p. 147).

When the entering substituent is electronegative in character, more examples can be found since the final disubstituted furan is stabilized by the presence of the negative substituent. α-Methylfuran metalates with sodium alkyls at the free α position (sodium being a strongly electronegative substituent).[100] The structure of the product may be shown by carbonation to the known acid (V–VII).[101] It should be emphasized that replacement of the hydrogen of the methyl group in

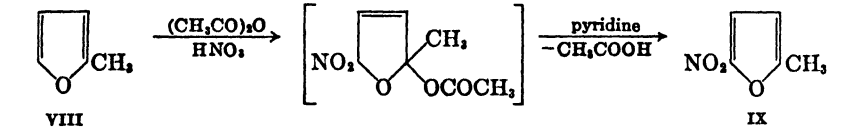
100 Morton and Patterson, *J. Am. Chem. Soc.*, **65**, 1339 (1943).
101 Gilman and Wright, *J. Am. Chem. Soc.*, **54**, 4108 (1932).

α-methylfuran does not occur under these conditions. In this, the substance differs from the corresponding benzene derivative, toluene.

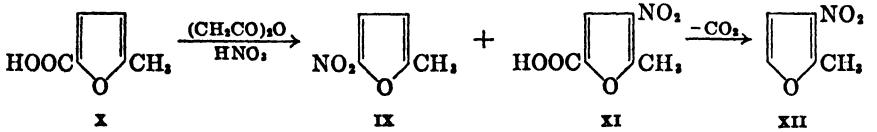


V VI VII

2-Methylfuran undergoes nitration with acetyl nitrate to yield 2-methyl-5-nitrofuran, presumably by intermediate addition of the reagent and subsequent loss of acetic acid (VIII–IX).[102] The structure of IX may be demonstrated indirectly by nitration of 5-methylfuroic acid (X) which yields a mixture of IX and the nitro acid (XI). Since



VIII IX



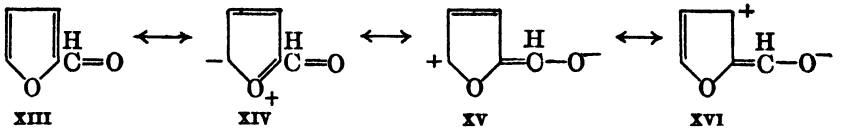
X IX XI XII

the nitromethylfuran (XII) obtained by decarboxylation of the nitro acid (XI) with copper and quinoline is not identical with IX, it follows that IX is formed in the second series by direct replacement of the carboxyl group during the nitration, and hence the structure of IX obtained by nitration of 2-methylfuran is proved.

Type II. The furan nucleus already carries an electronegative α substituent. Since the presence of a negative group tends to stabilize the nucleus, substitution in this type of compound in general proceeds with less danger of destruction of the nucleus than with Type I substitutions. On the other hand, as in the benzene series, the presence of the negative group inhibits further electrophilic substitution. The actual state of affairs, then, is somewhat of a compromise between these two factors, with the stability of the ring more than compensating for the more difficult substitution. The orientation in compounds of this type is dependent on the relative influences of a number of resonance forms, e.g., XIII–XVI. In furfural, the normal resonance of the furan ring will tend to direct a new substituent into the other α position. Contrary to the systems noted under Type I, the presence

[102] Rinkes, *Rec. trav. chim.*, 50, 981 (1931).

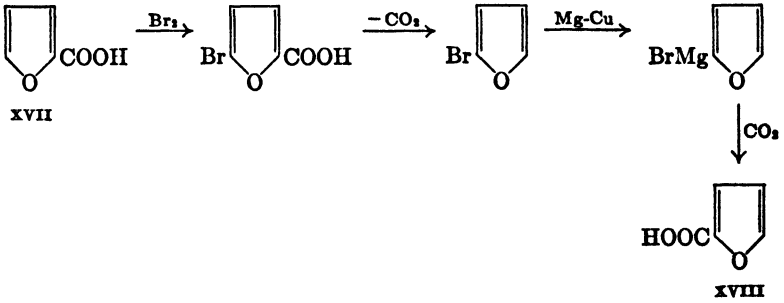
of the negative group in the present instance tends to withdraw electrons from this position (XV). Thus, in XVI, the positive center will



XIII XIV XV XVI

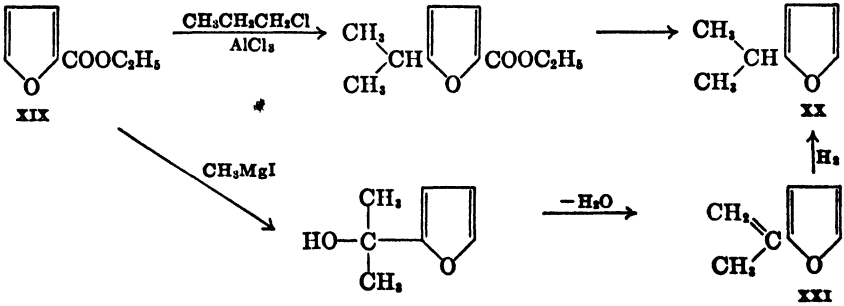
not be attacked by the usual reagents. There is then the possibility of attack at either of the other two positions. If the resonance due to the nucleus is more prominent than the electron-accepting effect of the negative group present, the new substituent will enter the free α position. This is the usual normal mode of substitution in compounds of this type, although a few less common instances of substitution in the β position have been noted.

As typical of the entrance of an electropositive group the easy halogenation of 2-furoic acid may be considered. The furan ring is attacked in the free α position, and the structure of the product can be shown by the reactions XVII–XVIII.[97] Likewise, ethyl 2-furoate



XVII XVIII

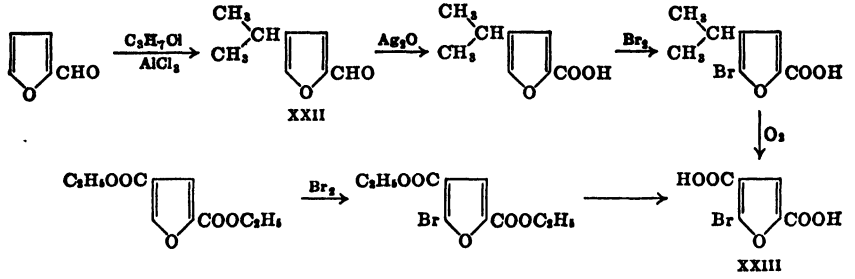
alkylates in the so-called normal fashion (XIX–XX).[80] This may be shown by conversion of the product to the known 2-isopropylfuran (XIX–XXI–XX).[103]



XIX XX XXI

[103] Reichstein, Zschokke, Gehring, and Rona, *Helv. Chim Acta*, **15**, 1118 (1932).

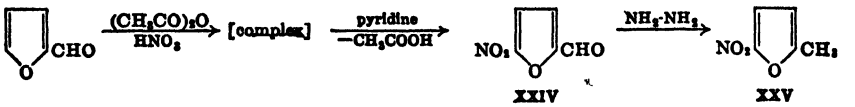
On the other hand, in the alkylation of furfural with isoproyl chloride the entering group assumes the β position,[104] a fact which becomes explicable on the basis of the stronger electronegativity of the aldehyde group as compared to the carbethoxy group by which the orienting effect of the ring is overcome. It is interesting that furan systems carrying a negative substituent undergo the Friedel-Crafts reaction, whereas the analogous benzene compounds do not. The β orientation can be readily shown by conversion of the product (XXII) to the known acid, 2-bromofuran-3,5-dicarboxylic acid (XXIII).[57] The deli-



XXIII

cate balance between the electronic effects due to the nucleus and those due to the substituent are strikingly demonstrated by the fact that, with higher alkyl halides, furfural follows the normal reaction course yielding the α-substituted product.

Introduction of a second electronegative substituent into furan is the reaction usually encountered. The products carrying two negative substituents show little tendency to undergo further substitution and are characterized by relative stability. The new substituent always enters the free α position as would be predicted. Thus, furfural on nitration yields 5-nitrofurfural (XXIV).[105] Derivatives of the latter, e.g., the semicarbazone, have assumed some importance as antibacterial agents.[106] The position of the nitro group in XXIV can be shown by conversion of XXIV to 2-methyl-5-nitrofuran by application of the



XXIV XXV

Wolff-Kishner reduction (XXIV–XXV).[101] Likewise, 5-nitro-2-furylphenyl ketone may be prepared either by Friedel-Crafts acylation of

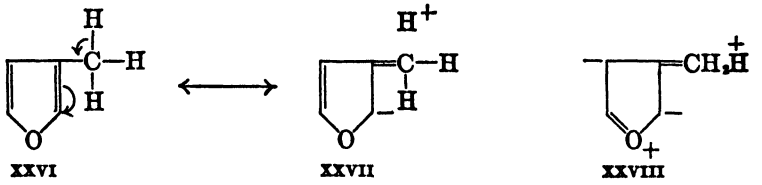
104 Gilman, Calloway, and Burtner, *J. Am. Chem. Soc.*, **57**, 906 (1935).

105 Gilman and Wright, *J. Am. Chem. Soc.*, **52**, 4165 (1930).

106 Downing, Hanson, and Lamb, *J. Am. Med. Assoc.*, **133**, 299 (1947); Shipley and Dodd, *Surg., Gynecol. and Obstet.*, **84**, 366 (1947).

2-nitrofuran with benzoyl chloride [80] or by nitration of 2-furylphenyl ketone with the acetyl nitrate reagent.[107] These reactions illustrate strikingly the effect of the nuclear resonance of furan as compared to benzene. In the first, the fact that nitrofuran will undergo the Friedel-Crafts reaction in contrast to nitrobenzene is emphasized; in the second reaction, the selective nitration of the furan nucleus in preference to the phenyl group is illustrated. Reactions such as these have led to the application of the term "super-aromatic" to furan. A more logical explanation appears to lie in the resonance characteristics of furan.

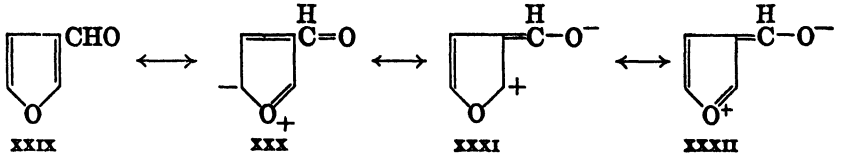
Introduction of a Second Substituent into a β-Substituted Furan. In a β-substituted furan, two free α positions are available. The nuclear resonance will direct the next entering group to one of these positions. β substitution has never been observed with such substances. Which α position is taken by the new group depends on whether the first substituent is *o,p*- or *m*-orienting. Positive (*o,p*-orienting) groups direct the new substituent to the adjacent α position by virtue of the contribution of the resonance form XXVII. A high electron density on the adjacent (*o*) β-carbon atom (XXVIII) is not



XXVI XXVII XXVIII

possible unless there is a low electron density on the oxygen. Such a form as this obviously plays a negligible part in the resonance of such a compound.

Negative (*m*-orienting) groups in the β position lead to a low electron density on the adjacent α-carbon atom, e.g., XXIX–XXXII.



XXIX XXX XXXI XXXII

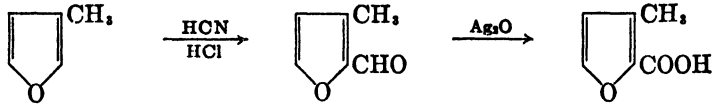
Since the resonance of the nucleus itself favors the α positions and since the presence of the negative β group partially cancels the high elec-

[107] Gilman and Young, *J. Am. Chem. Soc.*, **56**, 464 (1934).

tron density around the adjacent α-carbon atom, the new substituent will seek the opposite α position. The other β position drops from consideration by the same argument used above.

Type III. The furan nucleus already carries an electropositive β substituent. For reasons already stated dealing chiefly with the decreased stability of the furan ring when two positive substituents are present, introduction of a second positive group is very rarely encountered. The course of such reactions can best be predicted from a study of the reactions discussed below.

The introduction of an electronegative substituent into a furan carrying a positive β substituent is a more common occurrence due to the increased resonance stabilization. For example, β-methylfuran readily undergoes the Gattermann reaction without the aid of a catalyst,[108] and the position taken by the aldehyde group can be shown by oxidation to the known acid (XXXIII–XXXIV).[109] Nitration of β-hydroxyfuran will be considered elsewhere (p. 184).

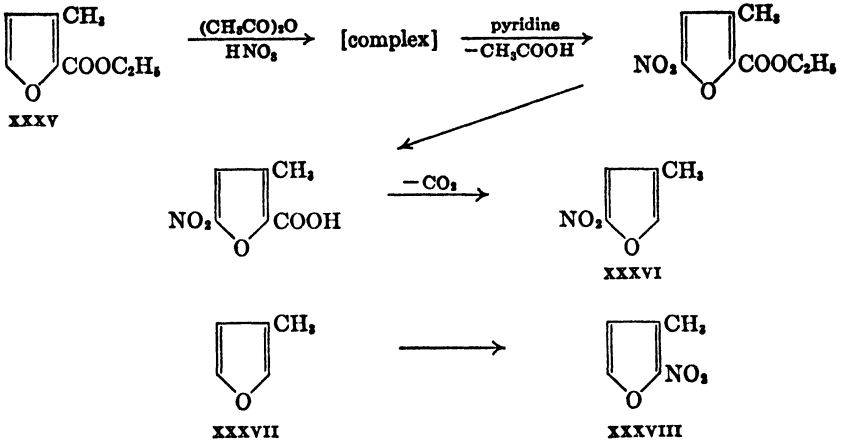


XXXIII XXXIV

Type IV. The furan nucleus already carries an electronegative β substituent. If the entering group is positive, it will take the α position opposite to the β substituent already present, e.g., in the bromination of 3-furoic acid, the 5-bromo derivative is formed. If the opposite α position is occupied, the new substituent will enter the adjacent α position. Thus, bromination of 3,5-dicarbomethoxyfuran results in the formation of the 2-bromo derivative.[91]

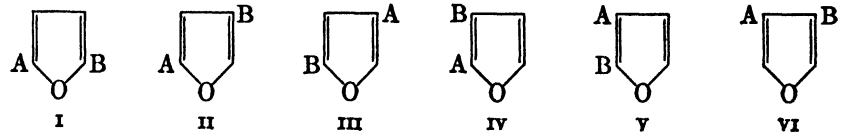
If the entering group is negative, again the opposite α position is taken. Nitration of furan-3-aldehyde by acetyl nitrate gives 5-nitrofuran-3-aldehyde [91] which can be reduced by the Wolff-Kishner method to 3-methyl-5-nitrofuran (XXXVI). The structure of XXXVI has been shown by synthesis (XXXV–XXXVI) [102] as well as by the nonidentity of XXXVI with the product (XXXVIII) of the nitration of 3-methylfuran. Although there is no absolute proof that the nitro group in XXXVI and XXXVIII is not in the free β position, assignment of this position to the nitro group is at variance with the effects of resonance in XXXV and XXXVII.

[108] Reichstein, Zschokke, and Georg, *Helv. Chim. Acta*, **14**, 1277 (1933).
[109] Gilman, Burtner, and Smith, *J. Am. Chem. Soc.*, **55**, 408 (1933).



Trisubstituted Furans

There are six possible disubstituted isomers of furan (I–VI), and definite orientation rules can be formulated for each isomer. In general, if one α position is available (as in II, III, IV, and V), it will be

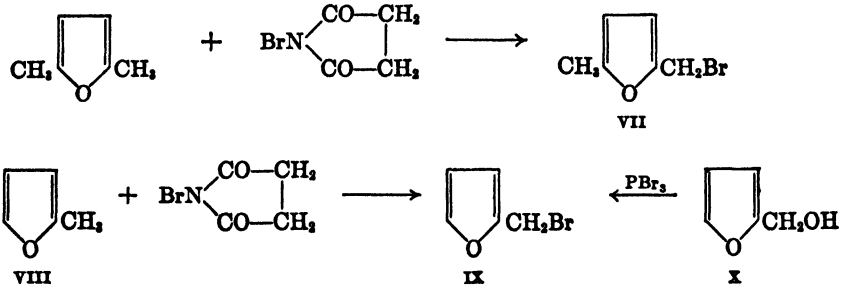


taken by the entering group, since in substitution reactions the orienting influence of the ring is greater than that of a substituent. (See p. 152 for the alkylation of furfural which represents an exception.) If two α positions are available (as in VI), the orienting influences of the substituents already present will direct the new group *ortho* or *meta* to the β substituents in accordance with their character. If two β positions are available (as in I), again the entering group is directed *ortho* or *meta* with respect to the groups already present, as would be predicted.

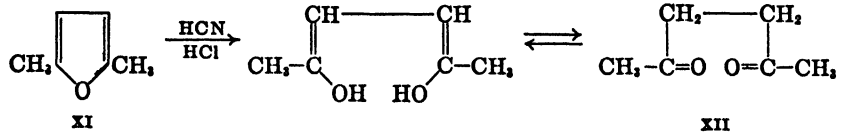
Type I. The furan carries two α substituents, both identical and positive. There is no orientation problem with this type. For instance, nitration [110] or mercuration [111] of 2,5-dimethylfuran can lead only to the 2,3,5-trisubstituted derivative.

110 Gilman and Burtner, *Rec. trav. chim.*, **51**, 667 (1932).
111 Gilman and Young, *Rec. trav. chim.*, **51**, 701 (1932).

There are, however, interesting examples of other reactions of such compounds. When 2,5-dimethylfuran is treated with N-bromosuccinimide in carbon tetrachloride, one of the side-chain hydrogens is replaced.[112] The structure of the product (VII) is inferred from the similar conversion of 2-methylfuran to furfuryl bromide (VIII–IX), which in turn can be prepared from furfuryl alcohol (X–IX).[113]



2,5-Dimethylfuran does not undergo the Gattermann reaction. Rather, ring opening occurs with formation of acetonylacetone (XI–XII), a reaction which is the reverse of that by which XI is prepared.[87]



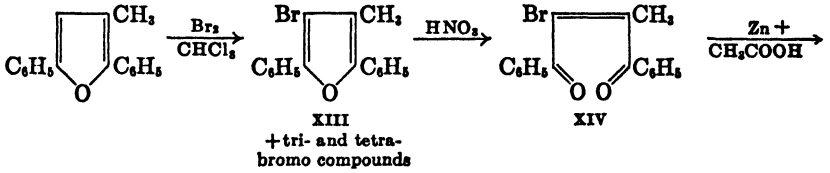
2,5-Diiodofuran prepared from the dimercuri compound undergoes replacement of one iodine on nitration and resists further mercuration.[91] No β nitration occurs.

Type II. The furan carries two α substituents, both positive but non-identical. Although several compounds of this type have been prepared, successful substitution reactions appear not to have been carried out with them. This is due to a combination of factors: the difficulty of introducing a substituent into the β position of furan, and the instability of the parent disubstituted derivative which renders the molecule susceptible to harsh reagents.

Type III. The furan carries two α substituents, both identical and negative. There is no orientation problem here. The parent substances are quite stable, owing to the presence of the negative groups. In general, further substitution is not possible. Furan-2,5-dicarboxylic

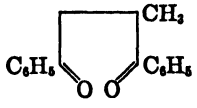
112 Buu-Hoï and Lecocq, *Compt. rend.*, **222**, 1441 (1946).
113 Zanetti and Bashour, *J. Am. Chem. Soc.*, **61**, 2249 (1939).

acid is not affected by aqua regia, fuming nitric acid, bromine, or fuming sulfuric acid.[111] However, not all such negatively substituted furans fail to undergo substitution. 2,5-Diphenyl-3-methylfuran brominates to yield the 4-bromo derivative (XIII).[47] Here the methyl group apparently exerts sufficient activating influence on the adjacent β position to overcome the tendency for substitution on the phenyl groups. The position taken by the bromine is shown by reactions XIII–XV.



XIII
+tri- and tetra-bromo compounds

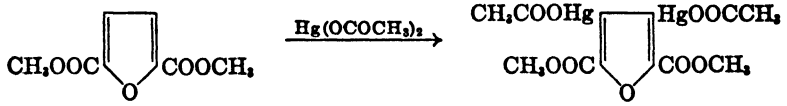
XIV



XV

A bromine in position 4 of XIII is the only type which is removable by zinc and acetic acid reduction in XIV and is stable to such reduction in XIII.

The diester (XVI) easily mercurates to yield a dimercuri acetate.[114]

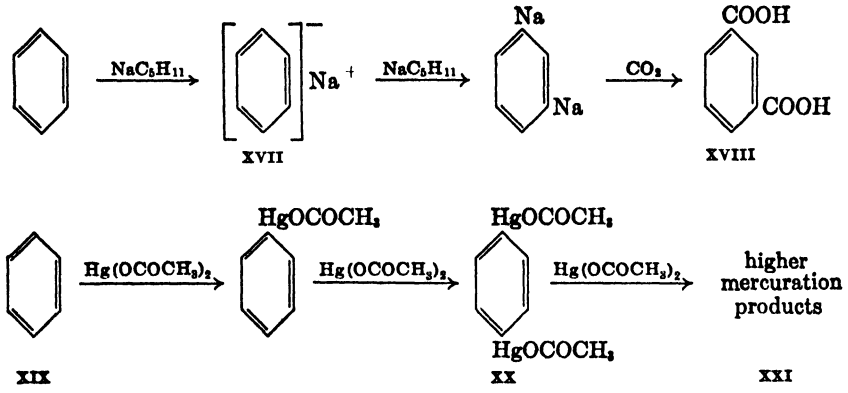


XVI

Furan itself can be mercurated to give successively mono-, di-, tri-, and tetra-substituted derivatives.[91] On the assumption based on the behavior of sodium as a substituting reagent in the benzene series, that the chloromercuri group is negative, such behavior at first appears to be an exception to the rule in the furan series. Closer analysis, however, brings the observed facts into line. Sodium has been shown to be a powerful *m*-directing substituent in the benzene series by the formation of isophthalic acid (XVIII) on carbonation of disodiophenyl.[115] It has been proposed that phenylsodium is an ion pair

114 Gilman, *Organic Chemistry*, 2nd ed., John Wiley & Sons, New York, 1943, p. 551.
115 Morton et al., *J. Am. Chem. Soc.*, 65, 1339 (1943).

(XVII), with the sodium ion being closely attracted to the nucleus. Since the nucleus is symmetrical, the negative charge is distributed equally over it. The positive sodium ion draws electrons from whatever carbon associates with it, thus acting as a *m*-directing group. On the other hand, mercuric chloride is relatively un-ionized, and hence no ion pair can form as obtains with sodiumphenyl. Even if such an ion pair formed, the chloromercuri ion is too weak to attract electrons from the nucleus. On the contrary, the chlorine with three unshared pairs of electrons can resonate in such a way as to donate electrons to the nucleus, thus bestowing *o,p*-orienting characteristics on the HgCl group. Substantiation for the above ideas is found in the results of the mercuration of benzene [116,117] which presumably proceeds as shown in XIX→XXI. It therefore becomes apparent that the mercuration of



furan falls into line with the generalizations given above, once the positive character of the mercuri substituent is recognized.

Type IV. The furan carries two α substituents, both negative but not identical. Most of the furan derivatives of this type are so unreactive as regards further substitution that such reactions rarely occur.[111,95] If substitution could be forced, the entering group would tend to go *meta* to the more strongly electronegative α substituent, although there is a reasonable probability that isomer formation would complicate the problem.

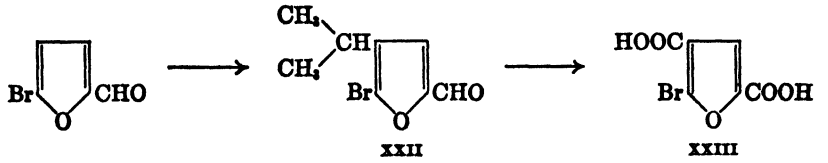
Type V. The furan carries two α substituents, one positive and one negative. A large number of such reactions can be found in the literature. In all of them, the entering group takes a position ad-

116 Dimroth, *Ber.*, **32**, 758 (1899).

117 Pesci, *Atti. accad. nazl. Lincei*, [5] **8**, I, 130 (1899).

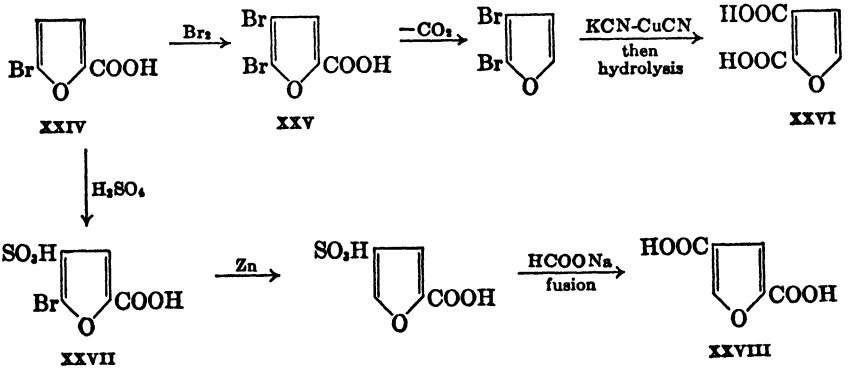
jacent to the positive *o,p*-directing α substituent. As illustrations a few typical examples are given.

5-Bromofurfural on alkylation with isopropyl chloride leads to 4-isopropyl-5-bromofurfural (XXII), the structure of which can be shown by oxidation to the known acid (XXIII) (p. 152).[105] Likewise,



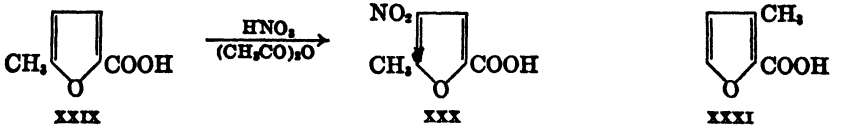
XXII XXIII

5-bromo-2-furoic acid, on bromination, gives the dibromo acid, XXV, in which the positions of the bromines can be shown by reactions XXIV–XXVI.[118] In a similar fashion, the acid (XXIV) sulfonates to XXVII in which the position of the sulfonic acid group may be shown by conversion to XXVIII.[119,120]



XXIV XXV XXVI XXVII XXVIII

In nitrations, it is more difficult to establish the position taken by the nitro group. Indirect evidence frequently allows this to be done. In the nitration of 5-methyl-2-furoic acid (XXIX), the position taken by the nitro group may be inferred from the easy esterification of the acid (XXX) with methanolic hydrogen chloride, whereas the hindered



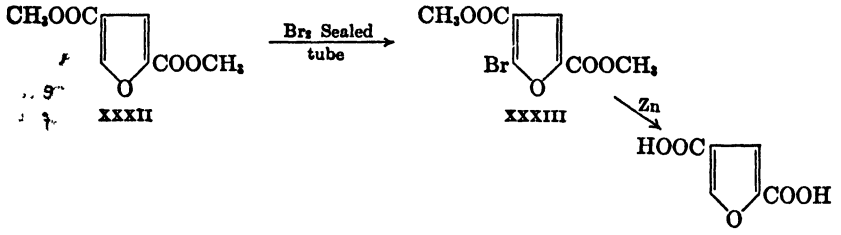
XXIX XXX XXXI

118 Hill and Sawyer, *Proc. Am. Acad. Sci.*, **21**, 135 (1885).
119 Gilman, Calloway, and Smith, *J. Am. Chem. Soc.*, **56**, 220 (1934).
120 Steinkopf, *Ann.*, **501**, 179 (1933).

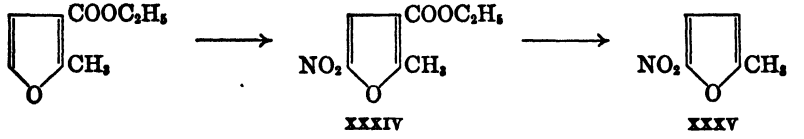
acid (XXXI) does not undergo esterification under these conditions.[121]

In substances of the type of II, III, IV, and V above, a free α position is available and should be taken by a new substituent regardless of the nature of the original substituents.

Type VI. The furan carries one α and one β′ substituent, either positive or negative. Very little concrete proof has been offered for the structures of the products obtained by further substitution of compounds of these types. It is obvious what should occur. The ester (XXXII) on bromination leads to XXXIII, from which the bromine may be removed by zinc in contradistinction to a β bromine.[57,122]



Type VII. The furan carries one positive α substituent and one adjacent negative β substituent. The new substituent will probably take the open α position because of the combined effects of the nuclear resonance and the negative substituent. For example, 2-methyl-3-carbethoxyfuran nitrates to yield XXXIV which can be converted to the known XXXV.[123]



Type VIII. The furan carries one negative α substituent and one adjacent positive substituent. In general, the free α position is taken by the new substituent. Only on alkylation of furans of this type containing a very powerful *m*-directing α group would the β position be taken, e.g., in the alkylation of 3-methylfurfural.

Type IX. The furan carries both substituents in the β positions. Which of the α positions will be taken by a new substituent has not been proved experimentally. However, one is on safe ground in predicting

121 Rinkes, *Rec. trav. chim.*, **51**, 350 (1932).
122 Gilman et al., *J. Am. Chem. Soc.*, **57**, 1146 (1935).
123 Gilman, Burtner, and Smith, *Rec. trav. chim.*, **51**, 407 (1932).

that the more strongly positive substituent will control the point of entrance of a third substituent.

Tetrasubstituted Furans

Here, obviously, there is no orientation problem. It also goes without saying that introduction of a fourth substituent into a trisubstituted furan is difficult if the three original groups are negative. Several examples of the formation of tetrasubstituted furans appear [110,124] which do not warrant detailed discussion.

REDUCTION OF FURAN AND ITS DERIVATIVES

Reduction of compounds of the furan series parallels closely reduction of compounds of the benzene series, except that fission of the furan ring introduces a new factor, not present in the benzene series, which must be taken into account. In general, cleavage of the ring may be avoided by proper attention to the temperature at which the reduction is carried out, higher temperatures tending to result in ring opening.

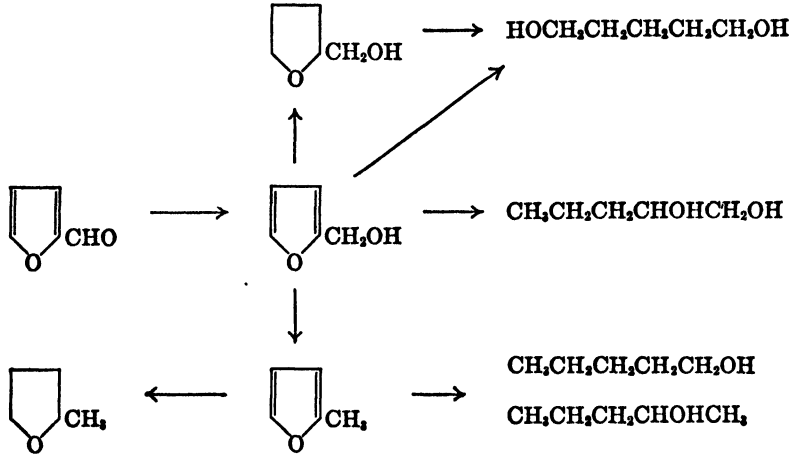
Comparatively little study has been given to the use of chemical, as contrasted with catalytic, reducing agents in the furan series, and the results reported are conflicting. The susceptibility of the furan ring to strong acids limits the number of such reagents. Yoder and Tollens [125] reported that pyromucic acid was not attacked by sodium amalgam, although in the same year Hill and Wheeler [126] reported the successful reduction of the nucleus in furan-2,5-dicarboxylic acid by the same reagent. Semmler [127] reduced furalacetophenone to furylphenylpropane with sodium and alcohol. No reduction of the furan ring was noted.

The use of platinum oxide for the catalytic reduction of various furan derivatives has been studied in detail by Kaufmann and Adams.[128] Furfural can be reduced quantitatively to furfuryl alcohol with platinum oxide, provided that the reduction is stopped after the absorption of one molecular equivalent of hydrogen. On further reduction, the ring is first saturated to yield tetrahydrofurfuryl alcohol together with smaller amounts of the products of reductive ring opening: pen-

124 Lutz and Kilber, *J. Am. Chem. Soc.*, **61**, 3010 (1939).
125 Yoder and Tollens, *Ber.*, **34**, 3462 (1901).
126 Hill and Wheeler, *Am. Chem. J.*, **25**, 463 (1901).
127 Semmler, *Ber.*, **39**, 726 (1906).
128 Kaufmann and Adams, *J. Am. Chem. Soc.*, **45**, 3029 (1923).

tanediols-1,2 and -1,5 and pentanol-1. Pyromucic acid yields the tetrahydro acid; furylacrylic acid yields furylpropionic acid; furoin yields a mixture of stereoisomeric 1,2-di(α-tetrahydrofuryl)ethylene glycols; furalacetone yields a mixture of 1-(α-tetrahydrofuryl)butanone-3 and 1-(α-tetrahydrofuryl)butanol-3; furalacetophenone yields a similar mixture of 1-(tetrahydrofuryl)-3-phenylpropanone-3 and the corresponding carbinol. It appears that the furan ring is more easily reduced than is the benzene ring, a circumstance wholly consistent with the resonance characteristics of furan. Kaufmann and Adams also made the interesting observation that a trace of iron in the platinum catalyst is a vital promoter for the reduction of the furan ring.

The reduction of furan derivatives with base-metal catalysts has received attention from a number of investigators.[7a,129-132] Connor and Adkins in an extended study of the reduction of furfuryl alcohol with a copper, chromium, barium oxide,[133] or nickel catalyst[134] at 175 atm. and 250° found that the main reactions are reduction to tetrahydrofurfuryl alcohol, accompanied or followed by direct hydrogenolysis, with cleavage occurring at each of the three C—O linkages as represented by the following scheme.



The reduction of furfural to furfuryl alcohol proceeds readily in a controllable fashion with a nickel-cobalt catalyst,[7a] which appears to

129 Connor and Adkins, *J. Am. Chem. Soc.*, **53**, 1091 (1931); **54**, 4678 (1932).
130 Burdick and Adkins, *J. Am. Chem. Soc.*, **56**, 438 (1934).
131 Peters, *Ind. Eng. Chem.*, **28**, 755 (1936); **31**, 178 (1939).
132 Rapoport and Rapoport, *J. Appl. Chem.* (*U.S.S.R.*), **11**, 723 (1938).
133 Connor, Folkers, and Adkins, *J. Am. Chem. Soc.*, **54**, 1139 (1932).
134 Covert, Connor, and Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932).

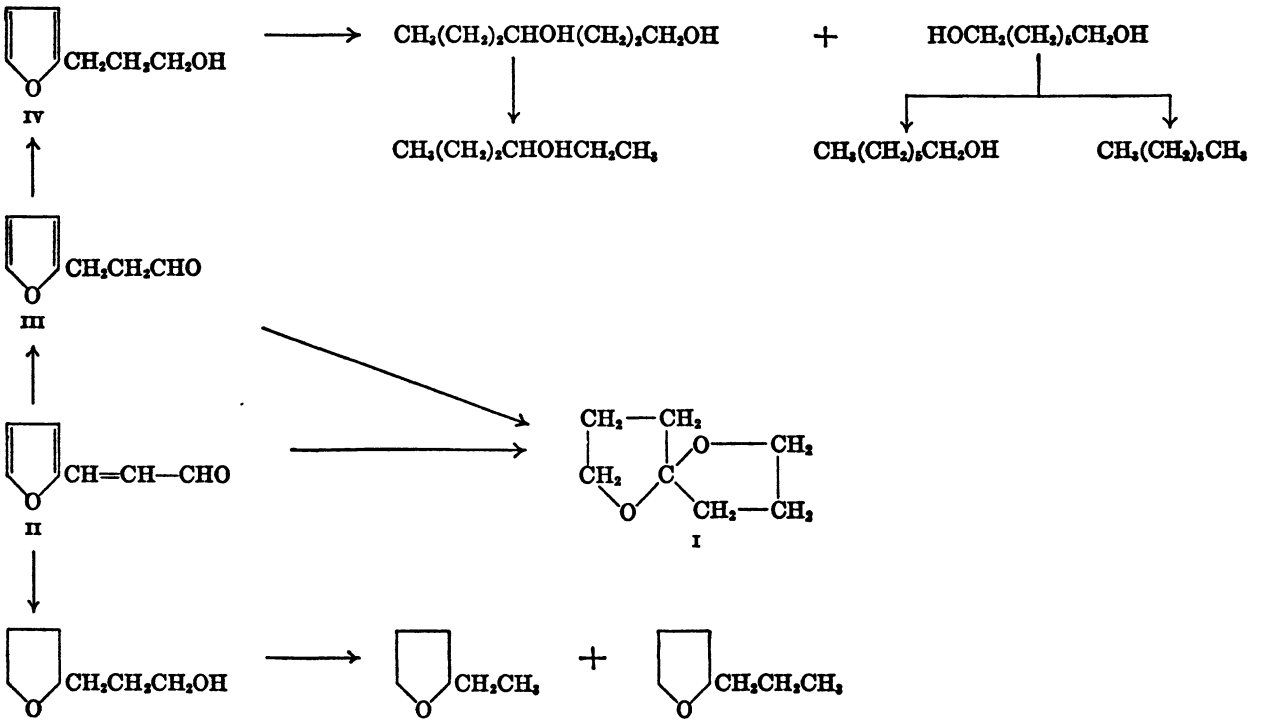
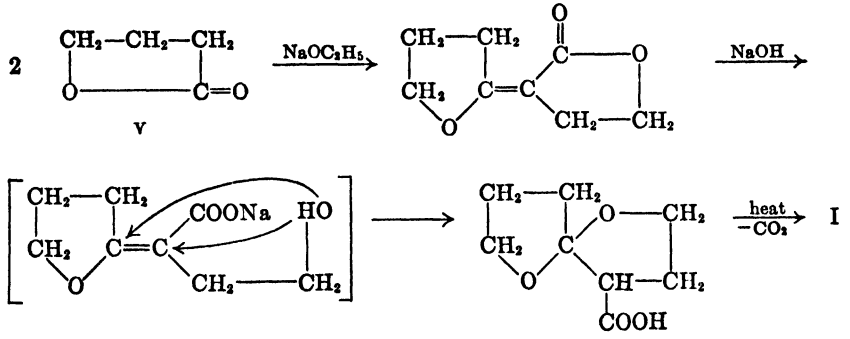

CH₂CH₂CH₂OH
O
IV
CH₃(CH₂)₂CHOH(CH₂)₃CH₂OH
+
HOCH₂(CH₂)₆CH₂OH
CH₃(CH₂)₂CHOHCH₂CH₃
CH₃(CH₂)₅CH₂OH
CH₃(CH₂)₃CH₃
CH₂CH₂CHO
O
III
CH=CH—CHO
O
II
CH₂—CH₂
O—CH₂
CH₂
C
O
CH₂—CH₂
I
CH₂CH₂CH₂OH
O
CH₂CH₃
+
CH₂CH₂CH₃

CHART 1

exert selective activity for the reduction of side chains. With higher temperatures, the reduction proceeds to 2-methylfuran and 2-methyltetrahydrofuran. Similarly, copper-chromium oxide at 150° results in almost quantitative reduction of furfural to furfuryl alcohol,[130] but at higher temperatures extensive hydrogenolysis occurs.

Burdick and Adkins in an extended study of the behavior of a number of furan derivatives over copper-chromium oxide and Raney nickel or nickel on kieselguhr report a wide variety of reactions involving hydrogenation, hydrogenolysis, or combinations of both. The products that have been obtained from furylacrolein are shown in Chart 1.

The formation of the substance 1,9-dioxa-5-spirononane (I) occurred to the extent of 25% when furylacrolein (II) was hydrogenated over Raney nickel at 160°.[135] This had previously been described by Fittig and Ström,[136] who prepared it by the reactions V–I. I apparently is

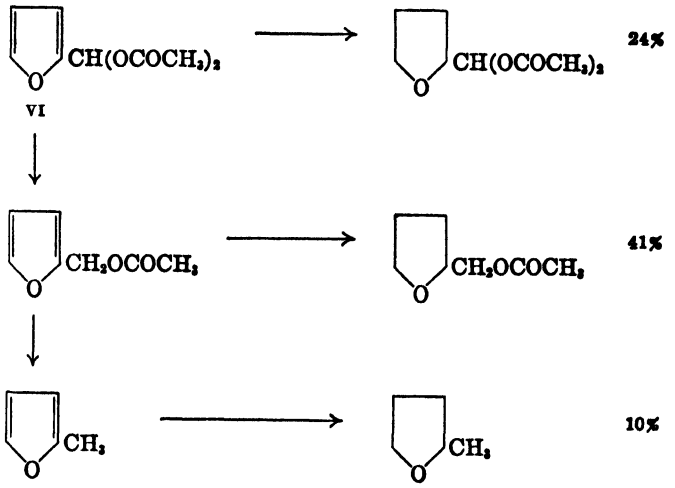


formed primarily from β-(2-furyl)propionaldehyde (III) since neither furylpropanol (IV) nor furylallyl alcohol yielded appreciable amounts of I under similar hydrogenation conditions.

In an attempt to prepare tetrahydrofurfural, a compound for which no completely satisfactory synthesis presently exists, Burdick and Adkins [130] encountered similar reactions in the reduction of furfural diacetate (VI) over nickel on kieselguhr at 160° and 100–200 atm. The same workers point out that Raney nickel is active at low temperatures, especially toward C=C bonds, and that either Raney nickel or nickel on kieselguhr are excellent catalysts for the saturation of C=C bonds in the side chain of a furan nucleus. Raney nickel is the best catalyst for cleavage of C to C bonds in primary alcohols. Copper-chromium oxide is rather inactive toward reduction of the nucleus

[135] Cf. Farlow, Burdick, and Adkins, *J. Am. Chem. Soc.*, **56**, 2498 (1934), for a correction of the structure originally assigned to the compound.

[136] Fittig and Ström, *Ann.*, **267**, 196 (1892).



but very effective in cleaving the ether linkage in furan and, at lower temperatures, for the hydrogenation of multiple linkages in side chains without affecting the nucleus. In the relative ease of reduction of the furan nucleus, the nature of the substituents sometimes plays a dominant role. An extreme instance of such an effect, which can be traced to the effect of conjugation of double bonds on the resonance forms of the nucleus, is the failure of the methyl ester of furan-2,5-dicarboxylic ester to undergo reduction with nickel.[137]

Mild reducing conditions have served for the preparation of various nitrogen derivatives of furan by procedures so set as to avoid reduction of the nucleus. Furylcyanide readily yields furfurylamine when hydrogenated over Raney nickel, preferably in the presence of ammonia, at room temperature.[138] Reductive amination of ammonia with furfural[139] and reduction of furfuraldehyde oxime[140] also lead to the same amine. More severe conditions yield the tetrahydro compound.

Catalytic reduction of furan derivatives can be carried out at elevated temperatures over copper-chromium oxide in the vapor phase without cleavage of the ring. Thus, Wilson[141] reports an 80% yield of 2-methylfuran by passage of the vapors of furfural over the catalyst at 280°. Schniepp, Geller, and Von Korff[142] obtained 92% of 2-methyl-

137 Haworth, Jones, and Wiggins, *J. Chem. Soc.*, 1 (1945).

138 Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).

139 Schwoegler and Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939).

140 Paul, *Bull. soc. chim. France*, [5] **4**, 1121 (1937).

141 Wilson, *J. Chem. Soc.*, 61 (1945).

142 Schniepp, Geller, and Van Korff, *J. Am. Chem. Soc.*, **69**, 672 (1947); cf. Lazier, U. S. pat. 2,077,422 (Apr. 20, 1937).

furan by passage of furfural vapor over copper-chromium oxide on activated charcoal [143] at 250°. On the other hand, at temperatures of 200° or below, the main product from the reduction of furfural over copper catalysts in the vapor phase at atmospheric pressure is furfuryl alcohol.[144] Bremner and Keeys have analyzed their own as well as the older data on such reductions and propose the following equations to explain the production of furfuryl alcohol at lower temperatures and 2-methylfuran at higher temperatures. The symbol F represents the furyl radical and M the catalyst. Equation 1 involves the

$$F{-}CHO + H_2 + M = F{-}CH_2OH + M \qquad (1)$$

$$F{-}CH_2OH + H^+ + M = F{-}CH_2^+ + H_2O + M^- \qquad (2)$$

$$F{-}\overset{+}{C}H_2 + F{-}CH_2OH + M = FCH_3 + F{-}CH_2O + M$$

$$\downarrow$$

$$F{-}CHO + H \qquad (3)$$

formation of furfuryl alcohol by simple addition of hydrogen. Equation 2 represents loss of a hydroxyl group from the alcohol with the formation of a carbonium ion which, because of stabilization by resonance, will have a relatively long period of residence on the catalyst during which time it will acquire a hydrogen atom to form methylfuran. The hydrogen transfer reaction between the carbonium ion and furfuryl alcohol, represented by equation 3, is based on analogy with the disproportionation of furfuryl alcohol to furfural and methylfuran noted by Paul.[145] Equation 2 is regarded as the rate-determining one.

$$2F{-}CH_2OH \rightarrow F{-}CH_3 + F{-}CHO + H_2O$$

PYROLYSIS OF FURAN DERIVATIVES

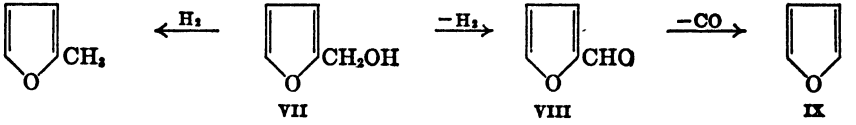
Furan derivatives undergo a variety of pyrolysis reactions. In some of these the nucleus remains intact, and in others rupture of the nucleus occurs. Several instances are reported in which side chains are eliminated at high temperatures under the influence of various catalysts. At temperatures in the neighborhood of 280°, furfural is decomposed in the vapor state to furan and carbon monoxide over nickel or cobalt

143 Lazier and Arnold, *Org. Syntheses Coll. Vol.* **2**, 142 (1943).

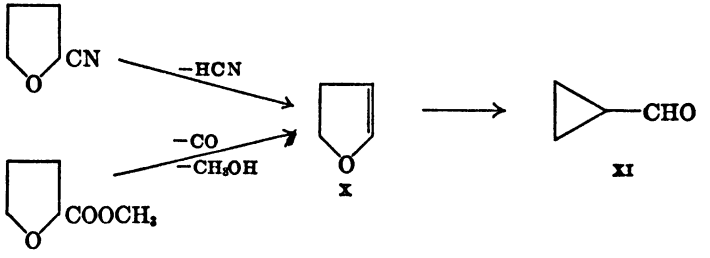
144 See Bremner and Keeys, *J. Chem. Soc.*, 1068 (1947), for a summary of the literature on this point.

145 Paul, *Bull. soc. chim. France*, [5] **2**, 2220 (1935).

catalysts. The amount of furan formed may be increased to about 65% by admixture of about ⅔ mole of hydrogen per mole of furfural. When furfuryl alcohol vapor is passed over Raney nickel at 150°, a mixture of furfural, furan, and 2-methylfuran results, the hydrogen for formation of the 2-methylfuran coming from dehydrogenation of furfuryl alcohol (VII–IX).[146]

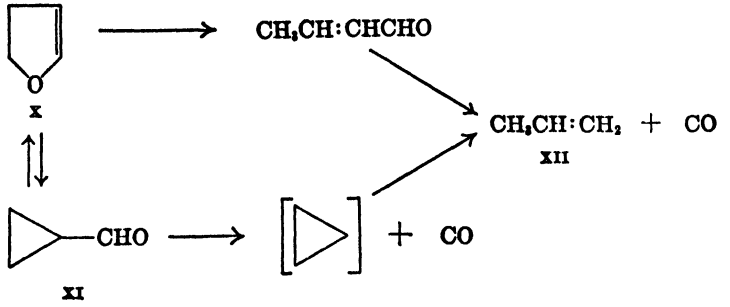


Passage of tetrahydrofurfuryl alcohol vapor over a variety of catalysts, of which nickel is the vital component, at 260–265° yields tetrahydrofuran as the main product (43–44%) along with carbon monoxide and hydrogen. An unexpected by-product is the hitherto unknown $\Delta^{2,3}$-dihydrofuran, yields of which increase to around 38% as the activity of a given catalyst decreases. Copper-nickel catalysts appear to be most effective in the formation of dihydrofuran. Some ring cleavage resulting in the formation of small amounts of *n*-butyraldehyde, methyl-*n*-propyl ketone, etc., also occurs.[147] When 2-cyanotetrahydrofuran or methyltetrahydrofuroate is passed over a dehydrating catalyst at 300–400°, 2,3-dihydrofuran (X) is also formed. At higher temperatures, X rearranges to cyclopropane aldehyde (XI).[148]



The interesting thermal interconversion of 2,3-dihydrofuran to cyclopropane aldehyde has been studied in more detail by Wilson,[149] and for the reactions noted at 500° over broken glass the scheme (X–XII) has been tentatively proposed. The reversibility of the reaction X–XI is

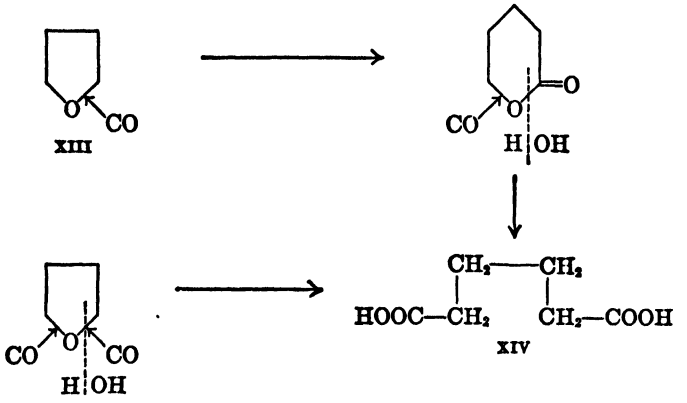
146 Paul, *Bull. soc. chim France*, [5] 5, 1592 (1938); 8, 507 (1941).
147 Wilson, *J. Chem. Soc.*, 52 (1945).
148 Wilson, *J. Chem. Soc.*, 58 (1945)
149 Wilson, *J. Am. Chem. Soc*, 69, 3002, 3004 (1947).



X XII XI

noteworthy. Dihydrofuran apparently behaves as a vinyl ether rearranging to the aldehyde.

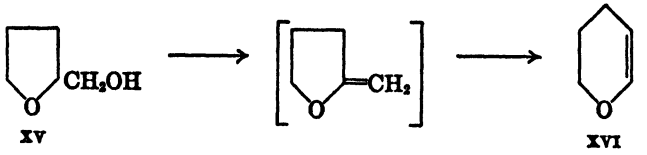
In the course of his investigations on the action of carbon monoxide on alcohols and ethers, Reppe [150] discovered a remarkable cleavage of tetrahydrofuran by reaction with carbon monoxide in the presence of metal carbonyls, preferably nickel carbonyl, and halogens at temperatures in the range of 200–300° and pressures of 150–300 atm. (XIII–XIV). The reaction can be controlled to yield either valerolactone or



XIII XIV

adipic acid (XIV) and can be realized in continuous operation with excellent yields.

The catalytic conversion of tetrahydrofurfuryl alcohol to dihydropyran (XV–XVI) when the vapor is passed over alumina at tempera-



XV XVI

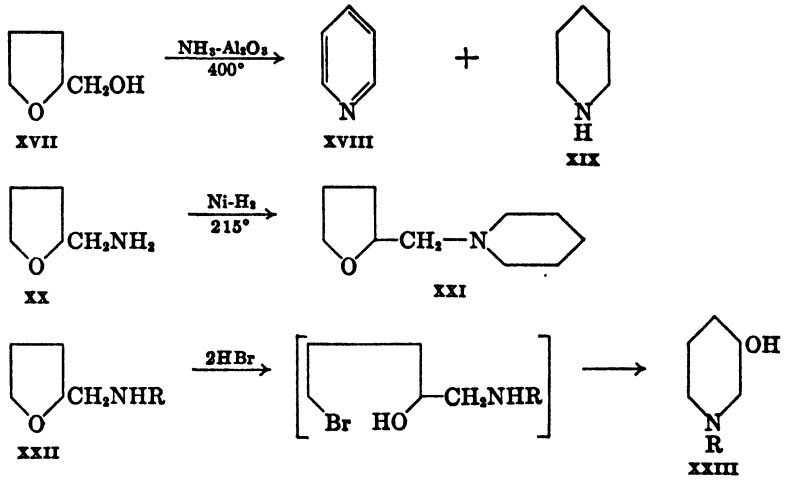
150 *U. S. Dept. Commerce, Office of Technical Services, Rept.* PB 1112, p. 26.

tures above 300°, a reaction first noted by Paul,[151] opens up a wide variety of substances derived from XVI (p. 348). The course of the dehydration can be pictured as involving a normal Wagner-Meerwein rearrangement of the primary dehydration product, which was not isolated.

When furan and its homologs are passed over alumina at 350° with hydrogen sulfide, low yields of the corresponding thiophenes are obtained.[152] If the tetrahydrofurans are treated similarly, the yields of tetrahydrothiophenes are much more favorable.

In similar fashion, furan yields pyrrole along with traces of indole, carbazole, and pyrrocoline when ammonia is substituted for hydrogen sulfide.[152,153] Primary aromatic or aliphatic amines may be substituted for ammonia, leading to N-substituted pyrroles. As in the conversion of furan derivatives to thiophenes, better yields of pyrrolidines result from tetrahydrofurans.

Furfuryl alcohol fails to react with ammonia under these conditions, but tetrahydrofurfuryl alcohol gives nitrogen heterocycles, generally in poor yields, by a reaction analogous to the formation of dihydropyran discussed above (XVII–XIX).[154] Other conversions of furan



151 Paul, *Bull. soc. chim. France*, [4] **53**, 1489 (1933); [5] **1**, 971 (1934). Cf. Schniepp and Geller [*J. Am. Chem. Soc.*, **68**, 1646 (1946)] for a complete literature review and a study of the reaction which resulted in excellent yields.

152 Yur'ev et al., *J. Gen. Chem.* (*U.S.S.R.*), **11**, 1128 (1941) [*C. A.*, **37**, 4071 (1943)]; *Ber.*, **69**, 1002 (1936).

153 Wilson, *J. Chem. Soc.*, 63 (1945).

154 Kline and Turkevich, *J. Am. Chem. Soc.*, **66**, 1710 (1944).

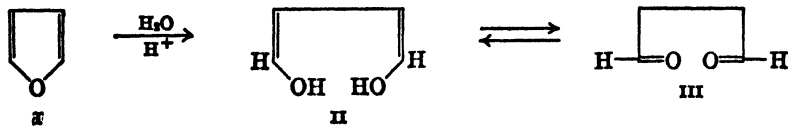
to heterocycles are shown in XX–XXI [155] and in XXII–XXIII.[156] (Cf. pp. 476 and 663 for a more detailed discussion.)

RING-OPENING REACTIONS OF FURAN

In addition to the reactions discussed above, opening of the furan ring either in compounds in which the furanoid system of double bonds is intact or in the reduced furans occurs readily under a wide variety of experimental conditions and reagents. In substantially all the reported ring openings, the reactions can be traced to the behavior of the derivative concerned as an ether, the extent and ease of ring cleavage and character of the products being for the most part determined by the degree of unsaturation present. Possible exceptions to this generalization may be found in certain pyrolytic reactions which furan derivatives undergo. These reactions are discussed on p. 166. It is by no means unlikely that, with fuller knowledge of these transformations, their courses may be found to fall into the same broad general pattern. Only with the lactones does the pattern depart from that characteristic of ethers, and the easy and familiar hydrolysis of these substances is readily ascribed to the presence of the internal ester grouping.

Ring opening of furans and their reduced derivatives by hydrogenolysis and pyrolytic reactions has already been considered. In the hydrogenolysis reactions, the behavior parallels exactly what would be expected of simple ethers.

The extreme susceptibility to acids of furan compounds in which the furanoid system of double bonds is intact can probably be attributed either to the lability manifested by vinyl ethers as a class or to the tendency which these substances, or the 1,4-diene system, show to undergo addition reactions. In all ring openings under the influence of acids, the initial product is a 1,4-dicarbonyl compound, and in this sense the process of ring opening may be regarded as a reversal of the process by which furans are formed from such dicarbonyl compounds. In a general over-all sense, this may be written as I–III. Whether the



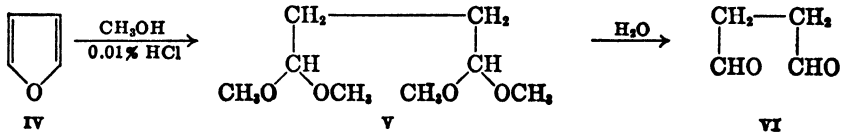
I II III

actual formation of the dicarbonyl compound may be preceded by addition of the elements of water, either in a 1,2 or a 1,4 fashion, and

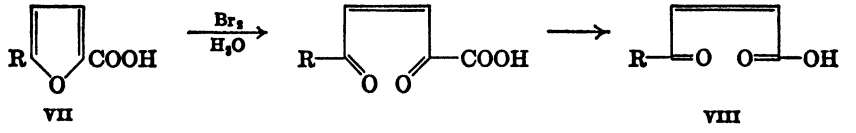
[155] Wilson, *J. Am. Chem. Soc.*, **67**, 693 (1945).
[156] Paul and Tchelitcheff, *Compt. rend.*, **221**, 560 (1945).

subsequent cleavage of the intermediate thus formed is a question which must be left unanswered at present. The stability of the products of ring cleavage is determined largely by the nature of the substituents present. If the opening is carried out in an oxidizing medium, the initial carbonyl compound is frequently oxidized.

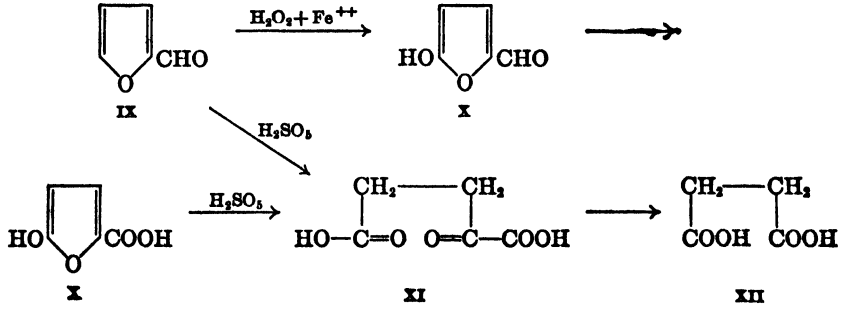
A typical example of the events which occur is the reactions of furan itself or α-methylfuran when heated with methyl alcoholic hydrogen chloride (IV–VI), a reaction noted by Harries,[157] which is accompanied



by extensive resinification and is noted for poor yields. With α-methylfuran, the product is the methylal of levulinic aldehyde, ketal formation not occurring under such conditions, as would be expected. Decarboxylation frequently accompanies ring opening of furan carboxylic acids, for example, in the action of bromine water on 2-furoic acid and 5-methyl-2-furoic acid (VII–VIII).[158] The formation of succinic



acid by the action of Caro's acid on furfural is easily explicable if one recalls the familiar chemistry of α-keto acids.[159,160] Here, hydroxylation in the 5 position has been postulated as preceding the actual ring opening of the unstable 5-hydroxyfurfural (IX–XII). A more in-



157 Harries, *Ber.*, **31**, 37 (1898); **34**, 1488 (1901).
158 Hill et al., *Am. Chem. J.*, **15**, 159 (1893); **19**, 650 (1897); *Ber.*, **23**, 452 (1890).
159 Cross, Bevan, and Heiberg, *J. Chem. Soc.*, **75**, 747 (1899).
160 Cross, Bevan, and Briggs, *Ber.*, **33**, 3132 (1900).

volved oxidative ring opening is that described by Milas [161] by the action of sodium chlorate catalyzed by osmium tetroxide or vanadium pentoxide on furfural, as represented in Chart 2. Hydroxylation in

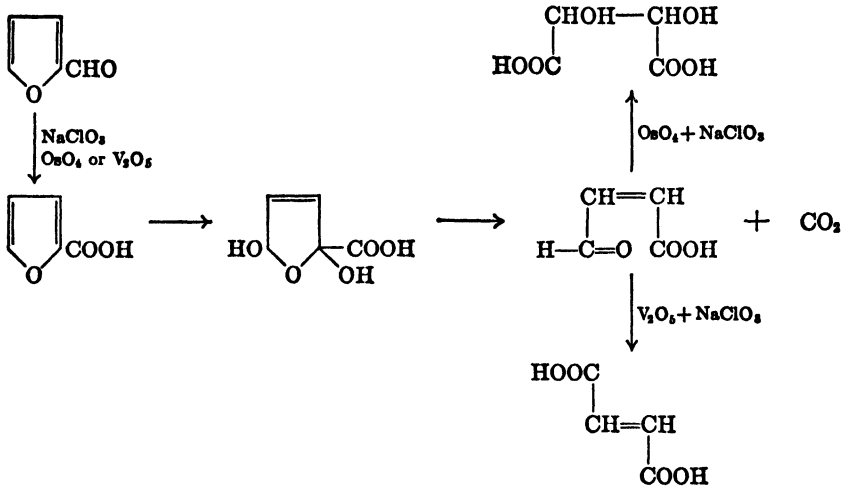
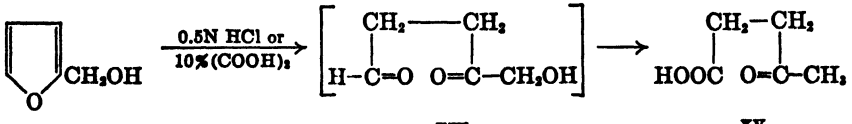


CHART 2

the 2 and 5 positions across the diene system is postulated as preceding the actual ring opening.

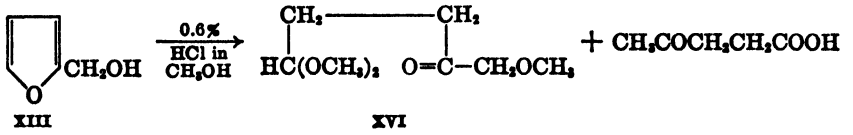
The ready conversion of furfuryl alcohol and certain of its derivatives into levulinic acid under the influence of dilute acid is a reaction which does not appear to be understood in its entirety at present. Largely as a result of the investigations of Pummerer and co-workers,[162,163] the reaction is formulated by XIII–XV. Evidence for the



XIII XIV XV

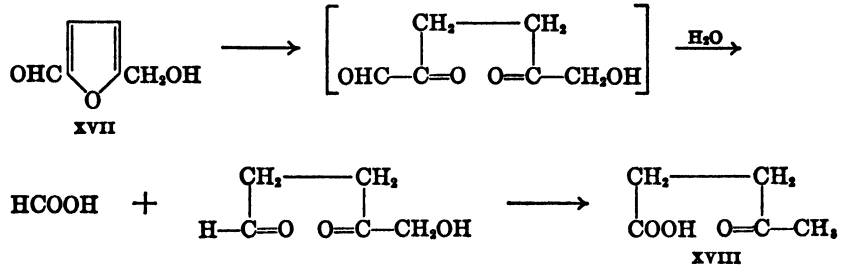
postulated intermediate (XIV) was obtained from a study of the action of methyl alcoholic hydrogen chloride on furfuryl alcohol in which the acetal (XVI) was actually isolated. It is thus suggested that the hydroxyketoaldehyde (XIV) is an intermediate in the formation of levulinic acid which in turn is formed by a sort of intramolecu-

161 Milas, *J. Am. Chem. Soc.*, **49**, 2005 (1927).
162 Pummerer and Gump, *Ber.*, **56**, 999 (1923).
163 Pummerer, Guyot, and Birkofer, *Ber.*, **68**, 480 (1935).



XIII XVI

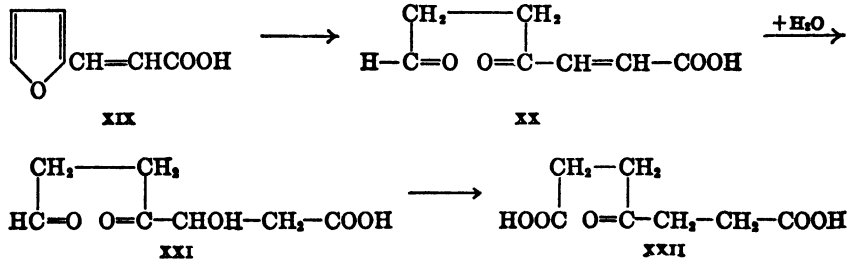
lar disproportionation resembling a Cannizzaro reaction. Levulinic acid also results from the action of dilute acids on 5-hydroxymethylfurfural,[163] for which a similar reaction is suggested with the addition of an extra step involving hydrolytic cleavage of formic acid (XVII–XVIII). Kinetic data supporting such a mechanism has been obtained



XVII XVIII

by Teunissen,[164] who also noted that the velocity of the reaction varied with the acid employed.

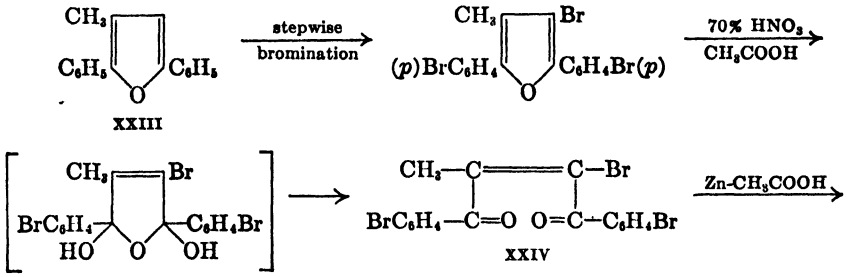
In an attempt to prepare ethyl β-(2-furyl)acrylate by the action of alcoholic hydrogen chloride on the acid (XIX), Marckwald[165] obtained γ-ketopimelic acid (XXII) instead of the expected acrylic ester. Water is necessary for the reaction, and investigation showed that, if the alcoholic hydrogen chloride contains 3.5 parts of water per part of ester, optimum conversion to XXII results. The course of this reaction can be explained on the basis of the Pummerer suggestions discussed above (XIX–XXII).[166]



XIX XX XXI XXII

164 Teunissen, *Rec. trav. chim.*, **49**, 784 (1930).
165 Marckwald, *Ber.*, **20**, 2813 (1887); **21**, 1398 (1888).
166 Cf. Volhard, *Ann.*, **253**, 235 (1889).

A reaction which appears to involve hydroxylation of the furan ring across the butadiene system in a 1,4 manner is the oxidative cleavage of certain 2,5-diphenylfurans by the action of mixtures of concentrated nitric acid and acetic acid.[47,167] This ring opening leads exclusively to formation of *cis*-dibenzoylethylene derivatives, which are sometimes difficultly accessible by other methods. Further, by operations, e.g., bromination, on the diphenylfuran, substituted dibenzoylethylenes can be prepared. From these, by reduction, substituted dibenzoylethanes or phenylhydrocarbons are accessible. The potentialities of this method as a source of organic compounds are illustrated in XXIII–XXVI.



XXIII

XXIV

$BrC_6H_4—CO—CH(CH_3)—CH_2—CO—C_6H_4Br$ ⟶

XXV

$BrC_6H_4CH_2CH(CH_3)CH_2CH_2C_6H_4Br$

XXVI

Ring cleavage, after hydration, of $\Delta^{2,3}$-dihydrofuran provides a convenient source of γ-hydroxybutyraldehyde.[168] Similarly, Paul [169] had shown earlier that 4,5-dihydro-2-methylfuran (XXVII) hydrolyzes to acetopropanol (XXIX). Schniepp, Geller, and von Korff [170] have studied the formation of acetopropanol directly from 2-methylfuran under combined reducing and hydrolytic conditions. Acetopropanol or 1,4-pentandiol can be prepared in 25–35% and 50–60% yields, respectively, by reductively cleaving the furan ring over a nickel catalyst in the presence of water and a trace of acid (0.01–0.10 weight per cent of

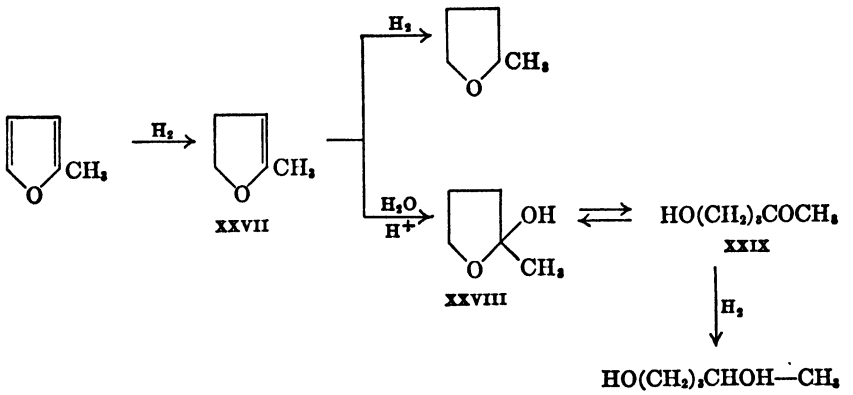
167 Lutz and McGinn, *J. Am. Chem. Soc.*, **64**, 2583 (1942).

168 Wilson, *J. Chem. Soc.*, 48 (1945).

169 Paul, *Bull. soc. chim. France*, [4] **53**, 417 (1933).

170 Schniepp, Geller, and von Korff, *J. Am. Chem. Soc.*, **69**, 672 (1947); cf. Topchiev, *Compt. rend. acad. sci. U.R.S.S.*, **19**, 497 (1938).

the reaction mixture of formic acid). The reactions are represented by XXVII–XXIX. The acidic conditions were necessary, presumably to accomplish hydration of the vinyl ether in XXVII, and the reaction



is analogous to the formation of δ-hydroxyvaleraldehyde from dihydropyran (p. 348). The ready interconvertibility of acetopropanol (XXIX) and XXVIII is shown by the conversion of XXIX to XXVIII merely by heating with water in the absence of acid.[171]

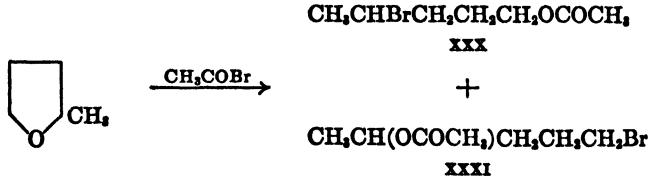
By ring opening of tetrahydrofuran and its derivatives, a wide variety of aliphatic compounds becomes available. The basic reactions involved differ in no sense from those commonly encountered in other saturated ether splittings.

Following earlier investigations by Paul [172] and Starr and Hixon [173] among others, Fried and Kleene [174] studied in some detail the action of hydrogen halides on tetrahydrofuran and its 2,5-dimethyl derivative. The general order of reactivity of the cyclic ether decreased in the order: HI, HBr, HCl; and the yields of the dihalides varied in the same order. Thus, by bubbling the dry hydrogen halide into the tetrahydrofuran, yields of the order of 75% and 60%, respectively, of 1,4-diiodo- or dibromo-butane were obtained as well as comparable yields of the 2,5-dihalogen hexanes from dimethyltetrahydrofuran. With hydrogen chloride, the reaction does not proceed beyond the halohydrin stage (59%) with tetrahydrofuran, and dimethyltetra-

171 Kyrides and Zienty, *J. Am. Chem. Soc.*, **68**, 1385 (1946).
172 Paul, *Bull. soc. chim. France*, [5] **8**, 1053 (1938).
173 Starr and Hixon, *J. Am. Chem. Soc.*, **56**, 1595 (1934).
174 Fried and Kleene, *J. Am. Chem. Soc.*, **63**, 2691 (1941).

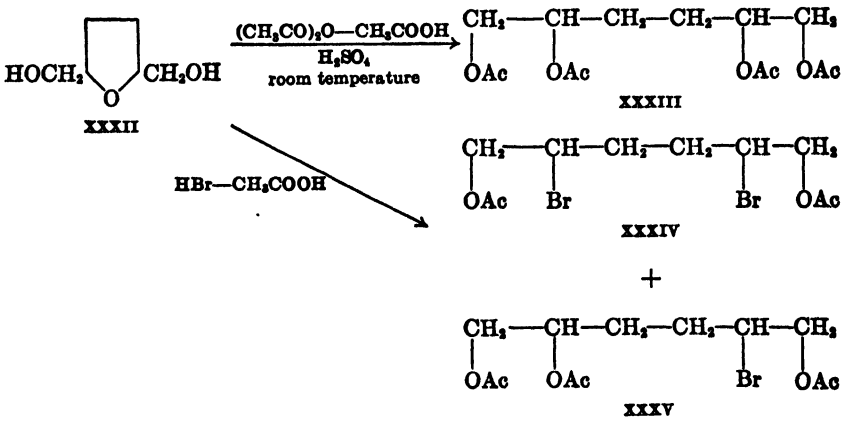
hydrofuran is not attacked. Addition of zinc chloride resulted in 56% of tetramethylene dichloride but in only 8% of 2,5-dichlorohexane.

The tetrahydrofuran ring is readily opened by acyl halides. Paul [175] obtained methyl α,δ-diacetoxyvalerate by the action of acetyl chloride on methyl α-furoate. Similarly, the action of acetic anhydride and zinc chloride on tetrahydrofurfuryl acetate gives 1,2,5-triacetoxypentane.[176] The action of acetyl halides on α-methyltetrahydrofuran can lead to two isomers, XXX and XXXI. Morell [177] studied this reac-



tion and found that, with acetyl bromide, the proportion of the isomers formed is influenced by the temperature at which the reaction is carried out, higher temperatures leading to increasing amounts of XXXI.

By ring cleavage of 2,5-bishydroxymethyltetrahydrofuran, Haworth, Jones, and Wiggins [137] obtained a variety of products (XXXII–



XXXV). From hydroxymethylfurfural, another series of substances was opened up, as shown in Chart 3.

[175] Paul, *Compt. rend.*, **212**, 401 (1941).
[176] Paul, *Bull. soc. chim. France*, [5] **8**, 369 (1941).
[177] Morell, U. S. pat. 2,424,184 (July 15, 1947).

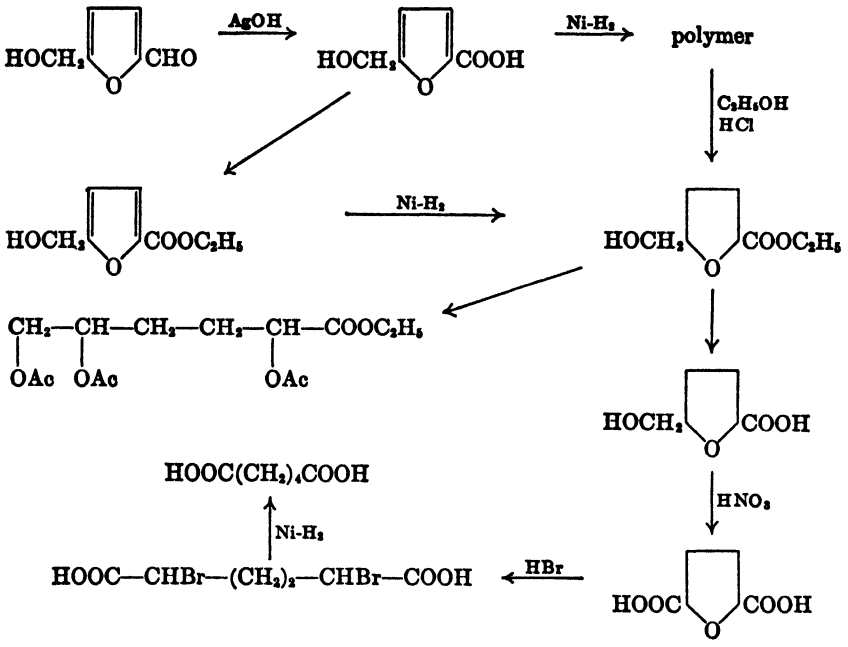


CHART 3

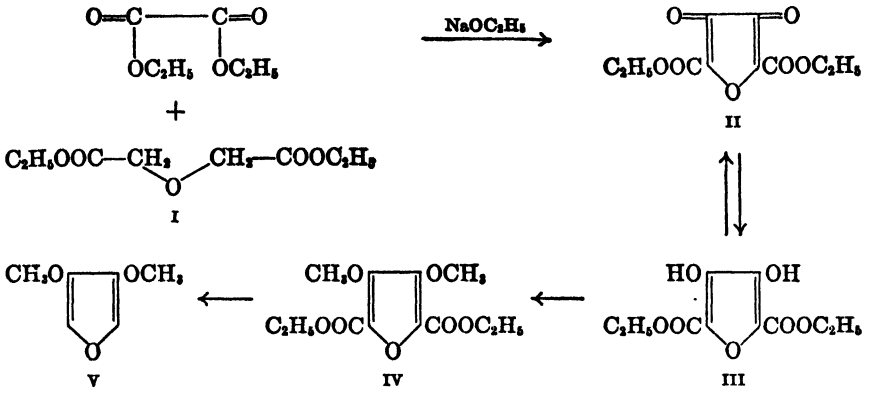
HYDROXY- AND AMINO-FURANS

Both the free hydroxy- and amino-furans in general are characterized by extreme instability and strong tendencies to pass spontaneously into resinous products. The one exception is to be found in $\Delta^{\beta,\gamma}$-butenolides, which can be considered the ketonic forms of 2-hydroxyfurans and are discussed elsewhere (p. 184). However, if the hydroxy or amino groups are protected by acylation or alkylation, the substances are reasonably stable.

The few 3-hydroxyfurans which have been described as reasonably stable in general have strongly electronegative groups in one or both of the α positions which exert a stabilizing effect on the molecule. Johnson and Johns [178] prepared 2,5-dicarbethoxy-3,4-dihydroxyfuran by condensation of ethyl oxalate with diethyl diglycolate (I), and Hinsberg [179] has prepared the corresponding methyl ester by the same method (I–III). Although Johnson and Johns considered that the

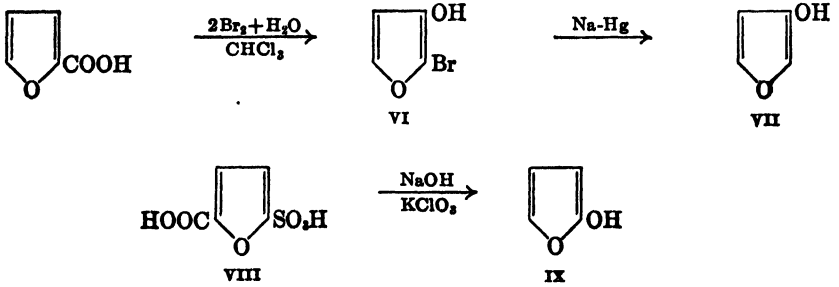
178 Johnson and Johns, *Am. Chem. J.*, **36**, 290 (1906).
179 Hinsberg, *Ber.*, **45**, 2413 (1913).

substance existed primarily in the keto form, Hoehn [180] prepared derivatives of the enol form, e.g., the bismethyl ether (IV) as well as the



diacetoxy and dibenzoxy derivatives, and noted the formation of copper and ammonium salts. By decarboxylation of the acid derived from IV, Hoehn obtained 3,4-dimethoxyfuran (V), which was characterized by its maleic anhydride addition compound.

The parent 2- and 3-hydroxyfurans have been reported recently by Hodgson and Davies.[181] In a careful reinvestigation of a reaction first noted by Limpricht,[182] it was found that bromination of furoic acid in chloroform in the presence of one equivalent of water gave a 72% yield of 2-bromo-3-hydroxyfuran (VI) from which 3-hydroxyfuran (VII)



was obtained by the action of sodium amalgam or sodium and alcohol. The amount of water present is critical; if none is present 3,5-dibromofuroic acid is formed,[183] and if too much is present ring rupture occurs.

180 Hoehn, *Iowa State College J. Sci.*, **11**, 66 (1936–1937).
181 Hodgson and Davies, *J. Chem. Soc.*, 806 (1939).
182 Limpricht, *Ann.*, **165**, 291 (1873).
183 Hill and Sawyer, *Ann.*, **232**, 42 (1885).

2-Hydroxyfuran has been reported to arise by treatment of 2-furoic acid-5-sulfonate (VIII-IX) [95] with sodium hydroxide and a little potassium chlorate at 200°. Both substances are described as non-reducing to Tollens' reagent and as darkening and resinifying readily. The 3-hydroxy compound was further characterized by its maleic anhydride addition compound.

The best insight into the properties of the 3-hydroxyfurans is obtained from the investigations of Kohler and co-workers [45,46] on 3-hydroxy-2,4,5-triphenylfuran (XII) and 3-hydroxy-2,5-diphenylfuran.

By treating 3-acetoxytriphenylfuran (X) with methylmagnesium iodide, the compound (XI) was obtained. By carefully controlled de-

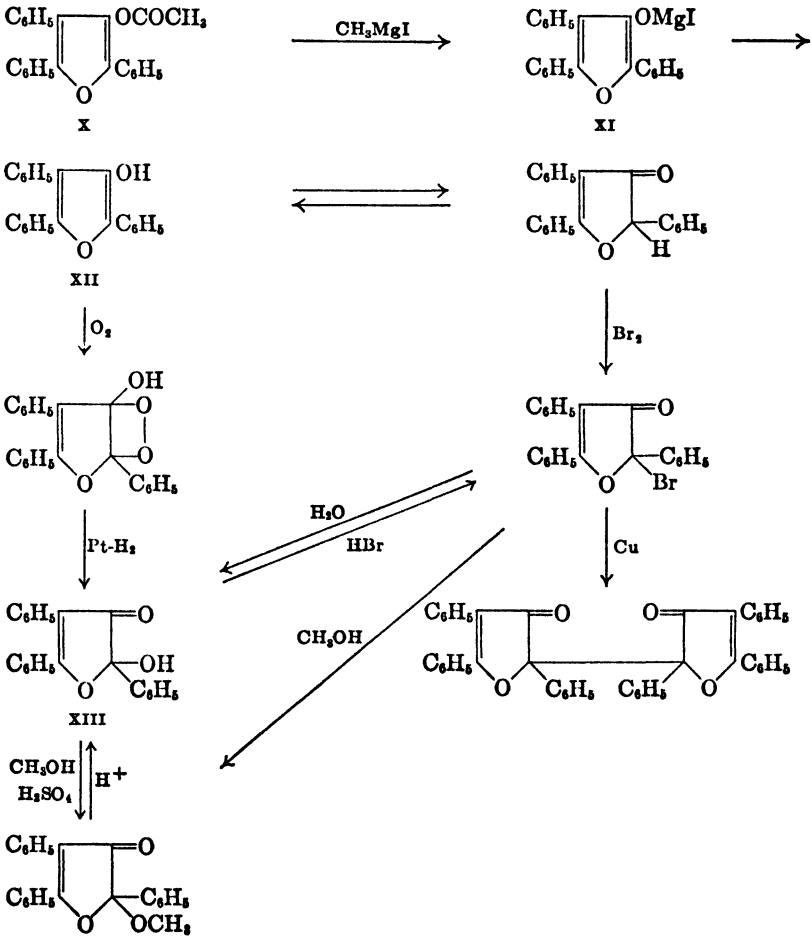
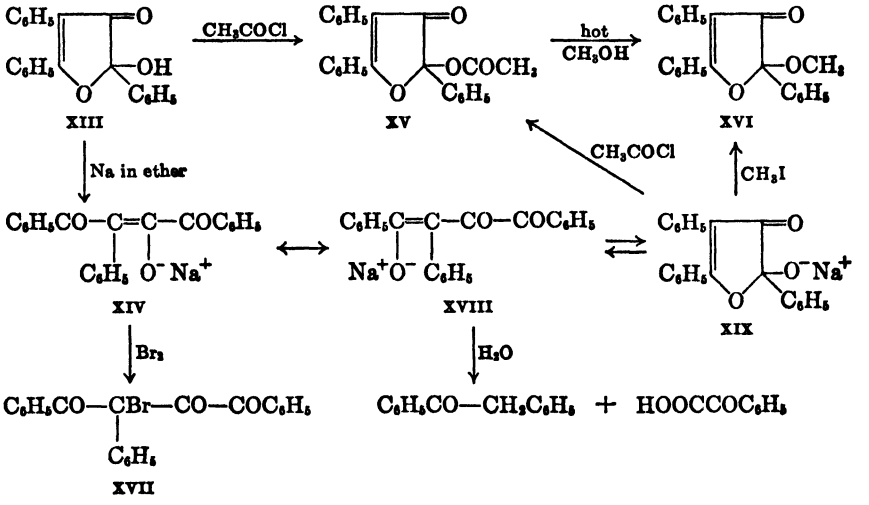


CHART 4

composition of this, it was possible to break down the over-all reaction, first noted by Thiele (XI–XII),[184] taking place when X is hydrolyzed by acid or alkali (Chart 4). Of particular interest is the behavior of the compound (XIV) obtained by the action of sodium on the hydroxyfuranone (XIII). By the action of acetyl chloride and methyl iodide, it is converted to the acetoxy and methoxy derivatives (XV and XVI), respectively. On the other hand, bromine converts it to the open-chain bromo compound (XVII), and boiling water splits it

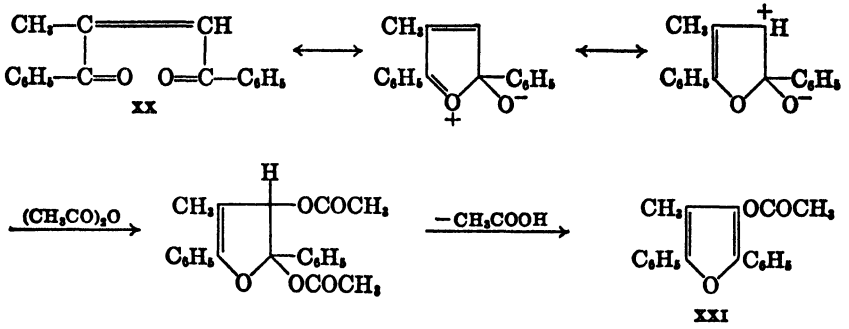


into desoxybenzoin and phenylglyoxylic acid. Solutions of the sodium compound apparently behave as a mixture of two different anions (XIV and XIX) in very mobile equilibrium. The ion (XIV) also resonates with a form (XVIII) from which the hydrolysis products are derived. Substantially the same behavior was noted with 2,5-diphenyl-3-hydroxyfuran.[46] Elimination of the phenyl group in the 4 position has virtually no effect on the chemical properties of the substance. Both β-hydroxyfurans behave like exceedingly reactive enolic forms of the ketones.

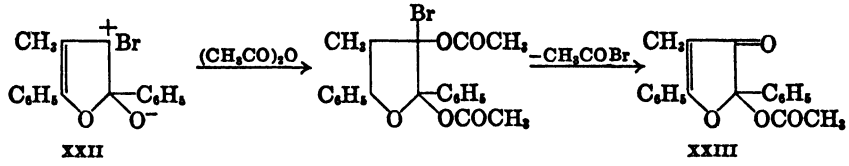
Derivatives of 2,5-diphenyl-3-hydroxyfuran, as well as of the hydroxyfuranones of the above type have also been prepared from unsaturated 1,4-diketones by Lutz and co-workers,[42,48] although the mechanism suggested by Lutz in his earlier papers for the formation of the compounds requires simplification in the light of the studies of Kohler[45,46] (see p. 132). For example, *cis*-dibenzoylmethylethylene

[184] Thiele, *Ber.*, **31**, 1249 (1898).

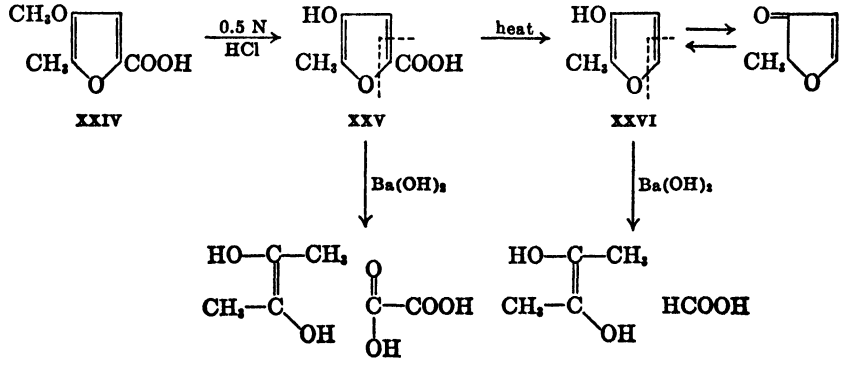
(XX) is converted to the acetoxyfuran (XXI) by the action of acetic anhydride-sulfuric acid. The steps shown in XX–XXI, based on a



suggestion of Smedley,[185] are put forward to account for this conversion. The *trans* form of the diketone does not undergo the reaction. If, as in the case of a completely substituted dibenzoylethylene, no hydrogen is available for furanization, the formation of hydroxyfuranones is still possible, provided proper substituents are present, e.g., XXII–XXIII.



Finally, a derivative of β-hydroxyfuran, 4-methoxy-5-methyl-2-furoic acid (XXIV), has been prepared by the action of methyl alcoholic hydrogen chloride on 5-ketorhamnonic lactone.[186] On treatment

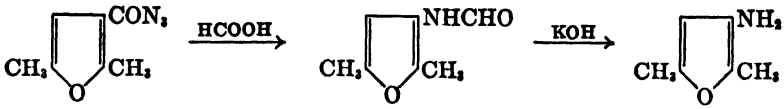


185 Smedley, *J. Chem. Soc.*, **75**, 219 (1909).

186 Votoček and Malachta, *Collection Czechoslov. Chem. Communs.*, **1**, 449 (1929); **4**, 87 (1932).

with 0.5 *N* hydrochloric acid, this passed to the free hydroxyfuran acid (XXV) which, when heated, lost carbon dioxide to give 2-methyl-3-hydroxyfuran (XXVI). From the results of Zerewitinoff active hydrogen determinations, it becomes apparent that XXVI exists predominately in the keto form. The acid (XXV) is readily hydrolyzed by barium hydroxide to acetoin and oxalic acid, and the hydroxyfuran is similarly cleaved to acetoin and, presumably, formic acid.

The only unequivocal way in which aminofurans or their derivatives have been prepared is by the Curtius degradation of the appropriate furan acid azides (XXVII–XXVIII).[187,188] A number of 2-



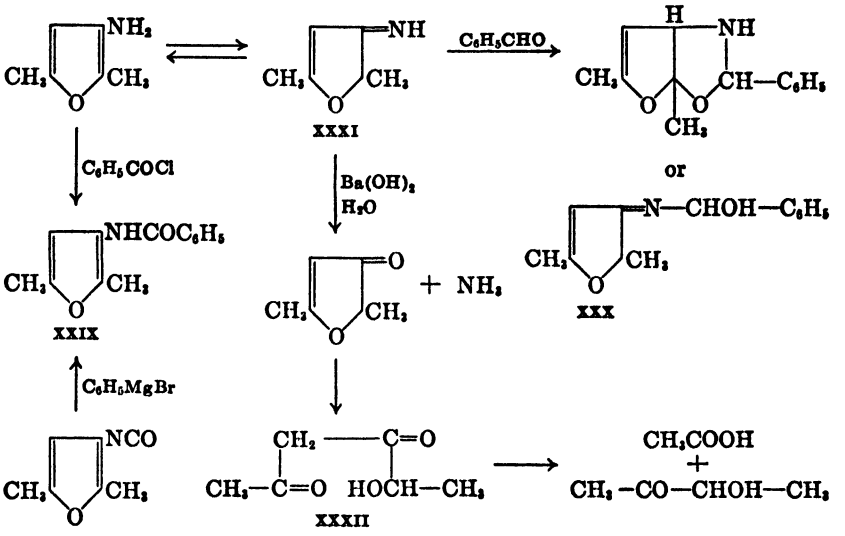
XXVII XXVIII

and 3-furylamines have thus been prepared. The intermediate isocyanates can, in general, be isolated,[189] and they react normally to yield ureas, carbamates, etc. The free 3-aminofurans are unstable and discolor rapidly in air with the formation of soft resins. As amines, they give strong isocyanide tests, but, paralleling the hydroxyfurans, they probably exist largely in the ketimine form. Thus, although the benzoyl derivatives are identical with those formed by the action of Grignard reagent on the isocyanates and are undoubtedly derived from the eneamine form (XXIX), benzaldehyde forms an addition compound (XXX), presumably from the ketimine form, which cannot be dehydrated to a Schiff base. Treatment of 2,5-dimethyl-3-aminofuran with barium hydroxide results apparently in direct hydrolysis of the amine, followed by subsequent decomposition of the hydroxyfuran in a manner analogous to the decomposition of the 3-hydroxyfurans (XXXI–XXXII) (p. 181). The diazotization of 3-aminofurans proceeds abnormally and resembles a nitrosation reaction. Although the diazonium compound couples with β-naphthol to yield a dye, it fails to undergo the usual replacement reactions. Little is known of the behavior of the 2-aminofurans.

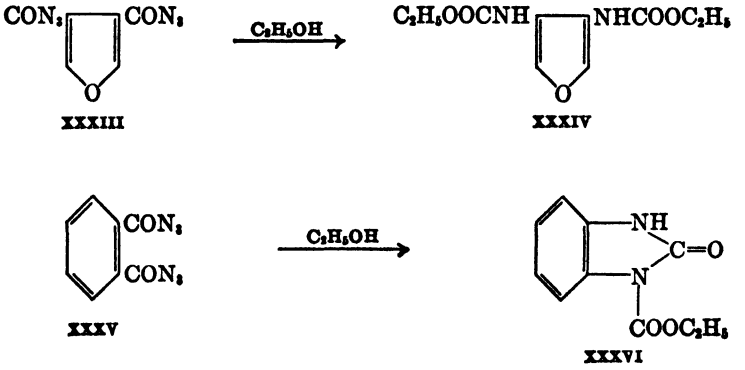
Of interest in connection with the synthesis of the furan analog of biotin, oxybiotin, is 3,4-diaminofuran. This has been prepared in the form of its urethan [190,191] by decomposition of the azide in the pres-

187 Blomquist and Stevenson, *J. Am. Chem. Soc.*, **56**, 146 (1934).
188 Stevenson and Johnson, *J. Am. Chem. Soc.*, **59**, 2525 (1937).
189 Singleton and Edwards, *J. Am. Chem. Soc.*, **60**, 540 (1938).
190 Hofmann and Bridgwater, *J. Am. Chem. Soc.*, **67**, 738 (1945).
191 Hofmann, *J. Am. Chem. Soc.*, **67**, 1459 (1945).

ence of alcohol. The reaction of the diazide of furan-3,4-dicarboxylic acid (XXXIII) with alcohol presents a distinct difference from the



behavior of the diazide of phthalic acid. The diurethane (XXXIV) is formed readily, whereas the corresponding reaction with phthalic acid leads to an imidazole derivative (XXXV–XXXVI).[192] Presum-



ably the difference is due to steric factors which create difficulty in fusing another five-membered ring to furan. On reduction of the furan nucleus, this difficulty disappears.[191]

Nitrosation or nitration of 2-hydroxyfuran and 3-hydroxyfuran is reported to lead to 2-hydroxy-5-nitroso- (or nitro-) furan and 2-ni-

[192] Stork, *J. Am. Chem. Soc.*, **67**, 884 (1945).

troso- (or nitro-) 3-hydroxyfuran, respectively (Chart 5).[193] Reduction of either the nitroso or nitro compounds is reported to lead to the

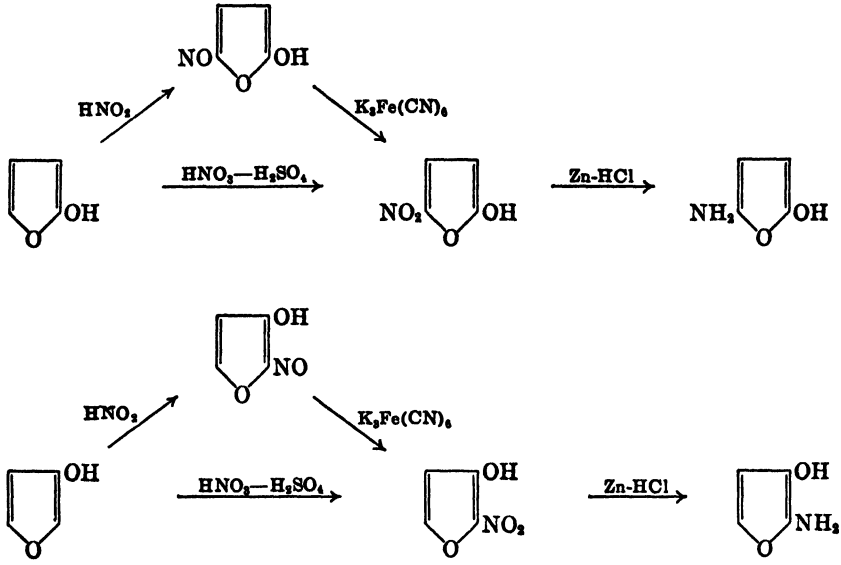


CHART 5

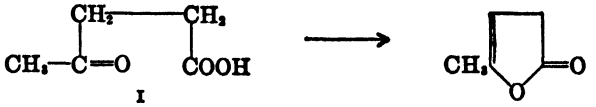
hydroxyaminofurans. Assignment of the positions taken by the entering groups was made on the basis of furan orientation rules. It is noteworthy that the sensitive hydroxyfuran apparently withstands this vigorous treatment. No mention is made of instability of the aminofurans. The properties of these compounds as described are so inconsistent with those expected that a reinvestigation of the above reactions would be most welcome.

THE UNSATURATED γ-LACTONES

Syntheses of $\Delta^{\beta,\gamma}$-Butenolides. If one regards simple $\Delta^{\beta,\gamma}$-unsaturated lactones of the type of α-angelica lactone as the keto tautomers of α-hydroxyfurans, then a variety of methods becomes available for their synthesis. Conversion of a γ-keto acid to the lactone occurs readily when the acid is heated with acetic anhydride, acetyl chloride, or mixtures of the two (I–II),[194–197] or occasionally merely by slow

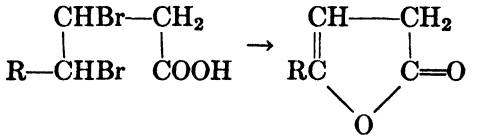
193 Hodgson and Davies, *J. Chem. Soc.*, 1013 (1939).
194 Thiele, Tischbein, and Lossow, *Ann.*, **319**, 180 (1901).
195 Kuhn and Jerchel, *Ber.*, **76**, 413 (1943).
196 Jacobs and Scott, *J. Biol. Chem.*, **87**, 601 (1930).
197 Lukes, *Collection Czechoslov. Chem. Communs.*, **1**, 461 (1929) among others.

distillation.[198,199] In such syntheses, it appears to be a necessary condition that the enol of a keto acid be available for ring closure. All



I II

attempts at similar ring closure of an aldehydo acid through its enol have so far met with failure.[200–202] A second synthesis proceeds by simultaneous hydrolysis and dehydrobromination of β,γ-dibromo acids by boiling them with water or sodium carbonate solution,[195,199,203] or by thermal decomposition of the dibromo acid, sometimes in the presence of quinoline (III–IV).[199,204]



III IV

Reactions of $\Delta^{\beta,\gamma}$-Butenolides. Lactones of this class are readily isomerized to $\Delta^{\alpha,\beta}$-butenolides, which in general are more stable, by the action of organic bases such as triethylamine,[194,197] although there is some evidence to indicate that an equilibrium exists between the two double-bond isomers, the relative proportions of the two at equilibrium being conditioned by the substituents present. Hydrolysis of the lactones results in the formation of the precursor keto acids. The $\Delta^{\beta,\gamma}$-butenolides may be distinguished from the $\Delta^{\alpha,\beta}$-isomers by color reactions with alkaline nitroprusside or with ferricyanide, provided that the tests are carried out under carefully controlled conditions.[201]

Perhaps the most characteristic behavior of this type of lactone is that shown on catalytic reduction. The furan ring is more easily opened than it is with other furan compounds, and the product of the reductive ring opening arises from cleavage in only one mode (V–VII). Thus, with α-angelica lactone, reduction over platinum oxide results in

198 Wolff, *Ann.*, **229**, 251 (1885).

199 Jacobs and Scott, *J. Biol. Chem.*, **93**, 139 (1931).

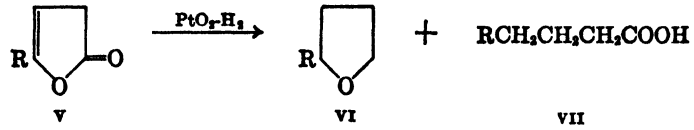
200 Carrierre, *Ann. chim.*, [9] **17**, 38 (1922).

201 Paist, Blout, Uhle, and Elderfield, *J. Org. Chem.*, **6**, 273 (1941).

202 Fried and Elderfield, *J. Org. Chem.*, **6**, 566 (1941).

203 Lespieau, *Bull. soc. chim. France*, [3] **33**, 466 (1905); cf. Blaise and Courtot, *ibid.*, [3] **35**, 989 (1906).

204 Bardhan, *J. Chem. Soc.*, 2616 (1928).

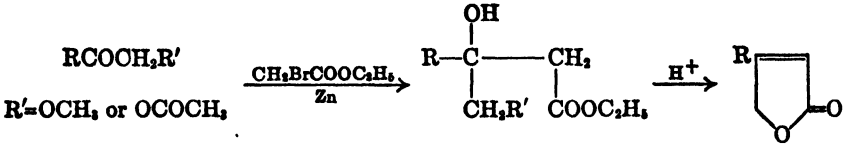


V VI VII

practically quantitative conversion to valeric acid.[196] The extent to which ring opening occurs varies with the nature and position of substituents present in the lactone.[196,199] In all cases, products of reduction consist of mixtures of the saturated lactone and derived desoxy acid. The mechanism of the reduction is not clear. It does not proceed over the saturated lactones, since these are stable to further reduction. Likewise, it apparently does not proceed by preliminary cleavage to the γ-keto acid, since levulinic acid behaves quite differently on hydrogenation.

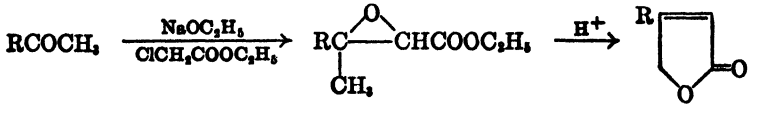
Syntheses of $\Delta^{\alpha,\beta}$-Butenolides. Several syntheses for these substances have been developed, largely because of the recognition of the presence of such a grouping in the cardiac aglycones and of the antibiotic activity of the class as a whole. As indicated above, the $\Delta^{\beta,\gamma}$-butenolides may be isomerized to $\Delta^{\alpha,\beta}$ compounds.

A convenient synthesis which was developed independently and simultaneously in two different laboratories [205,206] proceeds from α-methoxy- or acetoxy-ketones by application of the Reformatsky reaction, followed by hydrolysis and dehydration of the intermediate products (VIII–X).



VIII IX X

A second synthesis proceeds from a simple methyl ketone [207] and makes use of the Darzens condensation (XI–XIII). A variation of this synthesis is shown in XIV–XV.

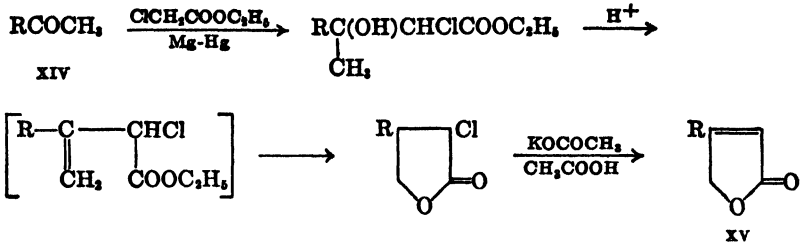


XI XII XIII

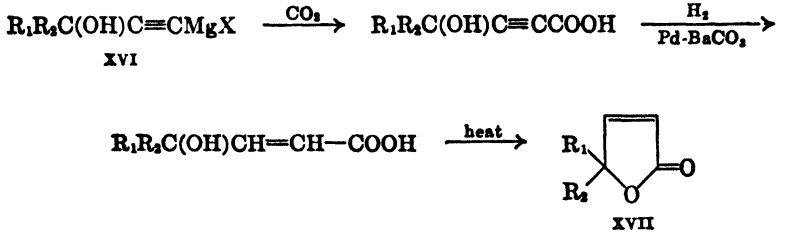
205 Elderfield et al., *J. Org. Chem.*, **6**, 260, 270, 273, 289 (1941); **7**, 362, 374, 383, 444 (1942).

206 Ruzicka et al., *Helv. Chim. Acta*, **24**, 76, 716 (1941), and later papers.

207 Blout and Elderfield, *J. Org. Chem.*, **8**, 29 (1943).

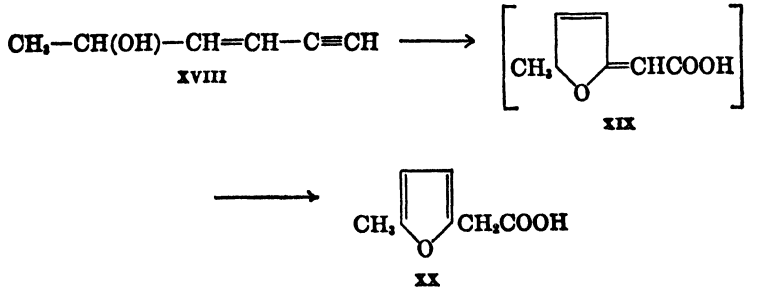


A third synthesis of $\Delta^{\alpha,\beta}$-butenolides, which can also be applied to the preparation of the analogous hexeno lactones, has been developed by Haynes and Jones [208] and is shown in XVI–XVII. The requisite



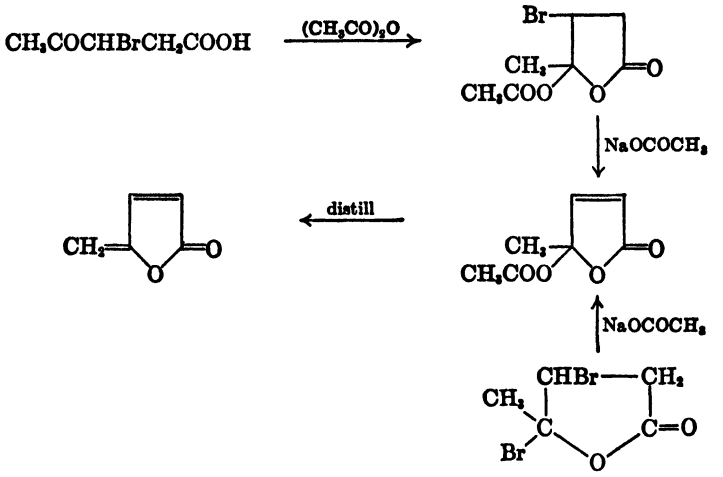
acetylenic carbinols are readily obtained by condensation of a ketone with acetylene. In the carboxylation reaction, the vital factor of solvent was apparently overlooked by previous investigators; if the solvent is benzene in which the Grignard complex is moderately soluble, yields of 80–90% are reported. Selective reduction of the acetylenic bond to the ethylene is carried out by stopping the reaction when about 90% of 1 mole of hydrogen has been absorbed, and lactonization is accomplished usually by distillation.

In the carboxylation of XVIII, an appreciable amount of XX is formed, presumably by way of the intermediate (XIX), by intramolecular hydration analogous to that described by Heilbron et al.[209]

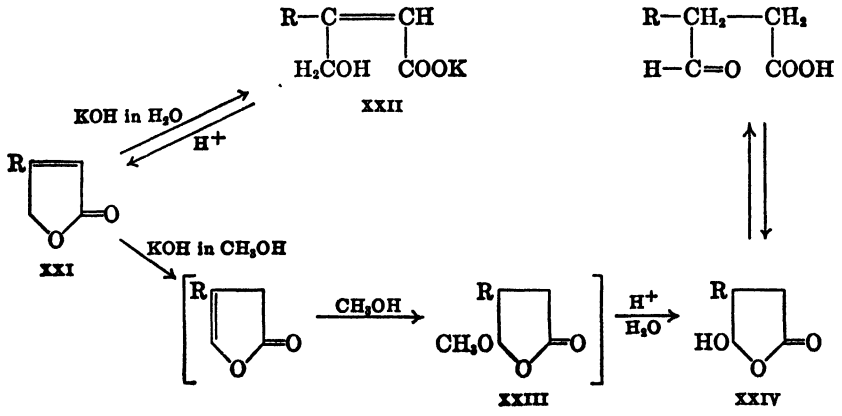


[208] Haynes and Jones, *J. Chem. Soc.*, 503, 954 (1946).
[209] Heilbron et al., *J. Chem. Soc.*, 54 (1946).

Still a fourth method of obtaining $\Delta^{\alpha,\beta}$-butenolides of the type of protoanemonine, the structure of which has been demonstrated by Asahina and Fujita (p. 191), is represented by the following sequence, as worked out by these authors.



Reactions of $\Delta^{\alpha,\beta}$-Butenolides. In contrast to the $\Delta^{\beta,\gamma}$-butenolides, the $\Delta^{\alpha,\beta}$ compounds (XXI) do not undergo cleavage on catalytic reduction but are converted to the saturated lactones. The action of alkali on these compounds is very characteristic.[201] Two distinct reactions have been noted, depending on whether water is present or absent in the reaction medium. In aqueous solutions, the lactone



undergoes hydrolysis to the salt of the acid (XXII) from which the parent lactone may be re-formed on acidification. In alcoholic solu-

tion, however, the double bond is apparently shifted to the β,γ position irreversibly, and the resulting intermediate vinyl ether adds the elements of alcohol to yield the acetal (XXIII). On acidification, the acetal is hydrolyzed, yielding the hydroxylactone (XXIV) as the product isolated from the reaction. XXIV exists in equilibrium with the open-chain aldehydo acid, and derivatives of both forms may be prepared. Whether a similar reaction takes place with such butenolides carrying the substituent in the γ position, e.g., α-angelica lactone, has not been determined.

The addition of SH groups to the double bond in the $\Delta^{\alpha,\beta}$-butenolides is considered on p. 195.

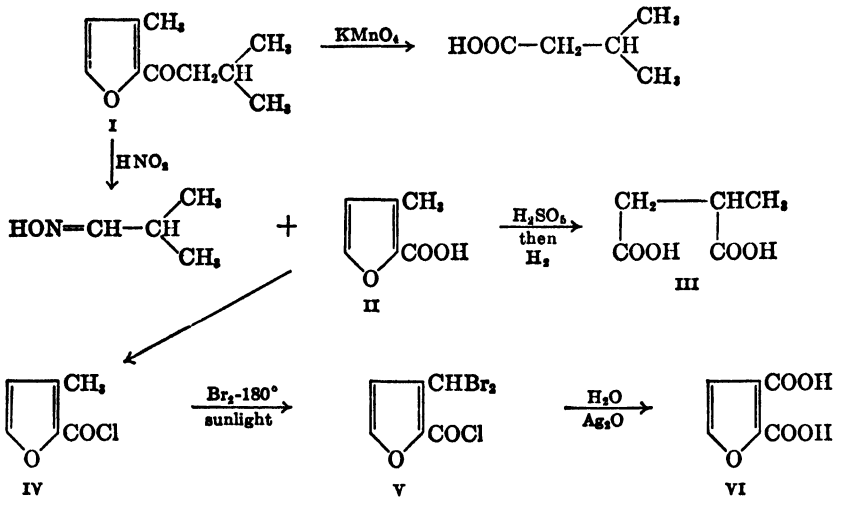
NATURALLY OCCURRING FURAN DERIVATIVES

Simple monocyclic furan derivatives are found occasionally in natural products, although as a group such substances are not of widespread occurrence.

Of these the simplest is furan-3-carboxylic acid, which occurs in the root bark of *Evonymus atropurpureus* [210] and in the root of *Phaseolus multiflorus* Link.[211] Its structure was settled unequivocably by synthesis by Reichstein and Zschokke (p. 199).

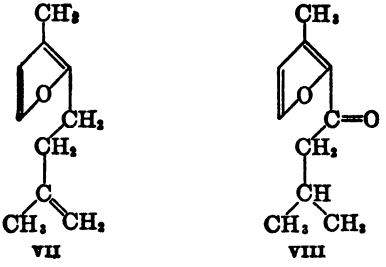
Asahina and Murayama [212] isolated a ketone, Elsholtzia ketone, from the ethereal oil of *Elsholtzia cristata* Willd., the structure of which was demonstrated by Asahina.[213] The ketone, 2-isovaleryl-3-methylfuran (I), on oxidation with permanganate gives isovaleric acid and on reaction with nitrous acid undergoes a remarkable cleavage, yielding Elsholtzia acid (II) and the oxime of isobutyric aldehyde. This cleavage is discussed in detail on p. 206. These observations serve to characterize the isovaleryl and methyl groups in I but still leave their positions undetermined. The possibilities were narrowed to three, 3-methylfuran-2-carboxylic acid, 4-methylfuran-2-carboxylic acid, and 3-methylfuran-4-carboxylic acid by oxidation of II with Caro's acid,[160] yielding an unsaturated acid which on reduction gave methyl succinic acid (III). A choice among the three was made by conversion of II to furan-2,3-dicarboxylic acid, as shown by II–VI. The structures assigned to both Elsholtzia ketone and acid by Asahina have

210 Rogerson, *J. Chem. Soc.*, **101**, 1044 (1912).
211 Power and Salway, *Chem. Zentr.*, **84**, I, 1931 (1913).
212 Asahina and Murayama, *Arch. Pharm.*, **252**, 435 (1914).
213 Asahina, *Acta Phytochim. Japan*, **2**, 1 (1924–1926).



been confirmed by synthesis of both compounds by Reichstein, Zschokke, and Georg.[108]

Apparently closely related to Elsholtzia ketone (VIII) is perillon, for which the structure of a 2-isopentenyl-3-methylfuran (VII) has

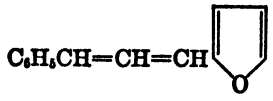


been suggested. It should be pointed out that the misnomer perillon was deliberately adopted to avoid confusion with the hydrocarbon perylen. The relationship of both substances to the terpenes and the role of the isoprene rule is apparent from the formulas.

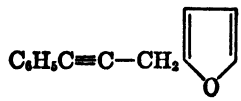
A curious furan derivative, carlina oxide, has been found by Semmler [214] in the steam volatile products from the root of *Carlina acaulis*. It has been assigned one of the three structures, IX, X, or XI, largely on the basis of the formation of 1-phenyl-3-(α-furyl)propane on reduction.[215]

[214] Semmler, *Ber.*, **39**, 726 (1906).

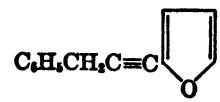
[215] Semmler and Ascher, *Ber.*, **42**, 2355 (1909).



IX



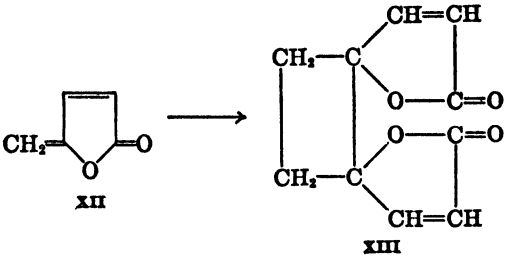
X



XI

Of more importance are unsaturated γ-lactones which can be regarded as derivatives of furan, often as the keto tautomers of hydroxyfurans. The important members of the digitalis-strophanthus group of cardiac aglycones are derived from $\Delta^{\alpha,\beta}$-butenolide or 2-keto-$\Delta^{3,4}$-dihydrofuran carrying a reduced cyclopentanophenanthrene ring system as a substituent in the 4 position. The structural chemistry of these substances has been dealt with adequately elsewhere,[216] and the chemistry of the butenolides is considered on p. 186.

Interest has been stimulated in the simple unsaturated lactones by the discovery of pronounced antibiotic properties manifested by many of them.[217] Many naturally occurring substances containing an unsaturated lactone, among which may be mentioned protoanemonine, penicillic acid, clavacin, and crepin, manifest such antibiotic action by the possession of strong antibacterial properties against both Gram-positive and Gram-negative bacteria. One of the simplest of such substances is protoanemonine, first isolated from buttercups by Asahina and Fujita [218] and later from *Anemone pulsatilla* by Baer, Holden, and Seegal.[219] The structure of protoanemonine (XII) which rapidly dimerizes to anemonine (XIII) has been demonstrated by Asahina



XII XIII

and Fujita,[218] who also synthesized the substance (p. 188). Baer, Holden, and Seegal [219] have investigated the relationship of the structure of simple unsaturated γ-lactones to antibacterial action. Both

216 Gilman, *Organic Chemistry*, John Wiley & Sons, New York, 1943, Vol. II, p. 1427, among others.

217 For a review of the development of this field see Haynes and Jones, *J. Chem. Soc.*, 954 (1946).

218 Asahina and Fujita, *Acta Phytochim. Japan*, 1, 1 (1922).

219 Baer, Holden, and Seegal, *J. Biol. Chem.*, 162, 65 (1946).

α- and β-angelica lactone as well as anemonine showed antibacterial properties, although all three were weaker than protoanemonine. Hydrolysis of the lactone as well as saturation of the double bond destroys activity. However, unsaturation per se is unable to account for such activity, since both acetylacrylic acid, the hydrolysis product of XII, or vinylacrylic acid or ester were likewise inactive. Furthermore, the antibiotic properties of such lactones are not confined to the furanoid γ-lactones but are also shown by pyranoid δ-lactones.[217]

Another antibiotic of the same general chemical class as protoanemonine is penicillic acid, first isolated by Black and Alsberg [220] from the metabolic products of cultures of *Penicillium puberulum* Bainier and subsequently from similar products of *P. cyclopium* Westling by Oxford and Raistrick.[221] The structure of the substance in its essential features has been demonstrated by Birkinshaw, Oxford, and Raistrick.[222] Penicillic acid (XIV) yields 1 mole of methane with the Zerewitinoff reagent, contains one acylatable hydroxyl group, forms a dibromide by addition of bromine, and readily absorbs 1 mole of hydrogen on catalytic reduction over palladium on charcoal to yield dihydropenicillic acid (XV). A second mole of hydrogen is absorbed more slowly, but no crystalline tetrahydro derivative has been isolated. Largely on the basis of its behavior towards alkali, the substance was originally considered to exist as an equilibrium mixture of the hydroxylactone (XIV) and the open-chain keto acid (XVI), by analogy with the behavior of other γ-carbonyl acids which frequently show similar tautomerism. However, Raphael [223] has shown on the basis of spectroscopic evidence that penicillic acid in all probability exists almost exclusively in the cyclic form (XIV). The ready consumption of one equivalent of alkali and the delayed reaction with hydroxylamine are therefore due to the great lability of the ring in XIV. Penicillic acid is also characterized by the ease with which carbon dioxide is lost and the easy cleavage of the enolic methyl ether. Thus, in reaction with phenylhydrazine the pyrazole derivative (XVIII) results, which is further broken down to the pyrazole (XIX) on oxidation with lead dioxide and subsequent treatment with cold sulfuric acid. This establishes the decomposition product from which the pyrazole (XVIII) arises as 2-methylpentene-1-dione-3,4 (XVII). The position of the carboxyl group involved in the lactone in penicillic acid was indicated by the isolation of γ-hydroxy-δ-methylhexanoic acid (XX) from the

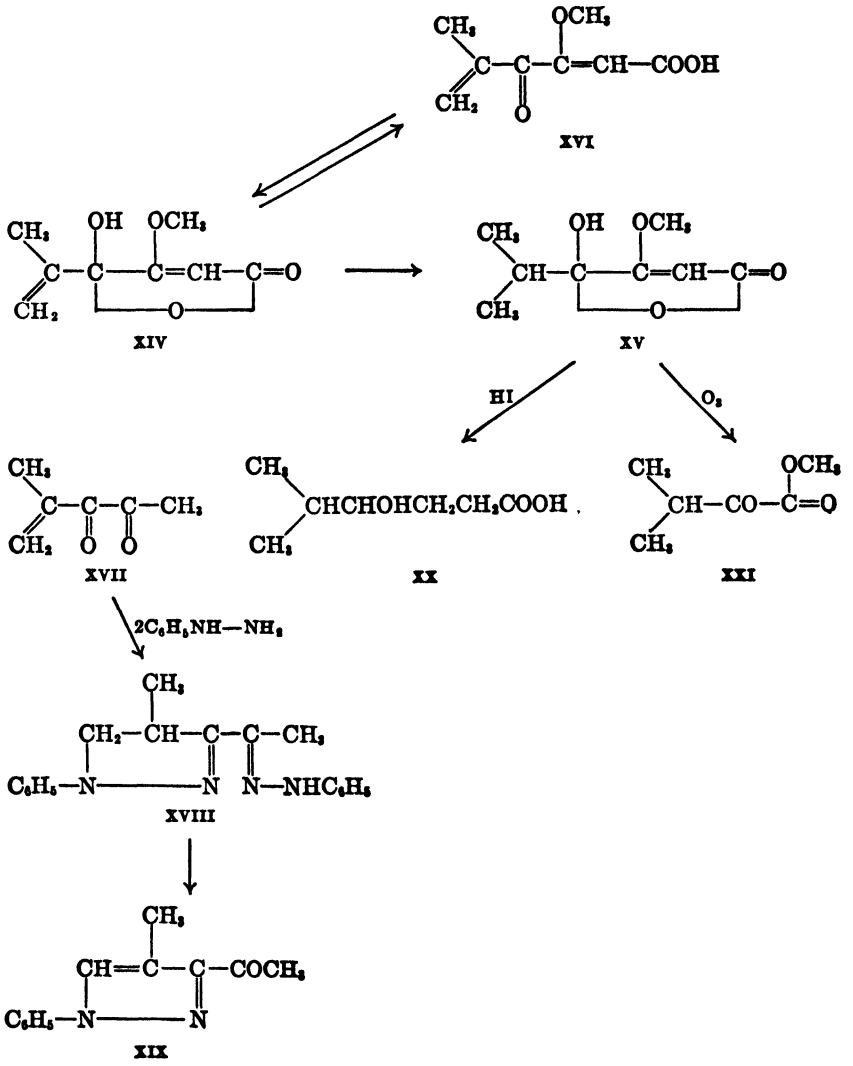
220 Black and Alsberg, *U. S. Dept. Agr. Bur. Plant Industry Bull.* 199 (1910); Alsberg and Black, *U. S. Dept. Agr. Bur. Plant Industry Bull.* 270 (1913).

221 Oxford and Raistrick, *Biochem. J.*, 29, 1599 (1935).

222 Birkinshaw, Oxford, and Raistrick, *Biochem. J.*, 30, 394 (1936).

223 Raphael, *J. Chem. Soc.*, 805 (1947).

products of the reduction of dihydropenicillic acid with hydriodic acid. Such an arrangement is consistent with the easy loss of carbon dioxide from XIV or XV. Finally, the enolic methoxyl group is placed by the

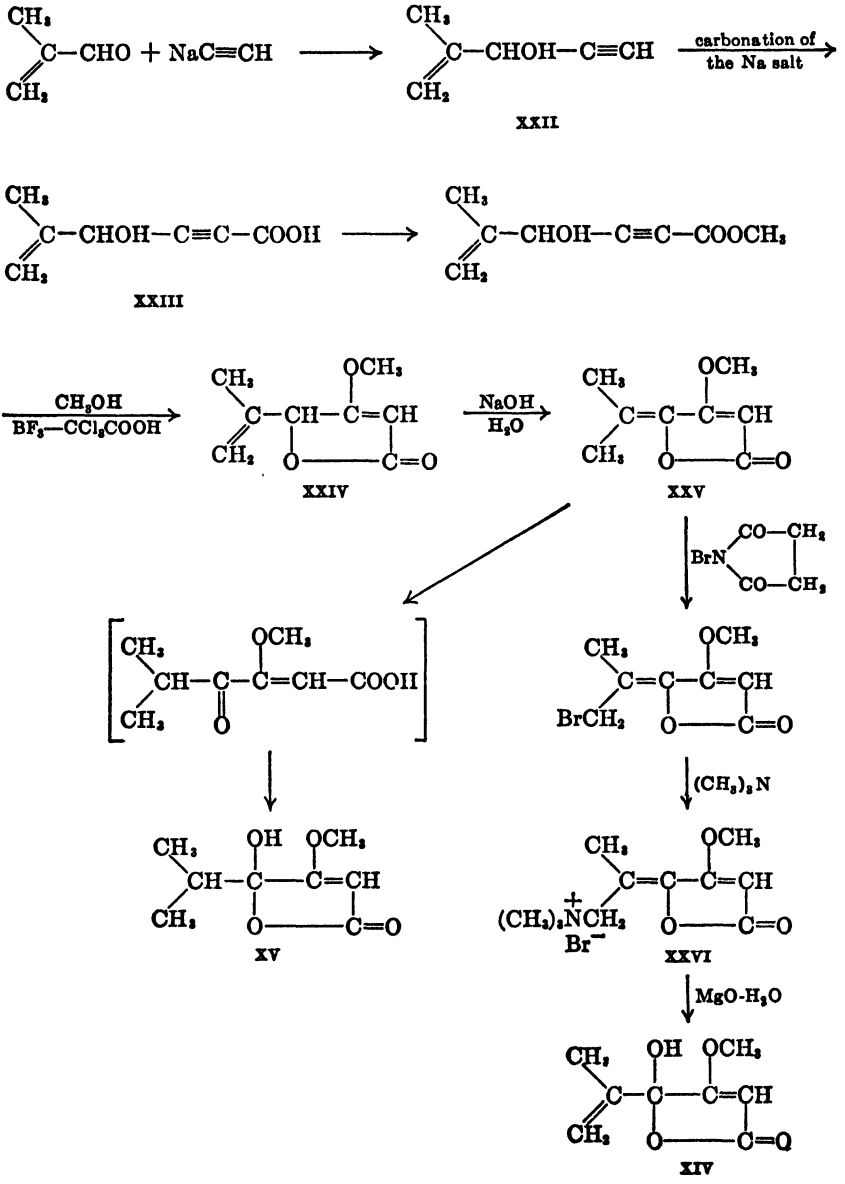


formation of methyl dimethylpyruvate (XXI) by the action of ozone on XV.

The structures assigned to penicillic acid and its dihydro derivative have received ample confirmation by synthesis of both substances.[224]

224 (*a*) Raphael, *J. Chem. Soc.*, 805 (1947); (*b*) *Nature*, **160**, 261 (1947); (*c*) *J. Chem. Soc.*, 1508 (1948).

For the synthesis of dihydropenicillic acid, advantage was taken of the condensation of sodium acetylide with α-methacrolein [225] to yield XXII, which was then carbonated as the sodium salt to yield the acid (XXIII).[226] The methyl ester of the acid (XXIII) on treatment with



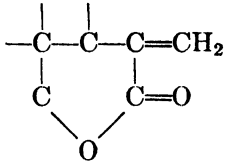
225 Heilbron et al., *J. Chem. Soc.*, 87 (1945).

226 Zoss and Hennion, *J. Am. Chem. Soc.*, 63, 1151 (1941).

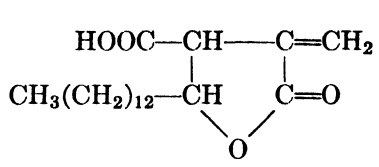
methanol in the presence of a catalyst of boron trifluoride-trichloroacetic acid [227] undergoes addition of methanol, accompanied by loss of methanol to establish the lactone (XXIV). On subjecting the lactone, XXIV, to the action of cold dilute sodium hydroxide solution, dihydropenicillic acid (XV) results. The formation of the latter is postulated to involve a prototropic change, followed by cleavage and reclosure of the lactone ring. The intermediate (XXV) can be isolated if ammonia replaces sodium hydroxide in the above reaction.

Raphael [224b] has also achieved the synthesis of penicillic acid itself (XXV–XIV). The passage from XXVI to XIV under the influence of magnesium oxide and water can be visualized as involving replacement of the trimethylamino group by hydroxyl, the replacement being accompanied by an allylic shift involving the double bond and hydroxyl group.

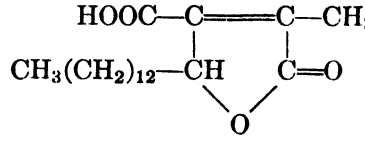
Another type of structure displaying antibacterial action is represented by the principle isolated from *Arctium minus* to which the partial structure XXVII has been assigned.[228] This is closely related, as far as the lactone is concerned, to protolichesterinic acid (XXVIII) and lichesterinic acid (XXIX).[229]



XXVII



XXVIII



XXIX

Among the theories which have been proposed to account for the antibiotic action of these unsaturated lactones is that offered by Cavallito and Haskell.[230] In this hypothesis, it is suggested that the double bond of the lactone undergoes addition of SH groups such as may be present in the protein constituents of bacteria, thus interfering with some essential process connected with growth of the bacteria. Although

227 Killian, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, **58**, 80 (1936).

228 Cavallito and Kirchner, *J. Am. Chem. Soc.*, **69**, 3030 (1947); Cavallito, Bailey, and Kirchner, *ibid.*, **67**, 948 (1945); Abraham et al., *Nature*, **158**, 744 (1946).

229 Asano and Kanematsu, *Ber.*, **65**, 1175 (1932).

230 Cavallito and Haskell, *J. Am. Chem. Soc.*, **67**, 1991 (1945).

this represents an attractive idea, there appears to be no evidence that it is exclusively the mechanism of antibiotic action.

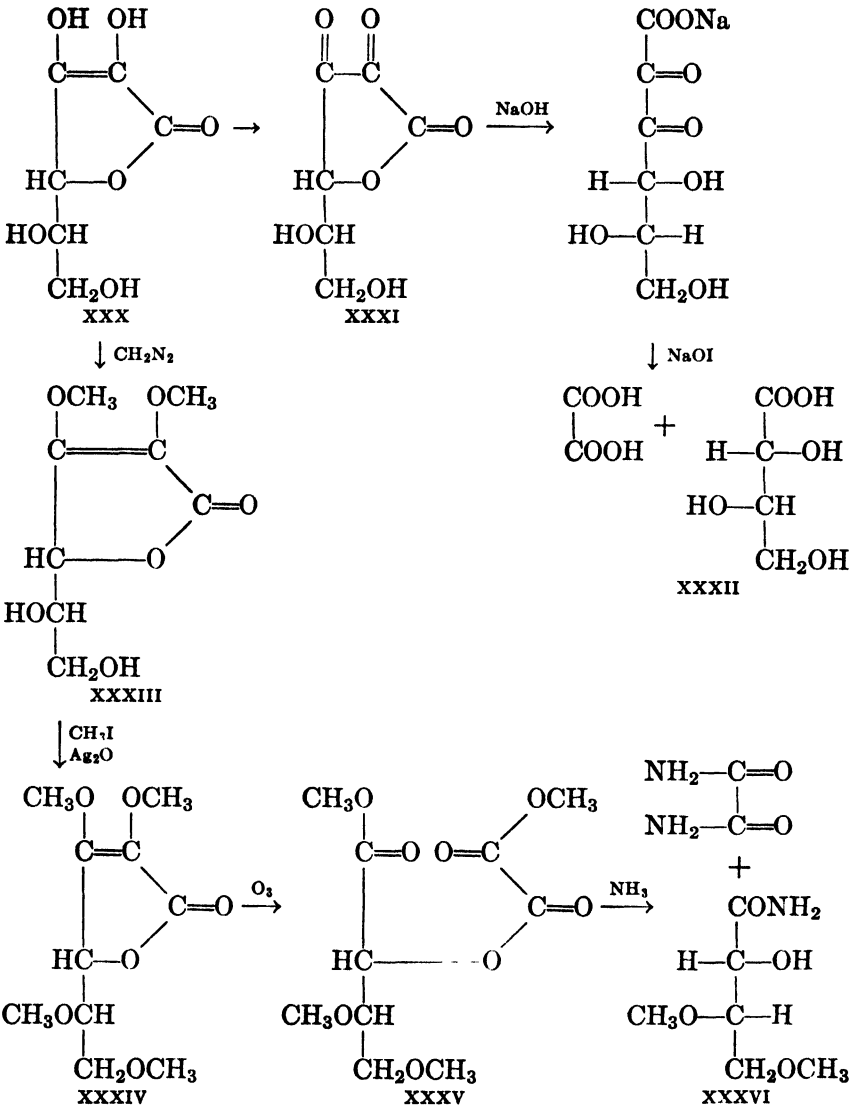
No discussion of naturally occurring furan derivatives would be complete without mention of ascorbic acid, or vitamin C, the anti-scorbutic vitamin. Although this substance is frequently considered under general carbohydrate chemistry, nevertheless the frequently found $\Delta^{\alpha,\beta}$-butenolide structure is perhaps the most characteristic feature of the molecule. In the present discussion, only the barest essentials of the chemistry of the vitamin will be presented. The reader is referred to the excellent review of Haworth and Hirst [231] for a rigorous treatment of this subject.

Just as penicillic acid is marked by the presence of an easily opened lactone, so ascorbic acid does not contain a free carboxyl group as such. However, the presence of two enolic hydroxyl groups does contribute to the acid properties of ascorbic acid. Ascorbic acid is characterized by its ability to undergo reversible oxidation to dehydroascorbic acid, either by titration in acid solution with such reagents as phenolindophenol, or in acid or neutral solution with iodine. The oxidation may also be accomplished by oxygen in the presence of traces of copper in aqueous solution under physiological *p*H conditions. However, the oxidation under these conditions proceeds further and ultimately involves disintegration of the molecule. Dehydroascorbic acid may be reduced to ascorbic acid with hydrogen sulfide or hydriodic acid.

The essentials of both the structural and stereochemical arrangements of ascorbic acid are apparent from the major degradations of ascorbic acid (XXX) and dehydroascorbic acid (XXXI). Oxidation of dehydroascorbic acid in alkaline solution with hypoiodite yields oxalic acid and *l*-threonic acid (XXXII). Methylation of ascorbic acid with diazomethane shows the presence of the two enolic hydroxyl groups and yields the dimethyl ether (XXXIII) which on further methylation with methyl iodide and silver oxide leads to the fully methylated lactone (XXXIX). Cleavage of XXXIV with ozone leads to the neutral ester XXXV which with ammonia yields oxamide and the amide of 3,4-dimethyl-*l*-threonic acid (XXXVI). By this series of reactions, the positions linked by the lactone ring are established. The vitamin may therefore be formulated, as first suggested by Hirst,[232] as the lactone of 2-keto-*l*-gulonic acid (XXX).

[231] Haworth and Hirst, *Ergeb. Vitamin- u. Hormonforsch.*, **2**, 160 (1938). Reprinted by Edwards Bros., Ann Arbor, Michigan.

[232] Hirst, *Chemistry & Industry*, **52**, 221 (1933).

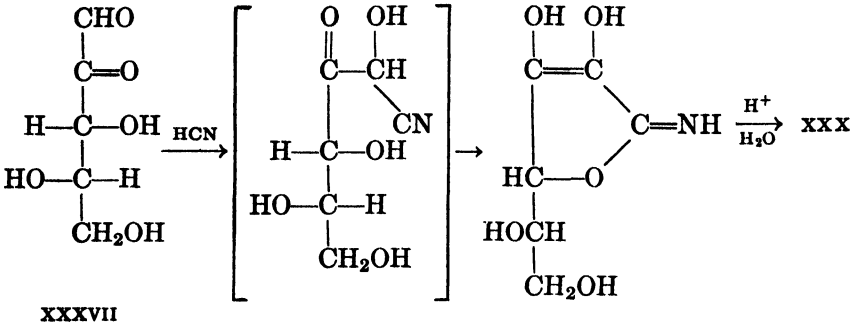


Various syntheses of ascorbic acid have furnished ample confirmation for the structure assigned to it. Of these, the first, described simultaneously by Haworth and Hirst [233] and by Reichstein and coworkers,[234] proceeds from *l*-xylosone, obtained with difficulty by a

[233] Haworth, Hirst, et al., *J. Chem. Soc.*, 1419 (1933); 62, 1192 (1934).

[234] Reichstein, Grüssner, and Oppenauer, *Helv. Chim. Acta*, 16, 561, 1019 (1933); 17, 510 (1934).

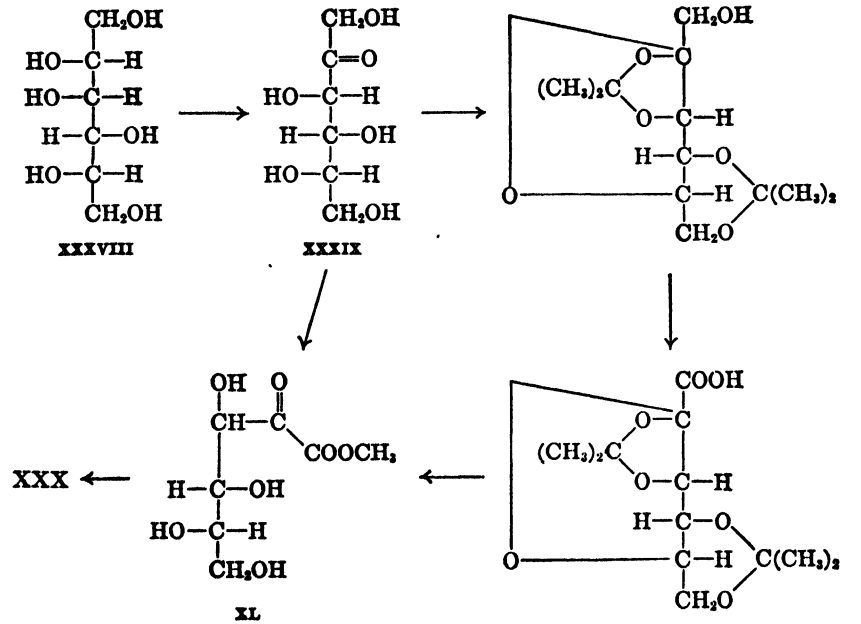
lengthy series of reactions from *d*-galactose. The essential steps in the synthesis are shown in XXXVII–XXX. Although interesting as pro-



XXXVII

viding the first confirmation by synthesis of the structure assigned to ascorbic acid, this synthesis is hardly practical because of the great difficulty involved in obtaining the requisite osone.

More convenient is a synthesis originally developed by Ohle et al.[235] and by Maurer and Schiedt[236] and applied by Reichstein and his collaborators to ascorbic acid.[237] This proceeds from *l*-sorbose (XXXIX), now available from *d*-sorbitol (XXXVIII) by bacterial oxidation, ac-



XXXVIII XXXIX XL

235 Ohle, Erlbach, and Carls, *Ber.*, **67**, 324, 555 (1934).
236 Maurer and Schiedt, *Ber.*, **66**, 1054 (1933); **67**, 1239 (1934).
237 Reichstein and Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).

cording to Bertrand.[238] The requisite *d*-sorbitol is commercially available by catalytic reduction of glucose. The steps involved are shown in XXXVIII–XXX. Another method involves the direct oxidation of *d*-sorbose (XXXIX) to 2-keto-*l*-gulonic acid (XL) by the action of nitric acid under carefully controlled conditions.[239] A wide variety of analogs of ascorbic acid have been made and are listed by Haworth and Hirst.[231]

FURAN CARBOXYLIC ACIDS

All the possible furan carboxylic acids in which the carboxyl group (or groups) are attached directly to the nucleus are known. These comprise two monocarboxylic acids, four dicarboxylic acids, two tricarboxylic acids, and one tetracarboxylic acid.

Furan Monocarboxylic Acids. Furan-2-carboxylic acid, 2- or α-furoic acid or pyromucic acid, is the commonest of the furan acids. It can be prepared by decarboxylation of the 2,5 acid, dehydromucic acid, or, more conveniently, from furfural. Oxidation of furfural by potassium dichromate and dilute sulfuric acid results in a 75% yield of the acid.[240] Application of the Cannizzaro reaction to furfural also results in a good yield of the acid.[240,241] The acid is purified with difficulty, best by vacuum sublimation, and can be kept without deterioration if stabilized by the addition of 1% of urea.

Furan-3- (or β-) carboxylic acid occurs naturally (p. 189). Its synthesis has been accomplished[242] by selective decarboxylation of either furan-2,4-dicarboxylic acid[59] or furan-2,3-dicarboxylic acid (p. 201).

Furan Dicarboxylic Acids. Furan-2,3-dicarboxylic acid can be prepared, although in poor yield, by application of the Feist-Benary synthesis from chloroacetaldehyde and acetonedicarboxylic ester (p. 132) or by an indirect method by oxidation of 2-methylfuran-3-carboxylic acid.

Furan-2,4-dicarboxylic acid is most conveniently prepared from methylcoumalate (p. 136). It may also be prepared by heating the 2,3,5-tricarboxylic acid (p. 136) at 250° until one molecule of carbon dioxide is given off.[60]

Furan-2,5-dicarboxylic acid, or dehydromucic acid, is easily derived from ring closure of hexose dicarboxylic acids (p. 127).

238 Schlubach and Vorwerk, *Ber.*, **66**, 1251 (1933).
239 Haworth, *Nature*, **134**, 724 (1934).
240 Hurd, Garrett, and Osborne, *J. Am. Chem. Soc.*, **55**, 1082 (1933).
241 Wilson, *Org. Syntheses Coll. Vol.* **1**, 276 (1941).
242 Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 268 (1932).

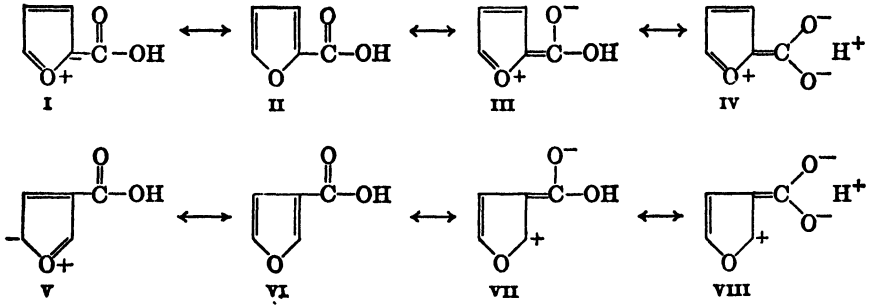
The most convenient synthesis for furan-3,4-dicarboxylic acid is by application of the Diels-Alder reaction to furan, using acetylenedicarboxylic ester, followed by subsequent partial reduction and cleavage of the initial product of the reaction (p. 140). Selective decarboxylation of furan-2,3,4-tricarboxylic acid also leads to the 3,4 acid.[243]

Furan Tricarboxylic Acids. The preparation of furan-2,3,4-tricarboxylic acid has already been described (p. 128).

Furan-2,3,5-tricarboxylic acid can be prepared as described on p. 136.

Furan Tetracarboxylic Acid. The preparation of this acid is given on p. 129.

Reactions of the Furan Carboxylic Acids. In view of the differences between the various positions in the furan nucleus, it is only reasonable that differences should manifest themselves in the behavior of the furan acids. In general, a β-carboxyfuran is a weaker acid than an α acid.[242,244] Examination of the resonance forms for the two furoic acids (I–IV and V–VIII) indicates why this should be so and also shows why



the α acids are more stable than are the β acids. In the α acid, the nuclear resonance enhances that of the carboxyl group with resultant increase in stability and acid strength. Such a situation does not occur with the β acid. A similar argument can be made in favor of increased stability of other negatively α-substituted furans as compared to the corresponding β derivatives. The general conclusion is borne out by the fact that, in practically all cases, the melting points of such β-substituted furans are lower than the α derivatives, indicating greater stability for the α series. On the other hand, this relationship appears to reverse itself when the substituents are positive.

[243] Reichstein et al., *Helv. Chim. Acta*, **16**, 276 (1933).

[244] Catlin, *Iowa State Coll. J. Sci.*, **10**, 65 (1935) [*C. A.*, **30**, 935 (1936)].

In the furan series, no detailed data on the relationship of the effect of substituents on reactivity of the acids, such as ionization constants and hydrolysis constants of the esters, are available. In the benzene series, studies of this nature have provided useful data in the form of the substituent constants (σ) and reaction constants (ρ) for the *m* and *p* series.[245] Only for the ionization of the 5-substituted 2-furoic acids can such values be derived from the data of Catlin from which a value for ρ of +1.394 can be assigned. The α acids may be distinguished from the β acids by their behavior when ferric chloride is added to their saturated aqueous solutions. The α acids furnish a precipitate, whereas the β acids do not.[246]

Perhaps the sharpest contrast between the α and β acids is found in their behavior on decarboxylation. Without exception, an α-carboxyl group will undergo loss of carbon dioxide in preference to a β-carboxyl group in the same molecule. However, the ease with which such decarboxylation takes place varies with the relative positions of the carboxyl groups concerned. Thus, furan-2,3-dicarboxylic acid readily loses its α-carboxyl group merely when heated, but the 2-carboxyl group in the 2,4 acid is removed only when heated with copper and quinoline. With the 2,4 acid the reaction can be controlled to yield the 4 acid provided it is stopped after evolution of 1 mole of carbon dioxide.[242] The sodium salts of α-furoic acids undergo replacement of the carboxyl group by the chloromercuri group, whereas the β-furoic acids do not.[66,91]

Both α- and β-furoic acids readily undergo the Arndt-Eistert reaction.[86,247] This method is recommended as more suitable for the preparation of chloromethylfuryl ketones than the direct chloroacetylation of furan by the Friedel-Crafts type of reaction.

The furan-2,3- and furan-2,4-dicarboxylic acids show interesting differences in their behavior when heated. The 2,3 acid fails to yield a cyclic acid anhydride,[176] whereas 2,5-diphenylfuran-3,4-dicarboxylic acid readily gives a cyclic anhydride on heating.[248] The 2,3 acid and its derivatives also show differences from the analogous phthalic acid. Whereas the oxime of phthaldehydic acid readily gives an internal anhydride when heated and *o*-cyanobenzoic acid passes to phthalimide under similar circumstances, furan-2,3-dicarboxylic acid does not. The

245 Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, 1940, pp. 184 ff.

246 Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 1107 (1932).

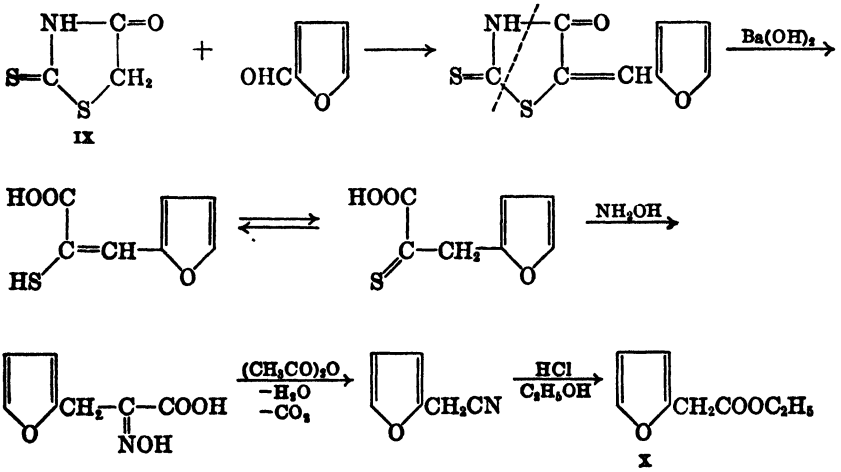
247 (*a*) Reichstein and Morsman, *Helv. Chim. Acta*, **17**, 1119 (1934); (*b*) Burger and Harnest, *J. Am. Chem. Soc.*, **65**, 2382 (1943).

248 Perkin, *J. Chem. Soc.*, **47**, 269 (1885).

oxime of furan-2-carboxylic acid-3-aldehyde is unchanged when heated at 190° or at 225° in vacuum. On treatment with acetic anhydride, the oxime dehydrates normally to yield 3-cyano-2-furoic acid, but the latter does not yield a substance analogous to phthalimide.[176]

Homologous Furan Carboxylic Acids. The various methylfuroic acids can for the most part be prepared by methods already discussed, among which the Feist-Benary synthesis is probably the most useful. Therefore, no protracted discussion of these will be given. Of the other homologous furan acids, those in which the carboxyl group, or groups, are removed by one or more carbon atoms from the nucleus merit discussion.

2-Furylacetic acid is one of the more difficultly accessible of such acids. Owing to the failure of 2-furfuryl chloride to yield 2-furylacetonitrile on reaction with potassium cyanide (p. 141), this apparently simple method of preparation fails. Of the alternative methods for the synthesis of 2-furylacetic acid, that of Gränacher [249] appears to be the most convenient. It proceeds from rhodanine (IX), easily prepared from ammonium dithiocarbamate and sodium chloroacetate, by the reactions IX–X. As will be seen, it is preferable to proceed to the ester since the free acid is very easily decarboxylated.

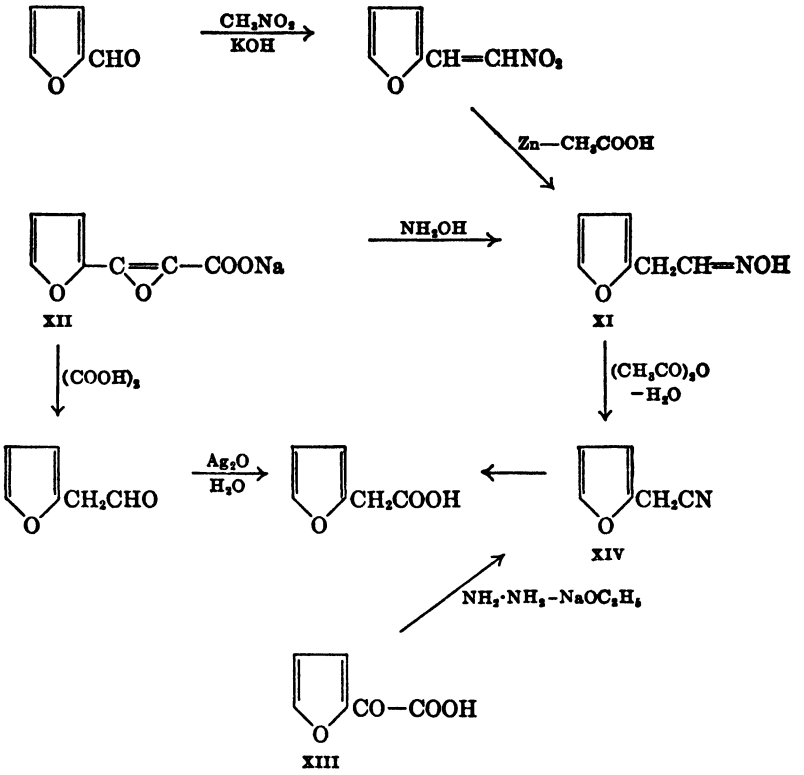


Two other syntheses for 2-furylacetic acid proceed through the intermediate 2-furylacetaldehyde oxime (XI) [76] and XII,[250] respec-

[249] Gränacher, *Helv. Chim. Acta*, **5**, 610 (1922). The preparation of rhodanine is described in *Org. Syntheses*, **27**, 73 (1947).

[250] Reichstein, *Ber.*, **63**, 749 (1930); Asahina and Fujita, *Chem. Zentr.*, **94**, I, 757 (1933).

tively. To these should be added the modification of Fischer,[251] developed by Reichstein [250] (XIII–XIV).



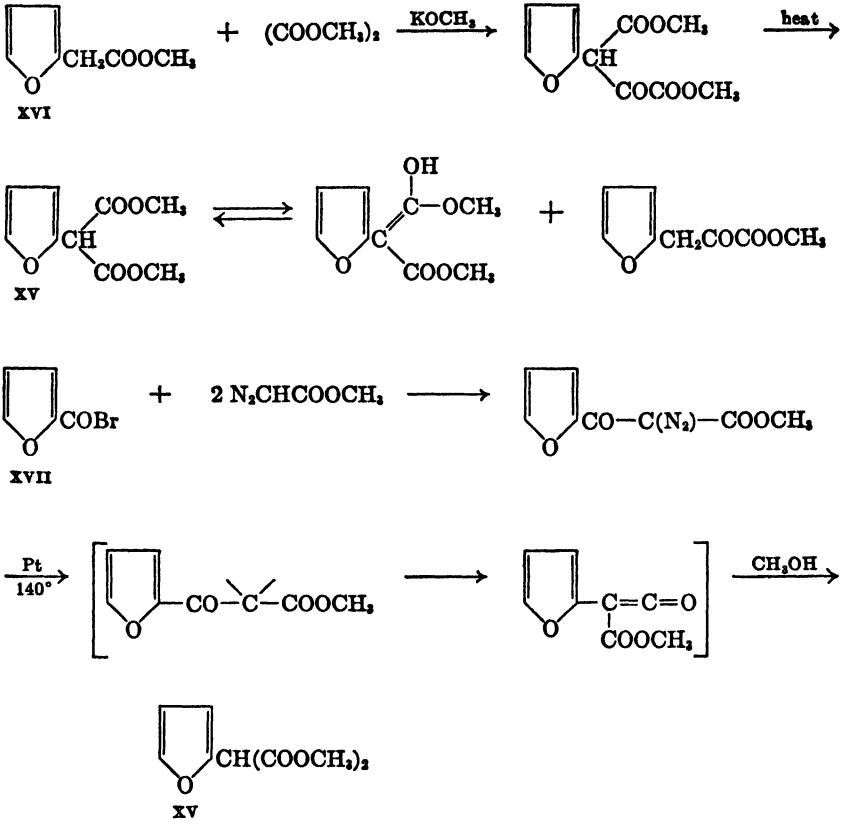
2-Furylacrylic acid is of academic interest only, since its important ester cannot conveniently be prepared from the acid (p. 173). The ethyl ester of 2-furylacrylic acid, however, serves as an intermediate for the synthesis of a number of furan derivatives. It is easily made by condensation of furfural with ethyl acetate in the presence of sodium.[252]

2-Furylmalonic ester (XV) has been prepared by two methods,[247a] the first of which (XVI–XV) is analogous to a preparation of phenylmalonic ester.[253] The second synthesis (XVII–XV) is a strict analog of the familiar Arndt-Eistert synthesis. 2-Furylmalonic ester undergoes all the reactions of phenylmalonic ester except that the furyl radi-

251 Fischer, *Ber.*, **46**, 891 (1913).

252 Claisen, *Ber.*, **24**, 144 (1891).

253 Wislicenus, *Ber.*, **27**, 792, 1091 (1894); Rising and Stieglitz, *J. Am. Chem. Soc.*, **40**, 723 (1918).



cal is about equal to two phenyl groups as far as negativity is concerned. The easy decarboxylation of the acid, as well as the difficulty connected with the direct esterification of such acids as furylacetic and furylacrylic acids without attendant decomposition, thus becomes apparent.

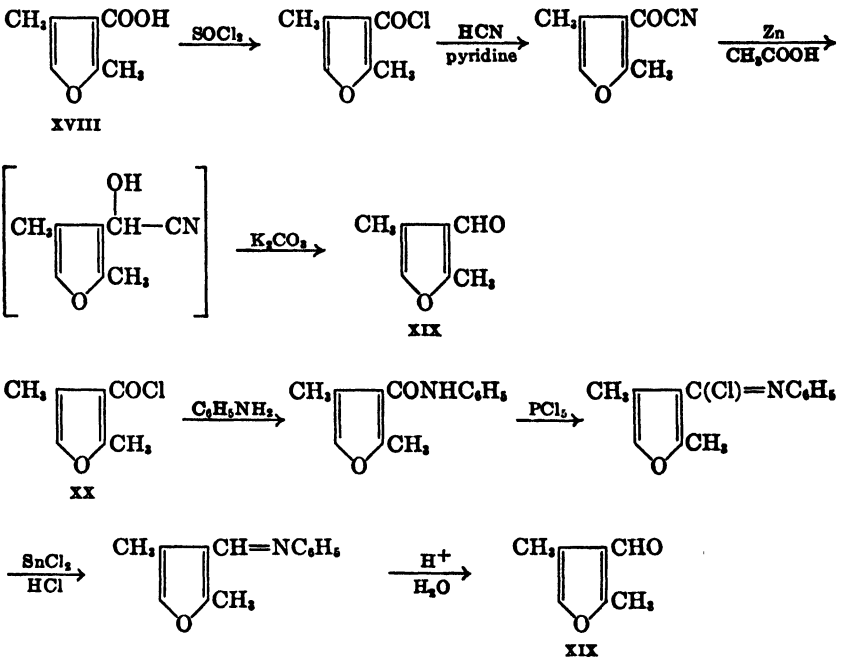
A number of esters of 2-furoylacetic acid have been prepared by condensation of ethyl 2-furoate with the appropriate acetic acid esters.[254]

CARBONYL DERIVATIVES OF FURAN

Aldehydes. Only the β-aldehydo derivatives of furan will be treated, since the α-aldehydo compounds, by and large, can be obtained by reactions which lead to furfural or its derivatives or by application of the

254 Bouveault, *Bull. soc. chim. France*, [3] **25**, 440 (1901); Torrey and Zanetti, *Am. Chem. J.*, **44**, 391 (1910); Zanetti and Beckmann, *J. Am. Chem. Soc.*, **50**, 1438 (1928).

Gattermann aldehyde synthesis. 3-Furanaldehyde has been prepared by Gilman and Burtner [59b] by reduction of 3-furoyl chloride by the Rosenmund procedure. Reichstein and Zschokke [255] have prepared 2,4-dimethyl-3-furanaldehyde by application of general methods originally proposed by Claisen and Kolbe (XVIII–XIX). The second



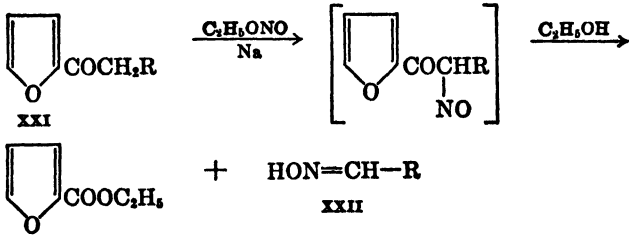
synthesis (XX–XIX) represents an adaptation of the conventional Sönn and Mueller method and proceeds in better yield than does the first. 2,4-Dimethyl-3-furanaldehyde is described as a colorless liquid, unstable in the air and very susceptible to alkali. Attempted oxidation with silver oxide to the acid, a reagent with which Reichstein has had great success in the α series, resulted in resinification. The structure of the aldehyde was shown by conversion to the original acid by dehydration of the oxime to the nitrile followed by saponification. The β-aldehyde differs from the α-aldehyde in its reaction with aromatic amines. With aniline acetate, it yields the normal anil, whereas the α-aldehydes undergo ring splitting with formation of deep blue derivatives of hydroxyglutaconic aldehyde.

Furfural parallels benzaldehyde very closely in its chemistry. Such deviations as may be noted, particularly as far as orientation is con-

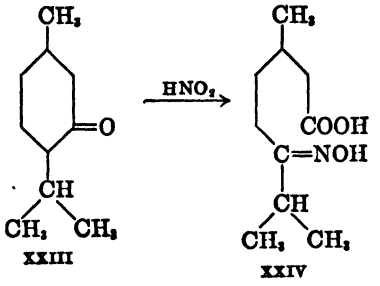
[255] Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 1105 (1932).

cerned, may be ascribed to the resonance effects of the nucleus discussed previously.

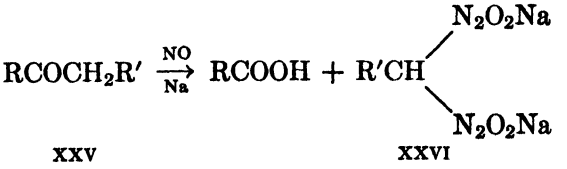
Ketones. Furyl ketones can be prepared by the usual acylation methods (p. 143). The α-furyl ketones, e.g., methyl, propyl, isoamyl, and phenyl, undergo a reaction with nitrous acid which seems to be peculiar to them.[176] When treated with nitrous acid, from ethyl nitrite, the 2-furoic acid and the oxime of the aldehyde carrying the other radical of the ketone are formed. A mechanism for this reaction



has been proposed (XXI–XXII). It is known that ketones containing the CO—CH linkage undergo such a split, e.g., menthone (XXIII–XXIV). The only analogy in which a ketone is cleaved in this fashion



between a CO and CH_2 group is found in Traube's observation on the action of sodium and nitric oxide on such substances (XXV–XXVI).[256]



[256] Traube, *Ann.*, **300**, 81 (1898). Cf. Woodward and Doering, *J. Am. Chem. Soc.*, **67**, 860 (1945).

MISCELLANEOUS FURAN DERIVATIVES

The 2-furfuryl halides are an exceedingly unstable group of substances. v. Braun and Köhler [257] prepared an ethereal solution of the bromide from the action of cyanogen bromide on 2-furfurylmethylamine. Gilman and Vernon [258] also prepared the chloride in solution, but all attempts at isolating it resulted in violent decomposition. Zanetti and Bashour [259] succeeded in isolating pure 2-furfuryl bromide by reaction of phosphorus tribromide on furfuryl alcohol under special conditions. The compound can be distilled, but rapid and sometimes explosive decomposition soon sets in. Apparently the decomposition of the halides is due to the effect of traces of halogen acids on the sensitive furan nucleus, and, once decomposition sets in, it is autocatalyzed by the acid liberated.

The furfuryl halides in solution serve as intermediates from which a variety of furfuryl ethers [260] and amines [261] may be prepared.

257 v. Braun and Köhler, *Ber.*, **51**, 87 (1918).

258 Gilman and Vernon, *J. Am. Chem. Soc.*, **46**, 2576 (1924).

259 Zanetti and Bashour, *J. Am. Chem. Soc.*, **61**, 2249 (1939).

260 Zanetti, *J. Am. Chem. Soc.*, **49**, 1065 (1927).

261 Zanetti and Beckmann, *J. Am. Chem. Soc.*, **50**, 2031 (1928); Zanetti and Bashour, *ibid.*, **61**, 3133 (1939); **62**, 742, 1511 (1940).

CHAPTER 5

THE CHEMISTRY OF THIOPHENE

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CONTENTS

HISTORICAL BACKGROUND

Victor Meyer stated that his discovery of thiophene in 1883 was due to an accident.[1] During a lecture, he wished to demonstrate the formation of indophenine, the deep blue product which is produced when a commercial grade of coal-tar benzene is mixed with isatin and concentrated sulfuric acid. Prior to this time, the formation of the blue substance was considered to be a characteristic test for benzene. Meyer, who was a careful and skillful experimenter, had obtained

1 Meyer, *Die Thiophengruppe*, Friedrich Vieweg und Sohn, Braunschweig, 1888, p. 1.

indophenine from coal-tar benzene just before the lecture and, consequently, was greatly surprised when he was unable to obtain the blue product during the lecture demonstration. After his assistant, Sandmeyer, had informed him that a different sample of benzene had been employed in the lecture experiment—benzene which had been prepared by decarboxylation of benzoic acid—Meyer immediately informed his audience that, when the explanation for the anomalous behavior of the benzene was found, it would be of considerable significance.

Meyer at once began a study of ordinary coal-tar benzene and soon found that it contained a small amount of an organic sulfur compound; it was from this substance, and not from the benzene, that indophenine was formed.[2]

Although the sulfur compound might have been some relatively unimportant derivative of benzene, this was found not to be the case. It proved, instead, to be a new parent compound which, although very different from benzene in composition and structure, was strikingly similar to it in certain physical and chemical properties, underwent a number of the typical reactions of benzene, and, in many instances, formed derivatives which resembled corresponding phenyl compounds.[3] In order to indicate this similarity and also the presence of sulfur, Meyer named the new compound thiophene and began immediately to study its properties.

Some idea of the intensity with which Meyer and his associates studied this subject can be gained from the appearance of one hundred and six publications on thiophene and its derivatives from his laboratory during a period of about five years. Considering the laborious manner in which thiophene had to be obtained and the poor laboratory equipment of those times, this achievement was most remarkable. In 1888, Meyer published his monograph [1] on thiophene and its derivatives, which contained a vast store of information concerning the fundamental chemistry of this unique heterocyclic compound.

INDOPHENINE

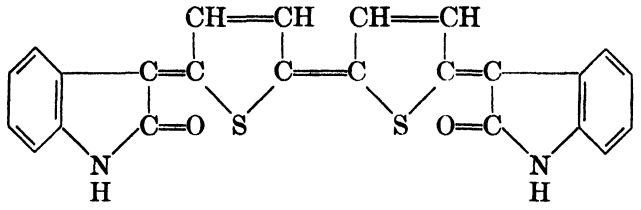
The formation of an intense blue color when isatin and concentrated sulfuric acid are added to coal-tar benzene was observed by Baeyer in

2 Meyer, *Ber.*, **15**, 2893 (1882); **16**, 1465 (1883).

3 Tables in which the melting and boiling points of corresponding thiophene and benzene compounds are compared can be found in Wilhelm Steinkopf's *Die Chemie des Thiophens*, Theodor Steinkopf, Dresden and Leipzig, 1941, pp. 15, 74, lithoprinted by Edwards Brothers, Ann Arbor, Michigan, 1944; and in Morton, *The Chemistry of Heterocyclic Compounds*, McGraw-Hill Book Company, New York, 1946, p. 41.

1879.[4] Since he thought that the indole derivative, isatin, had reacted with benzene to form a blue compound, he coined the term indophenine from the words indole and phenyl. Four years later, Meyer [2] discovered that the formation of indophenine was due to the interaction of isatin with thiophene.[5]

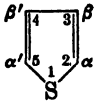
The formula assigned to indophenine by Schlenk and Blum [6] was established by the experimental work of Steinkopf and Hanske.[7]



indophenine

The term indophenine has now become a generic expression and refers to the colored product (red, violet, or blue) obtained by condensation of thiophene, or thiophene compounds that contain two nuclear hydrogen atoms in the 2,5 or 2,3 positions, with a 1,2-dicarbonyl compound such as isatin, alloxan, phenanthrenequinone, thianaphthenequinone, benzil, or esters of phenylglyoxylic or mesoxalic acid. This subject has been discussed in detail by Steinkopf.[8]

NOMENCLATURE



C_4H_4S	Thiophene
C_4H_3S—	Thienyl (phenyl)
$C_4H_3SCH_2$—	Thenyl (benzyl)
C_4H_3SCH=	Thenal or thenylidene (benzal or benzylidene)
C_4H_3SCO—	Thenoyl (benzoyl)

Most authors seem to prefer numbers, rather than Greek letters, to designate nuclear positions of the thiophene ring. However, it is some-

4 Baeyer, *Ber.*, **12**, 1309 (1879).

5 Schlenk [*Ann.*, **433**, 98 (1923)] recommends that the indophenine test should be performed in the following manner. A drop of thiophene, or a substance which contains thiophene, is added to a chloroform solution of isatin, and the solution is cooled in an ice bath. A blue color is produced upon the addition of cold, concentrated sulfuric acid.

6 Schlenk and Blum, *Ann.*, **433**, 95 (1923).

7 Steinkopf and Hanske, *Ann.*, **541**, 238 (1939).

8 Steinkopf, *Die Chemie des Thiophens*, Theodor Steinkopf, Dresden and Leipzig, 1941, pp. 125–133; lithoprinted by Edwards Brothers, Ann Arbor, Michigan, 1944.

times more practical to use α with reference to either the 2 or 5 position, and β to denote attachment to either the 3 or 4 carbon atom.

The nomenclature of thiophene radicals and of certain thiophene derivatives is patterned, to quite an extent, on that of corresponding compounds in the benzene series.[9]

Methylthiophene—thiotolene (toluene)
Dimethylthiophene—thioxene (xylene)
Aminothiophene—thiophenine (aniline)
Acetylthiophene—acetothienone (acetophenone)
Thenoylthiophene—thienone (benzophenone)
Benzoylthiophene—benzothienone
Thienylthenoylcarbinol—thenoin (benzoin)
Hydroxythiophene—thienol (phenol)
Methylhydroxythiophene—thiotenol (cresol)
Acetylaminothiophene—acetthiophenide (acetanilide)
Chloromethylthiophene—thenyl chloride (benzyl chloride)
Thiophenecarboxylic acid—thenoic acid, thiophenic acid (benzoic acid)
Thiophenecarbonyl chloride—thenoyl chloride (benzoyl chloride)

THIOPHENE AND HOMOLOGS[10]

Thiophene is a colorless, water-insoluble liquid which, when pure, has a benzene-like odor.

Accurate determinations have been made of some of the physical properties of very pure thiophene [11] and of 2- and 3-methylthiophene.[12]

Although the physical properties of thiophene and benzene are of the same order in most instances, the marked divergence in freezing points is one example of dissimilarity.

9 Possibly this attempt to coin analogous terms has been carried too far. Such trivial names as thioxene for dimethylthiophene and thiotenol for methylhydroxythiophene leave too much room for uncertainty regarding their exact meaning. The somewhat longer, but far more definite, systematic names seem preferable in some instances.

10 In the preparation of this chapter, extensive use was made of Steinkopf's admirable monograph, *Die Chemie des Thiophens*, ref. 8. The arrangement of some of the subject matter in this article is essentially the logical one adopted in the monograph. Since Steinkopf's treatment of certain phases of thiophene chemistry is more exhaustive, his book should be consulted for a more thorough discussion of many subjects, for tables of thiophene derivatives which have been described in the literature, and for additional references.

In this chapter, a later reference to a compound, which often discloses an improved process, has been mentioned in many instances rather than the original reference.

11 Fawcett and Rasmussen, *J. Am. Chem. Soc.*, **67**, 1705 (1945).

12 Fawcett, *J. Am. Chem. Soc.*, **68**, 1420 (1946).

	Thiophene [11]	Benzene
F.p., °C	−38.30	5.49
B.p., °C	84.12 (760 mm.)	80.10
n_D^{20}	1.5287	1.5014
d_4^{20}	1.0644	0.8791

Thiophene and some of its derivatives such as methyl-, dimethyl-, ethyl-, propyl-, and isopropyl-thiophene, bithienyl, and thianaphthene (benzothiophene) can be isolated from coal tar and shale oil.[13] Technical benzene contains a very small amount of thiophene.

A wide variety of compounds has been converted into thiophene: for example, erythritol, crotonic acid, butyric acid, paraldehyde, diethyl ether, diethyl sulfide, pyrrole, furan, ethylene, propene, butene, and butadiene. In some instances, the compound has been heated with sulfur, a phosphorus sulfide, or hydrogen sulfide, with or without a catalyst; in other cases, it has been passed through a hot tube. The reaction between acetylene and sulfur, usually in the presence of a catalyst, has been studied quite extensively. Thiophene obtained by this procedure is contaminated by a number of homologs and other products.[14] The interaction of sodium succinate and "phosphorus trisulfide" [15] represents the most convenient laboratory process for the preparation of thiophene.[16]

The manufacture of thiophene from butane and sulfur has been described.[17] It was suggested that the reaction may take place in the following manner.

13 Ref. 8, pp. 5–7.

14 Ref. 8, p. 9.

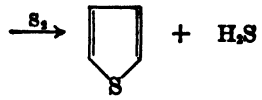
15 Many reactions are described in the organic chemical literature in which "phosphorus trisulfide" was employed, although the existence of such a phosphorus compound was in doubt even in 1886 [see Bidermann and Jacobson, *Ber.*, **19**, 2444 (1886), footnote 1]. Meyer (ref. 1, p. 39, footnote 1) stated, "It is to be understood that 'phosphorus trisulfide,' which actually does not exist, refers to the product obtained by heating a mixture of three parts of sulfur with two parts of red phosphorus." Permission has been received from Dr. John C. Pernert, Director of Research, Oldbury Electro-Chemical Company, to publish the following information. Samples of "phosphorus trisulfide" which were examined could be separated, by solvents, into phosphorus heptasulfide, P_4S_7, and phosphorus sesquisulfide, P_4S_3; the major portion was the heptasulfide. It is believed that only P_4S_3, P_4S_7, and P_4S_{10} can be obtained by direct action of phosphorus and sulfur at a high temperature. No instance was known to Dr. Pernert in which the heptasulfide could not be substituted satisfactorily for the trisulfide.

16 Volhard and Erdmann, *Ber.*, **18**, 454 (1885); *Org. Syntheses Coll. Vol.* **2**, 578 (1943).

17 Rasmussen, Hansford, and Sachanen, *Ind. Eng. Chem.*, **38**, 376 (1946).

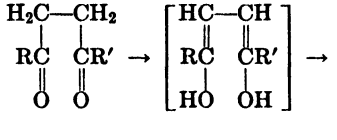
$$CH_3CH_2CH_2CH_3 \xrightarrow{\frac{1}{2}S_2} CH_3CH_2CH{=}CH_2(+ H_2S) \xrightarrow{\frac{1}{2}S_2}$$

$$CH_2{=}CH{-}CH{=}CH_2(+ H_2S)$$



Since 1945, the commercial availability of thiophene at a reasonable price has given a great impetus to the study and development of thiophene derivatives.

A general synthesis for thiophene and some of its derivatives is one in which a 1,4-dicarbonyl compound is heated with a phosphorus sulfide. Thiophene, a 2-substituted or a 2,5-disubstituted derivative, can be obtained from one of the compounds listed herewith. If one of the



R	R′	
H	H	Succinaldehyde
OH	OH	Succinic acid
OH	CH_3	Levulinic acid
OH	C_6H_5	γ-Benzoylpropionic acid
CH_3	CH_3	Acetonylacetone
CH_3	C_6H_5	Phenacylacetone
C_6H_5	C_6H_5	α,β-Dibenzoylethane

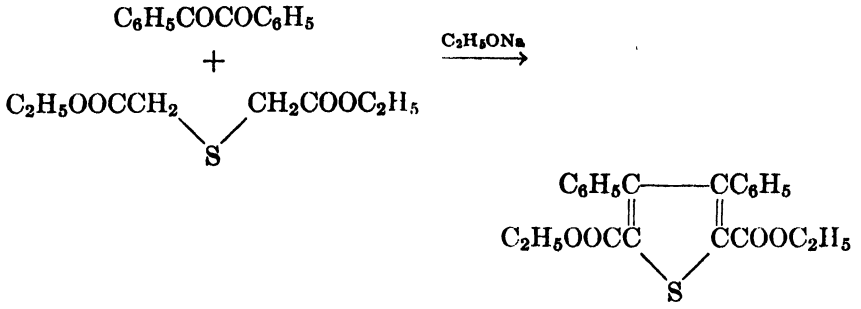
following compounds is employed, the thiophene produced will contain a substituent in the 3 or 4 position, or substituents in both the 3 and 4 positions: methyl-, ethyl-, α,α′-dimethyl-, α,α′-diethyl-, or phenylsuccinic acid, α-methyl-, β-methyl-, α,β-dimethyl-, α-ethyl-, or α-phenyl-levulinic acid, 3-methylacetonylacetone, or α,β-dibenzoyl-α-phenylethane. The sodium salt of the acid is commonly used.

Although α-hydroxy- and α-thiol-thiophenes are formed in some of these reactions, it is seldom possible to isolate them because they are reduced by the phosphorus sulfide.[18] An exception is the preparation of both 2-methyl- and 2-methyl-5-hydroxythiophene from levulinic acid or its sodium salt.[19–21]

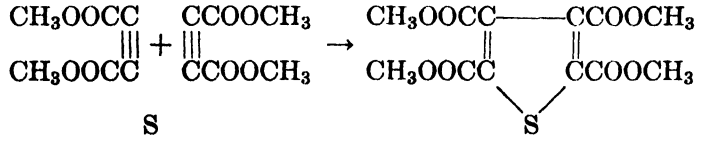
Appropriate condensations of 1,2-dicarbonyl compounds lead to thiophenes. This is shown by the interaction of diethyl thiodiacetate with glyoxal to form the diethyl ester of thiophene-2,5-dicarboxylic acid,

18 Paal, *Ber.*, **19**, 551 (1886).
19 Kues and Paal, *Ber.*, **19**, 555 (1886).
20 Vlastelitza, *J. Russ. Phys. Chem. Soc.*, **46**, 790 (1914) [*C. A.*, **9**, 1750 (1915)].
21 Chrzaszczewska, *Roczniki Chem.*, **5**, 33 (1925) [*C. A.*, **20**, 1078 (1926)].

and with benzil to produce diethyl 3,4-diphenylthiophene-2,5-dicarboxylate.[22]



Dimethyl acetylenedicarboxylate and sulfur react to yield tetramethyl thiophene-2,3,4,5-tetracarboxylate.[23]



When thiophene is passed through a red-hot tube, it is converted into 2,2-bithienyl and 3,3-bithienyl. Unlike thiophane (tetrahydrothiophene), thiophene cannot be oxidized to a sulfoxide or sulfone, nor will it react with methyl iodide to form a sulfonium iodide, although 3,4-diphenyl- and tetraphenyl-thiophene, as well as thianaphthene, form sulfones.

The thiophene ring is opened and sulfur is removed from the molecule by certain reagents. Although thiophene undergoes no change when boiled with sodium, which offers a process for its purification, it is decomposed by potassium with the formation of potassium sulfide. Hydrogen peroxide partially decomposes thiophene with the formation of sulfuric acid. Hydriodic acid, at 140°, converts thiophene into sulfur, hydrogen sulfide, and other products. Upon prolonged contact, thiophene is decomposed by concentrated sulfuric acid with the formation of sulfur dioxide. Thallium hydroxide transforms thiophene into succinaldehyde which is oxidized to thallium succinate during the experiment.[24] Fuming nitric acid reacts with tetrabromothiophene to

22 Hinsberg, *Ber.*, **43**, 901 (1910); **45**, 2413 (1912). Cf. p. 178 for an analogous reaction in the furan series.

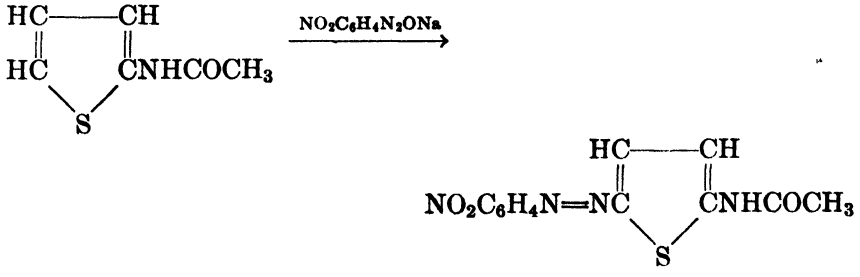
23 Michael, *Ber.*, **28**, 1633 (1895).

24 Morgan and Ledbury, *J. Chem. Soc.*, **121**, 2882 (1922).

form dibromomaleic acid.[25] 2-Bromo- or 2-iodo-thiophene and piperidine at 200–240° yield a substance which, when hydrogenated, is converted into 1,4-dipiperidinobutane.[26]

Many characteristic reactions of thiophene—sulfonation, nitration, halogenation, chloromethylation, mercuration with mercuric acetate, the Fittig reaction, the Friedel-Crafts reaction—are also characteristic reactions of benzene. This similarity in behavior has also been established for a number of thiophene derivatives and the corresponding phenyl compounds. In view of the differences, both in composition and structure, between thiophene and benzene, these analogies are so remarkable that in the past they have been responsible for an unwarranted tendency to regard the two parent substances, and too many of their corresponding derivatives, as practically equivalent compounds. With the further development of thiophene chemistry, the marked differences between the two groups of substances become more and more evident.

Nuclear hydrogen atoms of the thiophene nucleus, especially those in α positions, can be replaced under milder conditions than are required for the removal of benzene hydrogen atoms. Under identical conditions, thiophene reacts with certain reagents whereas benzene is unreactive. Thus, thiophene undergoes chloromethylation with great ease, undergoes, at least to a limited extent, the Mannich reaction, can be mercurated with mercuric chloride, and can be halogenated with N-chloroacetamide or bromocyanogen. Acetanilide will not couple with a diazonium salt, but 2-acetylaminothiophene reacts with sodium *p*-nitrobenzenediazotate and also with *p*-nitrobenzenediazonium chlo-



ride.[27] By treatment with chlorine, bromine, or mercuric acetate, all hydrogen atoms of thiophene can be replaced by halogen or acetoxy-

[25] Angeli and Ciamician, *Ber.*, **24**, 74, 1347 (1891). Cf. p. 139 for the analogous furan reaction.

[26] Thöl, *Ber.*, **28**, 2217 (1895).

[27] Hurd and Priestley, *J. Am. Chem. Soc.*, **69**, 859 (1947).

mercuri groups. Although thiophene can be nitrated under suitable conditions, it reacts vigorously with strong nitric acid and undergoes decomposition. Nitrothiophenes are converted, by reduction, into corresponding amino derivatives, but 2- and 3-aminothiophene are stable only in the absence of air.

For the detection and estimation of thiophene, colorimetric as well as precipitation tests may be employed. A characteristic color is produced by the interaction of thiophene with isatin and concentrated sulfuric acid (indophenine), with phenanthrenequinone and sulfuric acid, with amyl nitrite and sulfuric acid, with antimony pentachloride, and with a number of other reagents. Products of limited solubility are formed from thiophene and mercury salts. These tests are described in detail by Steinkopf.[8]

Thiophene homologs can be obtained by the Fittig reaction, by Clemmensen reduction of an acylthiophene, and by reaction between a suitable 1,4-dicarbonyl compound and a phosphorus sulfide. Thiophene has been alkylated by propene, butene-1, isobutene, pentene, cyclohexene, and isopropyl or *t*-butyl alcohol.[28] Certain homologs have been prepared by heating a semicarbazone of a carbonyl derivative of thiophene with moist potassium hydroxide,[29] or a similar hydrazone with sodium ethoxide,[30] and by interaction of sulfur and isoprene, dimethylbutadiene, or 3-methyl-1,3-pentadiene.[31]

2-Vinylthiophene is formed, in quantitative yield, by dehydration of 2-thienylmethylcarbinol, $(C_4H_3S)CH(OH)CH_3$, at its boiling point.[32] It has a styrene-like odor and polymerizes at room temperature. Dehydration of other carbinols has yielded unsaturated derivatives such as 2-(α-ethylpropenyl)thiophene.[33]

INTRODUCTION AND BEHAVIOR OF SUBSTITUENTS

It is only to a very limited extent, and with certain reservations, that any comparison can be made with respect to nuclear positions in thiophene and the *o*, *m*, and *p* positions in the benzene ring.[34]

28 Kutz and Corson, *J. Am. Chem. Soc.*, **68**, 1477 (1946).

29 Shepard, *J. Am. Chem. Soc.*, **54**, 2951 (1932).

30 Steinkopf, Frömmel, and Leo, *Ann.*, **546**, 199 (1941).

31 Shepard, Henne, and Midgley, *J. Am. Chem. Soc.*, **56**, 1355 (1934).

32 Kuhn and Dann, *Ann.*, **547**, 293 (1941); Nazzaro and Bullock, *J. Am. Chem. Soc.*, **68**, 2121 (1946).

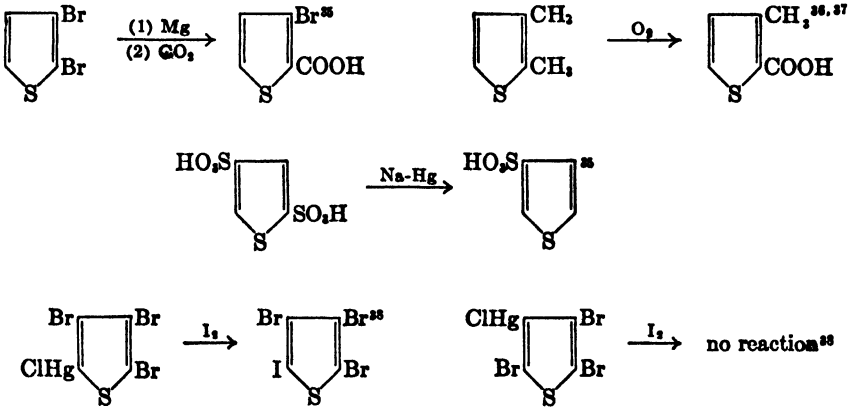
33 Domratschewa, *J. Russ. Phys. Chem. Soc.*, **46**, 864 (1914) [*C. A.*, **9**, 1754 (1915)].

34 Ref. 8, p. 26.

It becomes very evident, by a study of thiophene chemistry, that there is a marked tendency for an entering atom or group to replace an α- rather than a β-nuclear hydrogen atom, and for the removal, during a reaction, of an α instead of a β substituent. However, there is no simple rule to predict the nuclear position that will be taken by an entering substituent, or the behavior of the substituent after it has entered the ring. The nature of the entering substituent, the influence of a substituent already present, and the experimental conditions are factors which often play a determining role. To a certain extent, the resonance effects displayed by thiophene parallel those of furan, which have already been discussed (p. 137).

The formation of an α- instead of a β-substituted thiophene in such reactions as halogenation, sulfonation, nitration, mercuration, chloromethylation, and the Friedel-Crafts reaction illustrates the greater activity of an α-hydrogen atom.

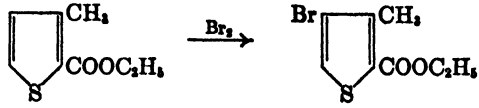
A few of the many reactions in which an α in preference to a β substituent is affected are indicated below.[35–37]



The manner in which the reactivity of nuclear hydrogen atoms and of other atoms or groups attached to the ring is influenced by the presence of certain substituents is shown by the following examples. Although chlorine converts tetrabromothiophene into tetrachlorothiophene, there is no replacement of bromine by chlorine when 3,4-

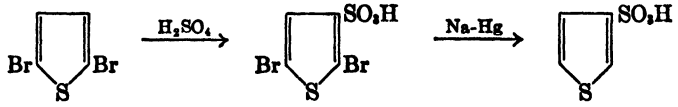
35 Steinkopf, Jacob, and Penz, *Ann.*, **512**, 136 (1934).
36 Steinkopf and Jacob, *Ann.*, **515**, 273 (1935).
37 Steinkopf and Hanske, *Ann.*, **527**, 264 (1937), footnote 4.
38 Steinkopf, Rösler, and Setzer, *Ann.*, **522**, 35 (1936).

dibromothiophene-2,5-dicarboxylic acid is treated with chlorine.[39] In the bromination of 2-carbethoxy-3-methylthiophene, a 4-bromo instead of a 5-bromo product is obtained.[40] In 2,5-dimethylthiophene, the

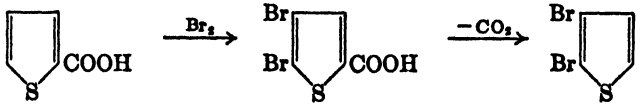


β-hydrogens are so reactive that they can be replaced easily by iodine on direct iodination,[36] by chloromercuri,[41] or by nitro groups.[42] 2-Nitro-3-iodothiophene is converted by bromine into tetrabromothiophene, but, when 2-nitro-3,4,5-tribromothiophene is treated with bromine, the nitro group is not replaced by halogen.[43]

Occasionally, a substituted thiophene, rather than thiophene itself, offers advantages for the preparation of a desired product. Substituents already present can block positions which would otherwise be taken by an entering group and can also exert a directing influence. After substitution has been effected, the unwanted substituents are then removed in some suitable manner. Direct sulfonation of thiophene produces thiophene-2-sulfonic acid, but, by the sulfonation of 2,5-dibromothiophene and subsequent removal of the bromine atoms with sodium amalgam, the 3-sulfonic acid can be obtained.[44] By the direct



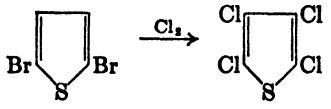
introduction of two bromine atoms into thiophene, 2,5-dibromo-, but not 2,3-dibromo-thiophene, is produced. However, the latter compound can be prepared by bromination of thiophene-2-carboxylic acid and decarboxylation of the dibromo derivative.[39]



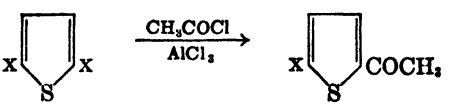
39 Steinkopf and Köhler, *Ann.*, **532**, 250 (1937).
40 Steinkopf and Nitschke, *Ann.*, **536**, 135 (1938).
41 Steinkopf and Bauermeister, *Ann.*, **403**, 50 (1914).
42 Steinkopf, Poulsson, and Herdey, *Ann.*, **536**, 128 (1938).
43 Steinkopf, Schmitt, and Fiedler, *Ann.*, **527**, 237 (1937).
44 Langer, *Ber.*, **18**, 553 (1885).

A considerable number of reactions are known in which an entering substituent displaces an atom or group already attached to the thiophene nucleus.[45–48]

bromine by chlorine[45,46]

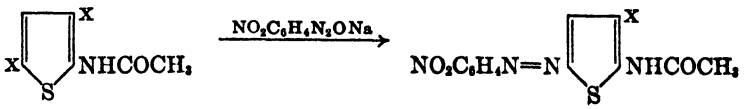


bromine or iodine by acetyl[47,48]



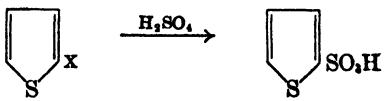
X=Br or I

bromine or iodine by *p*-nitrophenylazo[27]



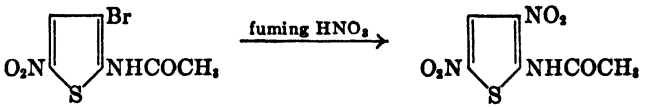
X=Br or I

bromine or iodine by a sulfonic acid group[25]

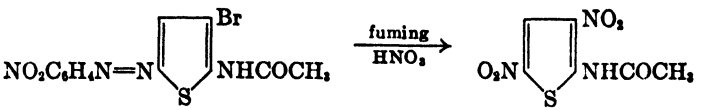


X=Br or I

bromine by nitro[49]



bromine and *p*-nitrophenylazo by nitro[27]



45 Weitz, *Ber.*, **17**, 792 (1884).

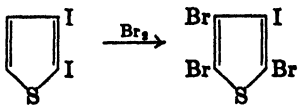
46 Rosenberg, *Ber.*, **19**, 650 (1886).

47 Gattermann and Römer, *Ber.*, **19**, 688 (1886).

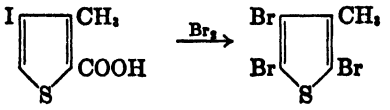
48 2,5-Dichlorothiophene reacts with acetyl chloride and aluminum chloride with the formation of 2,5-dichloro-3-acetylthiophene [Steinkopf and Köhler, *Ann.*, **532**, 265 (1937)]. See also Hartough and Kosak, *J. Am. Chem. Soc.*, **69**, 3093 (1947).

49 Priestley and Hurd, *J. Am. Chem. Soc.*, **69**, 1173 (1947).

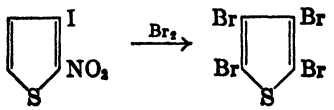
Iodine by bromine[48]



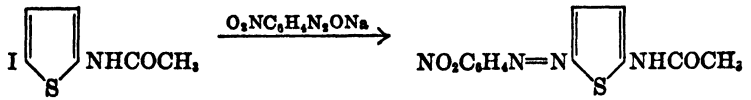
Iodine and carboxyl by bromine[50]



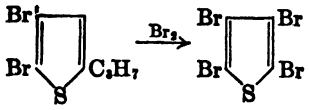
Iodine and nitro by bromine[48]



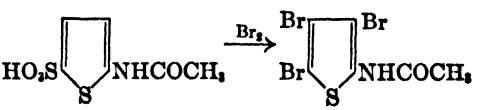
Iodine by *p*-nitrophenylazo[27]



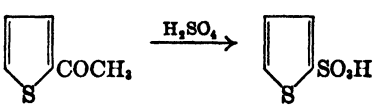
Propyl by bromine[39,51]



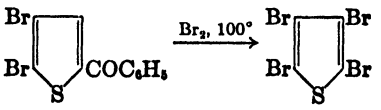
Sulfonic by bromine[27]



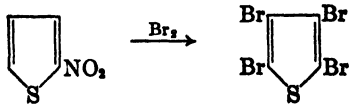
Acetyl by sulfonic[52,53]



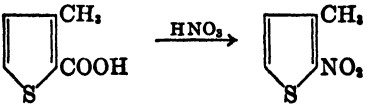
Benzoyl by bromine[54]



Nitro by bromine[55,56]



Carboxyl by nitro[56]



50 Steinkopf and Hanske, *Ann.*, **532**, 236 (1937).

51 Ruffi, *Ber.*, **20**, 1741 (1887). Tetrabromothiophene has been obtained by the action of bromine on 2-methylthiophene.[39]

52 Krekeler, *Ber.*, **19**, 674, 2627 (1886).

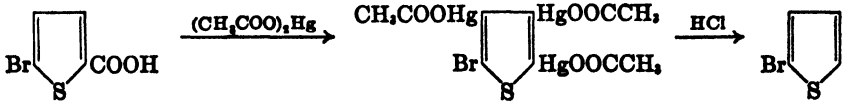
53 Muhlert, *Ber.*, **19**, 1620 (1886).

54 Marcusson, *Ber.*, **26**, 2457 (1893).

55 Bromination of 3-nitrothiophene yields 2,5-dibromo-3-nitrothiophene.[35] 2,4-Dinitro-, 2,5-dinitro-, and 2,3,4-tribromo-5-nitrothiophene are not attacked by bromine at ordinary temperature.[43]

56 Rinkes, *Rec. trav. chim.*, **52**, 1052 (1933).

carboxyl by acetoxymercuri[50,57,58]

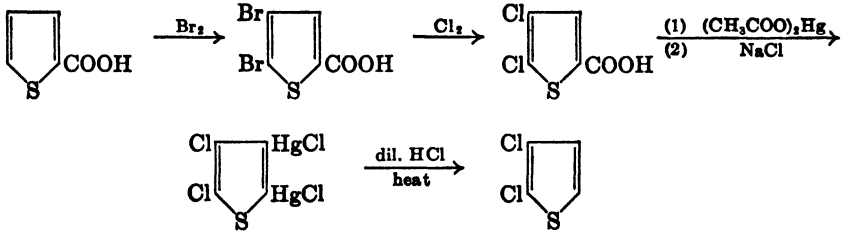


HALOTHIOPHENES

The ease with which thiophene is chlorinated is shown by the fact that, regardless of the amount of chlorine employed, a mixture of 2-chloro-, 2,5-dichloro-, 2,3,4-trichloro-, 2,3,5-trichloro-, and tetrachlorothiophene is formed. Since tetrachlorothiophene is a crystalline substance, it can be isolated from the mixture; however, the separation in pure form of the liquid chloro products from one another by distillation, at least on a small scale, is claimed to be an unsatisfactory procedure.[59] During chlorination, substances which have hitherto been considered to be hydrogen chloride addition products are formed, and they must be destroyed before a chlorothiophene can be obtained in a pure form.[60] This is accomplished by boiling the crude product with aqueous or alcoholic alkali. The same procedure must be employed in the preparation of at least some of the bromothiophenes.

2-Chlorothiophene has been obtained by chlorination with sulfuryl chloride.[61–63] Chlorination of thiophene with N-chloroacetamide yields a mixture of 2-chloro- and 2,5-dichloro-thiophene.[64]

Many chlorothiophenes, for example 2,3-dichlorothiophene, have been obtained only by indirect procedures.[39]



57 As a rule, a β-carboxyl group is not eliminated in this type of reaction.

58 The product to the right of the first arrow was not isolated but was converted, by hydrochloric acid, into 2-bromothiophene, which was identified in the form of its chloromercuri derivative.

59 Ref. 8, p. 38.

60 Coonradt and Hartough [*J. Am. Chem. Soc.*, **70**, 1158 (1948)] have shown that, upon chlorination of thiophene, substitution as well as chlorine addition products are obtained.

61 Thöl and Eberhard, *Ber.*, **26**, 2947 (1893).

62 Metcalf and Gunther, *J. Am. Chem. Soc.*, **69**, 2579 (1947).

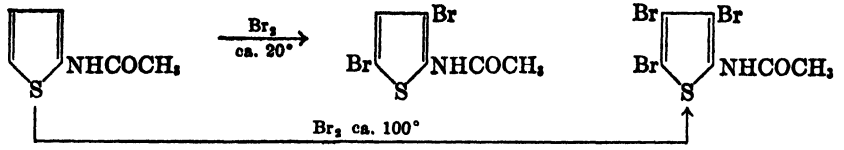
63 Campaigne and LeSuer, *J. Am. Chem. Soc.*, **70**, 415 (1948).

64 Steinkopf and Otto, *Ann.*, **424**, 61 (1920).

Chlorine can replace bromine or iodine in a variety of thiophene derivatives. Thus, tetrachlorothiophene has been obtained by chlorination of dibromothiophene.[45]

The preparation, separation, and purification of chlorothiophenes via mercury derivatives is described in the discussion of mercury compounds.

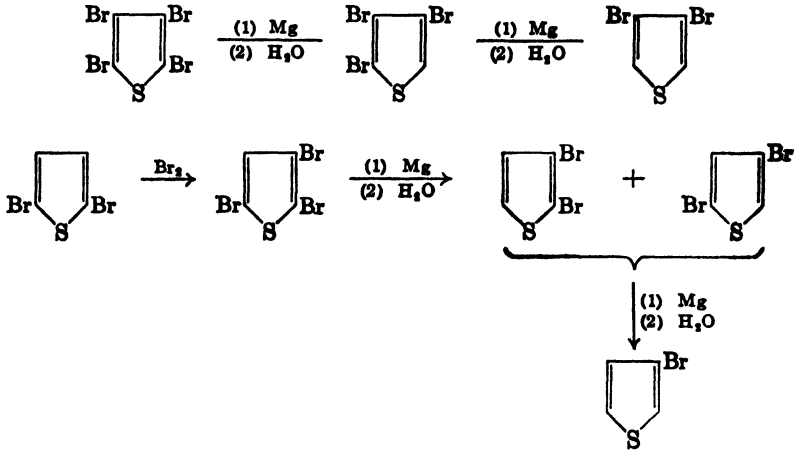
The most satisfactory process for the preparation of 2-bromothiophene is by the direct bromination of thiophene with the calculated amount of bromine.[65] Although some 2,5-dibromo- and a smaller amount of tribromo-thiophene are formed as by-products, the bromo derivatives can be separated by distillation. 2,3-Dibromothiophene can be obtained from 4,5-dibromothiophene-2-carboxylic acid by a procedure analogous to that leading to the 2,3-dichloro derivative.[39,66] The 2,3-dibromo derivative has been degraded to 3-bromothiophene.[66] 2,5-Dibromothiophene is produced in good yield by interaction of thiophene with two molecular equivalents of bromine,[67] and it reacts with one equivalent of bromine to yield the 2,3,5-tribromo compound.[68] Bromination of a 2-acetylaminothiophene at ordinary temperature yields a dibromo product, whereas at a higher temperature a tribromo derivative is formed.[27] Thiophene is converted by excess bromine into the tetrabromo derivative.[35]



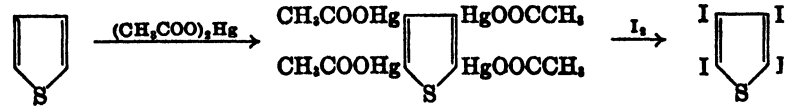
The "Grignard degradation," a term introduced by Steinkopf, refers to the transformation of a polyhalo compound, through the formation of a Grignard reagent and treatment of the Grignard reagent with water, into a product which contains one less halogen atom. It was used first to convert 2,5-dibromothiophene into the 2-bromo compound.[69] By means of this degradation, it is possible to eliminate one

65 Blicke and Burckhalter, *J. Am. Chem. Soc.*, **64**, 477 (1942).
66 Steinkopf, *Ann.*, **543**, 128 (1940).
67 Mozingo et al., *J. Am. Chem. Soc.*, **67**, 2092 (1945).
68 Rosenberg, *Ber.*, **18**, 1773 (1885).
69 Gattermann, *Ann.*, **393**, 230 (1912).

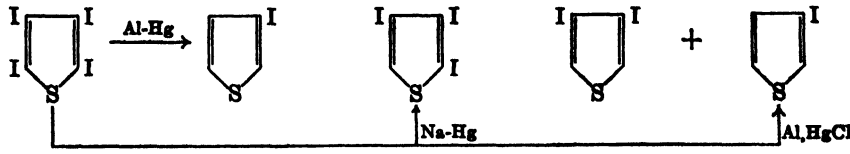
α-bromine at a time from tetrabromothiophene and to convert it, successively, into 2,3,4-tribromo- and 3,4-dibromo-thiophene. 2,3,5-Tribromothiophene, when subjected to this procedure, yields a mixture of the 2,3- and 2,4-dibromo compounds from which, by further degradation, 3-bromothiophene is obtained.[35] In the same manner, tetrachlorothiophene is converted into 2,3,4-trichlorothiophene.[35]



Only 2-iodo- [70] and 2,5-diiodo-thiophene can be synthesized by direct iodination of thiophene with iodine and mercuric oxide. Other iodothiophenes can be prepared indirectly by interaction of a chloromercuri or acetoxymercuri derivative with iodine. In the preparation of tetraiodothiophene from thiophene, it is not necessary to isolate the intermediate tetraacetoxymercurithiophene.[43] Several iodo deriva-

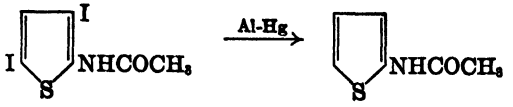


tives, such as 3-iodo-,[71] 3,4-diiodo-,[43] and 2,3,4-triiodo-thiophene,[43] have been obtained by removal of iodine from tetraiodothiophene with various reducing agents such as aluminum or sodium amalgam. 3-

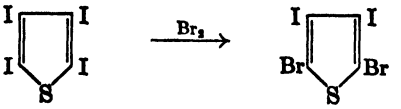


70 Meyer and Kreis, *Ber.*, **17**, 1558 (1884); *Org. Syntheses Coll. Vol.* **2**, 357 (1943).
71 Rinkes, *Rec. trav. chim.*, **53**, 643 (1934).

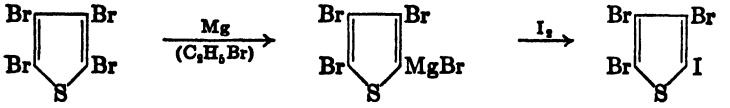
Iodothiophene can be iodinated with iodine and mercuric oxide to 2,3,5-triiodothiophene.[43] The removal of an α-bromine or iodine atom and, at least in certain instances, of iodine in the β position, can be accomplished with aluminum amalgam or other reducing agents.[49]



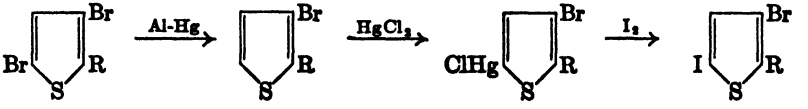
As the result of the extensive study made by Steinkopf and his associates,[72] the following statements can be made relative to the preparation of polyhalothiophenes that contain unlike halogen atoms. Chlorothiophenes can be brominated directly, and, if they contain a hydrogen atom in the α position, they can be iodinated with iodine and mercuric oxide. When iodothiophenes are chlorinated, iodine is replaced by chlorine. Bromine will displace iodine from the α but usually not from the β position.[43]



The α-bromine atom in a number of polybromothiophenes has been replaced by iodine by conversion of the bromo compound into a Grignard reagent and treatment of this substance with iodine.[35] The

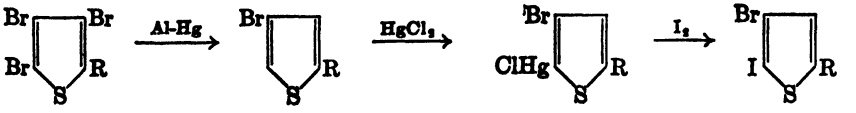


replacement of bromine by iodine has also been accomplished by the removal of bromine with aluminum amalgam, mercuration, and iodina-



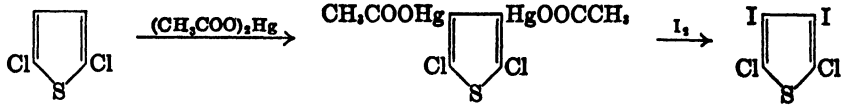
R=NHCOCH3

tion of the mercury derivative.[27] Iodine can be introduced by treat-

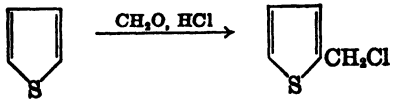


72 Ref. 8, p. 44.

ment of chloromercuri or acetoxymercuri derivatives of chloro- or bromo-thiophenes with iodine.[38,39]



It has not been found possible, for the direct halogenation process, to select conditions that will favor the entrance of chlorine or bromine, almost exclusively, either into the nucleus or into a side chain. Because of the greater reactivity of nuclear hydrogen atoms, halogenation in a side chain tends to take place only after all nuclear hydrogen atoms have been replaced. Direct chlorination of 2-methylthiophene (2-thiotolene) seems to produce a mixture of 3-chloro- and 5-chloro-2-methylthiophene.[73] With sulfuryl chloride, 2-methyl-5-(?)-chlorothiophene is obtained.[63] 2-Thenyl chloride (2-chloromethylthiophene) [74] can be obtained most readily by chloromethylation of thiophene.[75] It has been prepared also from 2-thenyl alcohol and hydrogen chloride.[76] When 2-thenyl chloride was allowed to react with magnesium, in the hope that the Grignard reagent would be formed, α,β-di-(2-thienyl)ethane was isolated.[65]



The discovery [77] that 3-thenyl bromide can be obtained from 3-methylthiophene and N-bromosuccinimide, in the presence of a catalytic amount of benzoyl peroxide, has made the synthesis of many 3-substituted thiophenes practical. Prepared by this method, the thenyl bromide contains a small amount of 2-bromo-3-methylthiophene which cannot be separated by distillation. The presence of the 2-bromo compound is shown by the fact that interaction of the mixture with magnesium and subsequent carbonation produce 3-methylthiophene-2-carboxylic acid; the principal reaction product is α,β-di-(3-thienyl)ethane. However, in many instances, the presence of the

[73] Ref. 8, p. 45.

[74] In contrast to benzyl chloride, this substance must be preserved in a refrigerator. A sealed tube which contained a sample of the material broke with explosive violence after several days.

[75] Blicke and Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946).

[76] Biedermann, *Ber.*, **19**, 636, 1615 (1886).

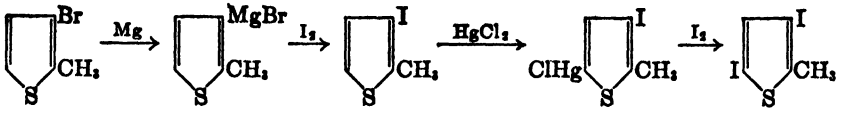
[77] Campaigne and LeSuer, *J. Am. Chem. Soc.*, **70**, 1555 (1948).

2-bromo derivative does not interfere with the successful utilization of the 3-thenyl bromide.

Bromination of 2-methylthiophene yields a mixture of 3-bromo-, 5-bromo-, and 3,5-dibromo-2-methylthiophene,[78] and by further bromination the 3,4,5-tribromo compound is obtained.[19,79] 2-Thenyl bromide, prepared from the corresponding alcohol and phosphorus tribromide,[80] is readily hydrolyzed, but it has been stated that 3,4,5-tribromo-2-thenyl bromide and the corresponding thenal bromide are relatively stable toward water.

By iodination of 2-methylthiophene, the 5-iodo derivative is obtained.[20] Other iodo derivatives have been synthesized by indirect methods. For example, 4-iodo- and 3,4-diiodo-2-methylthiophene [37] have been prepared by the following sequence of reactions: 2-methylthiophene → 3,4,5-triacetoxymercuri-2-methylthiophene → 3,4,5-triiodo-2-methylthiophene → Grignard degradation → 3,4-diiodo-2-methylthiophene + 4-iodo-2-methylthiophene.

3-Bromo-2-methylthiophene has been converted into 3-iodo- and 3,5-diiodo-2-methylthiophene in the following manner.[39]



The compound obtained by chlorination of 3-methylthiophene with chlorine [81] or sulfuryl chloride [63] seems to be the 2-chloro derivative.

Chlorination of 2,4,5-tribromo-3-methylthiophene converts this compound into the corresponding 2,4,5-trichloro derivative.[39] Only resinous material was obtained when the attempt was made to transform tribromo- or triiodo-2-methylthiophene, by chlorination, into trichloro-2-methylthiophene.

Bromine water reacts with 3-methylthiophene to produce only 2-bromo-3-methylthiophene. Depending on the experimental conditions, bromine can convert 3-methylthiophene into 2,5-dibromo- or 2,4,5-tribromo-3-methylthiophene, or 2,4,5-tribromo-3-thenyl bromide.[36]

2-Iodo-3-methylthiophene has been prepared by direct iodination and by treatment of 2-chloromercuri-3-methylthiophene with iodine.[40]

2,5-Dimethylthiophene (2,5-thioxene) reacts with bromine to form 3,4-dibromo-2,5-dimethyl-, 3,4-dibromo-2-methyl-(5-bromomethyl)-,

78 Steinkopf, *Ann.*, **513**, 281 (1934).
79 Egli, *Ber.*, **18**, 544 (1885).
80 v. Braun, Fussgänger, and Kühn, *Ann.*, **445**, 201 (1925).
81 Opolski, *Anz. Akad. Wiss. Krakau*, 730 (1904); *Chem. Zentr.*, **76**, I, 1255 (1905).

or 3,4-dibromo-2,5-di-(dibromomethyl)-thiophene.[80,82] The product obtained depends on the experimental conditions. In the last-mentioned compound, it is possible, by direct chlorination, to replace all the bromine atoms by chlorine.

β-(2-Thienyl)ethyl chloride has been obtained from 2-thienylmagnesium bromide and β-chloroethyl *p*-toluenesulfonate,[75] and the corresponding bromide from β-(2-thienyl)ethanol and phosphorus tribromide.[65]

The interaction of 2-thienylmagnesium bromide and γ-chloropropyl *p*-toluenesulfonate represents a convenient process for the synthesis of γ-(2-thienyl)propyl chloride. The chloride reacts with sodium iodide, in acetone solution, to form the iodide.[65]

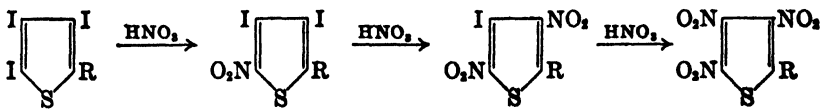
NITRO- AND AMINO-THIOPHENES

2-Nitrothiophene can be prepared in quite good yield from thiophene and fuming nitric acid with acetic anhydride as a solvent.[83] A small amount of the 3-nitro derivative is formed as a by-product.[84]

3-Nitrothiophene is obtained in pure form, although in low yield, by treatment of a mixture of 4- and 5-nitrothiophene-2-carboxylic acid, produced by nitration of thiophene-2-carboxylic acid, with mercuric acetate. During this process, the carboxyl group is replaced by an acetoxymercuri radical. After decomposition of the mercuration products with hot, dilute hydrochloric acid, the 3-nitrothiophene can be isolated without difficulty.[85]

Nitration of 2-nitrothiophene produces a mixture of 2,4- and 2,5-dinitro derivatives. 3-Nitrothiophene is converted by nitric acid into the 2,4-dinitro compound.[85]

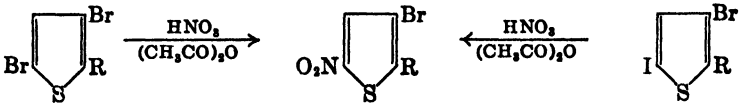
A trinitro derivative, which is not obtainable by direct nitration, can be prepared by the stepwise removal of iodine from a triiodo compound.[49]



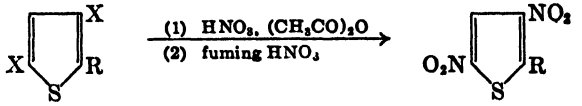
R=NHCOCH₃

82 Paal, *Ber.*, **18**, 2253 (1885).
83 Steinkopf, *Ann.*, **403**, 17 (1914).
84 Steinkopf and Höpner, *Ann.*, **501**, 174 (1933).
85 Steinkopf, *Ann.*, **545**, 38 (1940).

In a number of instances, it has been found that, by nitration, an α-bromine or α-iodine atom and, in some cases, bromine or iodine in the β position, can be replaced by a nitro group.[49]



R=NHCOCH$_3$



2-[83,86] and 3-Aminothiophene[84] (2- and 3-thiophenine) are liquids which change rapidly, in contact with atmospheric oxygen, into solid products of unknown structure. They are obtained by reduction of the corresponding nitro compounds with tin and hydrochloride acid and are isolated in the form of the stable addition products $2(C_4H_3S \cdot NH_2 \cdot HCl) \cdot SnCl_4$. The hydrochlorides are formed when the tin compounds are treated with hydrogen sulfide.

From the tin double salts 2-acetylamino- and 2-benzoylamino-thiophene can be prepared directly.[83] 2-Acetylaminothiophene, like acetanilide, will react with sodium to form a sodium derivative. Interaction of the sodium derivative with an alkyl halide produces a 2-alkylacetylamino derivative which, upon hydrolysis, is converted into a 2-alkylamino compound.

2-Aminothiophene and 4-aminothiophene-2-carboxylic acid, in the form of their tin double salts,[87] as well as several aminothiophene-arsonic acids,[88] can be diazotized. Diazonium salts and sodium diazotates couple with substituted aminothiophenes to yield azo dyes.[27]

Thiophene derivatives which contain an amino group in a side chain have been synthesized by various procedures. 2-Thienylmethylamine (2-thenylamine) can be prepared, in good yield, by decomposition of the addition product obtained from 2-thienylmethyl bromide and hexamethylenetetramine.[65] This amine, as well as di-(2-thienylmethyl)-amine, has been obtained by a Mannich-type reaction from thiophene, formaldehyde, and ammonium chloride.[89]

[86] Babasinian, *J. Am. Chem. Soc.*, **50**, 2748 (1928).

[87] Steinkopf and Müller, *Ann.*, **448**, 210 (1926).

[88] Finzi and Furlotti, *Gazz. chim. ital.*, **45**, II, 290 (1915). Finzi, *ibid.*, **60**, 159 (1930).

[89] Hartough, Lukasiewicz, and Murray, *J. Am. Chem. Soc.*, **68**, 1389 (1946); **70**, 1146 (1948).

α-(2-Thienyl)ethylamine has been prepared by reduction of 2-acetylthiophene oxime with sodium amalgam [90] and from 2-acetylthiophene by a modified Leuckart synthesis.[65] β-(2-Thienyl)ethylamine is obtained by a three-step process from β-(2-thienyl)acrylic acid [91] and from β-(2-thienyl)ethyl bromide and ammonia.[65] Interaction of γ-(2-thienyl)propyl iodide and ammonia yields γ-(2-thienyl)propylamine.[65]

HYDROXYTHIOPHENES

2-Hydroxythiophene has been obtained by the action of oxygen on 2-thienylmagnesium bromide in the presence of isopropylmagnesium bromide, and various substituted hydroxythiophenes have been prepared. The 3-hydroxy derivative has been prepared by the same method.[92] Both 2- and 3-hydroxythiophenes are unstable and decompose in a few days even at ice temperature. In this respect they resemble the hydroxyfurans.

2-Mercaptothiophene is formed in small amount when sodium succinate is heated with "phosphorus trisulfide," [93] and it has been obtained by reduction of the zinc salt of thiophene-2-sulfinic acid with tin and hydrochloric acid.[94] It is a yellow oil with a very unpleasant odor, oxidizes gradually in air, and forms dyes with diazonium salts.

2-Methyl-5-hydroxythiophene and also 2-methylthiophene are formed when levulinic acid is heated with phosphorus sulfide.[19,95] The hydroxy compound has a disagreeable odor and is decomposed by contact with air. The facts that it dissolves in alkali and forms an acetate and benzoate indicate that it exists in a hydroxy (phenolic) form. However, it also reacts with benzaldehyde to yield a benzal derivative, is oxidized by ferric chloride to an indigoid dye, and undergoes other reactions which support the assumption of a keto form.[96] The decomposition of the compound by alkali is accounted for by Steinkopf on the basis that the keto form represents a thiolactone.[97] 2,3-Dimethyl-5-hydroxythiophene is obtained as a by-product in the preparation of

90 Goldschmidt and Schulthess, *Ber.*, **20**, 1700 (1887).

91 Barger and Easson, *J. Chem. Soc.*, 2100 (1938).

92 Kreuz and Hurd, abstracts of papers, 113th meeting, American Chemical Society, Chicago, April 1948, p. 28L. Kreuz, Dissertation, Northwestern University, 1948. See also Thomas, *Compt. rend.*, **146**, 642 (1908).

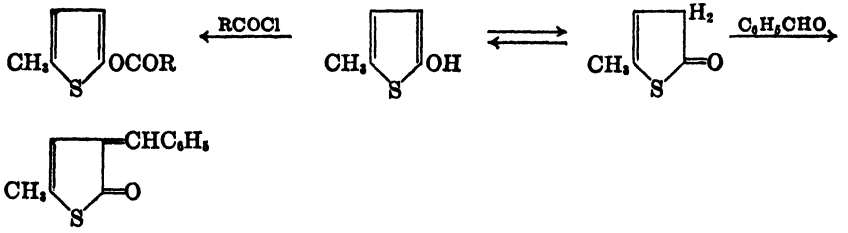
93 Meyer and Neure, *Ber.*, **20**, 1756 (1887).

94 Biedermann, *Ber.*, **19**, 1615 (1886).

95 Ref. 8, p. 34.

96 Steinkopf and Thormann, *Ann.*, **540**, 1 (1939).

97 Ref. 8, p. 63, footnote 3.



2,3-dimethylthiophene from β-methyllevulinic acid and "phosphorus trisulfide." [98]

Tautomerism has also been established for 2-phenyl-4-hydroxythiophene.[99] Among the reactions which it undergoes are the formation of a 5-oximino derivative with nitrous acid, oxidation by potassium ferricyanide to an indigoid dye, and conversion by bromine into 2-phenyl-3,5,5-tribromo-4-keto-4,5-dihydrothiophene.

3,4-Dihydroxythiophene is found to be so reactive towards oxygen that it can be isolated only in the form of its dibenzoate.[100] β-2-(3,4-Dihydroxythienyl)propionic acid seems to exist only in the dihydroxy form. It will not form a dioxime and, in solution, becomes blue-green when treated with ferric chloride.[101] A solution of δ-2-(3,4-dihydroxythienyl)valeric acid becomes deep blue upon the addition of ferric chloride solution.[102, 103]

2-Thenyl alcohol (2-thienylmethanol) has been prepared from thiophene-2-aldehyde by the Cannizzaro reaction,[76] by a crossed Cannizzaro reaction with formaldehyde,[104] and by the action of formaldehyde on 2-thienylmagnesium iodide.[105]

β-(2-Thienyl)ethanol can be obtained by interaction of 2-thienylmagnesium bromide and ethylene oxide;[65] with propylene oxide, α-methyl-β-(2-thienyl)ethanol is produced.[65]

THIOPHENEALDEHYDES

Thiophene-2-aldehyde is a colorless liquid which, in its odor and chemical behavior, greatly resembles benzaldehyde. It oxidizes in

98 Paal and Püschel, *Ber.*, **20**, 2557 (1887).
99 Friedländer and Kielbasinski, *Ber.*, **45**, 3389 (1912).
100 Farger, *J. Am. Chem. Soc.*, **67**, 2217 (1945).
101 Karrer and Kehrer, *Helv. Chim. Acta*, **27**, 142 (1944).
102 Karrer, Keller, and Usteri, *Helv. Chem. Acta*, **27**, 237 (1944).
103 See pp. 236 ff. for the behavior of other hydroxy acids.
104 Dunn and Dittmer, *J. Am. Chem. Soc.*, **68**, 256 (1946).
105 Steinkopf, *Ann.*, **540**, 14 (1939).

air to thiophene-2-carboxylic acid [106] and is converted by concentrated aqueous potassium hydroxide into a mixture of 2-thienylcarbinol and thiophene-2-carboxylic acid. Interaction with acetic anhydride and sodium acetate yields β-(2-thienyl)acrylic acid,[107] and with dimethylaniline and zinc chloride di-(*p*-dimethylaminophenyl)-2-thienylmethane is obtained.[108] The aldehyde condenses with thiophene, in the presence of phosphorus pentoxide, to produce tri-2-thienylmethane.[109] In many other instances,[110] its reactions parallel those of benzaldehyde; however, in solution, it undergoes resinification when treated with potassium cyanide, although 2,2′-thenoin can be isolated.[110a]

The best laboratory procedures for the preparation of the aldehyde involve the interaction of 2-thenyl chloride with hexamethylenetetramine and decomposition of the addition product that is formed (Sommelet reaction),[111] and the reaction of 2-thienylmagnesium bromide with ethyl orthoformate with subsequent hydrolysis of the diethyl acetal formed first.[112] In order to prevent oxidation, it is advisable to store the aldehyde in the form of the acetal.

$$\underset{\text{R = 2-thienyl}}{\text{RMgBr}} \xrightarrow{\text{HC(OC}_2\text{H}_5)_3} \text{RCH(OC}_2\text{H}_5)_2 \xrightarrow{\text{hydrolysis}} \text{RCHO}$$

Thiophene-3-aldehyde has been obtained from 3-thienylmagnesium iodide and ethyl orthoformate [113] and from 3-thenyl bromide by the Sommelet reaction.[77] In odor and in the ease with which it is oxidized, it resembles the 2-aldehyde. The 3-aldehyde condenses with rhodanine to form 3-thenalrhodanine, and with hippuric acid to yield 2-phenyl-4-(3-thenal)-5-oxazolone.[77]

Several dialdehydes have been synthesized, and 3,4-dibromothiophene-2,5-dialdehyde has been studied in some detail.[114]

106 Biedermann, *Ber.*, **19**, 636 (1886). In this reference, the aldehyde is called, incorrectly, the β-aldehyde.

107 Biedermann, *Ber.*, **19**, 1853 (1886).

108 Levi, *Ber.*, **20**, 513 (1887).

109 Nahke, *Ber.*, **30**, 2037 (1897).

110 Grischkewitsch-Trochimowski and Mazurewitsch, *J. Russ. Phys. Chem. Soc.*, **44**, 570 (1912) [*C. A.*, **6**, 2406 (1912)].

110a Deschamps, King, and Nord, *J. Org. Chem.*, **14**, 184 (1949).

111 Dunn, Waugh, and Dittmer, *J. Am. Chem. Soc.*, **68**, 2118 (1946).

112 Grischkewitsch-Trochimowski, *J. Russ. Phys. Chem. Soc.*, **43**, 206 (1911) [*C. A.*, **6**, 223 (1912)]. These investigators used 2-thienylmagnesium iodide; however, it is more advantageous to prepare the Grignard reagent from 2-bromothiophene.

113 Steinkopf and Schmitt, *Ann.*, **533**, 264 (1938).

114 Ref. 8, pp. 67–69.

2-Thienylglyoxal, $(C_4H_3S)COCHO$, is produced by hydrolysis of the isonitroso derivative obtained from 2-acetylthiophene [115] and by oxidation of 2-acetylthiophene with selenium dioxide.[116]

2-Thenoylacetaldehyde, $(C_4H_3S)COCH_2CHO$, is formed by condensation of 2-acetylthiophene and ethyl formate in the presence of sodium ethoxide.[117] It polymerizes spontaneously to 1,3,5-tri-(2-thenoyl)benzene.

ACYLTHIOPHENES

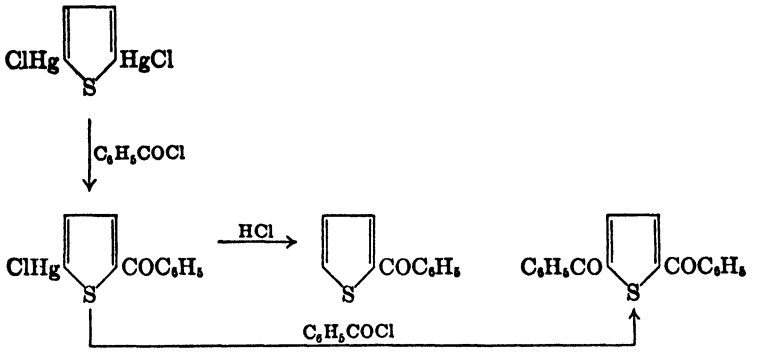
The Friedel-Crafts reaction is applicable for the preparation of acylthiophenes; 2-acetylthiophene (2-acetothienone) was obtained in 90% yield by this process.[66] However, unless proper precautions are observed, tarry products may be obtained owing to the action of aluminum chloride on thiophene. Since thiophene is such a reactive substance, condensation agents less active than aluminum chloride can be employed; for example, with stannic chloride [118–122] or titanium chloride,[123] ketones such as 2-acetylthiophene (2-acetothienone) and 2-benzoylthiophene (2-benzothienone) have been obtained in excellent yields. Benzene serves as a solvent in the presence of stannic chloride or titanium tetrachloride, since these inorganic chlorides will not initiate a reaction between benzene and the acid chloride.

It has been found that acylation of thiophene with acetic anhydride or benzoyl chloride is promoted by catalytic amounts of iodine and hydriodic acid [124] or boron trifluoride complexes,[125] and acylation with acetic or benzoic anhydride by catalytic quantities of zinc chloride.[124] Acylation with acetic anhydride, benzoyl chloride, phthalyl chloride, or adipyl chloride can be carried out with the aid of naturally occurring clays of the montmorillonite family, glauconite, or synthetic silica-metal gels.[126] Thiophene, 3-methyl-, and 2,5-dichloro-thiophene react with acid anhydrides or acid chlorides, in the presence of orthophos-

115 Fujise, *Biochem. Z.*, **236**, 241 (1931).
116 Kipnis and Ornfelt, *J. Am. Chem. Soc.*, **68**, 2734 (1946).
117 Kleber and Schwarz, *Ber.*, **45**, 2484 (1912).
118 Stadnikoff and Rakowsky, *Ber.*, **61**, 268 (1928).
119 Stadnikoff and Goldfarb, *Ber.*, **61**, 2341 (1928).
120 *Org. Syntheses Coll. Vol.* **2**, 8 (1943).
121 Cagniant and Deluzarche, *Compt. rend.*, **225**, 455 (1947).
122 Campaigne and Diedrich, *J. Am. Chem. Soc.*, **70**, 391 (1948).
123 Stadnikoff and Kaschtanoff, *Ber.*, **61**, 1389 (1928).
124 Hartough and Kosak, *J. Am. Chem. Soc.*, **68**, 2639 (1946); **69**, 1012 (1947).
125 Hartough and Kosak, *J. Am. Chem. Soc.*, **70**, 867 (1948).
126 Hartough, Kosak, and Sardella, *J. Am. Chem. Soc.*, **69**, 1014 (1947).

phoric acid, to form acyl derivatives, in many instances in very good yields.[127] Thiophene can be acylated with an aliphatic or aromatic acid and phosphorus pentoxide.[128]

Acylthiophenes have been prepared by interaction of a chloromercurithiophene and an acid chloride;[41,129,130] both mono- and di-acyl derivatives can be obtained by this procedure.[131] Ketones can be syn-



thesized also by condensation of thiophene or a homolog with an acid chloride in the presence of phosphorus pentoxide,[132,133] by the action of thienylmagnesium iodide on a nitrile,[134] or by heating the calcium salt of a thiophenecarboxylic acid.[113,135] 3-Acetylthiophene has been prepared by interaction of 3-thenoyl chloride with cadmium methyl.[77]

2-Thienyl phenyl diketone, a thiophene analog of benzil, has been studied, especially with respect to its oximes and potassium derivatives.[105] Thiophene-3-aldehyde in alcoholic solution is converted into 3,3′-thenoin by sodium cyanide.[77]

Acylthiophenes undergo the characteristic reactions of acylbenzenes, including the Mannich reaction.[136] 2-Acetyl- and 2-propionyl-thiophene react with acrylonitrile to form 1,1,1-tri-(β-cyanomethyl)methyl-2-thienyl ketone and γ-methyl-γ-thenoylpimelonitrile, respec-

127 Hartough and Kosak, *J. Am. Chem. Soc.*, **69**, 3093 (1947).

128 Hartough and Kosak, *J. Am. Chem. Soc.*, **69**, 3098 (1947). Cf. p. 144 for similarly catalyzed acylations of furan.

129 Volhard, *Ann.*, **267**, 172 (1892).

130 Steinkopf, *Ann.*, **424**, 23 (1920).

131 Steinkopf and Killingstad, *Ann.*, **532**, 288 (1937).

132 Steinkopf, *Ann.*, **413**, 343 (1917).

133 Steinkopf and Schubart, *Ann.*, **424**, 1 (1921).

134 Thomas and Couderc, *Bull. soc. chim. France*, [4] **23**, 288 (1918).

135 Gattermann, *Ber.*, **18**, 3013 (1885).

136 Blicke and Burckhalter, *J. Am. Chem. Soc.*, **64**, 451 (1942).

tively.[137] 2-Acetylthiophene condenses, without aid of a catalyst, with aniline and primary aliphatic amines to yield ketimines.[138]

THIOPHENECARBOXYLIC ACIDS

Thiophenecarboxylic acids can be obtained by many of the general procedures for the preparation of benzenecarboxylic acids.

The interaction of a thienylmagnesium halide with carbon dioxide probably represents the most convenient laboratory process and has been employed for the synthesis of thiophene-2-[139-141] and thiophene-3-carboxylic acid,[113] as well as for homologs of these acids.[37,50] 3,4,5-Trichloro- and 3,4,5-tribromo-thiophenecarboxylic acid have also been obtained by this procedure.[35]

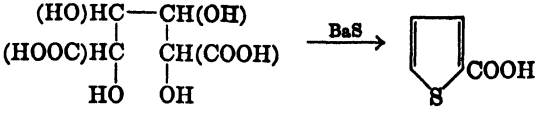
A number of thiophenecarboxylic acids have been prepared by oxidation of alkyl- or acetyl-thiophenes.[142,143] In addition to the desired carboxylic acid, a glyoxylic acid may also be produced[144] when an ethyl-[79] or acetyl-thiophene is oxidized.[145] 5-Halothiophene-2-carboxylic acids are formed by oxidation of a 5-halo-2-acetylthiophene,[47] and 2-nitrothiophene-3-carboxylic acid has been obtained by oxidation of 2-nitro-3-methylthiophene.[71]

2-Cyanothiophene, which can be synthesized by interaction of 2-thienylmagnesium bromide and cyanogen chloride[140] and by other procedures, yields thiophene-2-carboxylic acid on hydrolysis.[140]

The Wurtz synthesis and the Gattermann reaction have been used for the preparation of a few thiophenecarboxylic acids. Thus, 2-iodothiophene, ethyl chloroformate, and sodium amalgam react to form the 2-carboxylic acid;[146] iodoalkylthiophenes also take part in this synthesis.[147] Although thiophene does not react successfully, 3-methyl- and other alkyl-thiophenes react with carbamyl chloride and aluminum chloride to form amides which can then be hydrolyzed to the acids.[148]

137 Bruson and Riener, *J. Am. Chem. Soc.*, **70**, 214 (1948).
138 Hartough, *J. Am. Chem. Soc.*, **70**, 1282 (1948).
139 Schlenk and Ochs, *Ber.*, **48**, 676 (1915).
140 Steinkopf and Ohse, *Ann.*, **437**, 14 (1924).
141 Blicke and Zienty, *J. Am. Chem. Soc.*, **63**, 2945 (1941).
142 Hartough and Conley, *J. Am. Chem. Soc.*, **69**, 3096 (1947).
143 Ref. 8, p. 81.
144 Bradley, *Ber.*, **19**, 2115 (1886).
145 Peter, *Ber.*, **18**, 537 (1885).
146 Nahnsen, *Ber.*, **17**, 2192 (1884). The acid derivatives mentioned in this article are called, incorrectly, β compounds.
147 Levi, *Ber.*, **19**, 656 (1886).
148 Gattermann, *Ann.*, **244**, 58 (1888); Kitt, *Ber.*, **28**, 1807 (1895).

The preparation of thiophene-2-carboxylic acid from mucic acid and barium sulfide is an important reaction because it established the structure of this acid.[149]



The acid derivatives of the 2-carboxylic acid, such as the ethyl ester,[139] acid chloride,[146] amide,[146] anhydride,[140] hydrazide, and azide,[150] have been obtained by the conventional procedures.

Thiophene-3-aldehyde has been oxidized, by silver oxide, to thiophene-3-carboxylic acid in good yield.[77]

The formation of thiophene-2-carboxylic acid by interaction of a mixture of thiophene, mercury diethyl, and sodium with carbon dioxide,[151] and by carbonation of the product formed from thiophene and ethylmagnesium bromide in dimethylaniline at 160–170° [152] indicates that in these reactions thiophene must have been converted into a sodium derivative and into a Grignard reagent, respectively. It has been found that 2-chlorothiophene and metallic sodium or sodium amalgam react, in an inert solvent, above 50°, to form 2-thienylsodium in high yield; below 50°, a 2-halothiophene is converted into a 2-halo-5-thienylsodium. By carbonation of the metallic derivatives, thiophene-2-carboxylic acids are obtained.[153]

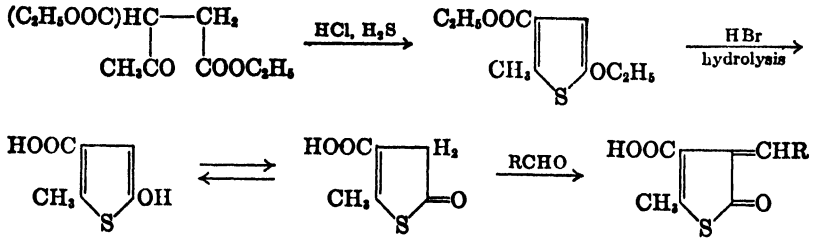
Chlorination of thiophene-2-carboxylic acid converts it into tetrachlorothiophene, but by bromination either 5-bromo-[35] or 4,5-dibromothiophene-2-carboxylic acid [35,39,154] is formed.

Nitration of the 2-carboxylic acid yields a mixture of 4-nitro- and 5-nitro-thiophene-2-carboxylic acid.[87,155] In order to prevent decarboxylation, certain acids are nitrated in the form of their esters.[56]

Hydroxy acids are obtained directly by condensation of aliphatic compounds.[156-158] An example is the synthesis of 2-methyl-5-hydroxythiophene-3-carboxylic acid which was prepared from the ethyl ester

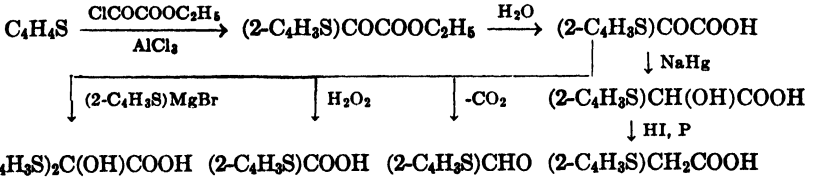
149 Paal and Tafel, *Ber.*, **18**, 456 (1885).
150 Curtius and Thyssen, *J. prakt. Chem.*, [2] **65**, 1 (1902).
151 Schorigin, *Ber.*, **43**, 1938 (1910).
152 Challenger and Gibson, *J. Chem. Soc.*, 305 (1940).
153 Schick and Hartough, *J. Am. Chem. Soc.*, **70**, 286 (1948).
154 Bonz, *Ber.*, **18**, 2308 (1885).
155 Rinkes, *Rec. trav. chim.*, **51**, 1134 (1932).
156 Benary and Baravian, *Ber.*, **48**, 593 (1915).
157 Benary and Silberstrom, *Ber.*, **52**, 1605 (1919).
158 Mitra, Chakrabarty, and Mitra, *J. Chem. Soc.*, 1116 (1939).

of β-carbethoxylevulinic acid.[158] Like many other, but not all,[159] hydroxy acids, it also exists in a keto form which undergoes condensation with aldehydes.



Thiophenecarboxylic acids in which the carboxyl group is not attached directly to the nucleus are of considerable interest, especially as intermediates for the synthesis of compounds of possible value as synthetic medicaments.

2-Thienylglyoxylic acid, $(2\text{-}C_4H_3S)COCOOH$, has been prepared by oxidation of 2-ethyl-[79] or 2-acetyl-thiophene [76,145] and by hydrolysis of 2-thenoyl cyanide.[105] Its synthesis from thiophene, ethyl oxalyl chloride, and aluminum chloride, with subsequent hydrolysis of the ethyl 2-thienylglyoxylate [160] which is formed, represents a good laboratory procedure.[161] This acid has been reduced to 2-thienylhydroxyacetic acid (2-thienylglycolic acid),[162] the thienyl analog of mandelic acid, and reduction of the latter substance with phosphorus and iodine yields 2-thienylacetic acid.[162] The glyoxylic acid reacts with 2-thienylmagnesium bromide to produce di-2-thienylhydroxyacetic acid,[161] the thienyl analog of benzilic acid, and when treated with hydrogen peroxide it is converted into thiophene-2-carboxylic acid.[163] At an elevated temperature, it loses carbon dioxide with the formation of the aldehyde.[164]



159 See refs. 101 and 102.

160 Steinkopf and Wolfram, *Ann.*, **437**, 22 (1924).

161 Blicke and Tsao, *J. Am. Chem. Soc.*, **66**, 1645 (1944).

162 Ernst, *Ber.*, **19**, 3278 (1886).

163 Holleman, *Rec. trav. chim.*, **23**, 169 (1904).

164 The decarboxylation in aniline has been described by du Vigneaud et al. [*J. Biol. Chem.*, **159**, 385 (1945)].

Since 2-thenyl chloride can easily be obtained by chloromethylation of thiophene and then converted into the cyanide,[75] hydrolysis of the cyanide [141] furnishes a practical method for the preparation of the acetic acid. By the Arndt-Eistert procedure, 2-thenoyl chloride can be converted into 2-thienylacetic acid.[141,165]

Acids that have been obtained by condensation of thiophene with succinic,[166] methylsuccinic,[167] glutaric,[168,169] or phthalic anhydride,[170,171] or from 2,5-dimethylthiophene and succinic anhydride,[42] in the presence of aluminum chloride, are essential intermediates in the preparation of certain bicyclic compounds. β-(2-Thenoyl)propionic acid, for example, after reduction to γ-(2-thienyl)butyric acid and conversion into the acid chloride, can be cyclized, by stannic chloride, to 4-keto-4,5,6,7-tetrahydrothianaphthene.[166]

Thiophenedicarboxylic acids are prepared by oxidation of dialkyl-, alkylacetyl-, or alkyl-thiophenecarboxylic acids. The 2,5-dicarboxylic acid has been obtained by oxidation of 2-methyl- [147] or 2-ethyl-5-acetylthiophene,[172] by reaction of 2,5-dibromothiophene, ethyl chloroformate, and sodium amalgam,[173] by hydrolysis of its dinitrile,[174] and by condensation of a 1,2-dicarbonyl compound, such as benzil, with diethyl thiodiacetate, and subsequent hydrolysis [22] (cf. p. 214).

THIOPHENESULFONIC ACIDS

When commercial benzene is shaken with concentrated sulfuric acid at room temperature for several hours, practically all the thiophene which it contains is converted into thiophene-2-sulfonic acid and only a very small amount of the benzene is sulfonated.[175] After separation and dilution of the sulfuric acid layer, the addition of lead carbonate converts the thiophenesulfonic acid into the water-soluble lead salt. By treatment of the aqueous solution with hydrogen sulfide, a solution

165 Arndt and Eistert, Ger. pat. 650,706 (1937) [*C. A.*, **32**, 595 (1938)].
166 Fieser and Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).
167 Kitchen and Sandin, *J. Am. Chem. Soc.*, **67**, 1645 (1945).
168 Melville et al., *J. Biol. Chem.*, **146**, 487 (1942).
169 Cagniant and Deluzarche, *Compt. rend.*, **222**, 1301 (1946).
170 Steinkopf, *Ann.*, **407**, 94 (1915).
171 Steinkopf, Barlag, and v. Petersdorff, *Ann.*, **540**, 7 (1939).
172 Schleicher, *Ber.*, **18**, 3015 (1885).
173 Bonz, *Ber.*, **18**, 2305 (1885).
174 Jackel, *Ber.*, **19**, 184 (1886).
175 Thiophene can be removed from benzene with aluminum chloride [Holmes and Beeman, *Ind. Eng. Chem.*, **26**, 172 (1934)].

of the sulfonic acid is obtained, and, after removal of the water, the sulfonic acid remains as a hygroscopic, crystalline material. It was by the aid of the sulfonic acid that Victor Meyer was able to isolate thiophene. Thiophene is produced by dry or steam distillation [176] of the sulfonic acid or by destructive distillation of a mixture of the lead salt of the sulfonic acid and ammonium chloride.[2] By the sulfonation of thiophene with 95% sulfuric acid, thiophene-2-sulfonic acid is obtained in 69–76% yield.[110]

In a number of instances, an α-acyl group is replaced by a sulfonic acid radical during sulfonation.[52,53,177] With pyrosulfuric acid, it is possible to convert 2-isobutyrylthiophene into a sulfonic acid without loss of the acyl group.[178]

Thiophene-3-sulfonic acid has been prepared by removal of the bromine atoms, with sodium amalgam, from 2,5-dibromothiophene-3-sulfonic acid.[44] Sodium amalgam also eliminates a sulfonyl chloride radical from thiophene-2,4-disulfonyl chloride with the production of thiophene-3-sulfonyl chloride.[35] Thiophene-2,4-disulfonyl chloride, and also the 2,5-disulfonyl chloride, is formed by sulfonation of thiophene-2-sulfonyl chloride and subsequent treatment of the mixture of sulfonic acids with phosphorus pentachloride.[84]

Thiophenesulfonic acids can be converted into the same series of derivatives which is characteristic of benzenesulfonic acids—esters, sulfonyl chlorides, sulfonamides, and sulfonanilides.[179]

Sulfonic acids cannot be halogenated, but it is possible to sulfonate certain halogenated thiophenes. During sulfonation, the halogen is removed from 2-bromo- and 2-iodo-thiophene.[35,44] 2-Nitrothiophene can be sulfonated,[180] and thiophene-2- and thiophene-3-sulfonyl chloride can be nitrated.[84]

The sulfonation of many thiophene compounds has been effected by the use of chlorosulfonic acid in order to obtain the sulfonyl chloride rather than the hygroscopic sulfonic acid. 2-Chlorothiophene reacts with chlorosulfonic acid to yield 2-chlorothiophene-5-sulfonyl chloride.[39]

176 Schulze, *Ber.*, **18**, 497 (1885).

177 Schleicher, *Ber.*, **19**, 660 (1886).

178 Krekeler, *Ber.*, **19**, 2623 (1886).

179 For tabulations of thiophenesulfonic acids and their derivatives, see *Organic Chemistry of Sulfur*, Suter, John Wiley & Sons, New York, 1944, p. 318, and Steinkopf, ref. 8, pp. 101 and 102.

180 Stadler, *Ber.*, **18**, 530 (1885).

The reduction of thiophene-2-sulfonyl chloride with zinc yields the zinc salt of thiophene-2-sulfinic acid.[45]

MERCURY DERIVATIVES

Extensive use has been made of mercury derivatives for the synthesis, isolation, purification, and identification of compounds in the thiophene series.

Thiophene reacts with mercuric chloride to form 2-chloromercuri- and 2,5-dichloromercuri-thiophene; in order to prevent a reversal of the reaction by the hydrochloric acid which is formed, sodium acetate is added to the reaction mixture.[129,131] In general, only an α-hydrogen can be replaced directly by a chloromercuri group at a low temperature.[131] Tetrachloromercurithiophene can be obtained, indirectly, in quantitative yield, by treatment of tetraacetoxymercurithiophene with sodium chloride.[182]

When thiophene, in acetic acid solution, is boiled with mercuric acetate or mercuric oxide, it is converted, quantitatively, into tetraacetoxymercurithiophene.[183] By the same procedure, all nuclear hydrogen atoms in thiophene homologs and halothiophenes can be replaced by acetoxymercuri groups.

It is difficult to introduce a chloromercuri group into thiophene-2-carboxylic acid with mercuric chloride.[184] When mercuric acetate reacts with this acid, it is decarboxylated and converted into tetraacetoxymercurithiophene.[185] Neither 2- nor 3-nitrothiophene can be mercurated with mercuric chloride,[41,85] but mercuric acetate converts 2-nitrothiophene into a diacetoxymercuri derivative, and 3-nitrothiophene into a triacetoxymercuri compound.[85] Although mercuric chloride does not react with 2,5-dichlorothiophene, mercuric acetate converts it into 2,5-dichloro-3,4-diacetoxymercurithiophene.[39] The dif-

181 According to Steinkopf and Bauermeister [*Ann.*, **403**, 50 (1914)], 2,5-dimethylthiophene reacts with mercuric chloride to yield a 3-chloromercuri derivative, but a number of other 2,5-dialkylthiophenes, such as the 2,5-diethyl compound, are unreactive toward mercuric chloride [Steinkopf, *Ann.*, **430**, 92 (1923)].

2-Thienyl ethyl ether exhibits an exceptional behavior in that it forms a dichloromercuri derivative in which one of the chloromercuri groups must occupy a β position [Steinkopf and Leonhardt, *Ann.*, **495**, 166 (1932)].

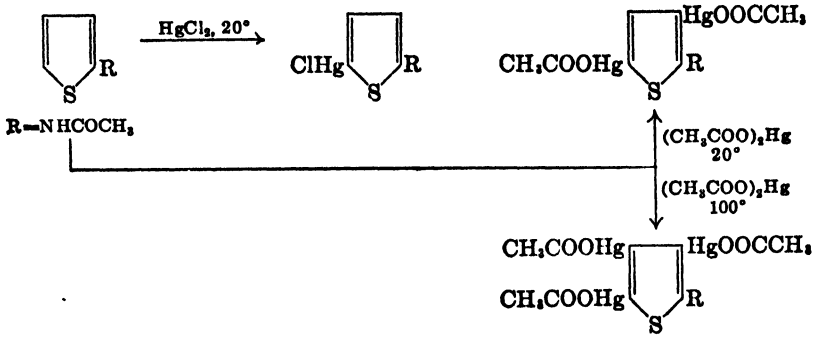
182 Ref. 8, p. 111.

183 Paolini and Silbermann, *Gazz. chim. ital.*, **45**, 385 (1915).

184 Steinkopf, *Ann.*, **413**, 310 (1916).

185 Ref. 8, p. 85.

ference in behavior between mercuric chloride and mercuric acetate is shown also by the following reaction scheme.[27]



It becomes evident from a study of mercuration reactions that, with mercuric acetate instead of mercuric chloride, a more highly mercurated product can be obtained and that in many instances mercuration can be effected under milder conditions. Benzene and its homologs do not react with mercuric chloride. However, by interaction with mercuric acetate, at about 110°, acetoxymercuribenzene can be obtained.[186]

Chloromercuri derivatives are less soluble than corresponding acetoxymercuri compounds and often can be purified with greater ease. When a chloromercuri or an acetoxymercuri derivative is boiled with dilute hydrochloric acid, the mercury radical is replaced by hydrogen. In these instances, a better yield of the mercury-free product is obtained when the chloromercuri derivative is employed.[187]

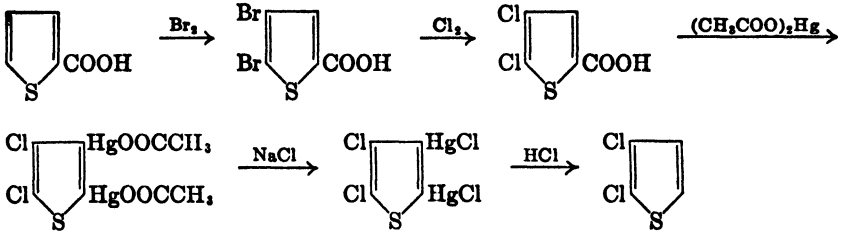
A thiophene-α-carboxylic acid, but not a β acid, is converted into an α-acetoxymercuri derivative when it is heated with mercuric acetate.[50] This transformation can be explained in the following manner.

$$RCOOH \rightarrow RCOOHgOOCCH_3 \rightarrow RHgOOCCH_3 + CO_2$$

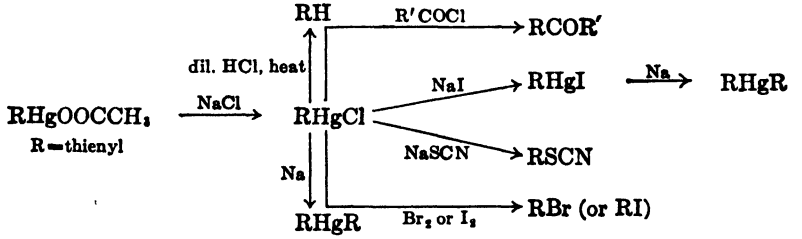
This reaction finds considerable application for the preparation of thiophene derivatives, for example, in the synthesis of 2,3-dichlorothiophene from 4,5-dibromothiophene-2-carboxylic acid.[39] Owing to decarboxylation and the formation of polychloro derivatives, 4,5-dichlorothiophene-2-carboxylic acid cannot be prepared by chlorination of thiophene-2-carboxylic acid.[39] However, the synthesis of 4,5-dibromothiophene-2-carboxylic acid, by bromination of thiophene-2-carboxylic acid, is a satisfactory procedure. In boiling acetic acid solu-

186 Roeder and Blasi, *Ber.*, **47**, 2751 (1914).
187 Ref. 35, p. 250, footnote 6.

tion, chlorine will displace the bromine from 4,5-dibromothiophene-2-carboxylic acid with the formation of the corresponding 4,5-dichloro acid. When the 4,5-dichloro acid is treated with mercuric acetate, 4,5-dichloro-2,3-diacetoxymercurithiophene is produced. This compound is converted, by the action of sodium chloride, into the corresponding 2,3-dichloromercuri derivative, and the mercury is then removed by boiling the compound with dilute hydrochloric acid; the product is 2,3-dichlorothiophene.[39]



The reactions of the mercury compounds are summarized in the following scheme.



Attempts to bring about a reaction between a chloromercurithiophene and an alkyl halide have not been successful.[129]

Compounds of the dithienylmercury type react with a mercuric halide to form a halomercurithiophene.[184]

$$RHgR + HgX_2 \rightarrow 2RHgX$$

R = thienyl; X = Cl, Br, or I

MAGNESIUM COMPOUNDS

The usefulness and application of Grignard reagents is as great in the thiophene as in the benzene series. These reagents have been of special importance for the preparation of certain bromo- and iodothiophenes, since one or more undesired bromine or iodine atoms in a polyhalothiophene can be replaced easily by hydrogen, by the Grignard degradation (cf. p. 222).

Under the usual conditions, 2-chlorothiophene, like chlorobenzene,[188] will not react with magnesium to form a Grignard reagent, but the 2-bromo and the 2-iodo compounds can be converted readily into Grignard reagents. The formation of dithienyls or dithienylalkanes as by-products takes place only to a slight extent, except with 2-bromo-5-phenylthiophene,[189] 2-thenyl chloride,[65] and 2-thenyl bromide.[77]

In order to prepare a Grignard reagent from a 3-bromo-, a 3-iodo-, a polybromo- or a polyiodo-thiophene, it is necessary to add methyl bromide, methyl iodide, or ethyl bromide to the reaction mixture.[35,190]

Only one of the nuclear halogens in a polyhalothiophene will react with magnesium, and, as in other instances, an α-halogen is by far the more reactive. The behavior of 2,5-dichloro-3,4-diiodothiophene is very unusual in that both β-iodine atoms seem to react with magnesium; after carbonation of the Grignard reagent, 2,5-dichlorothiophene-3,4-dicarboxylic acid is obtained.[191]

The use of thienylmagnesium halides for the synthesis of various types of thiophene derivatives is entirely similar to that of phenylmagnesium halides for the preparation of benzene derivatives and has been mentioned in other places.

OTHER METALLIC DERIVATIVES

In addition to the compounds that contain mercury or magnesium, arsenicals, analogous in structure to those that are well known in the benzene series, have been described.[88,184,192] Examples of such compounds are $RAsCl_2$, R_2AsCl, R_3As, RAs=AsR, RAsO, $R_2AsOAsR_2$, $RAsO(OH)_2$, and $R_2AsO(OH)$, in which R represents a 2-thienyl or a substituted 2-thienyl group. Many of the general processes applicable to the phenyl analogs are employed for their preparation. For example, oxidation of 2-thienyldichloroarsine yields 2-thienylarsonic acid, and reduction of the latter acid with hypophosphorous acid produces 2,2′-arsenothiophene. However, two general procedures for the direct introduction of arsenic into compounds of the benzene series, the Bechamp and the Bart reactions, are not serviceable.

188 Magnesium and boiling chlorobenzene do react slowly to form a Grignard reagent [Blicke and Monroe, *J. Am. Chem. Soc.*, **57**, 720 (1935), footnote 5; see also Schorygin and Issaguljanz, *Chem. Zentr.*, **107**, II, 2345 (1936); *C. A.*, **30**, 4157 (1936)].

189 Steinkopf, v. Petersdorff, and Gording, *Ann.*, **527**, 272 (1937).

190 Grignard, *Compt. rend.*, **198**, 625 (1934).

191 Steinkopf and Köhler, *Ann.*, **532**, 250 (1937).

192 Finzi, *Gazz. chim. ital.*, **45**, II, 280 (1915); **55**, 824 (1925); **62**, 244 (1932).

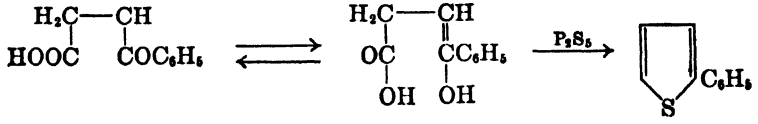
Organometallic derivatives of boron,[193] thallium,[194] silicon,[194] germanium,[193] tin,[194–196] lead,[194,195,197] phosphorus,[198] antimony,[193] bismuth,[194] and tellurium [193,194] have been obtained, in many instances, by interaction of 2-thienylmagnesium bromide or iodide with the required metallic halide.

$$4(C_4H_3S)MgI + SnCl_4 \rightarrow (C_4H_3S)_4Sn$$

$$2(C_4H_3S)MgBr + TlCl_3 \rightarrow (C_4H_3S)_2TlCl + (C_4H_3S)_2TlBr \xrightarrow{NaBr} (C_4H_3S)_2TlBr$$

ARYLTHIOPHENES

2-Phenyl- [21,199] and 3-phenyl-,[21,200] 2,4-diphenyl-,[201] 2,5-diphenyl-,[202] and 3,4-diphenyl-,[203] 2,3,5-triphenyl- [204] and tetraphenyl-thiophene [205–207] and some of the corresponding tolyl compounds represent known arylthiophenes. Many products of this type can be obtained by condensation of a 1,4-dicarbonyl compound with a phosphorus sulfide. Thus, 2-phenylthiophene is formed from β-benzoylpropionic acid [199] or its sodium salt.[21] The ketodihydrothiophene, which may be formed as an intermediate in this reaction, is reduced by the phosphorus sulfide to the thiophene. 2-Arylthiophenes have also been ob-



tained by addition of sodium hydroxide to a mixture of diazotized aromatic amine and an aromatic-type substance such as benzene, thio-

193 Krause and Renwanz, *Ber.*, **65**, 777 (1932).

194 Krause and Renwanz, *Ber.*, **62**, 1710 (1929).

195 Krause and Renwanz, *Ber.*, **60**, 1582 (1927).

196 Bobaschinskaja and Kotscheschkow, *J. Ser. A. J. allgem. Chem.*, **8**, 1850 (1938) [*C. A.*, **38**, 5820 (1939)].

197 Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932).

198 Sachs, *Ber.*, **25**, 1514 (1892); Kosolopoff, *J. Am. Chem Soc.*, **69**, 2248 (1947).

199 Kues and Paal, *Ber.*, **19**, 3141 (1886).

200 See also Brown and Voronkov [*J. Gen. Chem (U.S.S.R.)*, **17**, 1162 (1947); *C. A.*, **42**, 1591 (1948)] for the preparation of 3-phenylthiophene and some of its homologs.

201 Glass and Reid, *J. Am. Chem. Soc.*, **51**, 3428 (1929).

202 Kapf and Paal, *Ber.*, **21**, 3053 (1888).

203 Hinsberg, *Ber.*, **48**, 1611 (1915).

204 Smith, *J. Chem. Soc.*, **57**, 643 (1890).

205 Laurent, *Ann.*, **52**, 354 (1844).

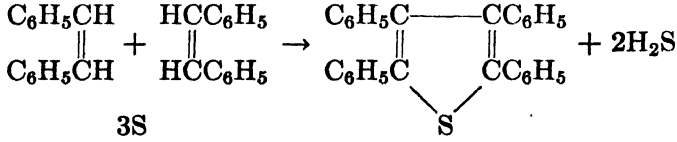
206 Baumann and Fromm, *Ber.*, **24**, 1441 (1891).

207 Baumann and Klett, *Ber.*, **24**, 3307 (1891).

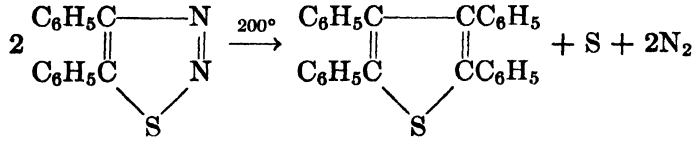
phene, or pyridine; a "diazo oxide" is formed which reacts with the "aromatic" nucleus to produce a biaryl type, for example, a 2-arylthiophene.[208]

$$RN_2ON_2R + 2R'H \rightarrow 2RR' + N_2 + H_2O$$
R = aryl; R' = 2-thienyl

Tetraphenylthiophene, which seems to be the oldest thiophene compound known, has been studied quite extensively. In 1844, it was found [205] that distillation of polymeric thiobenzaldehyde yields a substance which was named thionessal, and in 1891 [206, 207] it was shown that, during the distillation process, stilbene and sulfur are formed, and that it is from the interaction of these substances that thionessal is produced. After the recognition of this fact, it was not difficult to establish the structure of thionessal as tetraphenylthiophene.

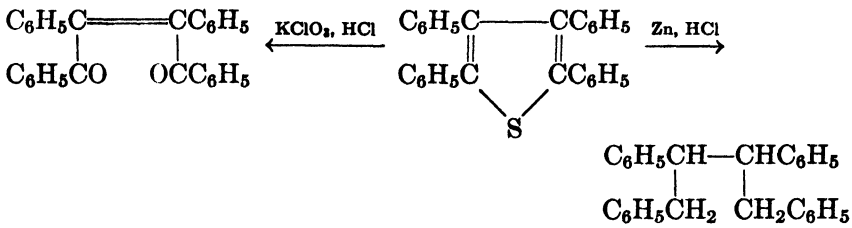


At least ten different derivatives of benzene are known to yield tetraphenylthiophene when they are heated alone or with sulfur, or are subjected to some other treatment. Especially interesting is the conversion, by heat, of 4,5-diphenylthiodiazole into tetraphenylthiophene; [209] the thiophene is obtained in good yield.



The tetraphenyl compound is characterized by its great stability toward heat. It can be sublimed, it distils unchanged at 460°, and its vapors can be passed over red-hot iron or copper with only slight decomposition; [210] fusion with alkali leaves it unchanged. By oxidation it is converted into *cis*-α,α'-dibenzoylstilbene,[210, 211] and by reduction into 1,2,3,4-tetraphenylbutane.[212]

208 Gomberg and Bachmann, *J. Am. Chem. Soc.*, **46**, 2339 (1924).
209 Staudinger and Siegwart, *Ber.*, **49**, 1918 (1916).
210 Dorn, *Ann.*, **153**, 349 (1870).
211 Fleischer, *Ann.*, **144**, 195 (1867); Berlin, *Ann.*, **153**, 130 (1870).
212 Fromm and Achert, *Ber.*, **36**, 534 (1903).



Hydrogen peroxide converts tetraphenylthiophene into a sulfone; zinc with a mixture of acetic and hydrochloric acid reduces the sulfone to the thiophene.[208]

THIENYLALKANES AND DERIVATIVES

Monothienylalkanes, that is, alkylthiophenes, can be obtained by many of the general reactions applicable to the synthesis of phenylalkanes. The same statement can be made with respect to the preparation of polythienylalkanes and mixed polysubstituted alkanes in which the substituents may be both phenyl and thienyl.

The following formulations indicate the manner in which substituted methanes have been obtained.

$$C_6H_5CH_2OH + C_4H_4S + \xrightarrow[CH_3COOH]{H_2SO_4} C_6H_5CH_2(C_4H_3S)\ ^{213}$$

$$(C_6H_5)_2CHOH + C_4H_4S + P_2O_5 \rightarrow (C_6H_5)_2CH(C_4H_3S)\ ^{214}$$

$$C_6H_5CHO + 2C_4H_4S + P_2O_5 \rightarrow C_6H_5CH(C_4H_3S)_2\ ^{215}$$

$$C_6H_5CHCl_2 + 2C_4H_4S + AlCl_3 \rightarrow C_6H_5CH(C_4H_3S)_2\ ^{215}$$

$$(C_4H_3S)CHO + 2C_4H_4S + P_2O_5 \rightarrow (C_4H_3S)_3CH\ ^{109}$$

$$(C_6H_5)_3COH + C_4H_4S + P_2O_5 \rightarrow (C_6H_5)_3C(C_4H_3S)\ ^{216}$$

Derivatives of ethane, propane, and other aliphatic hydrocarbons are formed by interaction of thiophene with an aldehyde in the presence of a condensation agent. In this manner, α,α-di-(2-thienyl)ethane is obtained from paraldehyde, and α,α-di-(2-thienyl)propane from propionaldehyde.[109]

Chloral condenses with thiophene to produce α,α-di-(2-thienyl)-β,β,β-trichloroethane,[217] a substance which can be converted into α,α-

213 Peter, *Ber.*, **17**, 1341 (1884).

214 Levi, *Ber.*, **19**, 1623 (1886).

215 Thöl and Nahke, *Ber.*, **29**, 2205 (1896).

216 Weisse, *Ber.*, **28**, 1537 (1895); **29**, 1402 (1896).

217 A product, analogous to DDT, has been obtained by interaction of 2-chlorothiophene with chloral under suitable conditions [Truitt, Mattison, and Richardson, *J. Am. Chem. Soc.*, **70**, 79 (1948)].

di-(2-thienyl)-β,β-dichloroethylene by treatment with alcoholic potassium hydroxide.[218]

Di- and tri-substituted carbinols have been obtained by well-known general procedures such as reduction of a ketone and interaction of a ketone or ester with a Grignard reagent.

$$C_6H_5CO(C_4H_3S) \xrightarrow{Al\text{-}Hg} C_6H_5CH(OH)(C_4H_3S)\ ^{218}$$

$$C_6H_5CO(C_4H_3S) \xrightarrow{(C_4H_3S)MgI} C_6H_5(C_4H_3S)_2COH\ ^{219}$$

$$C_6H_5COOC_2H_5 \xrightarrow{2(C_4H_3S)MgI} C_6H_5(C_4H_3S)_2COH\ ^{220}$$

When 2-acetylthiophene is reduced with aluminum isopropoxide in isopropyl alcohol, 2-thienylmethylcarbinol is obtained in 50% yield; $(C_4H_3S)CH(CH_3)OCH(CH_3)_2$, α-(2-thienyl)ethyl isopropyl ether, and $(C_4H_3S)(CH_3)CHOCH(CH_3)(C_4H_3S)$, di-$\alpha,\alpha'$-(2-thienyl)diethyl ether, are obtained as by-products.[32,33,122]

Tri-(2-thienyl)carbinol has been prepared by interaction of 2-thienylmagnesium iodide with di-(2-thienyl) ketone,[221] or with ethyl thienyl-2-carboxylate.[139] However, the compound is so unstable that it can be isolated only in the form of a derivative such as the perchlorate.

2-Thienyldi-(*p*-dimethylaminophenyl)carbinol reacts with mineral acids to form a dye which resembles malachite green.[108]

BITHIENYLS AND POLYTHIENYLS

Thiophene and benzene undergo similar transformations when they are passed through a red-hot tube. Thiophene is converted into 2,2'-bithienyl and also, to some extent, into 3,3'-bithienyl.[222,223] Although it was not isolated, it seems probable that 2,3'-bithienyl may also be formed. 2,2'-Bithienyl can be synthesized by heating 2-iodothiophene with silver [224] or copper [225] and by reaction between anhydrous cupric chloride and 2-thienylmagnesium bromide.[226] The bithienyl can be

218 Minnis, *J. Am. Chem. Soc.*, **51**, 2143 (1929).

219 Thomas and Couderc, *Bull. soc. chim. France*, [4] **23**, 326 (1918).

220 Gomberg and Jickling, *J. Am. Chem. Soc.*, **35**, 446 (1913).

221 Tschitschibabin and Dawrilow, *J. Russ. Phys. Chem. Soc.*, **46**, 1614 (1914) [*C. A.*, **9**, 2069 (1915)].

222 Nahnsen, *Ber.*, **17**, 789 (1884).

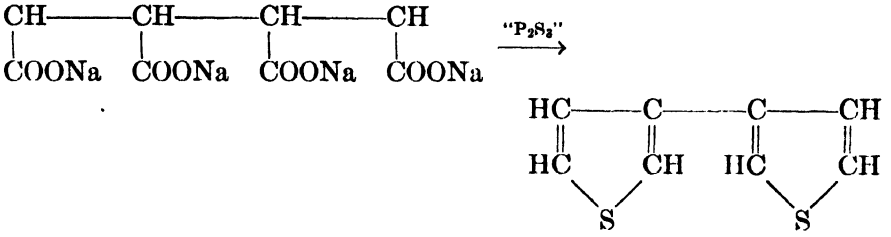
223 Auwers and Bredt, *Ber.*, **27**, 1741 (1894).

224 Eberhard, *Ber.*, **27**, 2919 (1894).

225 Cf. the preparation of 5,5'-dimethyl-2,2'-bithienyl [Steinkopf, Leitsmann, Müller, and Wilhelm, *Ann.*, **541**, 260 (1939)].

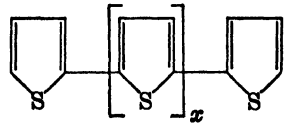
226 Steinkopf and Roch, *Ann.*, **482**, 251 (1930).

halogenated,[222,227] sulfonated,[146] and nitrated.[227] Chloro- and bromobithienyls are formed also by the action of concentrated sulfuric acid on chloro- and bromo-thiophenes.[59,228] Homologs can be obtained by the general procedures which have been mentioned,[229] as well as by degradation of indophenines.[7] 3,3′-Bithienyl has been prepared by the action of "phosphorus trisulfide" on the tetrasodium salt of butane-1,2,3,4-tetracarboxylic acid.[228]



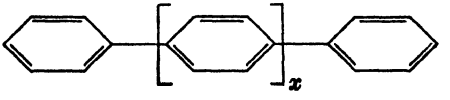
It is interesting to note that 2,2′,5,5′-tetraethyl-3,3′-bithienyl was isolated as a by-product when the hydrazone of 2-ethyl-5-acetylthiophene was treated with sodium ethoxide in order to convert the hydrazone into 2,5-diethylthiophene.[30] 2,3′-Bithienyl is known only in the form of derivatives.[156]

Polythienyls,[189,227,229] such as α-ter-, α-quater-, α-quinqui-, and α-sexi-thienyl, are obtained as by-products in the preparation of 2.2′-dithienyl from 2-iodothiophene and copper. It has been assumed that



α-polythienyls

x = 0, colorless
x = 3, greenish yellow
x = 4, yellow
x = 5, orange
x = 6, light red
x = 7, red



polyphenyls
(colorless)

the formation of these products is due to the decomposition of the cupric iodide, produced during the reaction, into cuprous iodide and iodine. The bithienyl is iodinated by the iodine, and the iodobithienyl, iodothiophene, and some of the excess copper then react to form the terthienyl. The terthienyl is then iodinated and reacts with iodothiophene to form quaterthienyl, and so on.

227 Steinkopf and Köhler, *Ann.*, **522**, 17 (1936).
228 Thöl and Schultz, *Ber.*, **27**, 2834 (1894).
229 Steinkopf, Leitsmann, and Hofmann, *Ann.*, **546**, 180 (1941).

It has been found that some α-polythienyls can be separated from one another by a chromatographic process, and their extinction curves have been reported.[230] In contrast, the polyphenyls are colorless. α-Terthienyl has been isolated from a certain variety of the common marigold.[231,232]

THIENYL DERIVATIVES OF HETEROCYCLIC COMPOUNDS

Thienyl derivatives of pyridine and quinoline have been obtained by syntheses analogous to those employed for phenyl derivatives of these two parent heterocyclics. For example, benzaldehyde condenses with acetophenone, under proper conditions, to form benzaldiacetophenone, $C_6H_5CH(CH_2COC_6H_5)_2$,[233] which is converted, by hydroxylamine hydrochloride, into 2,4,6-triphenylpyridine.[234] From 2-thenaldiacetophenone, 2,6-diphenyl-4-(2-thienyl)pyridine is obtained,[235] and, when 2-acetylthiophene is substituted for acetophenone, it is possible to prepare 2,6-di-(2-thienyl)-4-phenyl- and 2,4,6-tri-(2-thienyl)-pyridine.[235]

Condensation of thiophene-2-aldehyde with ethyl acetoacetate and ammonia yields diethyl 2,6-dimethyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate. This substance can be oxidized with nitrous acid to the corresponding pyridine derivative which upon hydrolysis yields the 3,5-dicarboxylic acid.[110]

A number of compounds analogous to cinchophen (atophan, 2-phenylquinoline-4-carboxylic acid) have been prepared by condensation of isatin with acylthiophenes.[236–239] In contrast to the colorless cinchophen, the thienyl derivatives are yellow or red. They can be decarboxylated by distillation over soda lime.

A few other thiophene derivatives of heterocyclic compounds are known, such as 2-(2-thienyl)indole,[240] ethyl 5-(2-thienyl)isoxazole-3-

230 Sease and Zechmeister, *J. Am. Chem. Soc.*, **69**, 270 (1947).
231 Zechmeister and Sease, *J. Am. Chem. Soc.*, **69**, 273 (1947).
232 See Steinkopf (ref. 8, pp. 149–152) for a lengthier discussion of polythienyls.
233 Konstanecki and Rossbach, *Ber.*, **29**, 1488 (1896).
234 Wislicenus and Newmann, *Ann.*, **302**, 240 (1898).
235 Steinkopf and Popp, *Ann.*, **540**, 24 (1939).
236 Hartmann and Wybert, *Helv. Chim. Acta*, **2**, 60 (1919).
237 Steinkopf and v. Petersdorff, *Ann.*, **543**, 119 (1940).
238 Steinkopf and Kühnel, *Ann.*, **545**, 35 (1940), footnote 1.
239 Steinkopf and Engelmann, *Ann.*, **546**, 205 (1941).
240 Brunck, *Ann.*, **272**, 201 (1893).

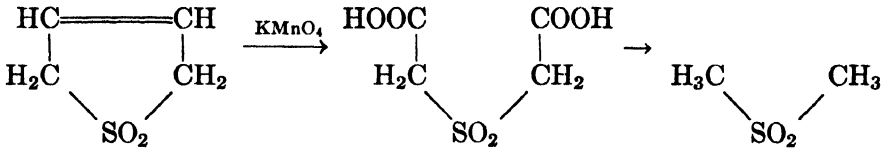
carboxylate,[241,242] ethyl 3-(2-thienyl)pyrazole-2-carboxylate [242] and 2-(2-thienyl)benzothiazole.[243]

DI- AND TETRA-HYDROTHIOPHENES

Dihydrothiophene is also called thiolene, and for tetrahydrothiophene the shorter term, thiophane,[244] is used quite frequently; other names for the tetrahydro compound are tetramethylene sulfide and thiolane.

2,5-Dihydrothiophene is formed, in poor yield, by the action of sodium sulfide on 1,4-dibromo-2-butene. It reacts with methyl iodide to form a sulfonium iodide.[245]

By interaction of butadiene and sulfur dioxide, monomeric, as well as polymeric, butadiene sulfones are obtained. Isoprene and dimethylbutadiene behave in a similar manner.[246–248] Monomeric butadiene sulfone, which is considered to be the sulfone of 2,5-dihydrothiophene, decomposes quantitatively, at 120–130°, into butadiene and sulfur dioxide.[246] It is soluble in water and organic solvents but decolorizes permanganate and bromine only in aqueous solution.[246] By permanganate oxidation, it is converted into the sulfone of thiodiglycolic acid (thio-*bis*-acetic acid), and then into dimethyl sulfone.[246] It reacts slowly, but quantitatively, with piperidine to form 3-piperidinothio-



phane sulfone.[249] 2,5-Dihydrothiophene sulfone, when treated with alkali, is transformed into a mixture of 2,3-dihydrothiophene sulfone and the sulfone of 3-hydroxythiophane.[248,249] The 2,3-dihydrothio-

241 Angeli, *Ber.*, **24**, 232 (1891).

242 Salvatori, *Gazz. chim. ital.*, **21**, 268 (1891).

243 Bogert and Stull, *J. Am. Chem. Soc.*, **48**, 248 (1926); **49**, 2011 (1927).

244 It is easy to mistake thiophane for thiophene; hence there is a distinct advantage in the longer term, tetrahydrothiophene.

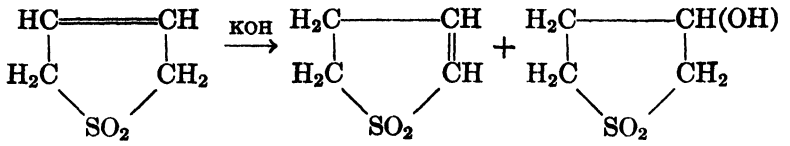
245 Slobodin, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 714 (1938) [*C. A.*, **33**, 1316 (1939)].

246 Staudinger and Ritzenthaler, *Ber.*, **68**, 455 (1935).

247 U. S. pat. 2,384,376 [*C. A.*, **40**, 344 (1946)] and U. S. pat. 2,402,891 [*C. A.*, **40**, 7229 (1946)].

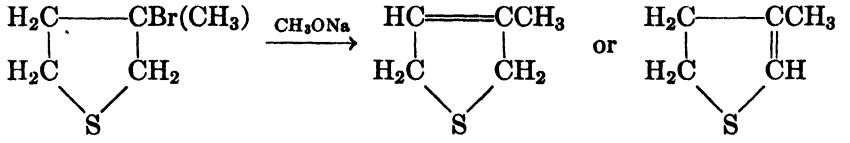
248 de Roy van Zuydewijn, *Rec. trav. chim.*, **56**, 1047 (1937).

249 Backer and Strating, *Rec. trav. chim.*, **62**, 815 (1943).

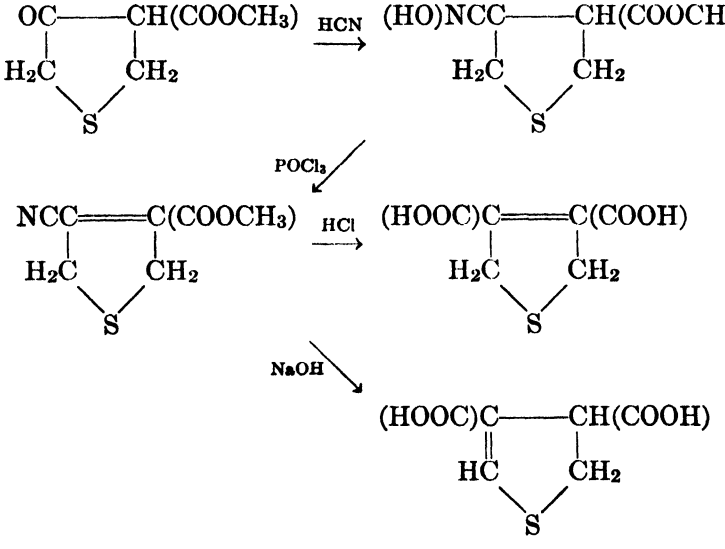


phene undergoes a Diels-Alder reaction with butadiene, 2,3-dimethylbutadiene, and cyclopentadiene.[250]

A methyldihydrothiophene, which may be either 3-methyl-2,5-dihydro- or 3-methyl-4,5-dihydro-thiophene, is produced by elimination of hydrobromic acid from 3-methyl-3-bromothiophane with sodium methoxide.[251]



When 3-carbomethoxy-4-ketothiophane is converted into the cyanohydrin, and the cyanohydrin is dehydrated to 3-carbomethoxy-4-cyanodihydrothiophene, the latter ester is hydrolyzed to 2,5-dihydrothiophene-3,4-dicarboxylic acid; however, when sodium hydroxide is employed for the hydrolysis, the reaction product is 2,3-dihydrothiophene-3,4-dicarboxylic acid.[252]



250 Alder, Rickert, and Windemuth, *Ber.*, **71**, 2455 (1938).
251 Karrer and Kleso, *Helv. Chim. Acta*, **27**, 1285 (1944).
252 Baker, Querry, and Kadish, *J. Org. Chem.*, **13**, 123 (1948).

It has been stated (p. 229) in the discussion of hydroxythiophenes that 2-hydroxy-5-methylthiophene can react as 2-keto-5-methyl-2,3-dihydrothiophene.[96]

Thiophane, a liquid which boils at 119°, has a very disagreeable, penetrating odor. It forms a sulfone and a methylsulfonium iodide. This is a characteristic behavior of thiophane compounds which is in distinct contrast to that of thiophene and its derivatives. However, a few thiophene derivatives, such as 3,4-diphenyl- and tetraphenylthiophene and thianaphthene, represent exceptions to this statement in that they do form sulfones. There is very little available information concerning sulfoxide formation, but it has been reported that oxidation of 2-methylthiophane with nitric acid yields a sulfoxide, whereas oxidation with potassium permanganate produces a sulfone.[253] Since thiophene often poisons hydrogenation catalytic agents, this effect can be overcome by hydrogenation and subsequent oxidation which converts the thiophene into thiophane sulfone.[254]

Thiophane, as well as a variety of its derivatives, can be obtained by treatment of a 1,4-dibromo compound with sodium sulfide. Thus, tetramethylene bromide, 1,4-dibromopentane, 1,4-dibromo-2,3-dihydroxybutane, and α,α'-dibromoadipic acid yield thiophane,[253,255] 2-methylthiophane,[253,256] 3,4-dihydroxythiophane,[257] and thiophane-2,5-dicarboxylic acid,[258] respectively.

By hydrogenation with a palladium catalyst, thiophene and 2-bromothiophene can be converted into thiophane, and δ-(2-thienyl)valeric acid into δ-(2-thiophyl)valeric acid.[67] (The term "thiophyl" represents the radical derived from thiophane by loss of an hydrogen.) The dehydrogenation of thiophane to thiophene, in 32% yield, has been accomplished with a platinum-carbon catalyst.[259]

A considerable number of thiophane homologs have been isolated from petroleum and shale oil.[260] They form addition products with mercuric chloride from which they can be liberated by the action of hydrogen sulfide.

253 Grischkewitsch-Trochimowski, *J. Russ. Phys. Chem. Soc.*, 48, 901 (1916) [*C. A.*, 11, 785 (1917)]. See also Surrey, Hammer, and Suter, *J. Am. Chem. Soc.*, 66, 1933 (1944).

254 Maxted, *J. Chem. Soc.*, 204 (1945).

255 v. Braun and Trumpler, *Ber.*, 43, 545 (1910).

256 v. Braun, *Ber.*, 43, 3223 (1910).

257 Kilmer et al., *J. Biol. Chem.*, 145, 495 (1942).

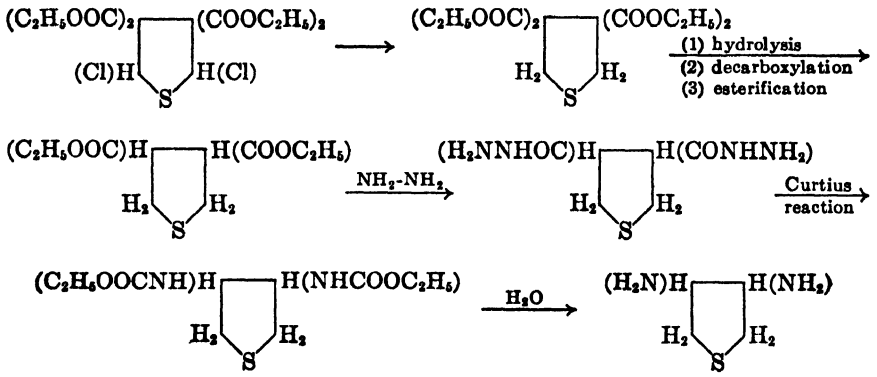
258 Ger. pat. 405,017; *Chem. Zentr.*, 96, I, 1912 (1925). See also Marvel and Williams, *J. Am. Chem. Soc.*, 61, 2714 (1939).

259 Jurjew and Borissow, *Ber.*, 69, 1395 (1936).

260 Ref. 8, pp. 6, 7, 104, and 105.

Chlorination of certain iodothiophenes has produced chlorothiophanes; for example, 2-iodothiophene is converted into octachlorothiophane [261] and 2,4,5-triiodo-3-methylthiophene into 2,2,3,4,4,5,5-heptachloro-3-methylthiophane.[39] Although butadiene and sulfur chloride form butadienetetrachloride, methylbutadiene (isoprene) and dimethylbutadiene react with the sulfur compound to yield 3,4-dichloro-3-methyl- and 3,4-dichloro-3,4-dimethyl-thiophane, respectively.[262] 3,4-Dihydroxythiophene, obtained by the action of sodium sulfide on 1,4-dibromo-2,3-dihydroxybutane, is converted by hydrobromic acid into 3,4-dibromothiophane.[257] It was not found possible to replace the bromine atoms by amino groups.

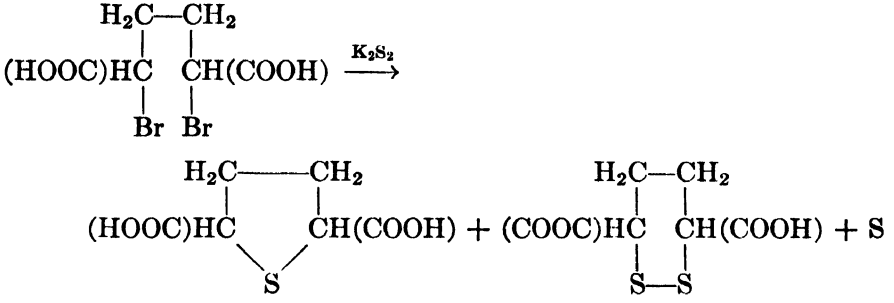
An attempt has been made to prepare 2,5-diaminothiophane by conversion of the diethyl ester of thiophane-2,5-dicarboxylic acid into the dihydrazide, transformation of the latter substance into 2,5-di-(carbethoxyamino)thiophane, and hydrolysis of the diurethane to the diamine. However, hydrolysis with either acid or alkali produced hydrogen sulfide, ammonia, and succinaldehyde, instead of the diamino compound.[263] 3,4-Diaminothiophane has been obtained by the procedure which is outlined below.[257] It has been shown that this diamine



possesses a *trans* configuration.[264] An isomeric 3,4-diaminothiophane is produced by treatment of 2,3-diaminobutane-1,4-disulfonic acid with sodium sulfide.[265] This diamine represents the *cis* modification [264] which can also be obtained from either the *cis* or *trans* form of thiophane-3,4-dicarboxylic acid.[266]

261 Willgerodt, *J. prakt. Chem.*, **33**, 150 (1886).
262 Backer and Strating, *Rec. trav. chim.*, **54**, 52 (1935).
263 Brown and Kilmer, *J. Am. Chem. Soc.*, **65**, 1674 (1943).
264 Baker, Bernstein, and Safir, *J. Org. Chem.*, **12**, 155 (1947).
265 Kilmer and McKennis, *J. Biol. Chem.*, **152**, 103 (1944).
266 Baker et al., *J. Org. Chem.*, **12**, 174 (1947).

Thiophanecarboxylic acids can be prepared from the corresponding thiophenecarboxylic acids by reduction with sodium amalgam in an alkaline medium.[267] Racemic thiophane-2,5-*trans*-dicarboxylic acid is formed in high yield by the interaction of racemic dibromoadipic acid and sodium sulfide.[268] The thiophane acid has been resolved into the optically active forms. Reaction between dibromoadipic acid and potassium disulfide takes place in the following manner.



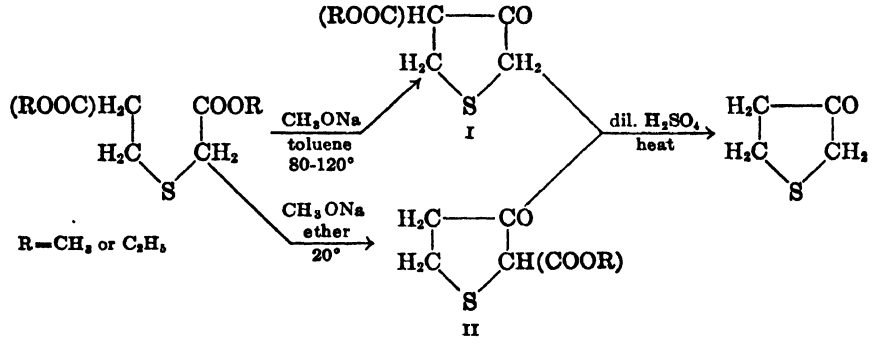
Thiophane-3,4-dicarboxylic acids have been studied extensively in connection with the synthesis of biotin and related compounds.[264, 266, 269–273]

Certain 2,3,4-trisubstituted thiophanes are also of special interest in connection with the determination of the structure and the synthesis of biotin.

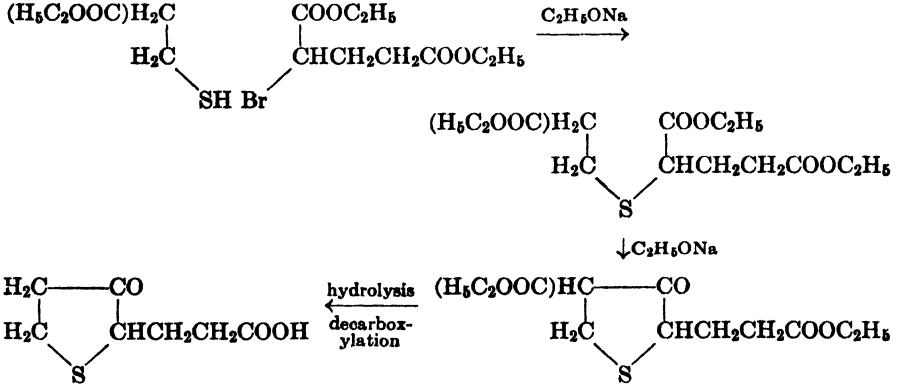
A considerable number of 3-ketothiophanes (3-thiophanones) have been prepared, especially those which contain an ω-carboxyalkyl group in the 2 position and some other substituent, such as a hydroxyl or carbethoxy radical, in the 4 position. The Dieckmann condensation is convenient for the preparation of such compounds. A characteristic example is the cyclization of carbethoxymethyl β-carbethoxyethyl sulfide under the influence of sodium, sodium ethoxide, or sodamide in some solvent such as ether, benzene, or toluene. Various investigators have reported that the main reaction product is 4-carbethoxy-3-ketothiophane (I),[274] 2-carbethoxy-3-ketothiophane (II) [275] or a mixture

267 Ernst, *Ber.*, **19**, 3274 (1886); **20**, 518 (1887).
268 Fredga, *J. prakt. Chem.*, **150**, 124 (1938).
269 Baker et al., *J. Org. Chem.*, **12**, 138 (1947).
270 Brown et al., *J. Org. Chem.*, **12**, 160 (1947).
271 Baker et al., *J. Org. Chem.*, **12**, 167 (1947).
272 Baker et al., *J. Org. Chem.*, **12**, 186 (1947).
273 Baker, McEwen, and Kinley, *J. Org. Chem.*, **12**, 322 (1947).
274 Karrer and Schmid, *Helv. Chim. Acta*, **27**, 116 (1944).
275 Buchman and Cohen, *J. Am. Chem. Soc.*, **66**, 847 (1944).

of these two substances.[276,277] Subsequently, it was found[278,279] that the direction of cyclization is dependent on the experimental conditions. When the dimethyl ester is cyclized with sodium methoxide in ether at room temperature, at least 75–80% of the 2-carbomethoxy ester (II) and a small amount of the 4-carbomethoxy derivative (I) are formed.[280]



However, when the cyclization is effected with sodium methoxide in toluene at 80–120°, the main product is the 4-carbomethoxy ester and there is no evidence that any of the isomeric ester is formed. Both the 2 and the 4 ester, when hydrolyzed with dilute sulfuric acid, produce 3-ketothiophane in good yield. 3-Ketothiophane has been obtained in the same manner from the ethyl ester.[274] The ketone condenses with benzaldehyde and with furfural to yield a yellow 2,4-dibenzylidene and a red 2,4-difurfurylidene derivative[279] and reacts with Grignard compounds and other reagents in the expected manner.[251]



276 Avison et al., *Nature*, **154**, 459 (1944).

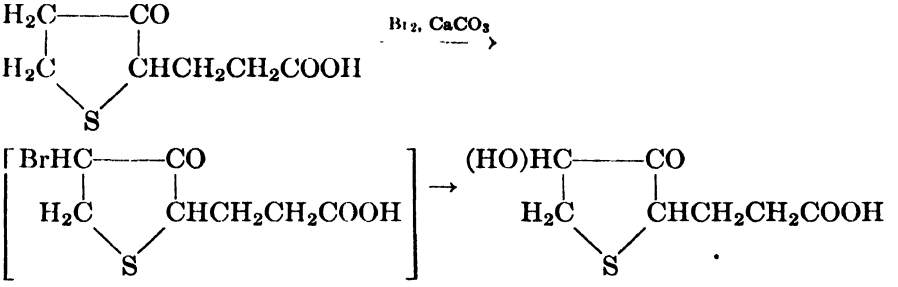
277 Karrer and Schmid, *Helv. Chim. Acta*, **27**, 124 (1944).

278 Woodward and Eastman, *J. Am. Chem. Soc.*, **66**, 849 (1944).

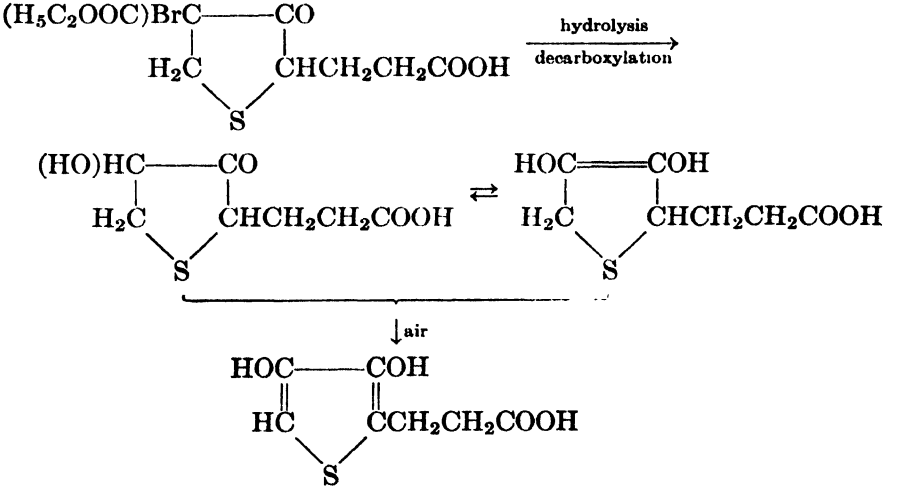
279 Woodward and Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946).

280 Derivatives of 2-carboxalkyl- and of 4-carboxalkyl-3-ketothiophanes react with ferric chloride to form colored products [Brown et al., *J. Org. Chem.*, **12**, 160 (1947)].

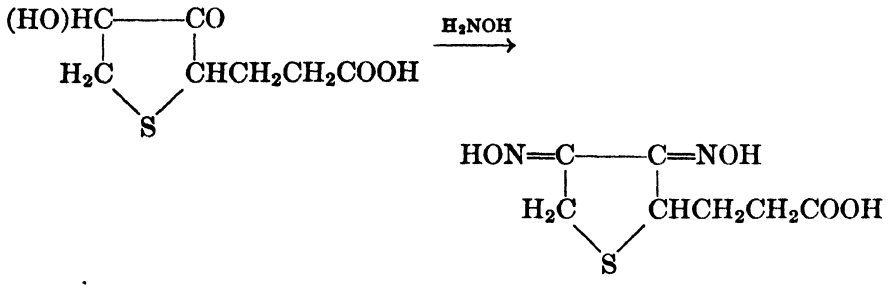
The preparation of a trisubstituted thiophane, such as β-2-(3-keto-4-carbethoxythiophyl)propionic acid, has been accomplished by allowing ethyl β-mercaptopropionate to react with the diethyl ester of α-bromoglutaric acid, as shown above. After ring closure by the Dieckmann reaction, the diethyl ester is hydrolyzed; during this process, the 4-carboxyl group is removed by decarboxylation, and β-2-(3-keto-thiophyl)propionic acid is formed.[101] By bromination of the latter substance, in the presence of calcium carbonate, β-2-(3-keto-4-hydroxythiophyl)propionic acid is produced. The unstable, intermediate 4-bromo derivative was not isolated.[101]



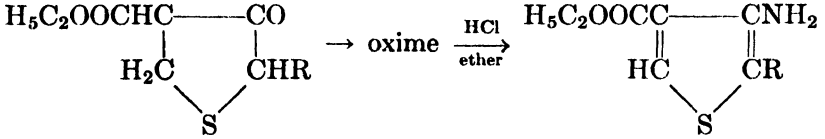
In an attempt to obtain β-2-(3-keto-4-hydroxythiophyl)propionic acid by hydrolysis and decarboxylation of β-2-(3-keto-4-bromo-4-carbethoxythiophyl)propionic acid, the reaction product was found to be not the desired thiophane derivative but β-2-(3,4-dihydroxythienyl)-propionic acid. It was assumed that the production of the thiophene compound was due to oxidation of the hydroxyketo acid by air during the preparative procedure.[101]



β-2-(3-Keto-4-hydroxythiophyl)propionic acid reacts with hydroxylamine to form a *dioxime*. Phenylhydrazine also reacts in an analogous manner.[101] It is not possible to reduce the dioxime to a



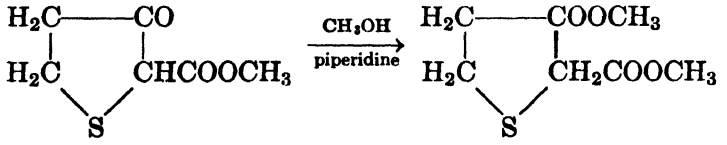
diamine since nitrogen is removed from the molecule during the reduction process. From 3-ketothiophanes, such as those shown below, the preparation of oximes and their conversion into amines takes place very readily.[281] The fact that the oximes can be reduced to the amines



R = $(CH_2)_3OC_6H_5$ or $(CH_2)_3OCH_2C_6H_5$

in good yields, with dehydrogenation of the ring merely in an ether solution of hydrogen chloride at room temperature, makes these reactions of unusual interest.

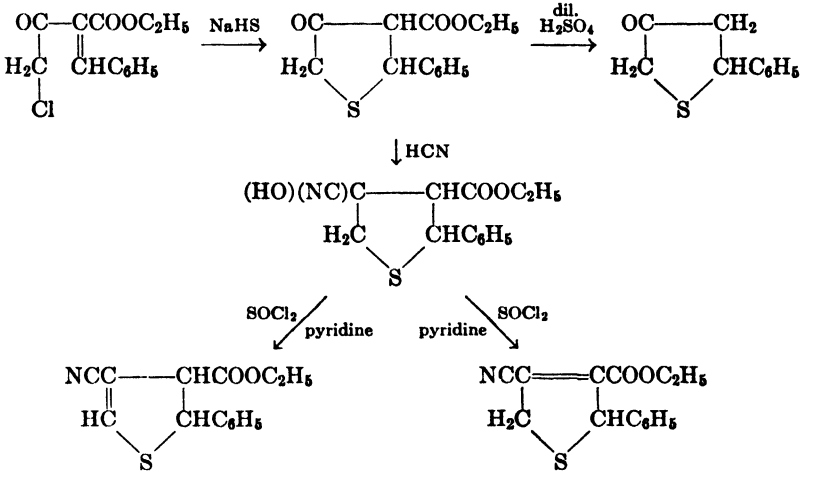
Ring opening in the case of methyl 3-ketothiophane-2-carboxylate takes place very readily when the ester is boiled with methyl alcohol containing a few drops of piperidine. It is converted, quantitatively, into carbomethoxymethyl β-carbomethoxyethyl sulfide. An isomeric ester, methyl 3-ketothiophane-4-carboxylate, when treated in the same manner, remains unchanged.[279]



3-Ketothiophanes which contain a substituent in the 5 position, such as 5-phenyl-3-ketothiophane (2-phenyl-4-ketothiophane), also are known. Ethyl α-benzylidene-γ-chloroacetoacetate, obtained by con-

281 Cheney and Piening, *J. Am. Chem. Soc.*, **67**, 729 (1945).

densation of ethyl γ-chloroacetoacetate with benzaldehyde in the presence of piperidine acetate, reacts with sodium hydrosulfide to form the corresponding γ-mercapto derivative. Cyclization takes place during the condensation through addition of the mercapto radical to the double bond,[282] and 2-phenyl-3-carbethoxy-4-ketothiophane is formed. Oxidation of this compound with hydrogen peroxide in acetic acid solution, for a relatively short time, produces the sulfoxide; after oxidation over a longer period, the sulfone is obtained.[283] Addition of hydrocyanic acid to 2-phenyl-3-carbethoxy-4-ketothiophane produces 2-phenyl-3-carbethoxy-4-hydroxy-4-cyanothiophane, which reacts with thionyl chloride in pyridine to produce two isomeric dihydrothiophenes. If the reaction is carried out at a low temperature, the principal prod-



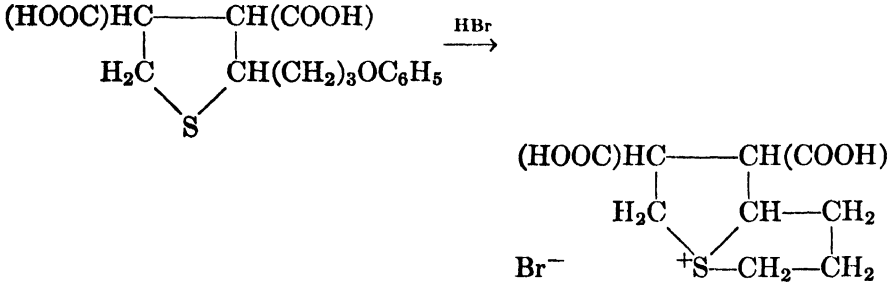
uct seems to be 2-phenyl-3-carbethoxy-4-cyano-2,3-dihydrothiophene; at room temperature, the main product is 2-phenyl-3-carbethoxy-4-cyano-2,5-dihydrothiophene. The structures of these compounds are based on their absorption spectra. When 2-phenyl-3-carbethoxy-4-ketothiophane is hydrolyzed, decarboxylation also takes place and 2-phenyl-4-ketothiophane is formed.[283]

It has been found in many instances that carboxylic acids, formed by the hydrolysis of esters of 3-ketothiophane-2- and 3-ketothiophane-4-carboxylic acids with dilute sulfuric acid, undergo decarboxylation during the process of hydrolysis,[269, 274, 277, 279, 283–286] a behavior which

282 See Baker et al. [*J. Org. Chem.*, **12**, 138 (1947)] for similar reactions.
283 Surrey, Hammer, and Suter, *J. Am. Chem. Soc.*, **66**, 1933 (1944).
284 Schmid, *Helv. Chim. Acta*, **27**, 127 (1944).
285 Harris et al., *J. Am. Chem. Soc.*, **66**, 1757 (1944).
286 Ghosh, McOmie, and Wilson, *J. Chem. Soc.*, 705 (1945).

is not surprising in view of the general instability of β-keto acids. Hydrolysis of 2-phenyl-3-carbethoxy-4-ketothiophane with dilute sulfuric acid converts it into 2-phenyl-4-ketothiophane, but, when the ester is hydrolyzed with 5% sodium hydroxide solution, it is decomposed with the formation of cinnamic acid.[283]

When 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-carboxylic acid is refluxed with 48% hydrobromic acid for 20 min., a 59% yield of the water-soluble 1,2-trimethylene-3,4-dicarboxythiophanium bromide instead of the 2-(γ-bromopropyl) derivative is obtained.[269] It has been suggested [270] that similar sulfonium compounds may have been formed in the Grüssner biotin synthesis (p. 268).



In a study of the usefulness of alkylene sulfides as alkylation agents, it has been found that ethylene sulfide and ethyl cyanoacetate, in the presence of sodium ethoxide, react to form a substance which, presumably, is ethyl β-mercaptoethylcyanoacetate. This product cyclizes spontaneously to form ethyl 2-iminothiophane-3-carboxylate (ethyl 2-amino-4,5-dihydrothiophene-3-carboxylate).[287]

BIOTIN [288]

It has been known, definitely, since 1901 that for optimal growth yeast requires a material which was given the name, bios.[289] This

287 Snyder and Alexander, *J. Am. Chem. Soc.*, **70**, 217 (1948).

288 Several general articles on the subject of biotin have been published: "The Structure of Biotin," du Vigneaud, *Science*, **96**, 455 (1942); "The Chemistry and Biochemistry of Biotin," Hofmann, *Advances in Enzymol.*, **3**, 289 (1943); "Synthesis and Stereochemistry of Biotin and Related Products," Harris, *J. Chem. Education*, **24**, 459 (1947); "Biotin and Related Compounds," Edith Ju-Hwa Chu, *Chemistry & Industry*, **8**, 115 (1948). Brief summaries, with many references to original articles, are to be found in the *Ann. Repts. Progress Chem.* (*Chem. Soc. London*), **38–41**.

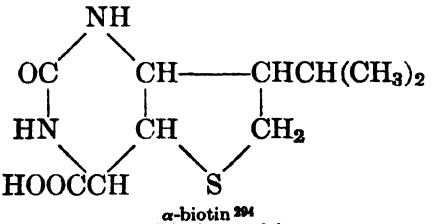
289 Bios was obtained from boiled yeast cells, peptone, and other sources. One of its constituents, biotin, is synthesized by many strains of yeast (but not in adequate amounts), by many varieties of bacteria, and by some molds.

substance was found to consist of several components. Bios I was identified as *meso*-inositol. In 1935, Kögl [290] separated a product, which he called biotin, from bios II, and a year later Kögl and Tönnis described the isolation of the crystalline methyl ester of biotin [291] from egg yolk. The ester was found to be very active in promotion of the growth of yeast. The empirical formula for biotin methyl ester was stated to be $C_{11}H_{18}O_3N_2S$ by Kögl in 1937.

In other biological investigations, entirely independent of those on bios, the observations were made that a diet high in egg white produces a severe dermatitis and other effects in rats, and it was then found that certain foods, such as liver, eggs, and milk, contain a substance, vitamin H, which offers protection against egg-white toxicity.[292]

György and co-workers, in 1940, suggested that biotin, vitamin H, and coenzyme R are identical substances. Coenzyme R, found in yeast and liver, was known to promote growth and respiration in a legume-nodule organism. During the same year, György and associates isolated crystalline biotin methyl ester from liver and claimed that it was identical with the substance which Kögl had obtained from egg yolk. Kögl maintains that there are two distinct biotins. He calls the substance isolated from egg yolk α-biotin, that from liver β-biotin.

On the basis of degradation studies, α-biotin [293] and β-biotin were assigned the formulas shown below.



α-biotin [294]
(original formula)

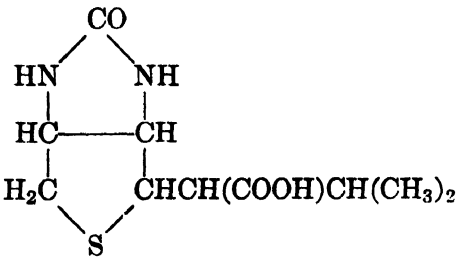
290 Kögl, *Ber.*, **68** (A), 16 (1935).

291 Biotin, which contains a carboxyl group, was converted into its methyl ester by the methanol and hydrogen chloride which were used during the isolation process. From 250 kg. of dried egg yolks, 1.1 mg. of crystalline material was obtained [Kögl and Tönnis, *Z. physiol. Chem.*, **242**, 43 (1936)]. The ester described originally was not a pure compound [Kögl and Pons, *Z. physiol. Chem.*, **269**, 61 (1941)].

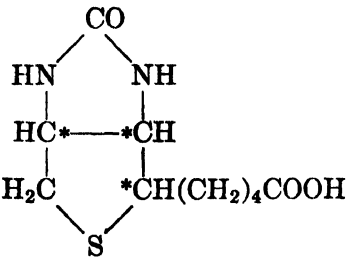
292 This toxicity is produced by avidin, a raw egg-white protein, which causes biotin deficiency by the formation of a nonabsorbable, avidin-biotin complex.

293 Kögl et al., *Z. physiol. Chem.*, **279**, 121 (1943). See also *Ann. Repts. Progress Chem.* (*Chem. Soc. London*), **41**, 215 (1944) for a summary of this work and for other references.

294 Preliminary studies for the synthesis of an α-biotin of this structure have been published by Ghosh, McOmie, and Wilson [*J. Chem. Soc.*, 705 (1945)].



α-biotin[295] (revised formula)



β-biotin

In the American literature, β-biotin is commonly referred to merely as biotin,[296] and this practice will be followed in the subsequent discussion.

Chemical names such as the following have been assigned to biotin: hexahydro-2-oxo-1-thieno[3,4]imidazole-4-valeric acid,[297] 2-(ω-carboxybutyl)-3,4-(2′-oxotetrahydroimidazol)thiophan,[298] and 2-(δ-carboxybutyl)-5-ketoimidazolido[4,5,c,*cis*]thiophane.[272] If the divalent radical —HNCONH— is called ureylene (analogous to phenylene), biotin can be named much more simply as 2-(δ-carboxybutyl)-3,4-ureylenethiophane.

The earliest experiments indicated that biotin is not an amino acid and that it does not contain any ethylenic bonds. The sulfur atom cannot be removed from the molecule by the action of alkali, hydriodic acid, zinc and hydrochloric acid, or bromine water. The assumption that the sulfur atom is present in biotin as a thio ether gained support from the fact that oxidation of biotin with potassium permanganate, or hydrogen peroxide in acetic acid solution, converts it into a sulfone; biotin methyl ester reacts with methyl iodide to form a sulfonium iodide.

From the information, gained mainly from degradation studies, du Vigneaud, in 1942, assigned a structure to biotin which was later confirmed by its synthesis in other laboratories. Some of the experiments

[295] Kögl and Borg, *Z. physiol. Chem.*, **281**, 65 (1944). The synthesis of 2-isopropyl-4,5-ureylenecaproic acid, a desthio-α-biotin, has been described by Brown and Ferger [*J. Am. Chem. Soc.*, **68**, 1507 (1946)]. This substance is a structural isomer of desthiobiotin, but its configuration was not determined. Unlike desthiobiotin, it does not promote the growth of yeast or inhibit the growth of *L. casei*.

[296] This term more specifically indicates the naturally occurring dextrorotatory as well as the synthetic *d* form [Harris et al., *J. Am. Chem. Soc.*, **67**, 2096 (1945)].

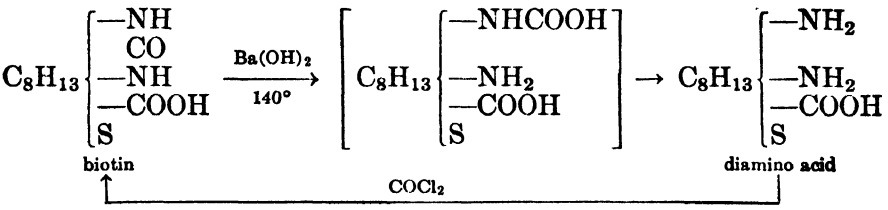
[297] Harris et al., *J. Am. Chem. Soc.*, **66**, 1756 (1944).

[298] Grüssner, Bourquin, and Schnider, *Helv. Chim. Acta*, **28**, 517 (1945).

and deductions made by du Vigneaud and his associates are related in the following discussion.[299]

Hydrolysis of biotin methyl ester with cold alkali yields crystalline, dextrorotatory biotin which, on the basis of titration curves, is a monocarboxylic acid. The empirical formula was established by analysis to be $C_{10}H_{16}O_3N_2S$. Information obtained from preliminary experiments, and the ratio of carbon to hydrogen, indicated that biotin contains a ring system which is bicyclic.

The discovery that biotin is converted into a diamino acid by treatment with barium hydroxide proved to be of the greatest importance. The diamino acid reacts with phosgene to form biotin in almost quantitative yield.[300] These reactions are very good evidence for the assumption of a cyclic urea structure in the molecule.



The fact that adipic acid, $HOOC(CH_2)_4COOH$, was isolated from the oxidation products of the diamino acid and the demonstration that one of the carboxyl groups of adipic acid was the carboxyl group originally present in the diamino acid led to the assumption that an *n*-valeric acid side chain might be present in the diamino acid and hence in biotin. If this assumption were correct, the location of five of the nine carbon atoms in the diamino acid would have been established. It seemed very probable that the four remaining carbon atoms and the sulfur atom of the diamino acid were united in the form of a saturated cyclic structure, but the location of the sulfur atom in the ring and the exact nuclear positions to which the ureylene radical and the side chain are attached remained to be determined.[301]

Although it is evident that interaction of the diamino acid with phosgene produces a cyclic urea, this reaction gives no indication of

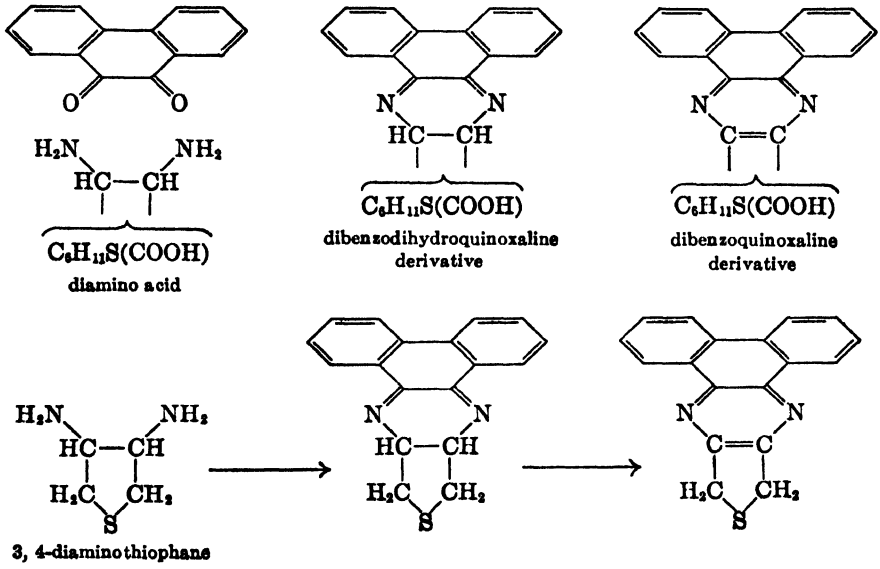
299 The study of biotin was greatly facilitated by the discovery that it could be obtained quite easily, and in a pure state, from milk concentrates [Melville, *J. Biol. Chem.*, 142, 615 (1942)].

300 Hofmann et al., *J. Biol. Chem.*, 141, 207 (1941).

301 The article by du Vigneaud [*Science*, 96, 455 (1942)] should be read for a more detailed discussion of the experimental data and the arguments in favor of these assumptions.

whether the diamino acid is a 1,2- or a 1,3-diamine; from a 1,2-diamine, a five-membered ring, and from a 1,3-diamine, a six-membered cyclic structure would be obtained. Since the diamino acid reacts with phenanthrenequinone to yield a condensation product, it appeared that the two amino groups were attached to adjacent carbon atoms. As far as is known, 1,3-diamines do not condense with phenanthrenequinone.

From the behavior of the condensation product, it seemed that a dibenzoquinoxaline rather than a dibenzodihydroquinoxaline derivative had been isolated. In order to obtain more positive evidence that the latter type of product had been formed, 3,4-diaminothiophane [257] was condensed with phenanthrenequinone, and a portion of the dibenzodihydroquinoxaline derivative which was produced was heated at 200° whereby it was oxidized to the dibenzoquinoxaline derivative.[302]

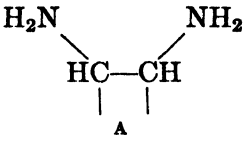


It was then shown that the ultraviolet absorption spectra of the dibenzoquinoxaline derivative of the diamino acid and that of the dibenzoquinoxaline derivative of 3,4-diaminothiophane are quite similar and entirely different from the absorption spectrum of the dibenzodihydroquinoxaline derivative of 3,4-diaminothiophane.

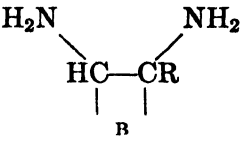
These experiments indicated not only that the diamino acid is a 1,2-diamine but, furthermore, that the two amino groups are part of a

[302] Hofmann, *J. Biol. Chem.*, **145**, 503 (1942).

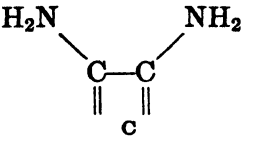
structural unit such as that represented by A or D. A dihydroquinoxaline can be obtained from a compound which contains a unit such as



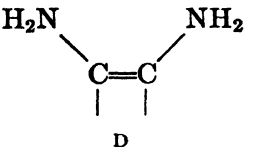
A



B



C

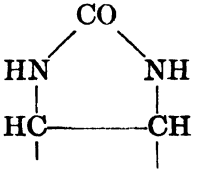


D

A or C; a quinoxaline derivative can be formed from D and, by the loss of two hydrogen atoms, from A but not from B or C.

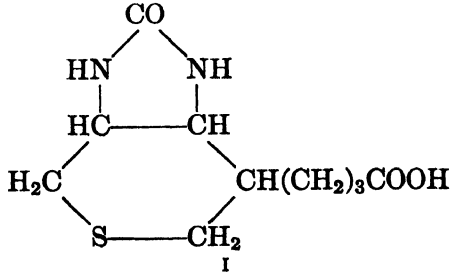
The formation of a quinoxaline also indicates that any side chain (R; e.g., a valeric acid side chain) present in the diamino acid, as well as in biotin, must be linked to a carbon atom other than one of those shown in A; the side chain cannot be attached in the manner shown in B.

Although it seemed definitely established that biotin contained the structural unit E, there was still some uncertainty with respect to the exact nature of the side chain. It seemed probable that this is a valeric acid side chain (a δ-carboxybutyl radical); nevertheless, the

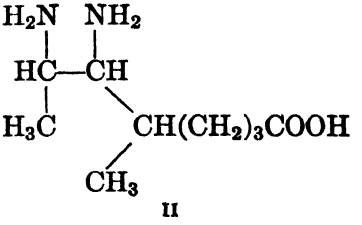


E

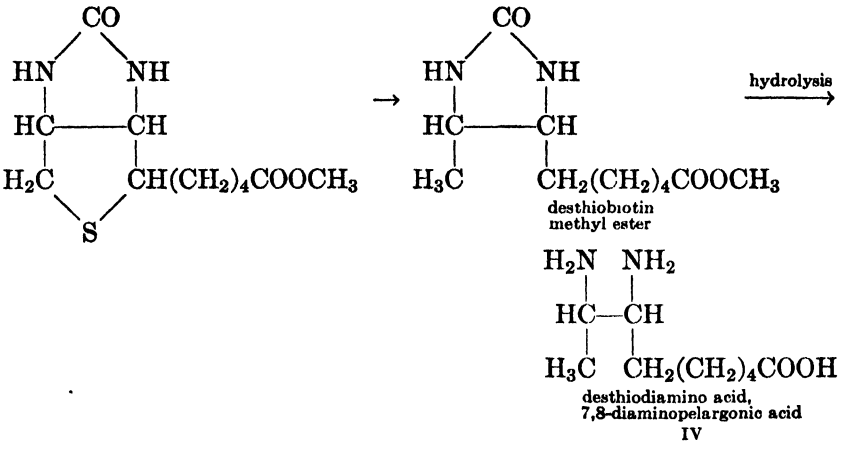
possibility that it might be a γ-carboxypropyl group had to be given consideration. In the latter case, formula I would represent a possible structure for biotin.



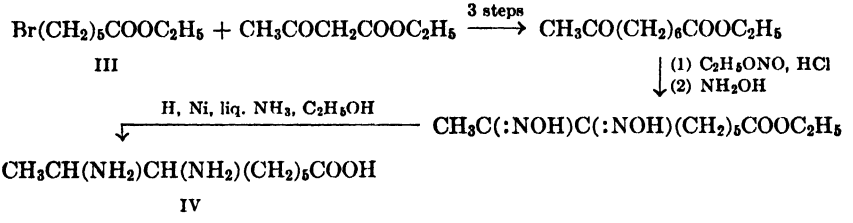
I



II



When the sulfur in biotin methyl ester was removed with Rancy nickel [303] and replaced by two hydrogen atoms, desthiobiotin methyl ester [304] was obtained which yielded a desthiodiamino acid on hydrolysis.[305] The structure of the latter substance, 7,8-diaminopelargonic acid (IV), was established by its synthesis (III–IV).[305] Oxidation of the desthiodiamino acid with periodic acid yields pimelic acid, $HOOC(CH_2)_5COOH$. If the desthiodiamino acid had been a compound which possessed structure II, oxidation would have converted it into α-methyladipic acid.[305] By the same procedures, compound I would



have been converted into the desthiodiamino acid (II) (5-methyl-6,7-diaminocaprylic acid). By interaction with phosgene, the desthiodiamino acid was converted into desthiobiotin.[306]

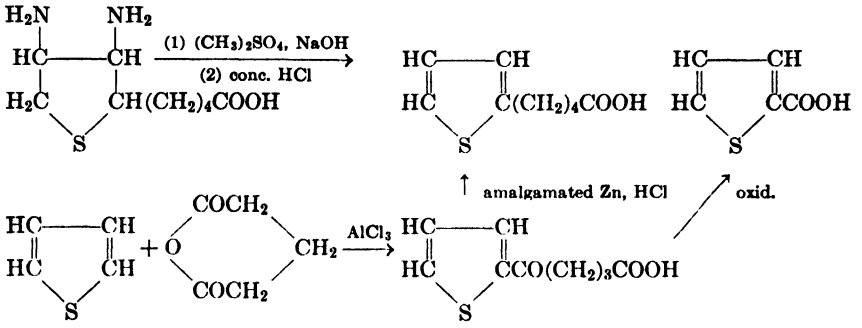
303 The procedure was discovered by Mozingo et al., *J. Am. Chem. Soc.*, **65**, 1013 (1943).

304 Desthiobiotin (7,8-ureylenepelargonic acid) has been synthesized from the diethyl ester of α-acetosuberic acid [Bourquin, Schnider, and Grüssner, *Helv. Chim. Acta*, **28**, 528 (1945)] and of α-carbethoxysuberic acid [Wood and du Vigneaud, *J. Am. Chem. Soc.*, **67**, 210 (1945)], and from 4-methyl-imidazolone-2 [Duschinsky and Dolan, *J. Am. Chem Soc.*, **67**, 2079 (1945)].

305 du Vigneaud et al., *J. Biol. Chem.*, **146**, 475 (1942).

306 Melville, *J. Am. Chem. Soc.*, **66**, 1422 (1944).

Positive proof of the structure of the nucleus which contained the sulfur atom and the exact nature and location of the side chain was obtained in the following manner. The diamino acid was degraded, by a modified Hofmann exhaustive methylation procedure, to δ-(2-thienyl)valeric acid.[168]



The synthesis of *dl*-biotin has been achieved by Harris,[297,307,308] by Grüssner,[298,309] and by Baker[272] and their associates. Resolution of the racemate by Wolf and co-workers[310] and by Baker et al.[272] yielded synthetic *d*-biotin which proved to be identical with natural biotin.

Since the diamino acid, 2-(δ-carboxybutyl)-3,4-diaminothiophane, obtained by hydrolysis of natural biotin, combined very readily with phosgene to produce biotin, it was expected that a total synthesis of biotin could be achieved if the diamino acid were made available by a synthetic procedure.

Several syntheses of the diamino acid have been described, each of which consists of a number of steps. In each synthesis, an available aliphatic compound is transformed into a sulfide which can be cyclized to a 4-substituted or a 2,4-disubstituted 3-ketothiophane by a Dieckmann reaction. The ketothiophane is then modified, by a series of reactions, until the required diamino acid is obtained. The Grüssner biotin synthesis represents a slight variation of this general procedure in that phosgene is condensed not with a diamino acid but with 2-(δ-bromobutyl)-3,4-diaminothiophane which had been obtained from the corresponding 2-(δ-methoxybutyl) compound (B). The last two stages in this synthesis then consist in the conversion of the δ-bromobutyl radical into a δ-carboxybutyl group.

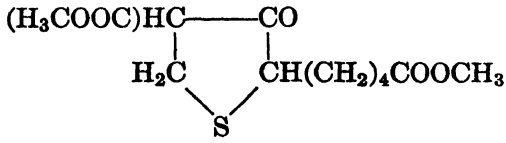
307 Harris et al., *Science*, **97**, 447 (1943).

308 Harris et al., *J. Am. Chem. Soc.*, **67**, 2096 (1945).

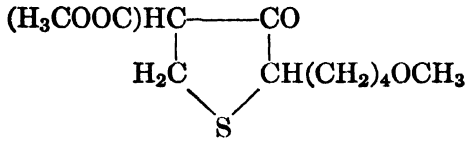
309 Schnider, Bourquin, and Grüssner [*Helv. Chim. Acta*, **28**, 510 (1945)] also synthesized 2-methyl-3,4-ureylenethiophane.

310 Wolf et al., *J. Am. Chem. Soc.*, **67**, 2100 (1945).

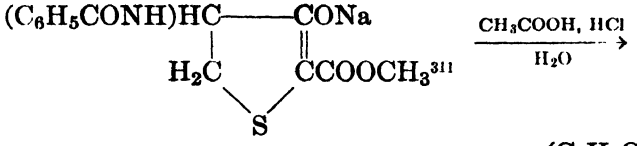
3-Ketothiophanes are fundamentally important intermediates in each of the three biotin syntheses which have been described in the literature. The syntheses of thiophanes A, B, and C, utilized by Baker, Grüssner, and Harris, respectively, are described below.

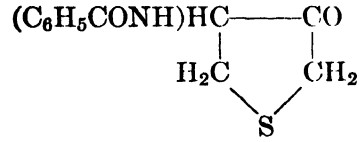


A (Baker)



B (Grüssner)

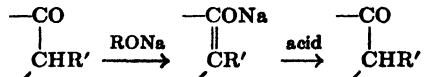




C (Harris)

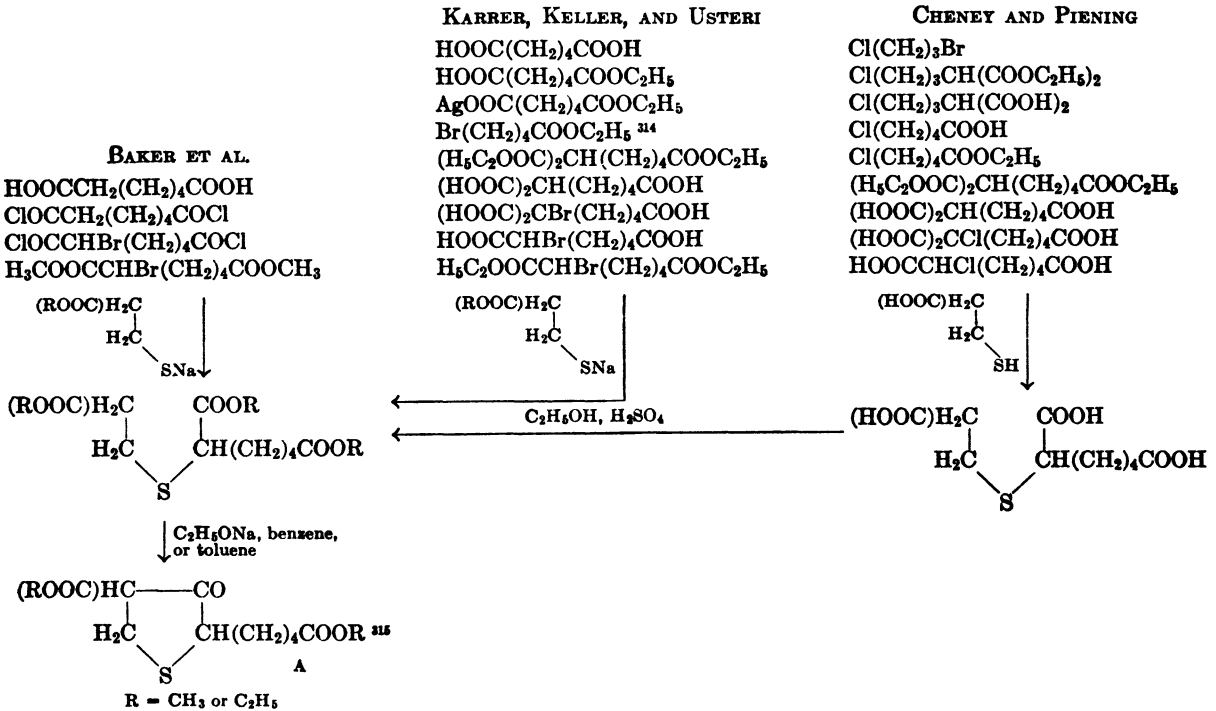
Procedures for the preparation of the 2,4-disubstituted 3-ketothiophane [A,2-(δ-carbomethoxybutyl)-3-keto-4-carbomethoxythiophane] employed by Baker and his associates in their biotin synthesis have been described by them,[271] by Cheney and Piening,[312,313] and also by Karrer, Keller, and Usteri.[102,313] The intermediates in each of these procedures are listed below in the order in which they were prepared.

311 The 3-ketothiophane, which is formed by the Dieckmann reaction, is converted into a sodium derivative by the sodium methoxide or ethoxide used to effect the cyclization. The sodium derivative may be isolated [Harris et al., *J. Am. Chem. Soc.*, **66**, 1757 (1944)] or transformed into the 3-keto derivative by acidification of the reaction mixture. Obviously, the sodium compound is a dihydrothiophene and not a thiophane; unless this derivative is isolated, it is not customary to indicate its formation in a reaction scheme. The precipitation of the sodium derivative in their reaction mixture is mentioned by Cheney and Piening.[312]



312 Cheney and Piening, *J. Am. Chem. Soc.*, **67**, 731 (1945).

313 These investigators prepared the diethyl ester.



314 The preparation of bromo compounds by treatment of a silver salt with bromine has been described by Hunsdiecker and Hunsdiecker [*Ber.*, **75**, 291 (1942)]. See also Lüttringhaus and Schade, *ibid.*, **74**, 1565 (1941), and *Org. Syntheses*, **26**, 52 (1946).

315 Proof that ring closure took place in the manner indicated has been furnished by Cheney and Piening [*J. Am. Chem. Soc.*, **67**, 729 (1945)] and by Baker et al. [*J. Org. Chem.*, **12**, 167 (1947)].

The transformation of one compound into another was accomplished by well-known reactions which include the Hell-Volhard-Zelinsky reaction, the malonic ester synthesis, and the Dieckmann cyclization process.

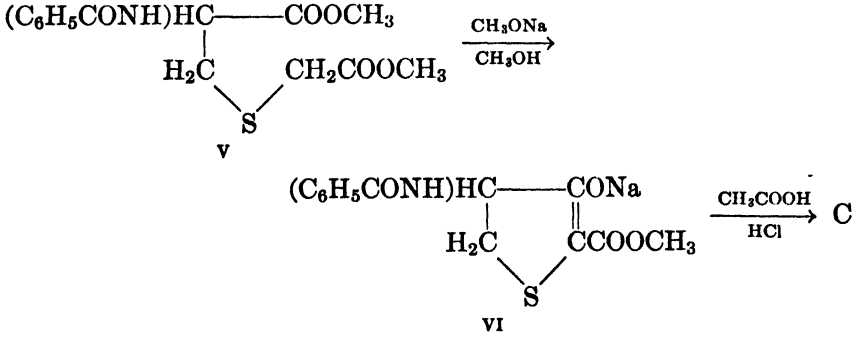
In the syntheses which have been formulated above, it has not always been necessary to isolate each intermediate. Thus, in the Baker synthesis, pimelic acid can be converted into the bromo ester without isolation of the acid chlorides.

The thiophane B, used by Grüssner et al., had been obtained previously by Schmid.[284] In this instance, the synthetic process begins with 1,4-dibromobutane which is converted into 1-bromo-4-methoxybutane and, eventually, into ethyl 2-bromo-6-methoxycaproate. This ester is condensed with ethyl β-mercaptopropionate to yield a sulfide,

$$H_5C_2OOCCH_2CH_2SCH(CH_2CH_2CH_2CH_2OCH_3)COOC_2H_5$$

which can be cyclized to thiophane B.

For the synthesis of thiophane C, Harris et al. employed β-(carboxymethylmercapto)alanine which had been prepared by other investigators from *l*-cystine [316] or *l*-cysteine [317] and chloroacetic acid in alkaline solution. By benzoylation and then esterification, the alanine is converted into the methyl ester of *l*-N-benzoyl-β-(carbomethoxymethylmercapto)alanine (V). This substance is cyclized with sodium methoxide to the sodium derivative of the 3-ketothiophane (VI). The sodium derivative is isolated and treated with acid, whereupon methyl *dl*-3-keto-4-benzamidothiophane-2-carboxylate is obtained.[318] Race-



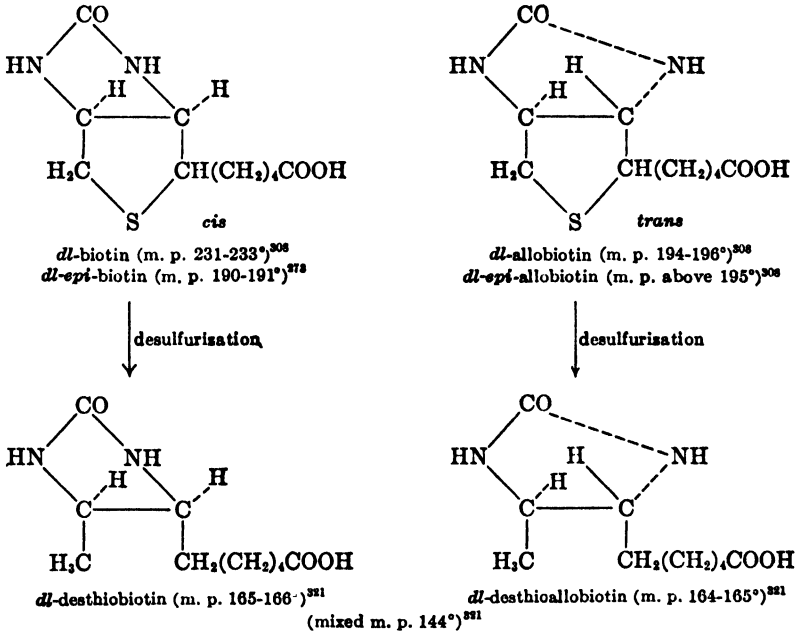
316 Blood and Lewis, *J. Biol. Chem.*, **139**, 407 (1941).

317 Michaelis and Shubert, *J. Biol. Chem.*, **106**, 331 (1934).

318 It was found also that serine could serve as the initial material for the synthesis of this thiophane [Harris et al., *J. Am. Chem. Soc.*, **66**, 1757 (1944)].

mization took place during the ring closure. When the keto ester or the sodium derivative is treated with a mixture of acetic and hydrochloric acid, hydrolysis and decarboxylation take place with the formation of 3-keto-4-benzamidothiophane (C).

During the next phases of the biotin syntheses—the transformation of the 3-ketothiophanes, by means of a series of intermediates, into 3,4-diaminothiophanes—it was found that certain intermediates are mixtures of stereoisomeric racemates. These products are separated, and each stereoisomer is subjected, individually, to the series of reactions necessary for its conversion into the diaminothiophane. Depending on the particular configuration of the racemic 2-(δ-carboxybutyl)-3,4-diaminothiophane [319] which condenses with phosgene, the reaction product is *dl*-biotin, *dl-epi*-biotin, *dl*-allobiotin, or *dl-epi*-allobiotin.[320] The stereochemical relationships of these compounds are shown by the following formulas.



dl-biotin (m. p. 231-233°)[308]
dl-epi-biotin (m. p. 190-191°)[278]

dl-allobiotin (m. p. 194-196°)[308]
dl-epi-allobiotin (m. p. above 195°)[308]

dl-desthiobiotin (m. p. 165-166°)[321]

dl-desthioallobiotin (m. p. 164-165°)[321]
(mixed m. p. 144°)[321]

319 This substance, like biotin, contains three asymmetric carbon atoms and should exist in eight optically active and four racemic modifications; in two of the racemates, the positions of the amino groups must represent a *cis* and, in the other two, a *trans* arrangement. The configuration of the side chain, attached to carbon atom 2 of the ring, has not been established.

320 This nomenclature was introduced by Harris et al., *J. Am. Chem. Soc.*, **67**, 2096 (1945).

321 Harris et al., *J. Am. Chem. Soc.*, **67**, 2102 (1945).

dl-Biotin and *dl-epi*-biotin are epimeric at position 2 of the thiophane ring; the same statement applies to *dl*-allobiotin and *dl-epi*-allobiotin.

dl-Desthiobiotin [322] is formed by the removal of sulfur, with Raney nickel catalyst, from synthetic *dl*-biotin [321] and also from *dl-epi*-biotin,[273] whereas desthioallobiotin is obtained by desulfurization of *dl*-allobiotin [321] and *dl-epi*-allobiotin.[273,321]

The manner in which Harris and his associates utilized thiophane C for the synthesis of *dl*-biotin and the two stereoisomeric racemates, *dl*-allobiotin and *dl-epi*-allobiotin, is illustrated below. Thiophane C, unlike A and B, is not substituted in the 2 position. It was found possible to introduce into this position a substituent which can easily be converted into the desired δ-carboxybutyl group by condensation of thiophane C with methyl γ-formylbutyrate; the latter compound was prepared from glutaric anhydride.

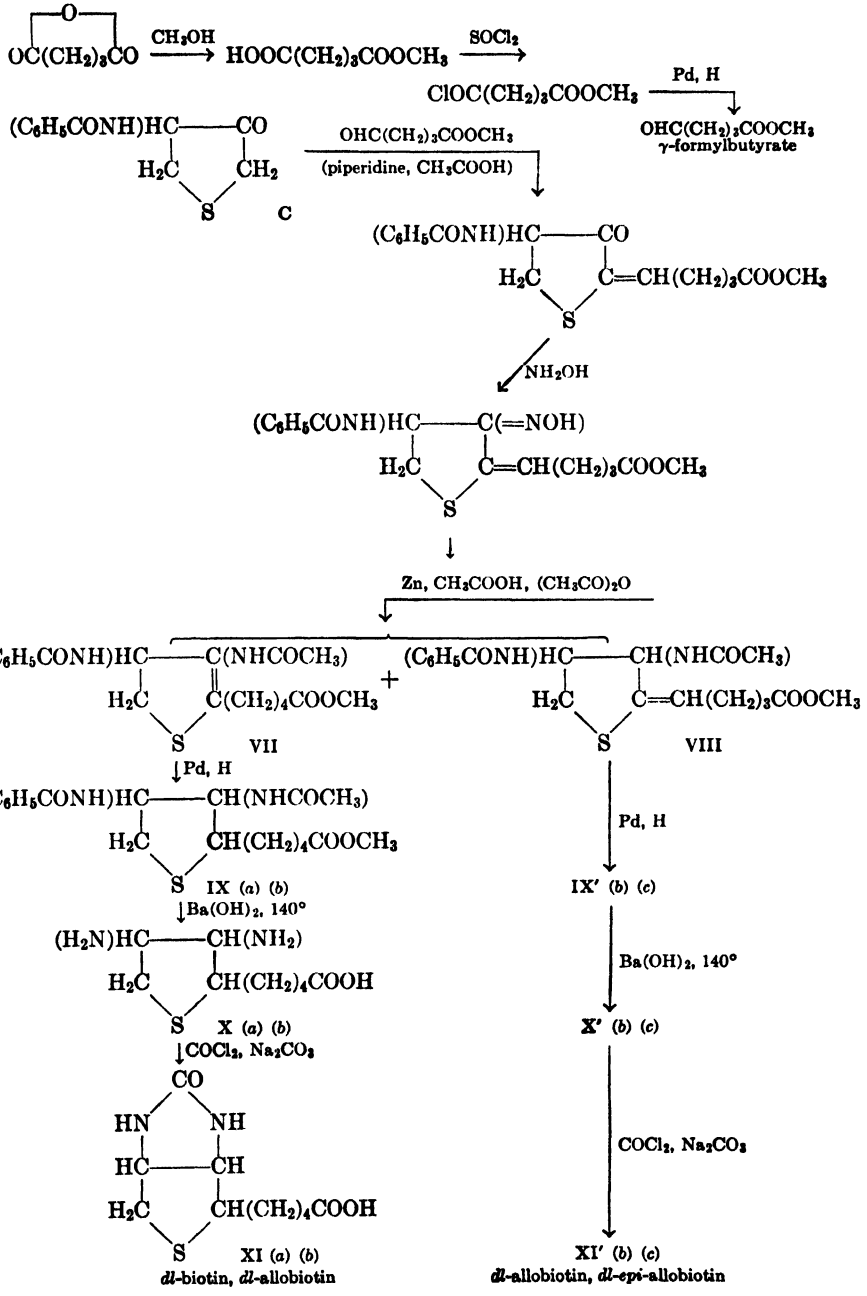
After the introduction of the 2 substituent into the thiophane and the preparation of the oxime, the 3-oximino radical is reduced with a mixture of zinc, acetic acid, and acetic anhydride. This process yields two structurally isomeric products; both represent the 3-acetylamino derivative, but one isomer appears to possess structure VII, the other isomer, structure VIII.[323] When the double bond in each compound (VII and VIII) is removed by hydrogenation, products of structure IX, the diamido esters, are obtained. Hydrolysis of the diamido esters yields the diamino acids (X), which react with phosgene to form products which possess the biotin structure XI.

Product IX, obtained from VII, is a mixture of two stereoisomeric racemates which are separated by fractional crystallization; they are called the *dl*-diamido ester [IX (*a*)] and the *dl*-allodiamido ester [IX (*b*)], and in subsequent experiments each racemate is treated separately. Hydrolysis of the *dl*-diamido ester [IX (*a*)] with barium hydroxide produces the *dl*-diamino acid [X (*a*)] which is converted, by phosgene, into *dl*-biotin [XI (*a*)]. When this biotin is resolved, the *d* form is found to be identical with natural biotin.[324] When the

322 It has been stated [Dittmer, Melville, and du Vigneaud, *Science*, **99**, 203 (1944)] that a yeast strain can convert desthiobiotin into biotin but, for *L. casei*, desthiobiotin cannot replace biotin [Melville et al., *ibid.*, **98**, 497 (1943)]. *dl*-Desthiobiotin is one-half as active as desthiobiotin, and *dl*-desthioallobiotin is inactive when tested by the yeast growth assay.[321]

323 Evidence for these structures has been presented by Harris et al. [*J. Am. Chem. Soc.*, **67**, 2102 (1945)].

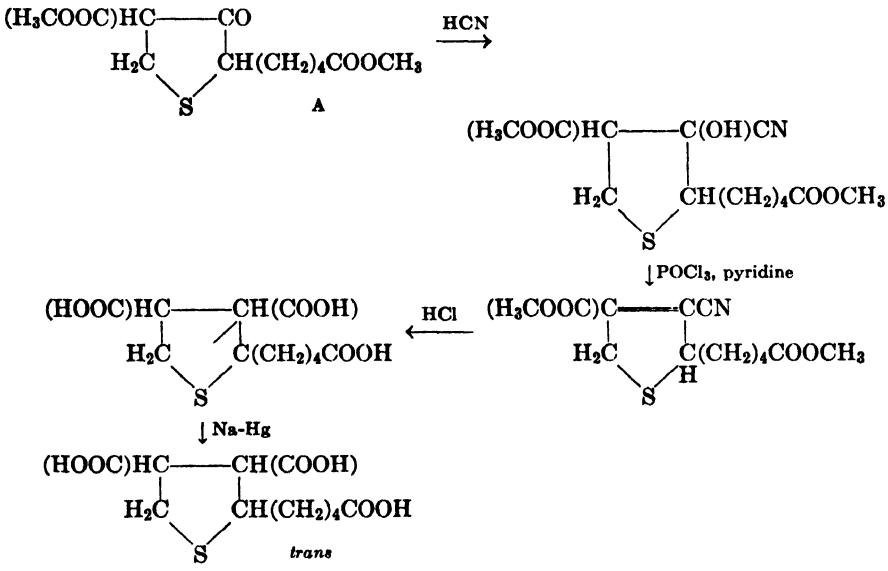
324 Initially, biotin was obtained by the resolution and hydrolysis of the *d*(−)-mandelic acid esters of *dl*-biotin [Harris et al., *Science*, **97**, 447 (1943); *J. Am. Chem. Soc.*, **66**, 1756 (1944); *ibid.*, **67**, 2096 (1945)]. Later, it was discovered that *l*(+)-arginine could be used very advantageously [Wolf et al., *J. Am. Chem. Soc.*, **67**, 2100 (1945)].


CH3OH
SOCl2
Pd, H
γ-formylbutyrate
OHC(CH2)3COOCH3
(piperidine, CH3COOH)
C
NH2OH
Zn, CH3COOH, (CH3CO)2O
VII
VIII
IX (a) (b)
IX' (b) (c)
Ba(OH)2, 140°
X (a) (b)
X' (b) (c)
COCl2, Na2CO3
XI (a) (b)
dl-biotin, dl-allobiotin
XI' (b) (c)
dl-allobiotin, dl-epi-allobiotin

dl-allodiamido ester [IX (*b*)] is treated in the same manner, *dl*-allobiotin [XI (*b*)] is obtained.

Product IX′, obtained from VIII, likewise is a mixture of two stereoisomeric racemates. One of these racemates is the *dl*-allodiamido ester [IX′ (*b*)]; the other is a new racemate and is called the *dl-epi*-allodiamido ester [IX′ (*c*)]. When the *dl-epi*-allodiamido ester is subjected to the reactions which have been mentioned, *dl-epi*-allobiotin [XI′ (*c*)] is produced.[325]

In a manner shown by the following reaction scheme, Baker et al. converted thiophane A, successively, into the cyanohydrin, the unsaturated cyanide, and carboxylic acid, in which the position of the double bond was not established,[326] and finally into the saturated acid, 2-(δ-carboxybutyl)thiophane-3,4-dicarboxylic acid.[271,327] It was



the *trans* isomer of this acid which Baker and his associates employed for the synthesis of compounds which possess a biotin structure. The *trans* configuration is established by the fact that the tricarboxylic acid

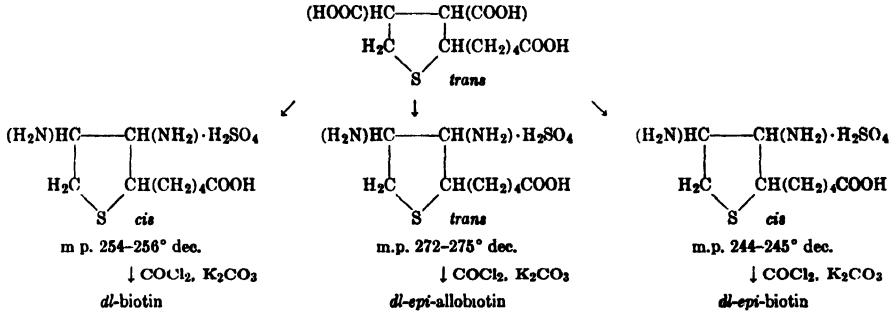
325 By the *L. arabinosus* assay, *dl*-biotin exhibits 50% of the activity of biotin, whereas *dl*-allobiotin and *dl-epi*-allobiotin are inactive. Against biotin deficiency in rats, induced by raw egg white, *dl*-biotin is one-half as effective as biotin, and *dl*-allobiotin is inactive [Harris et al., *J. Am. Chem. Soc.*, **67**, 2096 (1945)].

326 In the 2- or 5-alkyl-3-hydroxy-3-cyano-4-carbomethoxythiophanes, it has been shown that dehydration yields derivatives which have a double bond in the 3,4 position [Baker, Querry, and Kadish, *J. Org. Chem.*, **13**, 123 (1948)].

327 Another synthesis for this acid has been described by Brown et al., *J. Org. Chem.*, **12**, 160 (1947).

reacts with thionyl chloride to form a triacid chloride which, in turn, reacts with aniline to yield a trianilide. If the configuration had been *cis*, thionyl chloride would have converted the acid into a monoacid chloride anhydride, and this substance would have been transformed, by aniline, into an alkali-soluble monoanilide anilic acid.[270]

Through a series of reactions,[328] the 2-(δ-carboxybutyl)thiophane-*trans*-3,4-dicarboxylic acid is converted into a *cis*-2-(δ-carboxybutyl)-3,4-diaminothiophane which reacts with phosgene to produce *dl*-biotin.[272] By other processes, the tricarboxylic acid is transformed into a *trans*-2-(δ-carboxybutyl)-3,4-diaminothiophane which combines with phosgene to form *dl-epi*-allobiotin.[272] Finally, by other ingenious procedures, a *cis*-diamino acid can be obtained from the tricarboxylic acid which condenses with phosgene to yield *dl-epi*-biotin.[273]



Since *dl-epi*-biotin is converted by desulfurization with Raney nickel into *dl*-desthiobiotin, it must be epimeric to *dl*-biotin at position 2 of the thiophane ring. It shows no activity when assayed with *S. cerevisiea.*

The *dl*-biotin synthesis of Grüssner, Bourquin, and Schnider[298] is illustrated by the series of reactions on p. 274.

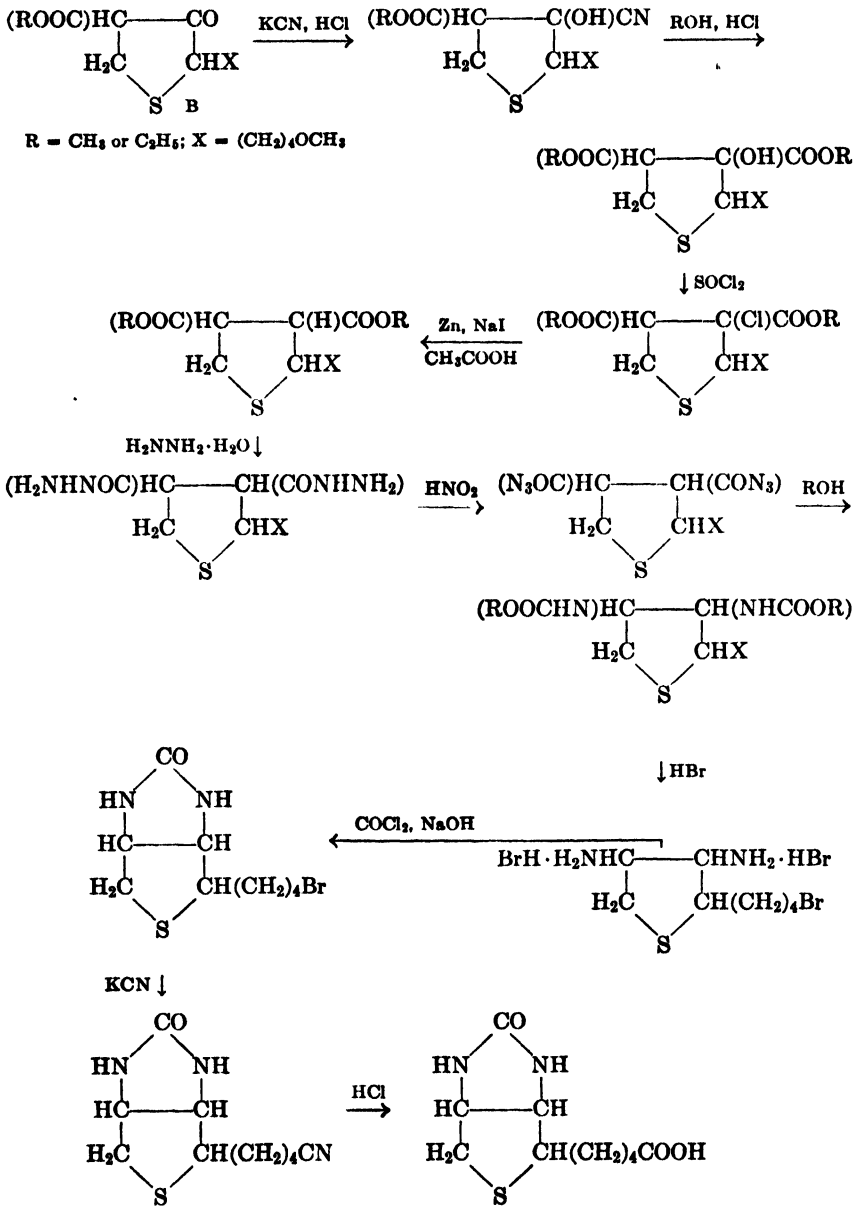
In addition to *dl*-biotin, other products were obtained which, originally, were considered to be isomeric biotins; later it was found that this view was erroneous, and the nature of the products remains unknown.[329]

dl-Dehydrobiotin, 2-(δ-carboxybutyl)-3,4-ureylene-2,5-dihydrothiophene, was synthesized by Safir, Bernstein, Baker, McEwen, and SubbaRow[330] in the hope that it could be hydrogenated with the for-

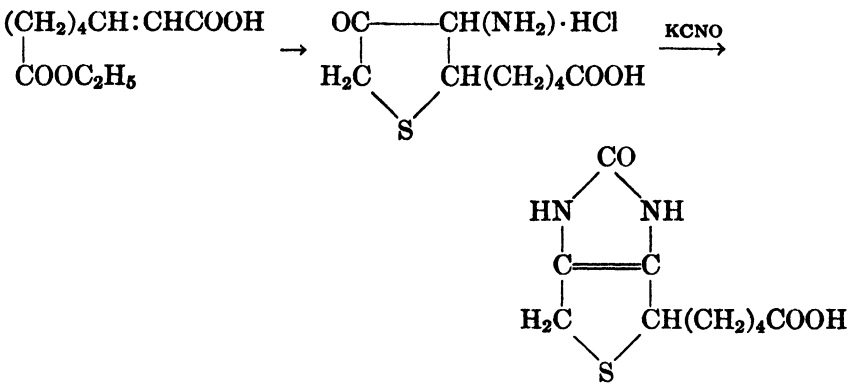
328 The original publications should be consulted for information relative to the nature of the many intermediates and to the manner in which their configurations were established at each step in the processes.

329 Grüssner, Bourquin, and Schnider, *Helv. Chim. Acta*, **29**, 770 (1946). See also Brown et al., *J. Org. Chem.*, **12**, 160 (1947), footnote 2.

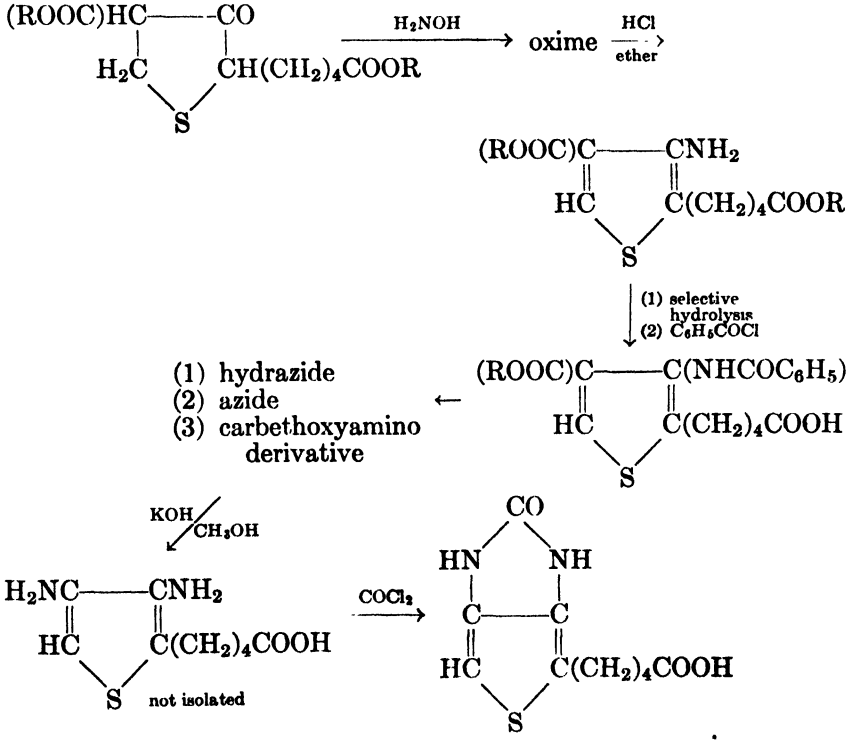
330 Safir et al., *J. Org. Chem.*, **12**, 475 (1947).



mation of *dl*-biotin. 7-Carbethoxy-2-heptenoic acid is converted, through a series of reactions, into 2-(δ-carboxybutyl)-3-amino-4-keto-thiophane hydrochloride which reacts with potassium cyanate to yield *dl*-dehydrobiotin. This substance is biologically inactive with *L. casei*.

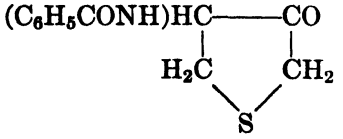


The synthesis of 2,3,4,5-tetradehydrobiotin, 2-(δ-carboxybutyl)-3,4-ureylenethiophene, the thiophene analog of biotin, has been achieved by Cheney and Piening.[312,331] The preparation of the required β-keto ester has already been described (p. 267). The tetradehydrobiotin cannot replace biotin for either *L. arabinosus* or *S. cerevisiae*.



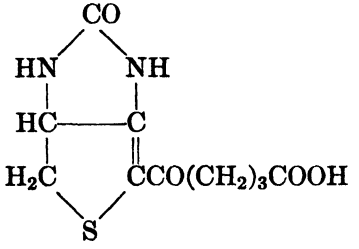
331 Cheney and Piening, *J. Am. Chem. Soc.*, **66**, 1040 (1944).

In an effort to synthesize biotin, Businger[332] was able to obtain 3-keto-4-benzoylaminothiophane from cysteine, but the oxime of this



compound behaves similarly to an oxime described by Karrer and Schmid[333] in that it cannot be reduced to an amine. Furthermore, although the 2-methylene group of the thiophane condenses with *p*-nitrobenzaldehyde, it will not react with an aliphatic aldehyde such as butyraldehyde. This behavior is in marked contrast to that of the thiophane utilized by Harris and collaborators in their biotin synthesis.

2-(γ-Carboxybutyryl)-3,4-ureylene-4,5-dihydrothiophene was also obtained by Businger,[332] but this compound could not be hydrogenated, either at the double bond or at the carbonyl group.



A total synthesis of *dl*-oxybiotin, 2-(δ-carboxybutyl)-3,4-ureylene-tetrahydrofuran, has been described by Hofmann.[334] It is stated that the activity of this substance, for certain organisms, equals that of *dl*-biotin. *dl*-Oxybiotin has also been synthesized by Duschinsky and Dolan.[335]

The synthesis of 3,4-diamino-5-methyltetron and of 2,3-diamino-4-methylbutyrolactone by Spiegelberg and Kirchensteiner[336] is also of interest in connection with the study of biotin.

Finally, attention should be called to analogs of biotin, prepared by English and co-workers,[337] in which the thiophane nucleus has been replaced by a benzene or a cyclohexane ring.

332 Businger, *Jubilee Volume Dedicated to Emil Christoph Barell*, Basle, 1946, p. 137.
333 Karrer and Schmid, *Helv. Chim. Acta*, **27**, 1280 (1944).
334 Hofmann, *J. Am. Chem. Soc.*, **67**, 1459 (1945).
335 Duschinsky and Dolan, ref. 332, p. 164.
336 Spiegelberg and Kirchensteiner, ref. 332, p. 149.
337 English et al., *J. Am. Chem. Soc.*, **67**, 295, 2263 (1945).

CHAPTER 6

THE CHEMISTRY OF PYRROLE AND ITS DERIVATIVES

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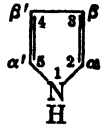
CONTENTS

SCOPE OF THE CHAPTER

The chemical literature now contains a number of reviews of the chemistry of the derivatives of pyrrole [1] summarizing the structural investigations of the naturally occurring pyrrole pigments. In the work which has had the major objective of elucidating these structures, many observations have been made of general interest to the organic chemist not primarily concerned with the problem of the structure of natural products. Chemists interested in the problem of organic synthesis will find the ring closures and transformations in the pyrrole series suggestive. Chemists interested primarily in organic reactions and their mechanisms will find in the pyrrole series much material for speculation and correlation. This chapter is directed primarily to these groups.

Conventional methods for denoting the various positions in the pyrrole nucleus parallel strictly those for the other monocyclic five-membered heterocycles. The use of Greek letters as well as numbers is common in the literature.



1 Fischer and Orth, *Die Chemie des Pyrrols*, Bd. I, Akademische Verlagsgesellschaft, Leipzig, 1934.

Fischer and Orth, *Die Chemie des Pyrrols*, Bd. II, 1 Hälfte, Akademische Verlagsgesellschaft, Leipzig, 1937.

Fischer and Stern, *Die Chemie des Pyrrols*, Bd. II, 2 Hälfte, Akademische Verlagsgesellschaft, Leipzig, 1940.

Gilman, *Organic Chemistry*, Vol. II, 2nd ed., John Wiley & Sons, New York, 1943: (*a*) Corwin, "The Chemistry of the Porphyrins," p. 1259; (*b*) Steele, "Chlorophyll," p. 1293. Fischer, "Ueber Hämin und Beziehungen zwischen Hämin und Chlorophyll," Nobel Prize Lecture, Stockholm. December 11, 1930; *Z. angew. Chem.*, **44**, 617 (1931).

Steele, *Chem. Revs.*, **20**, 1 (1937).

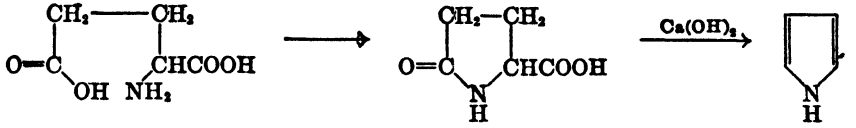
Fischer, *Naturwissenschaften*, **26**, 401 (1940).

Ann. Rev. Biochem., Ann. Reviews, Inc., Stanford University, California: (*a*) Fischer and Orth, **3**, 410 (1934); (*b*) Smith, James H. C., **6**, 496–507 (1937); (*c*) Lemberg, **7**, 421–437 (1938); (*d*) Mackinney, **9**, 459–471 (1939); (*e*) Drabkin, **11**, 531–568 (1942); (*f*) Rimington, **12**, 425–446 (1943); (*g*) Strain, **13**, 591 (1944); (*h*) Holden, **14**, 599 (1945).

Ann. Repts. Progress Chem. (*Chem. Soc. London*): (*a*) Linstead, **32**, 359–399 (1935); (*b*) Linstead, **34**, 369–389 (1937); (*c*) Stevens, **37**, 325–332 (1940).

HISTORICAL BACKGROUND

The existence of pyrrole in coal tar, bone oil, and, in general, in products obtained by the dry distillation of proteins was first surmised by Runge [2] in 1834, when he noticed that a substance was present in the ammonia liberated which would impart a red color to a wood splint moistened with mineral acid. Because of the fiery red color obtained, he called this unknown substance "pyrrole," meaning fiery oil, although he did not know its chemical constitution and supposed it to be a gas. It seems reasonable to suppose that the pyrrole formed by pyrolysis of proteins stems mainly from glutamic acid residues. Thus, it is known that glutamic acid (I) is converted to pyrrolidone α-carboxylic acid (II) on heating.[3] Pyrolysis of the calcium salt of this acid leads



I II III

to pyrrole (III).[4] It has been shown that the addition of chalk or barium hydroxide to bran or albumin increases the yield of pyrrole,[5] which is found in the non-basic oil fraction. It should be noted that proteins also contain preformed hydropyrrole rings in proline, pyrrolidine α-carboxylic acid, and β-hydroxyproline.

Pyrrole obtained from bone tar was first purified and analyzed by Anderson [6] in 1857. The preparation from ammonium mucate (IV)[7] or ammonium saccharate [8] soon superseded this source of pyrrole. The stoichiometry of this reaction may be made clear by the assumption of a hypothetical dienolic intermediate (V). The amide of pyrrole α-carboxylic acid (VI) has been isolated as a by-product in this reaction.[9] This method is still preferred for the preparation of pyrrole in the laboratory,[10] although its isolation from manufactured gas may

2 Runge, *Ann. Physik*, **31**, 67 (1834).

3 Menozzi and Appiani, *Gazz. chim. ital.*, **24**, I, 373 (1894).

4 Haitinger, *Monatsh.*, **3**, 228 (1882).

5 Laycock, *Chem. News*, **78**, 210, 223 (1898); Schutzenberger and Bourgeois, *Bull. soc. chim. France*, [2] **25**, 289 (1876).

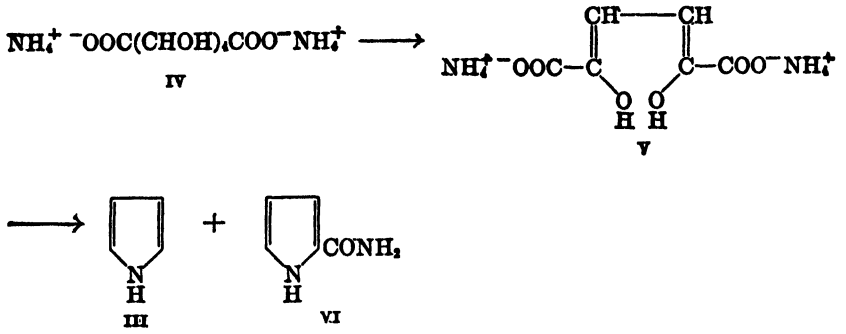
6 Anderson, *Trans. Roy. Soc. Edinburgh*, **21**, part IV, 571 (1857). See also *Ann.*, **105**, 349 (1858).

7 Schwanert, *Ann.*, **114**, 65 (1860); Ciamician, *Ber.*, **37**, 4200 (1904).

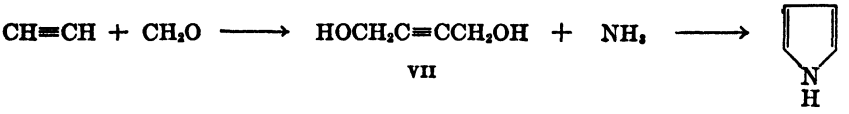
8 Fujita et al., *J. Soc. Chem. Ind., Japan*, **41**, 63 (1938) [*C. A.*, **32**, 6902 (1938)].

9 Schwanert, *Ann.*, **116**, 269 (1860); Ciamician and Silber, *Ber.*, **17**, 104 (1904).

10 Goldschmidt, *Z. Chem.*, **3**, 280 (1867); Gilman, *Org. Syntheses Coll. Vol.* **1**, 478, Second Edition (1941).



be feasible.[11] A promising method for future investigation is that of Reppe et al.,[12] who prepare pyrrole from acetylene, formaldehyde, and ammonia. The intermediate 2-butyne-1,4-diol (VII) reacts as succinic



dialdehyde. Numerous variations on this scheme are claimed to be feasible, so that many pyrroles and hydropyrroles should be available, provided that yields are satisfactory.

Interest in the chemistry of pyrrole derivatives was originally stimulated by the discovery that indole, which is benzopyrrole, is the fundamental nucleus in indigo, an important article of commerce, and that pyrrole itself is the building block of hemin, bilirubin, and chlorophyll. Early in the nineteenth century, Berzelius investigated the effects of many reagents upon blood, and it was in following up these studies that Teichmann[13] obtained the first crystals of hemin. In 1868, Hoppe-Seyler[14] undertook the preparation of crystalline hemin on a large scale for chemical study. He prepared the first porphyrin in 1871[15] and also demonstrated that hemin was in some way related to pyrrole by isolating "pyrrole" (probably a mixture of alkyl pyrroles) from the products of the dry distillation of hemin.[16]

11 Bunte and Steinbrunn, *Gas- u. Wasserfach*, **74**, 1193 (1931) [*C. A.*, **26**, 1418 (1932)].

12 Reppe et al., Ger. pat. 701,825 (Dec. 24, 1940) [*C. A.*, **35**, 7976 (1941)]. Cf. p. 127 for the analogous preparation of furan.

13 Teichmann, *Z. ration. Med., N.F.*, **3**, 375 (1853).

14 Hoppe-Seyler, *Med. Chem. Untersuchungen*, **3**, 379 (1868).

15 Hoppe-Seyler, *Med. Chem. Untersuchungen*, **4**, 540 (1871).

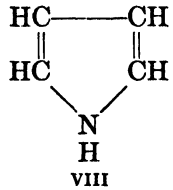
16 Hoppe-Seyler, *Med. Chem. Untersuchungen*, **4**, 524 (1871).

The study of the bile pigments goes back to alchemical times, but again Berzelius was the first modern investigator to make any progress in the examination. He studied methods for their separation and purification, and, owing to his labors, Tiedemann and Gmelin [17] were able to find a characteristic color test for the bile pigments. The Gmelin test is the most sensitive one known for these substances and is probably the most spectacular color display in all organic chemistry. Bilirubin was first obtained in crystals from the clots of internal hemorrhages by Virchow [18] and was called hematoidin. It was crystallized from the gallstones of cattle by Valentiner [19] in 1858. In 1864, Staedeler [20] published a remarkably accurate analysis of the compound. Since physiologists early recognized the close connection between the pigments of the blood and the bile, the demonstration of the relation of hemin to pyrrole immediately related bilirubin to pyrrole in the minds of chemists.

The study of chlorophyll was begun somewhat later and has through all its stages proved more difficult than that of either hemin or bilirubin. Again, it was Berzelius [21] who undertook the separation of the pigment from hawthorn leaves. The relationship between hemin and chlorophyll was correctly deduced from incorrect observations by Verdeil,[22] who maintained that both contained iron. The first correct evidence of their relation was obtained by Hoppe-Seyler [23] when he prepared a porphyrin from chlorophyll.

THE CONSTITUTION OF PYRROLE

In 1870, Baeyer and Emmerling [24] proposed a structural formula for pyrrole (VIII) in connection with their studies on the constitution of



VIII

17 Tiedemann and Gmelin, *Die Verdauung nach Versuchen*, Leipzig, 1826, pp. 1, 80.
18 Virchow, *Ann.*, **78**, 353 (1851).
19 Valentiner, *Günzberg's Z.*, 46 (1858).
20 Staedeler, *Ann.*, **132**, 323 (1864).
21 Berzelius, *Ann.*, **27**, 296 (1838).
22 Verdeil, *Compt. rend.*, **33**, 689 (1851).
23 Hoppe-Seyler, *Z. physiol. Chem.*, **3**, 339 (1879).
24 Baeyer and Emmerling, *Ber.*, **3**, 517 (1870).

indigo. This remains the only normal valence formula for pyrrole which has been seriously considered. In spite of this fact, some dissatisfaction with the formula has been felt for much the same reasons that the original formulation for benzene was felt to be inadequate. In his summary of the constitution of pyrrole, Hans Fischer [25] writes three alternative formulas for pyrrole and concludes that an exact answer to the question of structure will probably be reached by physical-chemical studies. Following this line of thought, it is useful to examine some of the physical evidence concerning the structure of pyrrole.

Direct Physical Investigations of Pyrrole. It has been proposed [26] to represent pyrrole as a resonating molecule. The organic chemist must first inquire, therefore, what direct physical determinations permit the conclusion that the pyrrole molecule is actually a resonating system.

One criterion of a resonating system which has been advanced to apply to pyrrole is stabilization.[27] The energy actually found by combustion differs by 23 kcal.[28] from that calculated from normal bond energies, and the direction is towards greater stability than that calculated for "normal" bonds. This stabilization energy is ascribed to resonance in the pyrrole molecule.

Closer examination reveals a number of uncertainties in this conclusion. It is outside the scope of this work to examine the validity of the assumptions on which this scheme is based. However, they have not gone unchallenged.[29] For the present purpose, let us accept these assumptions and examine only the data on which the conclusion is based.

Calorimetric data on compounds containing nitrogen are less satisfactory than many others for purposes of calculation of second-order effects, such as resonance stabilization. Workers in the field have frequently neglected to correct for the possibility of nitrite formation or for the possible presence of NO among the combustion products. Carbonaceous ashes which are frequently formed are assumed to be gra-

[25] Fischer and Orth, *Die Chemie des Pyrrols*, Bd. I, Akademische Verlagsgesellschaft, Leipzig, 1937, pp. 1, 13, 14. See also ref. 1.

[26] Ingold, *J. Chem. Soc.*, 1127 (1933); Pauling and Sherman, *J. Chem. Phys.*, **1**, 606 (1933).

[27] Pauling, *The Nature of the Chemical Bond*, 2nd ed., Cornell University Press, Ithaca, N. Y., 1940, p. 226.

[28] Schomaker and Pauling, *J. Am. Chem. Soc.*, **61**, 1778 (1939).

[29] Dietz, *J. Chem. Phys.*, **3**, 58 (1935); Wrinch, *Science*, **92**, 79 (1940).

phitic in the face of the fact that they may contain nitrogenous material in addition.[30]

For pyrrole, the calculations are based on the combustion data of Berthelot and André [31] made in 1899. These measurements were made before modern precision methods of calorimetry were introduced. They are also deficient in other respects. No criterion of purity of the pyrrole was given by the authors beyond a rough analysis which did not agree well with the theoretical values. The authors note that pure pyrrole always left a carbonaceous ash and that this difficulty was overcome by the admixture of a considerable amount (unspecified) of camphor. Although this admixture may have served to decrease the amount of nitric oxide formed during the combustion, it would also diminish the precision of the determination on pyrrole itself.

If the combustion products of pyrrole contained nitric oxide, correction for this error would tend to decrease the apparent resonance stabilization of the pyrrole molecule. If such an error were present in the combustion of the amines from which the normal C—N bond value was calculated, the opposite effect would be produced. From an examination of the combustion values obtained with other derivatives of pyrrole, Schomaker and Pauling conclude that a resonance energy of 31 kcal. per mole is more probable than that of 23 kcal., calculated from the determination of Berthelot and André. They specifically stated their lack of confidence in these data.[32] Until precise calorimetric determinations have been made on all the necessary nitrogenous materials in a state of high purity, judgment must be reserved as to the exact magnitude of resonance stabilization in pyrrole.

Another physical argument in the evaluation of resonance is based on bond lengths.[32] The only data that bear on the bond lengths in the pyrrole molecule are obtained by electron diffraction measurements.[32] These show the average ring bond length in the molecule but do not resolve sharply the different ring bonds. The average is very slightly smaller than the average calculated on the assumption that all the bonds are "normal" and have the minimum values assigned to "normal" bonds. The deviations in intensity of the electron diffraction photographs which would be caused by the assignment of the minimum "normal" bond lengths have not been published so that it is

30 For a summary of the literature on which most of these calculations are based, see Kharasch, *Bur. Standards J. Research*, **2**, 359 (1929).

31 Berthelot and André, *Ann. chim. phys.*, [7] **17**, 446 (1899).

32 Schomaker and Pauling, *J. Am. Chem. Soc.*, **61**, 1769 (1939).

not possible to judge whether the photographs obtained completely contradict the assumption of "normal" bond distances and thus exclude the simple Baeyer formula for pyrrole. With benzene, it is admitted [32] that the electron diffraction method is not sufficiently precise to decide between complete and "quite incomplete" resonance in the benzene ring, however.

Still another method of evaluating the resonance in molecules is to measure the heats of hydrogenation of the bonds [33] and to compare them with "normal" ethylenic double bonds. Unfortunately, this criterion is not available for pyrrole since its heat of hydrogenation has not been measured.

Finally, a searching analysis of the spectrum of a substance is capable of revealing the desired information. A complete analysis of the ultraviolet absorption spectrum of pyrrole is lacking.[34] Much progress has been made toward the interpretation of the infrared and Raman spectra, however.[35] From these studies, it is concluded that the pyrrole ring contains no ethylenic bond and that the "pyrrolenine" form, which has frequently been assigned to pyrrole, is entirely lacking. This analysis provides confirmation for the concept of resonance in the pyrrole ring, despite the fact that no Kekulé isomers can be written.

Physical Investigations Bearing Indirectly on Pyrrole. Even though incomplete, the direct physical investigations of pyrrole which have been cited lead to the conclusion that pyrrole is a resonating system. If we argue by analogy, then the great mass of physical evidence concerning the structure of benzene is applicable to pyrrole. One of the burdens of the argument in succeeding parts of this treatment will be to develop the logically necessary analogies between the pyrrole series and the benzene series.

Kistiakowsky's studies [33] on heats of hydrogenation provide quantitative confirmation for the qualitative fact long known to organic chemists that dihydrobenzene derivatives are less stable than the aromatic system itself and tend to revert to it. Exhaustive analyses of the infrared and Raman spectra [36] of benzene itself. as well as com-

[33] Conant and Kistiakowsky, *Chem. Revs.*, **20**, 181 (1937).

[34] For ultraviolet curves, see Menczel, *Z. physik. Chem.*, **125A**, 161 (1927).

[35] Bonino, *Atti accad. nazl. Lincei, Classe sci. fis mat. e nat.*, **25**, 502 (1937); Bonino, *Atti congr. intern. chim. 10th Congr. Rome, 1938*, **2**, 141 (1939); Manzoni-Ansidei, *Ricerca sci.*, **10**, 328 (1939); Zumwalt and Badger, *J. Chem. Phys.*, **7**, 629 (1939); Lord and Miller, *ibid.*, **10**, 328 (1942).

[36] Langseth and Lord, *Kgl. Danske Videnskab. Selskab, Mat. fys. Medd.*, **16**, No. 6 (1938) [*C. A.*, **32**, 3263 (1939)].

bustion data,[37] also confirm the conclusion that it is a stabilized system.[36]

It is recognized that phenol, catechol, and resorcinol are still aromatic systems, even though most of the typical substitution reactions of benzene have been made easier and the stability to oxidizing agents has been decreased. It follows that, if benzene is stabilized by resonance, these substances also owe their peculiar aromatic properties to the same source. There is no difficulty in formulating at least two normal valence structures which contribute to this resonance.

As was pointed out long ago [38] and as will be developed in greater detail, the derivatives of pyrrole are substances which are closely analogous in their reactions to the substituted phenols. This conclusion also agrees completely with the insistence of the early workers in the field that pyrrole derivatives are aromatic systems.[38] It follows, then, that the derivatives of pyrrole are stabilized by resonance. If we accept the conclusion as necessary, we are forced to seek possible electronic isomers of the Baeyer formula for pyrrole.

A clue to the answer to this difficulty may be obtained by a study of the behavior of pyrrole and its derivatives towards acids and bases. Pyrrole is not a base in the usual sense of the word. Even tetramethylpyrrole, which should be a stronger base, does not form salts which are stable in aqueous solutions. Pyrrole is vastly more acidic than ammonia. 2,4-Dimethyl-3,5-dicarbethoxypyrrole has been estimated to have an acidity similar to that of methanol.[39] The basic properties of simple pyrrole derivatives are negligibly weak in pyrrole chemistry. The formation of picrates by certain pyrroles is not necessarily to be regarded as true salt formation, since similar derivatives are formed with trinitrobenzene,[40] and picrates and trinitrobenzene derivatives of non-basic aromatic hydrocarbons are well known.[41] Moreover, salts of pyrroles with stronger acids than picric acid, such as hydrochloric acid, are not stable under the conditions that the picrates are stable. On the other hand, the acidic properties of pyrrole are so pronounced that they are of frequent value in preparative work, and the salts of certain substituted pyrroles with bases are stable in aqueous solutions.[42]

37 See ref. 27, pp. 124 et seq.

38 See the review by Ciamician, *Ber.*, **37**, 4201 (1904).

39 McEwen, *J. Am. Chem. Soc.*, **58**, 1124 (1936).

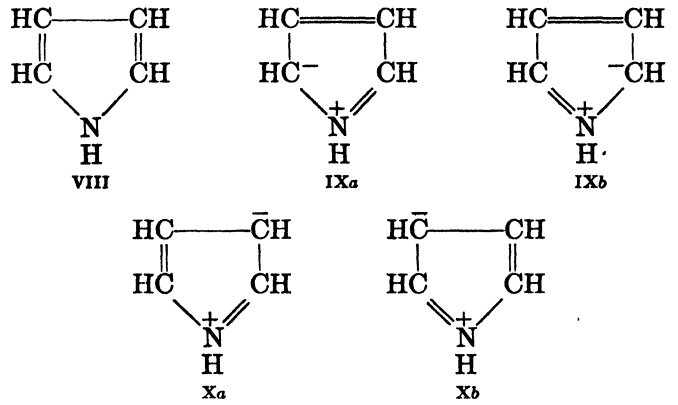
40 Van Romburgh, *Rec. trav. chim.*, **14**, 67 (1895).

41 See Pfeiffer, *Organische Molekülverbindungen*, F. Enke, Stuttgart, 1922, pp. 218 et seq.

42 Fischer and Ernst, *Ann.*, **447**, 155 (1926).

The structural feature of substituted amines which is responsible for basic properties is an unshared pair of electrons on the nitrogen.[48] The structural features of ammonium salts which are responsible for their acidity are the combination of quadrivalence and positive charge on the nitrogen atom and the presence of a hydrogen atom. Since pyrrole possesses only weakly basic properties, the Baeyer formula, with its unshared pair of electrons on nitrogen, does not adequately represent its reactions. Since acidity is distinctly detectable in pyrrole, it must be possible for pyrrole to react as an ammonium salt, that is, the nitrogen must have a positive charge and be quadrivalent.

A pyrrole formula incorporating these structural features was suggested by Pauling and Sherman [26] and almost simultaneously by Ingold.[26] The main components of the resonance of pyrrole are those listed below.



Although it may seem unduly cumbersome to represent a simple chemical substance by such a multiplicity of forms, the system has many advantages for predicting and correlating the reactions of pyrrole.

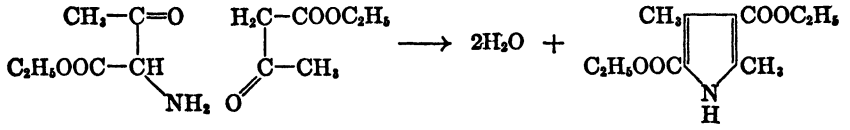
On the bases of both direct physical evidence and analogy, we may thus conclude that the pyrrole ring is a resonating system. The analogies which establish this are the lack of basicity of pyrrole, its acidity, and its pronounced resemblance to the resonating benzenoid systems. In this review, we shall adopt the convention of writing the classical formula for pyrrole with the implication that it is a symbol for the resonating system represented above, and specific citations of the charged forms will be made only when necessary.

[48] G. N. Lewis, *Valence*, Chemical Catalog Co., New York, 1923, p. 142.

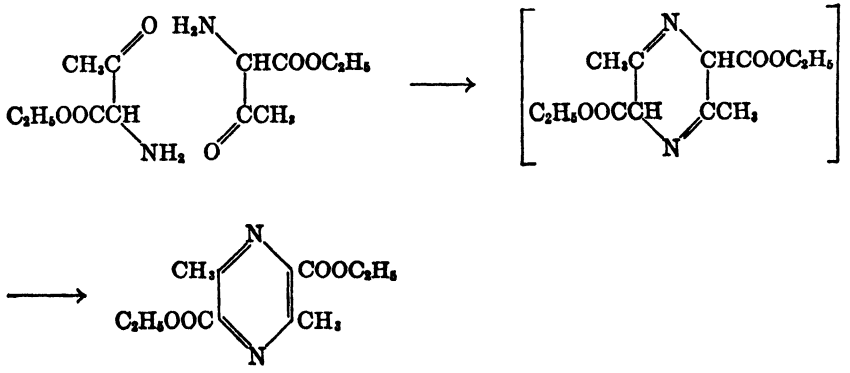
PYRROLE RING CLOSURES

Most pyrrole derivatives which have been used in natural product synthesis have been prepared by methods involving one or more substitution reactions after the original ring closure. For this reason, a solution to the problem of the preparation of a desired pyrrole derivative will in general involve a knowledge of the transformations which can be effected on the intact pyrrole system. These transformations will be discussed in the section on the reactions of pyrrole systems.

The most general reaction of ring closure in the field is the method discovered by Knorr.[44] This has been shown by Knorr and Lange[45] to involve the condensation of an α-amino ketone with a ketone having a reactive methylene group *alpha* to the carbonyl group. The type example is the condensation of α-aminoacetoacetic ester with acetoacetic ester.



The utility of the reaction is limited by the tendency of α-amino ketones toward self-condensation.[46] If the methylene ketone is not sufficiently reactive, the amino ketone will condense to form a pyrazine instead of a pyrrole.[47] This condensation proceeds so readily that



44 Knorr, *Ann.*, **236**, 318 (1886).

45 Knorr and Lange, *Ber.*, **35**, 3001 (1902).

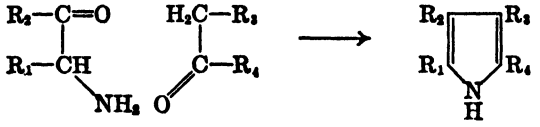
46 Treadwell, *Ber.*, **14**, 1461 (1881). See also Stoehr, *J. prakt. Chem.*, [2] **47**, 464 (1893).

47 Wleügel, *Ber.*, **15**, 1051 (1882).

α-amino ketones are, in general, not capable of independent existence and must be isolated as hydrochlorides.

As a matter of convenience, it is frequently possible to carry out the preparation and condensation of the α-amino ketone in the same operation. This can be accomplished because of the fact that a methylene ketone of the type of acetoacetic ester is not reduced by zinc dust in boiling glacial acetic acid, whereas an α-isonitrosoketone is readily reduced under these conditions to the corresponding α-amino ketone.[48]

If we represent the generalized reaction as follows,



the limitations of the reaction may be summarized thus.[45]

When R_1 is H or alkyl or aryl and the other substituents are favorable, the reaction is frequently useful but the yields may not be wholly satisfactory.

When R_1 is acyl or carbalkoxy and the other substituents are favorable, the yields are excellent.

R_2 may be alkyl, aryl, acyl, or carbalkoxy without seriously affecting the yield.

When R_3 is alkyl, the yields are poor or the reaction may fail. When R_3 is acyl or carbalkoxy, the yields are excellent.

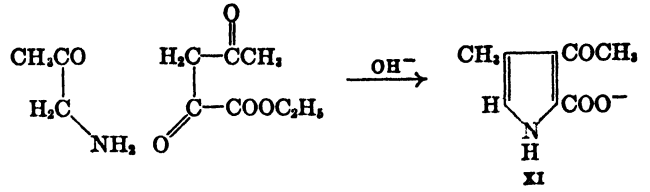
When R_4 is alkyl, aryl, acyl, or carbalkoxy, the yields are excellent.

Almström [49] has shown that the reaction may be further extended to the preparation of N-substituted pyrrole derivatives from secondary amino ketones.

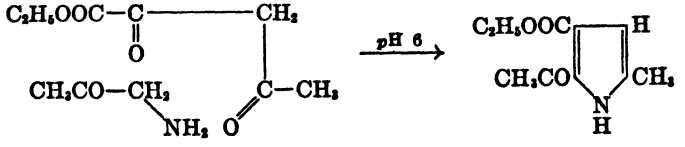
When the condensation is sluggish, it has been found possible to effect it by slow neutralization of the α-amino ketone hydrochloride in the presence of the desired methylene ketone. An especially interesting example of this variation of the technique is afforded by the condensation of α-aminoacetone with ethyl oxaloacetone, studied by Fischer, Sturm, and Friedrich.[50] Since ethyl oxaloacetone is an unsymmetrical diketone, several condensation possibilities appear, of which two actually take place.

[48] Corwin and Quattlebaum, *J. Am. Chem. Soc.*, **58**, 1083 (1936).
[49] Almström, *Ann.*, **409**, 291 (1915).
[50] Fischer, Sturm, and Friedrich, *Ann.*, **461**, 244 (1928).

It is possible to control the course of the condensation by controlling the *p*H of the condensing medium.[51] In alkali, compound XI is formed,



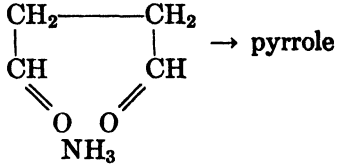
XI



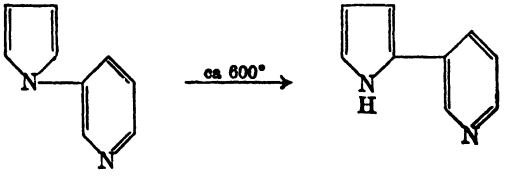
XII

whereas at *p*H 6 compound XII is obtained. Intermediate alkalinities give mixtures of the two substances.

If pyrrole prepared by the pyrolysis of proteins is formed from glutamic acid, then Runge's pyrolysis was the first synthetic pyrrole ring closure. Schwanert's method, using ammonium mucate, constitutes a second ring closure, the hypothetical mechanism for which, IV–III, p. 280, bears a formal resemblance to the synthesis of pyrrole from succindialdehyde and ammonia by Harries.[52] The ammonia method has



been used for the preparation of N-substituted pyrroles, by substitution of primary amines instead of ammonia. An application was that of Pictet and Crepieux to the synthesis of nicotine, in which the mucate of β-aminopyridine was distilled to give N-β-pyridylpyrrole (XIII).[53]



XIII

51 Fischer, Beyer, and Zaucker, *Ann.*, **486**, 55 (1931).

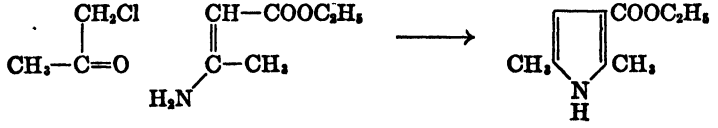
52 Harries, *Ber.*, **34**, 1488 (1901).

53 Pictet and Crepieux, *Ber.*, **28**, 1904 (1895).

It should be noted that the rearrangement of this substance from the N to the α position of the pyrrole ring is very difficult, requiring red heat.

The Harries synthesis is a special case of the Paal-Knorr synthesis from γ-diketones.[54] By this method, 2,5-dimethylpyrrole may be prepared from acetonylacetone, $CH_3COCH_2CH_2COCH_3$. Primary amines may also be substituted for ammonia.

The Hantzsch pyrrole synthesis, typified by the following example, has been discussed in some detail earlier in connection with a variation of the reaction which leads to the formation of furan derivatives (pp. 132 ff.).



REACTIONS OF PYRROLE SYSTEMS

The reactions of pyrrole systems may conveniently be classified into substitution reactions, reactions of substituents on the ring, condensation reactions, and reactions that destroy the pyrrole system, such as cleavage. Before proceeding to details of these reactions, formulation of a mechanistic basis for the reactions of the system will aid in understanding the reactivity of pyrrole derivatives. This is best done by considering the analogies between pyrroles and phenols.

Analogies between Pyrroles and Phenols

The chemistry of many of the aromatic-type heterocyclic compounds can be paralleled by selecting suitably substituted benzene derivatives as model compounds for the purposes of analogy. Frequently, the wider study which has been accorded the benzene derivatives makes this course a suggestive one for the understanding of isolated parts of heterocyclic chemistry. Thus, the analogies which Victor Meyer[55] drew between benzene and the derivatives of thiophene, as well as the differences which he noted, have been of the greatest aid in the logical organization of the chemistry of thiophene.

Early in the study of pyrrole derivatives, Ciamician[38] called attention to the similarity between the behavior of pyrroles and phenols.

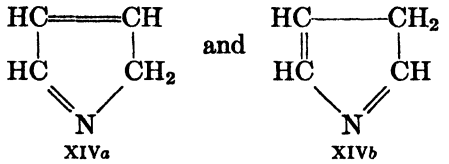
[54] Paal, *Ber.*, 18, 367 (1885); Knorr, *Ann.*, 236, 290 (1886).

[55] Victor Meyer, *Die Thiophengruppe*, Vieweg und Sohn, Braunschweig, 1888.

Later information as to aromatic structures and reactions permit these analogies to be refined, their sources understood, and their limitations marked, for it must be emphasized again that the analogies, although admittedly useful, are imperfect.

The So-Called Desmotropic Reactions of Pyrroles and Phenols

Fischer and Orth [1] state that α- and β-pyrrolenines (XIV*a* and *b*) can exist as desmotropes of pyrrole. Acceptance of this statement necessitates abandoning the concept of pyrrole as a resonating struc-

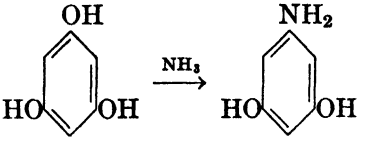


XIV*a* XIV*b*

ture since the resonance stabilization of either of the pyrrolenines must be much less than that of pyrrole. Beilstein [56] is much more conservative and says that pyrrole may react as the tautomeric pyrrolenine form.

There appears to be no basis whatsoever in the literature for the statement that either of the unsubstituted pyrrolenines can exist, and no claim to have isolated either of them has appeared. On further examination, the statement of Fischer and Orth that these substances can exist is based on the fact that derivatives of them have been prepared from pyrrole. This reduces, then, to Beilstein's argument that pyrrole may react as the pyrrolenine form. Let us examine the evidence and analogies for this statement.

In 1861, Hlasiwetz [57] discovered that phloroglucinol reacts with ammonia to give phloramine. This reaction was investigated further by Pollak,[58] who established the empirical formula for the amine and



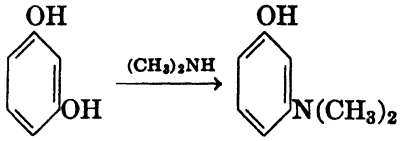
demonstrated that, under suitable conditions, the reaction can be reversed. The hydrolysis of 1,3,5-triaminobenzene hydrochloride forms

[56] Beilstein, *Handbuch der organischen Chemie*, 4 Aufl., Bd. XX. Springer, Berlin, 1935, p. 159.

[57] Hlasiwetz, *Ann.*, **119**, 202 (1861).

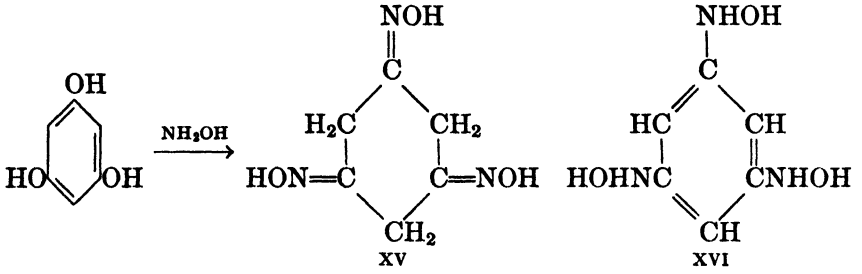
[58] Pollak, *Monatsh.*, **14**, 401 (1893).

a convenient method for preparing phloroglucinol. The reactions apply to other polyhydric phenols and polyaminobenzenes as well. Thus, a convenient method for preparing dimethyl-*m*-aminophenol is by the



action of dimethylamine and its sulfite on resorcinol.[59] *m*-Phenylenediamine can also be prepared by the action of ammonia, or preferably ammonium sulfite, on resorcinol.[60] In the naphthalene series, this reaction is known as the Bucherer reaction.[61]

In 1886, Baeyer [62] modified the amination cited above by the substitution of hydroxylamine for ammonia and claimed to have prepared the trioxime of the keto form of phloroglucinol (XV). It is curious that this compound, like many pyrroles, gives a pine-splint test.



Baeyer advanced no evidence for his claim that the compound so prepared was really a keto derivative and not an aromatic compound. He did not even consider the alternative formulation (XVI) which would be strictly analogous to the cases of phloramine and the derivatives of *m*-phenylenediamine. It is not now unprecedented that a compound lacking a keto group should give an "oxime" of the type formulated in compound XVI. Xanthydrol [63] and many substituted di- and tri-phenylcarbinols,[64] the carbinol bases of the triphenylmethane dyes,

[59] Ger. pat. 121,683 (July 31, 1900). See *Frdl.*, **6**, 192 (1900–1902).

[60] Ger. pat. 117,471 (Nov. 14, 1899). See *Frdl.*, **6**, 190 (1900–1902).

[61] For a review see *Organic Reactions*, Vol. 1, Chapter 5, John Wiley & Sons, New York, 1942.

[62] Baeyer, *Ber.*, **19**, 159 (1886).

[63] Fosse, *Bull. soc. chim. France*, [3] **35**, 1005 (1906); *Ann. chim.*, [9] **6**, 31 (1916). For a different example, see Wallach and Schrader, *Ann.*, **279**, 386 (1894), or Semmler, *Ber.*, **36**, 767 (1903).

[64] Weil, *Ber.*, **27**, 1404 (1894); **28**, 211 (1895); **38**, 275 (1905).

give such derivatives. Thus, the great weight of Baeyer's authority was lent to the unsubstantiated and logically inconclusive view that phenolic derivatives could isomerize freely to desmotropic forms.

It must be admitted that the direct chemical evidence on the opposite side of the argument is also inconclusive. Although the concepts of aromatic stability and of free isomerization of phloroglucinol are contradictory, conclusive evidence from classical organic methods is lacking on either side. On the other hand, the large body of evidence in favor of aromatic stabilization favors an aromatic formulation unless some force is at work which tends to counteract this stabilization. From the point of view of analogy, then, we may conclude that phloroglucinol should be aromatic and not ketonic.

The most reliable physical evidence bearing on this question is that from spectra. The evidence from Raman spectra [65] is that, in alcoholic solution, phloroglucinol is unequivocally trihydroxybenzene. Ultraviolet absorption spectra also lead to the conclusion that keto groups are absent in phloroglucinol.[66] From this evidence, we may conclude that any forces which may be at work in phloroglucinol to counteract its aromatic structure are not sufficient to accomplish this result and that the classical formulation is correct. The conclusion is still further substantiated by the calculations of Conant and Kistiakowsky, which show that the free energy of enolization of the hypothetical ketone form of phenol is -18.6 kcal.,[38] indicating that phenol is wholly enolic.

It is evident that the studies made of phenols provide no analogy for the conclusion that pyrrole should be formulated in the pyrrolenine form.

A much better case can be made for the conclusion that "pentachloropyrrole" is a derivative of α-pyrrolenine. This substance was first prepared by Anschütz and Schroeter [67] by the reaction of phosphorus pentachloride on β,β′-dichloromaleic imide. It was later prepared by Mazzara [68] by the action of SO_2Cl_2 upon pyrrole and upon tetrachloropyrrole. The fact that this substance can be reduced by means of sodium amalgam in acetic acid to tetrachloropyrrole may be cited as evidence that the material is a normal derivative of pyrrole (XVIII). Conversely, the fact that the material is hydrolyzed by hot water to yield the original dichloromaleic imide may be cited as evidence that the compound is not a pyrrole derivative and is, therefore, a pyrrol-

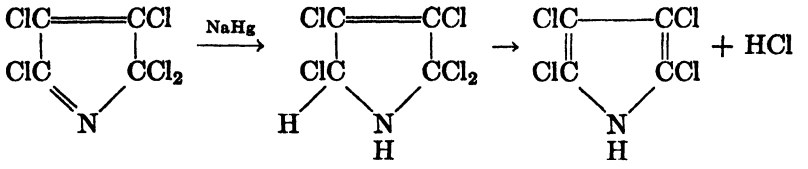
65 Kohlrausch, *Ber.*, **69**, 527 (1936).

66 Hartley, Dobbie, and Lauder, *J. Chem. Soc.*, **81**, 929 (1902). See also Hedley, *ibid.*, **89**, 730 (1906).

67 Anschütz and Schroeter, *Ann.*, **295**, 82 (1897).

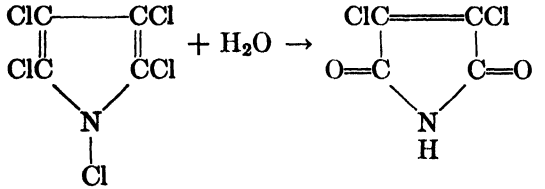
68 Mazzara, *Gazz. chim. ital.*, **32**, II, 30 (1902).

enine derivative (XVII). It is not impossible, as Anschütz and Schroeter saw, that the pyrrolenine derivative, if it exists, can be reduced to a pyrrole derivative. Conversely, it is not impossible that



XVII

an N-chloropyrrole derivative, if it exists, might be hydrolyzed to a maleic imide derivative.



XVIII

The above reaction would require a step of the following nature.

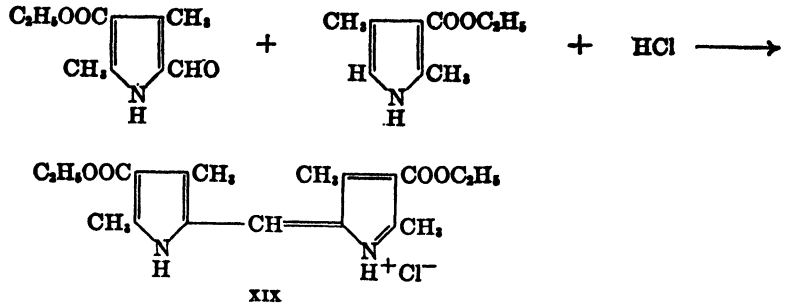
$$R_2NCl + HCl \rightarrow R_2NH + Cl_2$$

After this reaction, chlorine would be available to oxidize the pyrrole derivative formed to the maleic imide derivative. A final decision between these conflicting views will have to await a more subtle structural investigation. Meanwhile, the conclusion may be legitimately drawn that the chemistry of pentachloropyrrole affords no evidence for the existence of a pyrrolenine form of pyrrole or even of tetrachloropyrrole.

One type of pyrrolenine derivative is generally recognized in the literature. This is the type formed by condensation with carbonyl derivatives. The most important members of this class are the dipyrrylmethenes, which may be regarded as formed by the condensation of a substituted pyrrole with a pyrrole aldehyde.

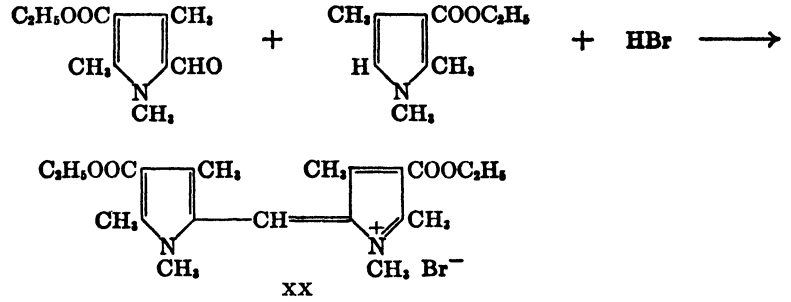
To argue that this reaction shows that the pyrrole with the free α position isomerizes before reacting [69] is to assume an arbitrary mechanism for the reaction. This assumption has no experimental support in the literature. It is much more reasonable, although equally unsupported by decisive mechanistic experiments, to assume a preliminary condensation to a substituted carbinol, followed by ionization. The

[69] Sidgwick, *The Organic Chemistry of Nitrogen*, revised by Taylor and Baker, Oxford, 1937, p. 482.



XIX

preliminary isomerization is definitely excluded by the following condensation.[70]



XX

The formulation of a dipyrrylmethene such as XIX or XX with fixed bonds on one side is entirely arbitrary, just as the formulation of benzene as one of the Kekule forms would be. These substances are resonating structures, and it is the resonance stabilization which makes the pyrrolenine form a stable one. This stabilization is lacking in unsubstituted pyrrolenine.

The dipyrrylmethenes illustrate one property of the pyrrolenines which sets them off sharply from the pyrroles, namely, their basicity. The methenes are bases which combine readily with mineral acids to form stable salts. This property, contrasting as it does with the lack of basicity of the pyrroles, shows that the pyrroles are not pyrrolenines and that they do not even *react* as pyrrolenines.

The final class of derivatives of pyrrolenine which will be considered comprises the alkylated pyrrolenines. If pyrrole or 2,3,4,5-tetramethylpyrrole is treated with methyl iodide and magnesium oxide in boiling ether, pentamethylpyrrolenine is formed.[71] Although the structural investigation of this particular compound is not complete, the analogies between the alkyl pyrrolenines and the alkyl indolenines,

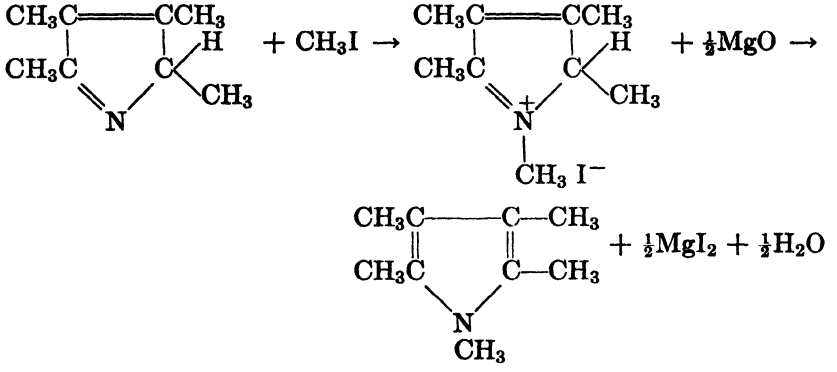
70 Brunings and Corwin, *J. Am. Chem. Soc.*, **64**, 593 (1942).

71 Plancher and Zambonini, *Atti reale accad. Lincei*, [5] **22**, II, 708 (1913).

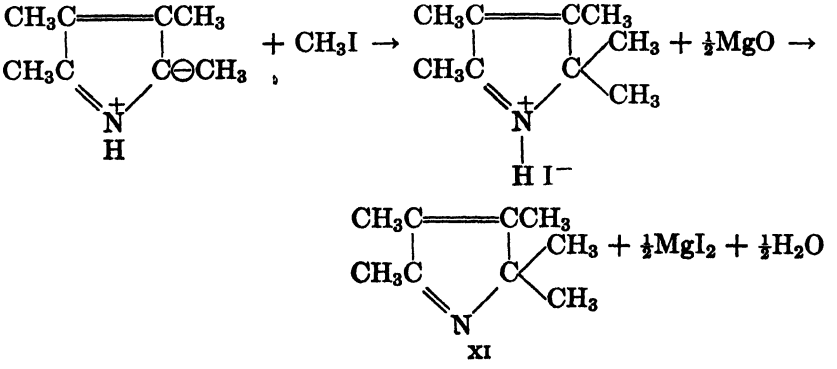
which have been more carefully examined, are so extensive as to suggest that their structures are analogous. The production of these substances is of great significance in the theory of pyrrole reactions.

The confusion which has arisen concerning the reactions of pyrroles is due to the assumption that an entering group takes the place vacated by a leaving group. In the pyrroles and the pyrrolenines, the structural feature which determines the outcome is not the position of the hydrogen atom being replaced but the position of an unshared pair of electrons which can bond with the entering group, in this case, the methyl group.

Following this reasoning, we should expect that tetramethyl α- (or β-) pyrrolenine, if it could exist, would have an unshared pair of electrons on the nitrogen and would alkylate there to give pentamethylpyrrole, as represented by the following equation.



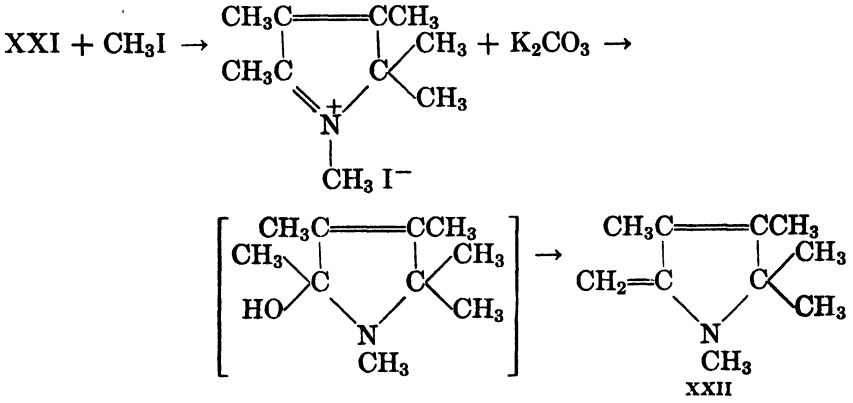
The behavior to be expected of tetramethylpyrrole would be different. Resonance would transfer electrons from the nitrogen to the carbons and C alkylation should result. This may be formally represented as follows.



XI

The experimental observation that pyrrole itself and the alkyl pyrroles alkylate not on nitrogen but on carbon and that tetramethylpyrrole, in particular, forms not pentamethylpyrrole but pentamethylpyrrolenine provides confirmation for the view that pyrroles react as resonating structures, not as pyrrolenines. This peculiarity extends to the indole series where it was first observed by Fischer and Steche.[72] The course of the alkylation can be represented as if the extra pair of electrons in pyrrole is not on nitrogen but on carbon. This is to say that, on a time average, IX*a*, IX*b*, X*a*, and X*b* come closer to representing pyrrole than formula VIII, for the purposes of correlating reactions.

Confirmation of the argument that tetramethylpyrrolenine, if it could exist, should alkylate on nitrogen is obtained by the reactions of pentamethylpyrrolenine. This substance, unlike the true pyrrole derivatives, is basic in its reaction. On alkylation, it forms an N-methyl derivative as is proved by the fact that the same compound can be obtained from the alkylation of N-methylpyrrole. This methiodide pseudomerizes and dehydrates in the presence of base, as represented by the following equations.[73] Compound XXII is called pentamethyl-

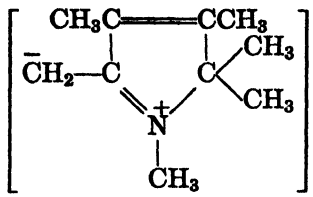


XXII

methylenepyrroline. One might expect it to alkylate further on the nitrogen with methyl iodide. Investigation shows, however, that it, like an alkyl pyrrole, methylates on carbon instead. This may be systematized by writing the reactive form of the substance as XXIII.

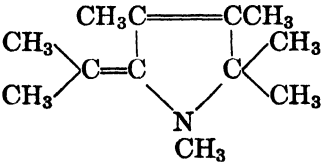
72 Fischer and Steche, *Ann.*, **242**, 348 (1887). See also Plancher, *Gazz. chim. ital.*, **28**, II, 30 (1898).

73 Plancher and Ravenna, *Atti reale accad. Lincei*, [5] **22**, II, 708 (1913).



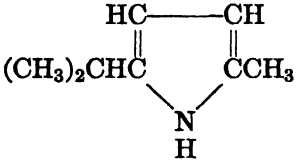
XXIII

$+ CH_3I + K_2CO_3 \rightarrow$



XXIV

The product (XXIV) is heptamethylmethylenepyrroline. That it is an isopropylidene derivative is proved by its preparation by the methylation of 2-methyl-5-isopropylpyrrole.

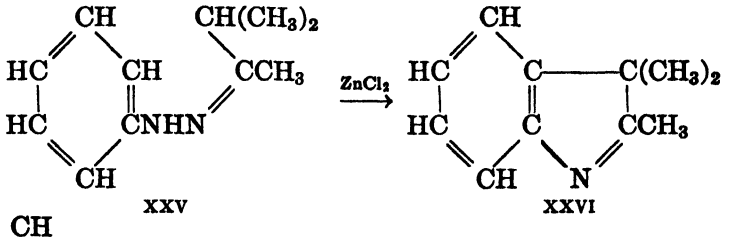


$+ CH_3I \rightarrow$ XXIV

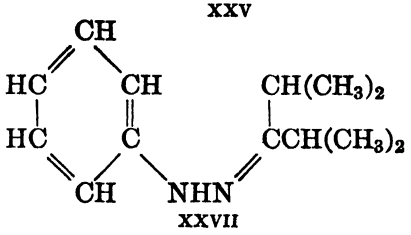
Whether the extra methyl group in pentamethylpyrrolenine (XXI) is on the α or the β position has not been established with certainty. Fischer's synthesis in the indole series, however, has made the position of the groups easier to determine in the indoles. All the compounds shown above have their analogs in the indole series, and certain key compounds have been synthesized independently.[74]

The phenylhydrazone of methylisopropyl ketone (XXV) condenses in the presence of zinc chloride to give trimethylindolenine (XXVI), the indole analog of pentamethylpyrrolenine (XXI), which can also be made by the methylation of indole or α-methylindole. The phenylhydrazone of diisopropyl ketone (XXVII) condenses to give dimethylisopropylindolenine (XXVIII), the analog of heptamethylmethylenepyrroline (XXIV). Compound XXIX can be made by the same series of reactions that leads to compound XXIV, the starting product being a methylated indole instead of a methylated pyrrole. These reactions lend support to the structural analogies drawn. In this treatment, the pyrrolenines are formulated as *alpha* instead of *beta*, as in the indole series, because of the fact that pyrrole directs *alpha*, whereas indole directs *beta*.

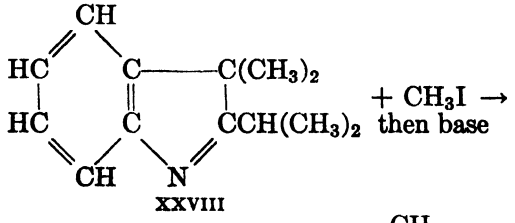
[74] Plancher, *Gazz. chim. ital.*, **28**, II, 80 (1898).



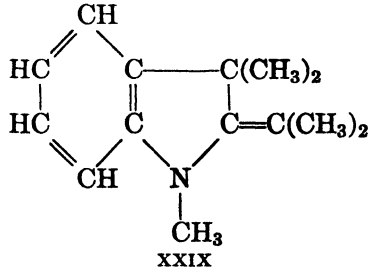
XXV XXVI



XXVII



XXVIII



XXIX

The reactions of the alkyl pyrrolenines and indolenines demonstrate that pyrrolenine would alkylate on nitrogen, in contrast to the pyrroles. By analogy, we conclude that no pyrrolenine is present in pyrrole. This strengthens the concept of the resonance stabilization of pyrrole, a principle which we shall adopt throughout the remainder of this review.

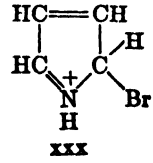
The Electronic Basis for Pyrrole-Phenol Analogies

In benzene substitution, an electron-attracting reagent can impart a positive charge to the ring only by depriving ring carbons of their full electronic octets. In phenol, however, a positive charge may be imparted to the ring by the process of sharing a previously unshared pair

on the oxygen, giving it a positive sign, without destroying octets. This facilitates substitution by electron-attracting reagents on the phenol systems. In substituted pyrroles, a positive charge may be imparted to the ring by a similar process, giving a charge to the nitrogen atom without destroying octets. Since ammonium salts are more stable than oxonium salts, such intermediate forms would be more stable in pyrrole than in a monohydric phenol, and pyrrole should substitute somewhat more readily than phenol. The material presented below will indicate that pyrrole is more nearly comparable to resorcinol in reactivity than to phenol.

The directive influence of the pyrrole ring can be correlated with this electronic concept. Let us formulate the course of a substitution by an electron-attracting reagent, such as bromine, with a pyrrole molecule as taking place in the following steps.[75]

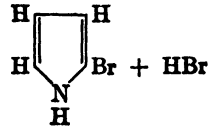
pyrrole + Br_2 ⟶ activated state I ⟶



+ Br^- ⟶

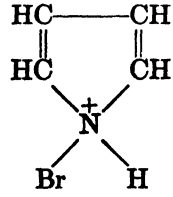
XXX

activated state II ⟶



The rate-determining step in this process is the formation of activated state I. The stability of this activated state is influenced by the stability of the intermediate (XXX). Alternative courses of the reaction which would lead to similar intermediates of differing stability should proceed at different rates, the greatest rate being associated with the course of the reaction which leads to the most stable intermediate. The problem is to estimate the relative stabilities of the intermediates.

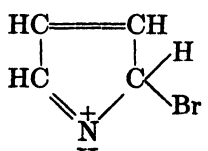
For N substitution on pyrrole, one form alone will be possible.



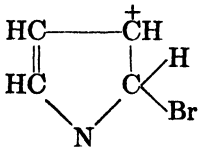
[75] Compare Branch and Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, New York, 1941, p. 473, and Wheland, *The Theory of Resonance*, John Wiley & Sons, New York, 1944, p. 258.

This intermediate would destroy the resonance of the pyrrole ring and would lead to the formation of an unstable N—Br bond. It should, therefore, be relatively unstable, and its instability should prevent rapid substitution on N.

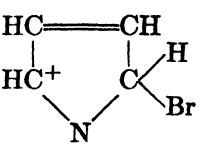
For α substitution three electronic isomers are possible. Of these XXXI is the most stable and XXXI*a* and XXXI*b* are less stable,



XXXI



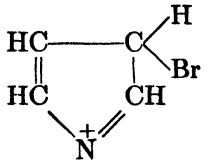
XXXI*a*



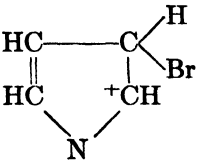
XXXI*b*

owing to the presence of open sextets. These would contribute less to the resonance of the intermediate than would XXXI.

For β substitution, only two electronic isomers are possible. Of these XXXII is the more stable. No form corresponding to XXXI*b* is



XXXII



XXXII*a*

possible. We conclude that there should be slightly less resonance stabilization of the intermediate for β substitution than for α substitution and that pyrrole should be α directing, in accordance with experimental observations. Accurate ratios between the velocities of substitution in the α and β positions are lacking in the literature, but substitution in either position takes place readily.

The Reactions of Decarboxylation and Carboxylation

In his review of pyrrole chemistry in 1904 Ciamician [38] stated quite clearly that methyl groups on the pyrrole ring enhance the "basic properties" of the pyrrole ring and that "negative radicals," or electron-attracting groups, enhance the acidic properties of the ring. This observation has fundamental significance for pyrrole reactivity as well as for acidity or basicity. Electron-attracting groups on the ring decrease the velocity of substitution reactions by electron-attracting re-

agents, whereas electron-repelling groups, like methyl and ethyl, increase the reaction velocity. The usual electron-attracting groups which have been studied in the pyrrole series are the carbethoxy, aldehyde, nitrile, nitro, acctyl, and bromo groups. The usual electron-repelling groups are methyl and ethyl. It is with these groups in various combinations on the pyrrole ring that we shall deal in most of our considerations of reactivity.

The reaction of the pyrrole series that affords best opportunity for comparisons of reactivity with the phenol series is not one of substitution but one of cleavage, namely, decarboxylation. The ease of decarboxylation of the pyrroles has often been considered one of the peculiarities of the system, although it is paralleled in certain other heterocyclic systems, notably the imidazole system and the furan system. The ease of decarboxylation of substituted pyrroles forms a striking analogy to the ease of decarboxylation of polyhydric phenol carboxylic acids.

In approaching the study of the relative reactivities of pyrroles and phenols to decarboxylation, we find that the available information is not to be regarded as strictly comparable. The ease of decarboxylation is markedly influenced by the presence of catalysts and by the manner of heating as well as by the tendency of the substance under investigation to form a liquid. An investigation of carefully purified materials in homogeneous systems under strictly comparable conditions should yield information of much value as to the forces at work in this particular reaction. Lacking this information, we can only make comparisons of the rough data which are available and which certainly show large qualitative differences.

The work of Pedersen [76] and of Wiig [77] on the kinetics of decarboxylation suggests that more than one competing mechanism of decarboxylation must be possible in these substances. In neither the pyrrole series nor the phenol series is it known definitely whether or not decarboxylation can follow alternative or competing routes. From extensive rather than intensive studies, Kharasch [78] concluded that decarboxylation could follow alternative, as opposed to competing, routes. One of these alternatives would be favored by a high concentration of electrons at the carboxyl group, the other by a low concentration of electrons at the same point.

[76] Pedersen, *J. Am. Chem. Soc.*, **51**, 2098 (1929); **58**, 240 (1936).

[77] Wiig, *J. Am. Chem. Soc.*, **52**, 4729 (1930); *J. Phys. Chem.*, **32**, 961 (1928); **34**, 596 (1930).

[78] Kharasch, Reinmuth, and Mayo, *J. Chem. Education*, **11**, 87 (1934).

Qualitative conclusions to be derived from a study of decarboxylations in the benzene series bear out this general idea, although such studies obviously cannot answer the question whether or not competing mechanisms are also at work in a given instance. Thus, decarboxylation of 2,4,6-trinitrobenzoic acid [79] and of 2,4,6-trihydroxybenzoic acid [80] is easy. Yet trinitrobenzene has three strongly electron-attracting groups and substitutes with electrophilic reagents with the greatest difficulty if at all,[81] whereas trihydroxybenzene is of exactly the opposite type with three groups which cause extremely easy electrophilic substitution in optimum positions for enhancing reactivity. Compounds of intermediate ease of substitution decarboxylate increasingly difficultly from each of these extremes, forcing the conclusion that there are at least two alternative routes of decarboxylation. Obviously, in the pyrrole series only that type which resembles the trihydroxybenzoic acid will be considered.

In the phenol series the same factors that make for marked increases in the ease of electrophilic substitution also make for an increase in the ease of decarboxylation. It is well known that benzoic acid may be distilled without decomposition. In like manner, *m*-hydroxybenzoic acid is quite stable to heating,[82] and the usual decarboxylation catalysts do not bring about evolution of carbon dioxide. On the other hand, *p*-hydroxybenzoic acid does decompose,[83] although it does not yield phenol completely. Incomplete evolution of carbon dioxide takes place at temperatures between 200–220°. Thus, the position which is activated by the OH group for substitution is also activated for decarboxylation. 2,4-Dihydroxybenzoic acid loses carbon dioxide completely at 194°,[84] indicating further activation for decarboxylation. 2,6-Dihydroxybenzoic acid loses carbon dioxide completely between 150–170°,[85] also indicating a high degree of activation, and 3,5-dihydroxybenzoic does not decarboxylate on dry distillation.[86] 2,4,6-Trihydroxybenzoic acid loses carbon dioxide appreciably at 100°,[80] and when water is added it decarboxylates completely below 100°. On the other hand, when the hydroxyl groups are not placed in the position of maximum activation, the effect noted is generally less. Thus, gallic

79 Ger. pat. 77,353 (Nov. 7, 1893). *Frdl.*, **4**, 34 (1894–1897).
80 Will and Albrecht, *Ber.*, **17**, 2103 (1884).
81 MacKerrow, *Ber.*, **24**, 2943 (1891).
82 Graebe, *Ann.*, **139**, 145 (1866).
83 Graebe and Eichengrün, *Ann.*, **269**, 325 (1892).
84 Tiemann and Parrisius, *Ber.*, **13**, 2359 (1880).
85 Senhofer and Brunner, *Sitzber. kgl. Akad. Wiss. Wien.*, **80**, II, 504 (1880).
86 Barth and Senhofer, *Ann.*, **159**, 226 (1871); **164**, 109 (1872).

acid, 3,4,5-trihydroxybenzoic acid, melts with decomposition into carbon dioxide and pyrogallol at a temperature of 225–240°,[87] indicating considerably greater stability than is found in the phloroglucinol carboxylic acid. In general, the addition of a carboxyl group, which decreases ease of electrophilic substitution in all positions, also decreases the ease of decarboxylation. A striking example of this is to be found in the resorcinol series where 2,6-dihydroxybenzoic acid loses carbon dioxide at 150–170°, whereas the addition of a carboxyl group in the 3 position raises the stability so that the compound melts above 300° without extensive decomposition.[85]

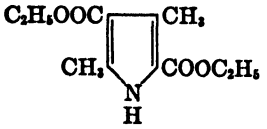
Pyrrole α-carboxylic acid evolves carbon dioxide at 192° [88] and the β acid decomposes at 161–162°.[89] This indicates the limit of reliability of the crude decarboxylation data, since the α position is more active in substitution than the β position. It does indicate that pyrrole is more active in both α and β positions than phenol, however, since the decarboxylations are complete at these temperatures. A comparison shows that the stabilities are closer to those of the isomeric resorcylic acids than to those of the derivatives of phenol, and the general ease of substitution in the pyrrole series bears out this analogy. It also seems clear that the pyrrole molecule is not so active as the phloroglucinol molecule.

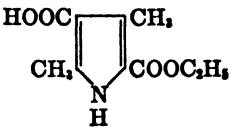
Another reaction which can afford some insight into the relative reactivities of the phenols and the pyrroles is the opposite of that given above, namely, carboxylation. Salicylic acid and *p*-hydroxybenzoic acid may each be prepared from phenol by the Kolbe synthesis, at temperatures as high as 250°.[90] With resorcinol, the conditions necessary to introduce the carboxyl group are much less severe. A mixture of 2,4- and 2,6-dihydroxybenzoic acids may be prepared from resorcinol by heating it with an aqueous solution of ammonium carbonate at 120–130° or with a solution of potassium carbonate at the reflux temperature.[91] The reaction with potassium carbonate proceeds smoothly on phloroglucinol at 60–70°.[80] Pyrrole α-carboxylic acid may be prepared from pyrrole under the same conditions which are successful for resorcinol,[88] again indicating reactivity intermediate between that of phenol and phloroglucinol and analogous to resorcinol.

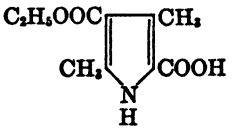
The correlation between decarboxylation temperature and reactivity is found to hold good with derivatives of Knorr's pyrrole (XXXIII).

87 Liebig, *Ann.*, **101**, 48 (1857).
88 Ciamician and Silber, *Ber.*, **17**, 1151 (1884).
89 Ciamician, *Monatsh.*, **1**, 625 (1880).
90 Kolbe, *J. prakt. Chem.*, [2] **10**, 95 (1874).
91 Bistrzycki and Kostanecki, *Ber.*, **18**, 1985 (1885).

The β acid (XXXIV) decarboxylates at about 270° [92] whereas the α acid (XXXV) decarboxylates at about 210°.[93] The reactivities of the decarboxylated compounds fall in the same order. The increased de-

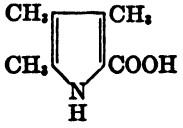

XXXIII

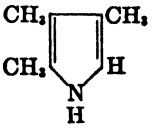

XXXIV

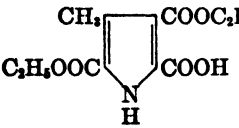

XXXV

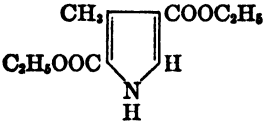
carboxylation temperature shows that compounds XXXIV and XXXV are less reactive than phenol, an effect produced by the strongly deactivating influence of the carbethoxy group in the molecules.

In the pyrrole series, an increase in the number of alkyl groups causes a decrease in the decarboxylation temperature, as would be expected from the generalizations which have been drawn. Thus, if compound XXXV is modified by the substitution of a methyl group for the β-carbethoxy group, (XXXVI), the decarboxylation temperature is lowered by more than 80° to 126°.[94] From this, one might predict that 2,3,4-trimethylpyrrole (XXXVII) should substitute much more readily than the β-carbethoxy analog. Unfortunately, reliable data to test this prediction are lacking.


XXXVI


XXXVII


XXXVIII


XXXIX

In the pyrrole series, as in the phenol series, it is possible to stabilize the carboxyl group against decarboxylation by adding electron-attracting groups. Thus, compound XXXVIII, stabilized by the substitution of two carbethoxy groups on the ring, does not decarboxylate, even under drastic conditions. It may be distilled without decomposition.[95]

92 Fischer and Walach, *Ber.*, **58**, 2820 (1925).
93 Knorr, *Ann.*, **236**, 323 (1886).
94 Fischer and Walach, *Ann.*, **450**, 126 (1926).
95 Corwin, Bailey, and Viohl, *J. Am. Chem. Soc.*, **64**, 1267 (1942).

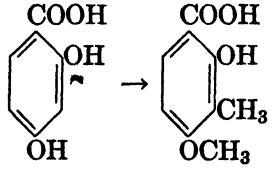
In line with this observation, the corresponding pyrrole with a free α position (XXXIX) condenses with formaldehyde difficultly and incompletely.[95]

Without discussing more than a small fraction of the analogies in the literature, it is apparent that the reactions of the phenol series and the pyrrole series are parallel. The probable electronic basis for the analogies has been developed, but the theory is not yet capable of predicting which one of the phenols pyrrole should most resemble. Recourse to rough experimental analogies leads us to conclude that the reactivity of pyrrole most nearly resembles that of resorcinol and that the substituted pyrroles should increase or decrease in reactivity from this base point much as substituted resorcinols do, with due allowance for the electronic differences between the systems.

Substitution Reactions of the Pyrrole System

Examples of nitrations,[96] and nitrosations [97] of pyrrole derivatives can be found in the literature, although the reactions have not been widely exploited for synthetic purposes. Reactions that have been of value are alkylation, halogenation and dehalogenation, introduction of aldehyde and ketone groups, and, for purposes of identification, diazo coupling reactions. These reactions will be considered separately.

Alkylation of Pyrroles. It has already been pointed out that pyrroles alkylate on carbon when treated with methyl iodide. This reaction finds analogies in the C alkylation of derivatives of resorcinol and phloroglucinol.[98] Thus, for example, Perkin [99] found that the following reaction takes place.



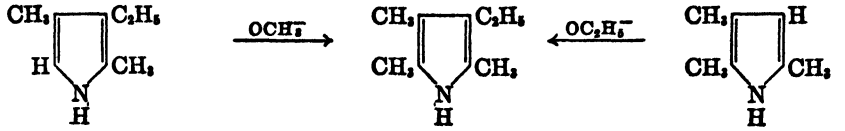
[96] Ciamician, *Ber.*, **18**, 1456 (1885); **19**, 1078 (1886). Angeli and Alessandri, *Atti reale accad. Lincei*, [5] **20**, I, 311 (1911); Fischer and Zerweck, *Ber.*, **55**, 1949 (1922); Küster and Maag, *Ber.*, **56**, 66 (1923).

[97] Angeli, Angelico, and Calvello, *Atti reale accad. Lincei*, [5] **11**, II, 16 (1902); Angelico, *ibid.*, [5] **14**, I, 699 (1905); Angeli and Marchetti, *ibid.*, [5] **16**, I, 271 (1907); Angelico and Calvello, *Gazz. chim. ital.*, **34**, I, 38 (1904); Fischer and Zelle, *Ann.*, **483**, 251 (1930).

[98] Herzig and Zeisel, *Monatsh.*, **9**, 217; 882; 1045 (1888); **10**, 144 (1889).

[99] Perkin, *Ber.*, **28**, 1051 (1895).

The reaction of alkylation with alkoxides, on the other hand, has been effectively exploited in the pyrrole series[100] but has no known analogy in the phenol series. It is to be expected that this reaction will proceed smoothly when sufficiently active phenols are employed. An example of this reaction is the preparation of phyllopyrrole.[101]



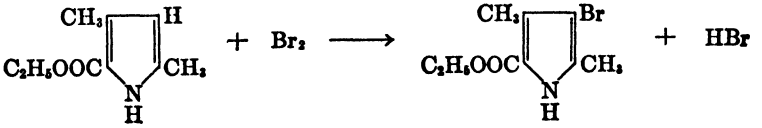
The reactions are performed in an autoclave at temperatures of 200–220°.

The preparation of N-ethylaniline[102] by the reaction of aniline and sodium ethoxide may be considered as an analogy to this reaction. In both cases the mechanism is obscure, however. Both the pyrrole and the aniline act as nucleophilic reagents, but the concept of a methoxide ion as electrophilic is unorthodox. The reaction requires closer investigation.

It has been found that the α position is more reactive than the β position in this reaction, as in other substitutions in the pyrrole ring.

Halogenation and Dehalogenation. Halogenation takes place most readily in the pyrrole series. The usual chlorinating agent is sulfuryl chloride, SO_2Cl_2.[103] Bromination is performed with elementary bromine, and iodination with triiodide ion, as a rule. The great reactivity of the pyrrole ring is emphasized by the fact that triiodide ion iodinates pyrrole derivatives with great rapidity. Thus, tetraiodopyrrole may be prepared from pyrrole and triiodide ion.[104]

An example of a normal pyrrole halogenation is the following.[105]



If the positions of the H and $COOC_2H_5$ groups are reversed, an "abnormal" bromination readily ensues.[106]

100 Fischer and Bartholomäus, *Z. physiol. Chem.*, **77**, 189; **80**, 6 (1912); Fischer and Hahn, *ibid.*, **84**, 259 (1913); Fischer and Röse, *ibid.*, **87**, 45 (1913).

101 Fischer and Bartholomäus, *Ber.*, **45**, 466 (1912).

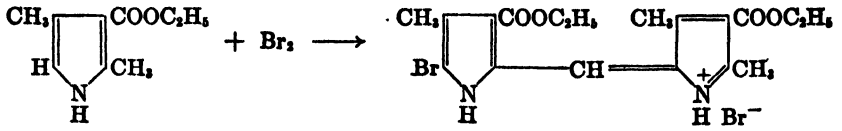
102 Nef, *Ann.*, **318**, 140 (1901).

103 Muzzara and Borgo, *Gazz. chim. ital.*, **35**, I. 477; II, 19 (1905).

104 Ciamician and Dennstedt, *Ber.*, **15**, 2582 (1882).

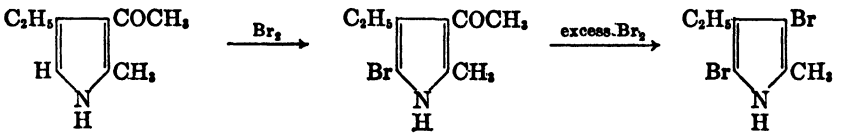
105 Fischer and Ernst, *Ann.*, **447**, 147 (1926).

106 Fischer, *Sitzber. math. physik. Klasse Akad. Wiss. München*, 410 (1915).



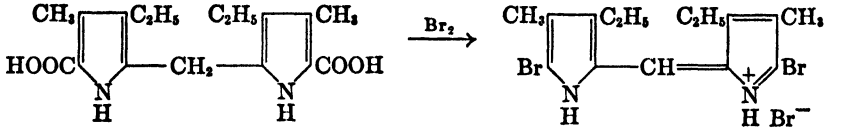
This reaction illustrates the fact that certain pyrroles undergo condensation so readily that the process of preparing simple ring-substituted pyrryl halides is complicated, if not impossible. Bromination at low temperatures leads to the normal 5-bromo derivative.[107] The reactivity of 2,4-dimethyl-3-ethylpyrrole is so great, however, that the mononuclear halide has not been isolated.

Another complication which occasionally causes difficulties in halogenations is the substitution of halogen for groups other than hydrogen. An example is the elimination of acetyl groups by bromine.[107]

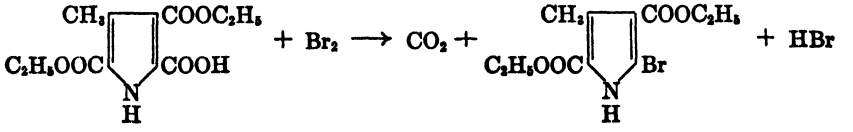


This and similar examples make it clear that the pyrrole ring is more reactive to bromine than is the acetyl group.

The replacement of carboxyl groups by bromine occurs frequently in pyrrole syntheses and constitutes a standard method for preparing reactive dipyrrylmethenes for porphyrin synthesis.[108]



This reaction accomplishes decarboxylation when other means fail.[109]

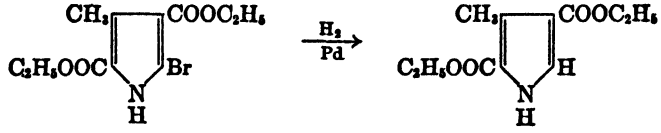


107 Fischer and Bäumler, *Ann.*, **468**, 58 (1929); Corwin and Viohl, *J. Am. Chem. Soc.*, **66**, 1143 (1944).

108 Fischer, Halbig, and Walach, *Ann.*, **452**, 283 (1927).

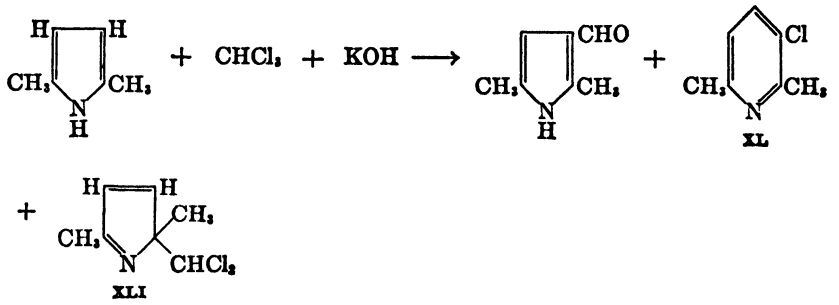
109 Corwin, Bailey, and Viohl, *J. Am. Chem. Soc.*, **64**, 1272 (1942).

Ring bromo- and iodo-pyrroles can be dehalogenated readily. The reduction of tetraiodopyrrole to pyrrole is accomplished with zinc and alkali.[110] Catalytic hydrogenation readily removes ring-bound bromine.[109] Thus, halogen atoms serve to protect the pyrrole ring



while other reactions are performed and may be removed at will by hydrogenation.

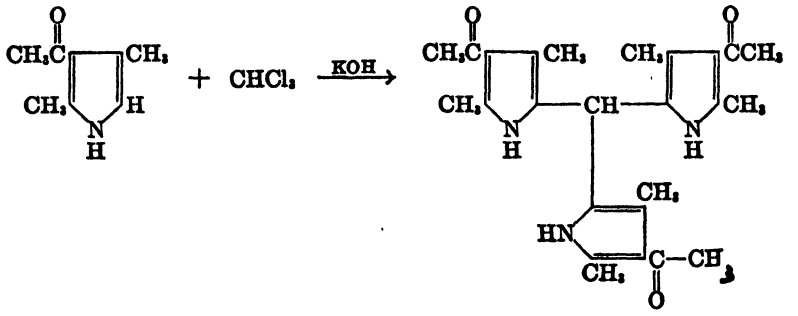
Introduction of Aldehyde and Ketone Groups. The first method for the preparation of a pyrrole aldehyde was the Reimer-Tiemann reaction,[111] which yields pyrrole α-aldehyde. The poor yields obtained make this an undesirable method for the preparation of aldehydes, except as a last resort. Plancher and Ponti [112] studied the reaction with some care and showed that the by-products formed are capable of accounting for the poor yields of aldehyde. When applied to 2,5-dimethylpyrrole, the reaction leads to 2,6-dimethyl-3-chloropyridine (XL) as well as to a pyrrolenine derivative (XLI). This pyrrolenine



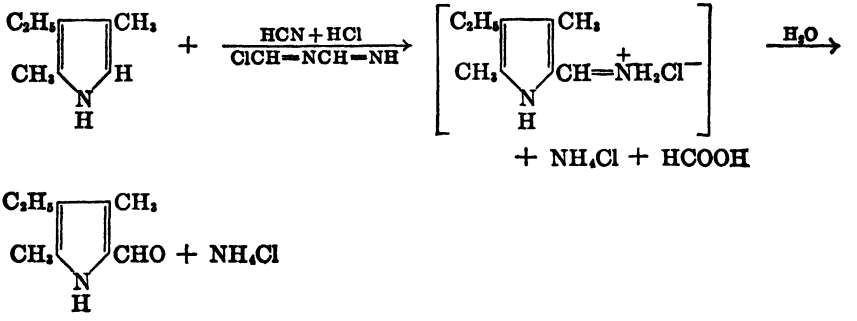
derivative (XLI) rearranges on treatment with sodium ethoxide in alcohol at 100° for 3 hr. to yield the pyridine derivative (XL).

The reaction with chloroform and alkali can also lead to the formation of tripyrrylmethanes.[113]

110 Ciamician and Silber, *Ber.*, **19**, 3027 (1886).
111 Bamberger and Djierdjian, *Ber.*, **33**, 536 (1900).
112 Plancher and Ponti, *Atti reale accad. Lincei*, [5] **18**, II, 469 (1909).
113 Fischer and Ammann, *Ber.*, **56**, 2320 (1923).



The most convenient method for introducing the aldehyde group is the Gattermann synthesis, employing HCN and HCl. The Gattermann procedure gives good results with reactive phenols, such as resorcinol, and with phenol[114] ethers. The pyrrole analogy is an obvious one. The method was introduced into pyrrole chemistry by Fischer and Zerweck.[115] The synthesis is capable of placing the formyl group in either the α or β position in the ring in excellent yields. In the course of the reaction, chloromethyleneformamidine (NH=CH—N=CHCl) is apparently produced.[116] This reacts with the pyrrole to form an aldimine hydrochloride which is usually isolated before hydrolysis to separate it from any unreacted pyrrole, which could condense to form a dipyrrylmethene. An example of the reaction is the formation of kryptopyrrole aldehyde.[117]



The value and safety of this reaction has been greatly improved by the modification introduced by Adams and Levine,[118] which employs

[114] Gattermann, *Ber.*, **31**, 1149 (1899); Gattermann and Schnitzspahn, *Ber.*, **31**, 1770 (1899). See also Hinkel, Ayling, and Morgan, *J. Chem. Soc.* 2793 (1932).

[115] Fischer and Zerweck, *Ber.*, **55**, 1942 (1922).

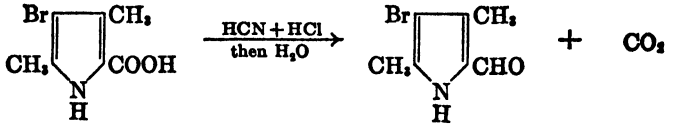
[116] Hinkel and Dunn, *J. Chem. Soc.*, 1834 (1930).

[117] Fischer and Schubert, *Ber.*, **56**, 1209 (1923).

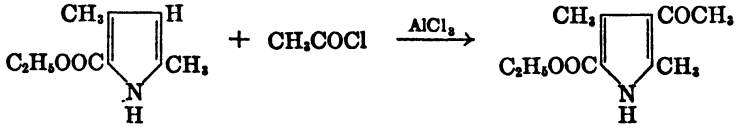
[118] Adams and Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923); Adams and Montgomery, *ibid.*, **46**, 1518 (1924).

anhydrous zinc cyanide instead of anhydrous hydrogen cyanide. This modification is preferable to the Fischer-Zerweck procedure in the pyrrole series.[119]

The Gattermann reaction, like halogenation, is capable of displacing carboxyl groups from the pyrrole ring.[120]



Keto groups can be introduced into pyrrole rings by the Houben-Hoesch synthesis, in which an aliphatic or aromatic nitrile is substituted for the hydrogen cyanide in the Gattermann method.[121] The method which has been employed most frequently, however, is the



Friedel-Crafts reaction.[122] The reactivity of the pyrrole ring is so great that it is frequently unnecessary to add aluminum chloride as a catalyst. Ciamician and Dennstedt first prepared α-acetylpyrrole by simply heating pyrrole with acetic anhydride.[123]

Most pyrryl ketones which are of value in synthesis can be prepared by ring synthesis, and when this is possible it is usually desirable.

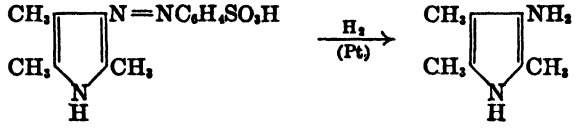
Azopyrroles. Our argument concerning the analogies of pyrrole systems with aromatic systems will be completed by a consideration of the reactions of pyrroles containing the azo group.

The coupling of pyrroles with diazotized aromatic amines was discovered in 1886 by Fischer and Hepp.[124] Numerous azo dyes containing the pyrrole ring have been prepared by subsequent investigators.[125] As with the phenols, the tendency to couple is so marked that the reaction takes place in acidic media. With pyrrole itself, a monazo dye is formed in acid and a bisazo dye is formed in base.

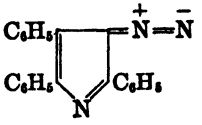
119 Corwin and Andrews, *J. Am. Chem. Soc.*, **58**, 1086 (1936).
120 Fischer and Ernst, *Ann.*, **447**, 148 (1926).
121 Fischer, Schueller, and Zerweck, *Ber.*, **55**, 2390 (1922).
122 Fischer and Schubert, *Z. physiol. Chem.*, **155**, 99 (1926).
123 Ciamician and Dennstedt, *Gazz. chim. ital.*, **13**, 445 (1883).
124 Fischer and Hepp, *Ber.*, **19**, 2251 (1886).
125 Fischer and Bartholomäus, *Z. physiol. Chem.*, **76**, 478 (1912); **87**, 257 (1913); *Ber.*, **45**, 1919 (1912).

The studies of Fischer and Bartholomäus [125] have shown that the α position is more reactive to coupling than the β position but that the α-azo dyes are less stable to light and air than the β-azo dyes. They recommend the coupling reaction for the separation and characterization of a mixture of pyrroles. Tetrasubstituted pyrroles will not couple. β-Pyrrylazo dyes can be isolated from the coupling mixture readily by crystallization. α-Pyrrylazo dyes can be recognized by their peculiar "spot test" reaction with diazotized *p*-nitroaniline. In this test, a solution of α-azo dye is treated with carbonate and placed on a filter paper. Diazotized *p*-nitroaniline is added. First the rim becomes purple, and finally the whole surface turns to an intense blue shade. β-Pyrrylazo dyes do not give this reaction.

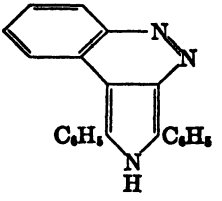
The reduction of pyrrylazo dyes serves as a method for the preparation of pyrrylamines.[126]



The diazotization and coupling of pyrrylamines has not been extensively studied. Certain pyrroles are known to form stable diazo compounds, however. Thus, 2,4,5-triphenyl-3-diazopyrrolenine may be represented by the following formula.[127]



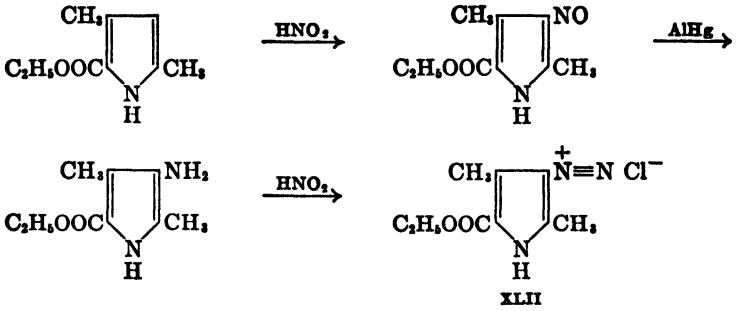
After being heated with dilute sulfuric acid, for a prolonged period, this isomerizes to a substance to which the following formula has been assigned.



[126] Fischer and Rothweiler, *Ber.*, **56**, 512 (1923).

[127] Angelico and Calvello, *Gazz. chim. ital.*, **31**, II, 4 (1901); Angelico and Labisi, *ibid.*, **40**, I, 411, 417 (1910).

The pyrryldiazonium chloride which may be prepared most readily in quantity for study is that from 2,4-dimethyl-3-amino-5-carbethoxy-

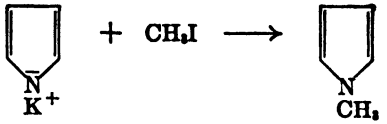


XLII

pyrrole.[128] This substance (XLII) exhibits great stability and couples readily with suitable phenols.

Substitutions on Nitrogen

Substitution on the pyrryl nitrogen can, in general, be accomplished only by previous removal of the hydrogen by a basic reagent. Thus, N-methylpyrrole [129] can be prepared by the reaction of methyl iodide with potassium pyrrole.[130] Convenient procedures for methylating the sodium salts of pyrroles have been worked out.[131]



N-carbethoxypyrrole may be prepared by the action of chloroformic ester on potassium pyrrole.[132]

The use of the Grignard reagent to secure activation of the pyrrole ring was introduced by Oddo.[133] However, reaction is not confined to the pyrryl nitrogen. Alkyl halides alkylate on C instead of on N,[134] and chloroformic ester reacts in both positions.[135]

128 Fischer and Zelle, *Ann.*, **483**, 251 (1930).

129 Hess and Wissing, *Ber.*, **47**, 1422 (1914).

130 Anderson, *Ann.*, **105**, 352 (1858).

131 Corwin and Quattlebaum, *J. Am. Chem. Soc.*, **58**, 1081 (1936).

132 Ciamician and Dennstedt, *Ber.*, **15**, 2579 (1882); Tschelinzeff and Maxoroff, *Ber.*, **60**, 194 (1927).

133 Oddo, *Ber.*, **43**, 1020 (1910).

134 Oddo and Mameli, *Gazz. chim. ital.*, **43**, II, 504 (1913); **44**, II, 162 (1914).

135 Signaigo and Adkins, *J. Am. Chem. Soc.*, **58**, 1122 (1936).

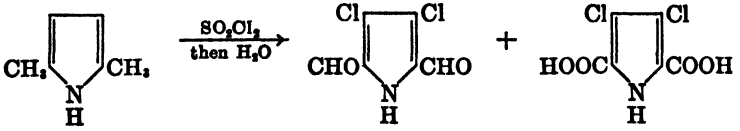
Two further substitutions on nitrogen occur in pyrrokol formation and in the condensation to dipyrrolopyridones, which will be discussed under pyrrole condensations.

From this review of selected substitution reactions in the pyrrole series, one may conclude that pyrroles, in general, resemble the more reactive phenols in the ease of their substitution, unless sufficient electron-attracting groups, such as carbethoxy, have been substituted to prevent easy reaction.

REACTIONS OF SUBSTITUENTS ON THE PYRROLE RING

It is difficult to draw analogies between the reactions of substituents on the pyrrole ring and those of substituted benzenoid hydrocarbons. This is due to the fact that the great mass of work on pyrroles has been carried out on compounds in which most of the ring positions are blocked, whereas in the benzene series the greatest mass of reactions has been performed on substances in which more than one ring position is open. Thus, for instance, toluene can be chlorinated on the methyl group by means of sulfuryl chloride.[136] It does not seem possible to halogenate a methyl group on a pyrrole ring without first attacking any free positions on the ring. To study side-chain halogenation alone, it is necessary to block the nuclear hydrogens with suitable substituents.

The reaction of methylated pyrroles with sulfuryl chloride was first studied by Colacicchi,[137] although the reagent had been used earlier by Mazzara and Borgo.[138] Colacicchi halogenated 2,5-dimethylpyrrole and obtained, after hydrolysis, 2,5-diformyl-3,4-dichloropyrrole and 2,5-dicarboxy-3,4-dichloropyrrole.



This reaction has been widely exploited by Fischer and his co-workers to prepare pyrryl aldehydes and acids.[139] The contrast between the reactivity of the α position and the β position is brought out most strikingly by this reaction, since only the preparation of α-aldehydes

136 Wohl, Ger. pat. 139,552 (June 16, 1901); *Frdl.*, **6**, 1287 (1900–1902).

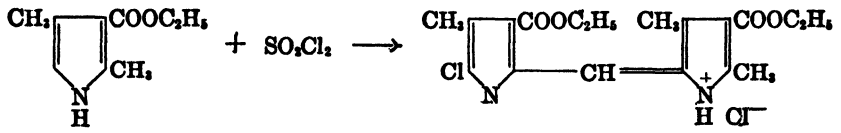
137 Colacicchi, *Atti reale accad. Lincei*, [5] **19**, II, 645 (1910).

138 Mazzara and Borgo, *Gazz. chim. ital.*, **32**, I, 512 (1902); **34**, I, 489 (1904).

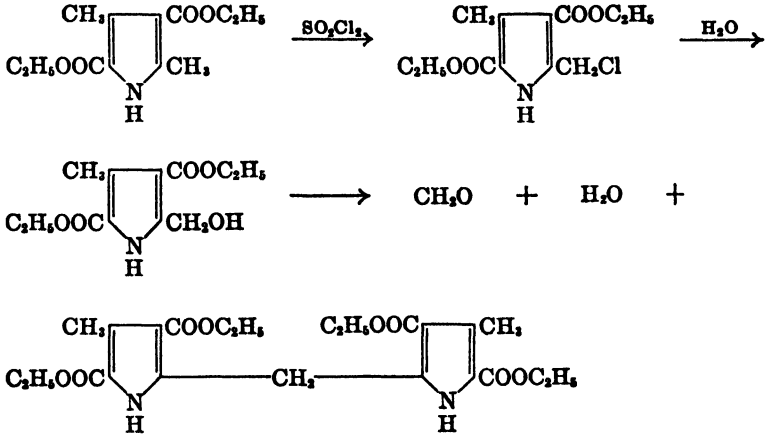
139 See Fischer, Sturm, and Friedrich, *Ann.*, **461**, 249 (1928).

and α-acids is feasible by this method. In general, the reaction has been performed in ether at 0°, although with 2,4-dimethyl-3,5-dicarbethoxypyrrole, in which the carbethoxy substituents make the α-methyl group less reactive, the use of glacial acetic acid makes trichlorination of the α-methyl group [95] possible.

As with bromination, this reaction is limited by the ability of 2-methylpyrroles with an open 5 position to condense.[139]



With 1 mole of sulfuryl chloride, it is usually possible to stop the chlorination at the monochloromethyl stage. This reaction has also been widely utilized in the preparation of dipyrrylmethanes,[95,139] since the pyrrylcarbinols formed by hydrolysis of the chloromethylpyrroles cleave readily to yield formaldehyde and also condense readily.[95,140]

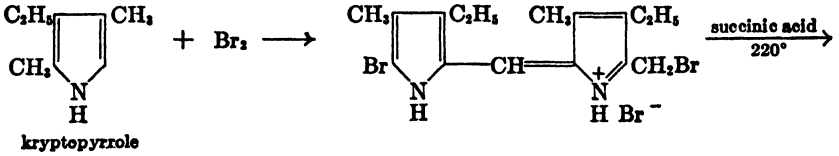


In contrast to sulfuryl chloride, bromine tends to monohalogenate α-methyl groups. For this reason, it has been even more widely used than sulfuryl chloride for the preparation of dipyrrylmethanes by the reaction given above. With 2,4-dimethyl-3,5-dicarbethoxyprrole,[141] 4 moles of bromine are necessary to secure monobromination, but with 2,4-dimethyl-3-ethyl-5-carbethoxypyrrole the reaction proceeds much more readily.[105]

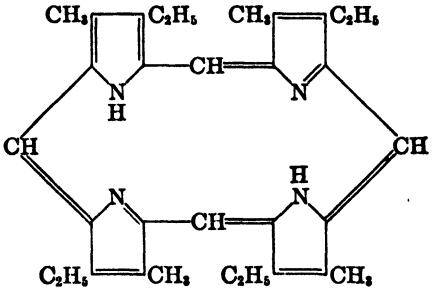
140 Fischer and Ernst, *Ann.*, **447**, 158 (1926).

141 Fischer and Scheyer, *Ann.*, **434**, 237 (1923).

The condensation of 2-methylpyrroles with an open 5 position brought about by halogenation was discovered by Fischer in the course of the investigation of the halogenation of kryptopyrrole and hemopyrrole,[106] 2,4-dimethyl-3-ethylpyrrole, and 2,3-dimethyl-4-ethylpyrrole, respectively. This reaction has been the most useful halogenation reaction in pyrrole chemistry, producing dipyrrylmethenes which in general can be condensed directly to porphyrins.[142]



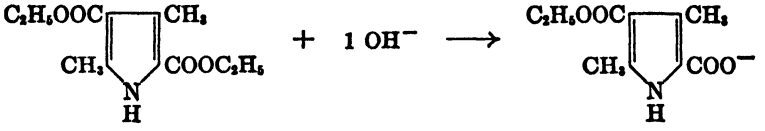
kryptopyrrole



etioporphyrin I

The fact that pyrrylmethyl groups have not been iodinated demonstrates clearly that the methyl groups are substantially less reactive than nuclear positions in the ring, since ring iodination takes place readily.

A useful property of the pyrrole ring is its ability to impart different reactivities to α and β ester groups. This leads to the characteristic selective hydrolysis of pyrryl esters. Selective hydrolysis with alkali was first accomplished by Knorr.[44]



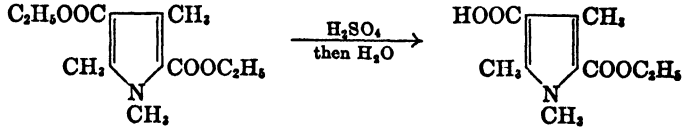
Sensitivity of the α position to attack by alkali seems to be a general property of pyrryl systems, since ester interchange as well as hydrolysis takes place on this position.[143] In pyrrole polyesters, the β

142 Fischer and Klarer, *Ann.*, **448**, 178 (1926).

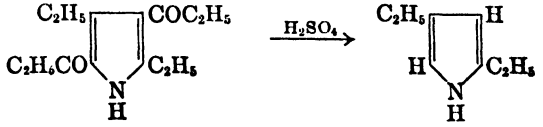
143 Corwin and Ellingson, *J. Am. Chem. Soc.*, **66**, 1146 (1944).

position can be attacked only by alkali in excess of the amount required to hydrolyze all esters in α positions.

In 1925, Fischer and Walach [144] discovered that concentrated sulfuric acid is capable of selective attack on the β position in the pyrrole ring. This opened the way to freeing the β position by decarboxylation so that any desired group could be substituted. It should be noted that the greater reactivity of the β position to sulfuric acid is not due solely to steric crowding,[145] since the β position is also attacked in 1,2,4-trimethyl-3,5-dicarbethoxypyrrole, where the steric effects on both α and β positions are equivalent.[131]



Pyrrylketones undergo cleavage by both acidic and basic catalysts. Thus, sulfuric acid will remove keto groups in what may be regarded as a reversal of the Friedel-Crafts synthesis.[146]



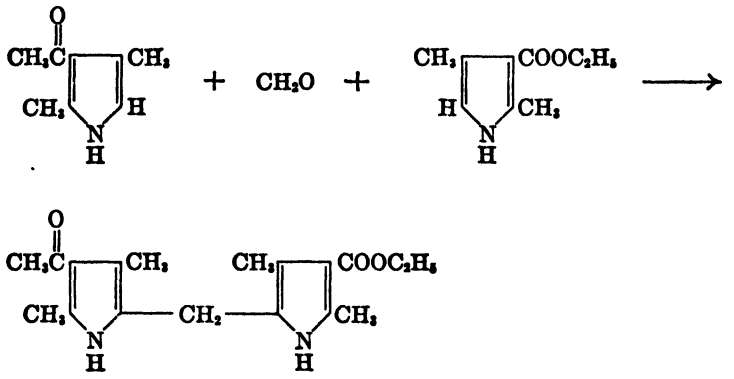
PYRROLE CONDENSATIONS

Dipyrrylmethanes. Because of the fact that many of the naturally occurring pyrrole pigments have pyrrole rings joined by carbon bridges, condensations leading to this type of structure have great importance in the field. The simplest compounds of this type are the dipyrrylmethanes which were first prepared by Pictet and Rillier in 1907.[147] These investigators condensed potassium pyrrole with methylene choride under pressure and obtained N,N′-dipyrrylmethane as well as α,α′-dipyrrylmethane. The procedure was simplified by Colacicchi who substituted formaldehyde for methylene chloride. With this reagent, mildly acidic conditions suffice to bring about reaction, and no reaction takes place on N. Formaldehyde will also react with pyrroles in alkaline solutions to form pyrrylcarbinols.[148] Thus, this reaction

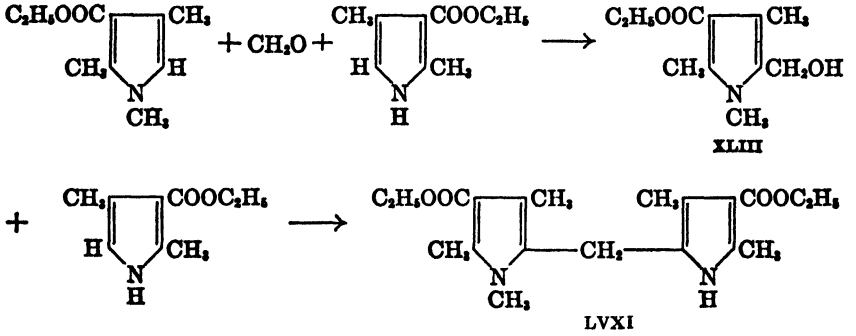
144 Fischer and Walach, *Ber.*, **58**, 2820 (1925).
145 Treffers and Hammett, *J. Am. Chem. Soc.*, **59**, 1708 (1937).
146 Fischer and Bartholomäus, *Z. physiol. Chem.*, **80**, 7 (1912).
147 Pictet and Rillier, *Ber.*, **40**, 1170 (1907).
148 Colacicchi, *Gazz. chim. ital.*, **42**, I, 10 (1912).

may be considered as analogous to the Bakelite condensation, except that in the pyrrole series it is usually undertaken under such conditions that polymerization is not possible.

Although the formaldehyde condensation commonly leads to symmetrical dipyrrylmethanes, it is adaptable to the preparation of unsymmetrical compounds as well.[149] On a purely statistical basis, one



should expect to obtain 25% of each of the symmetrical methanes and 50% of the unsymmetrical methanes by this process. In a similar unsymmetrical condensation, however, it was found possible to obtain 75% of the unsymmetrical methane (XLIV) after purification.[150] This suggests that the formaldehyde is exhausted by the more reactive component in the formation of the pyrrylcarbinol (XLIII) before the slower condensation to the methane takes place.



LVXI

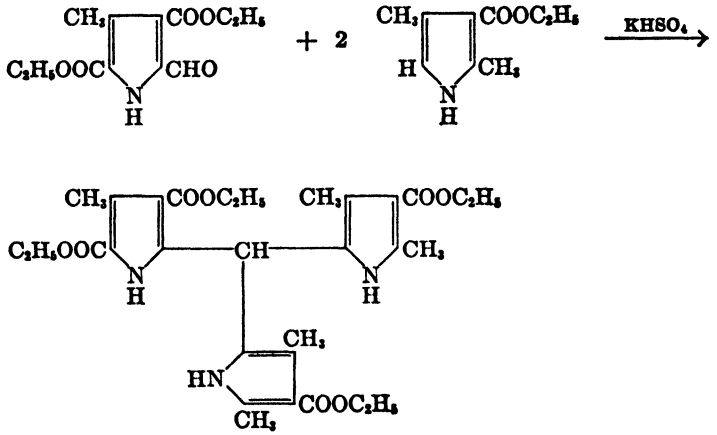
[149] Fischer and Bartholomäus, *Z. physiol. Chem.*, **87**, 261 (1913).
[150] Corwin and Brunings, *J. Am. Chem. Soc.*, **64**, 2112 (1942).

Unsymmetrical dipyrrylmethanes may be formed by a process similar to the last step indicated above, when one pyrrole with a free α position is not readily available. Bromomethyl [151] or alkoxymethyl [152] pyrroles may be substituted for carbinols of the type of XLIII.

Condensations to give α,β- or β,β-dipyrrylmethanes also proceed quite smoothly, although not so rapidly as those forming the corresponding α,α-methanes. As in other substitutions in the pyrrole ring, N-substituted methanes can be made only with metallic salts of the pyrrole. Bridge-substituted methanes may be prepared with properly substituted aldehydes or ketones in the condensation with pyrroles with a free α position.

Tripyrrylmethanes. The first tripyrrylmethane was prepared by Piloty, Krannich, and Will [153] in an attempt to apply the Reimer-Tiemann synthesis with chloroform and alkali to the production of pyrryl aldehydes. These investigators believed that they had obtained a dipyrrylcarbinol, and it was not until the subject was reinvestigated nine years later [154] that it became clear that tripyrrylmethanes had, in fact, been produced. It should be noted that Feist had prepared substituted phenyldipyrrylmethanes much earlier [155] by the condensation of derivatives of benzaldehyde with substituted pyrroles.

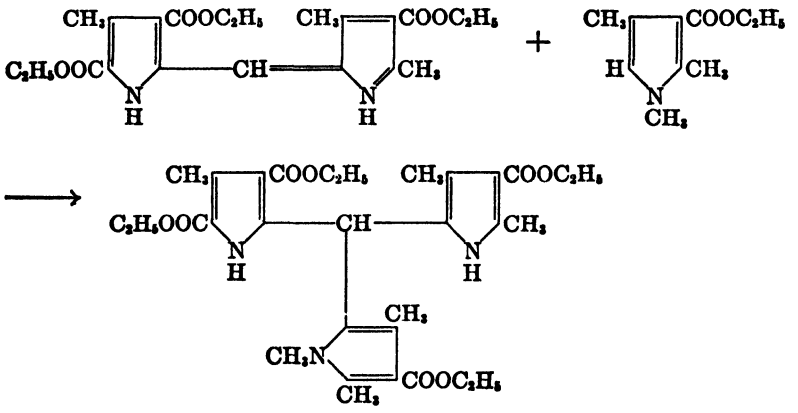
The Piloty method for preparing tripyrrylmethanes leads only to symmetrical substances. Derivatives with two different pyrrole rings



151 Fischer and Halbig, *Ann.*, **447**, 125 (1926).
152 Fischer and Adler, *Z. physiol. Chem.*, **197**, 266 (1931).
153 Piloty, Krannich, and Will, *Ber.*, **47**, 2536 (1914).
154 Fischer and Ammann, *Ber.*, **56**, 2319 (1923).
155 Feist, *Ber.*, **35**, 1647 (1902).

can be prepared by the Feist fusion method,[156] using a pyrryl aldehyde and a pyrrole derivative with a free nuclear position.

Completely unsymmetrical tripyrrylmethanes can be prepared by the condensation of a dipyrrylmethene with a pyrrole with a free position.[157]



The tripyrrylmethanes are of importance in pyrrole chemistry primarily because of their possible position as intermediates in the synthesis of dipyrrylmethenes. The reaction immediately preceding can be reversed by the addition of an acid, such as dry hydrogen chloride, which binds the dipyrrylmethene as a salt. This cleavage of tripyrrylmethanes was discovered by Piloty, Krannich, and Will,[158] who were misled into assigning the formula of dipyrryl carbinols to these substances because of the ease with which they are converted to dipyrrylmethenes. Piloty's intuition that the substances were intermediates in the synthesis of some dipyrrylmethenes was confirmed by later investigations.[119,157-159]

Tripyrrylmethanes are also of some interest because of the fact that they are leuco bases of tripyrrylmethene dyes, one of which, prodigiosin, has been isolated from a natural source.[160] The structural formula tentatively assigned to this substance is

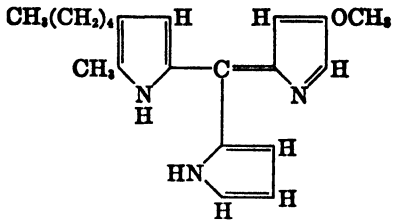
156 Fischer and Heyse, *Ann.*, **439**, 246 (1924).

157 Paden, Corwin, and Bailey, *J. Am. Chem. Soc.*, **62**, 418 (1940).

158 Corwin and Andrews, *J. Am. Chem. Soc.*, **59**, 1973 (1937).

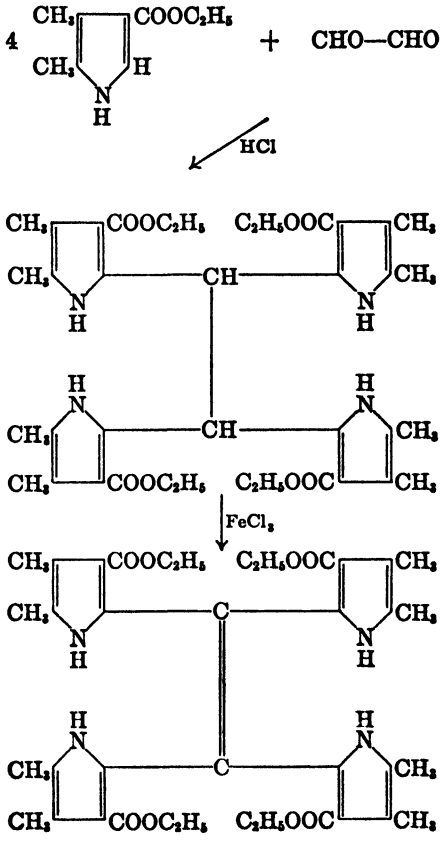
159 Corwin and Krieble, *J. Am. Chem. Soc.*, **63**, 1829 (1941).

160 Wrede and Hettche, *Ber.*, **62**, 2678 (1929); Wrede, *Z. physiol. Chem.*, **210**, 125 (1932); Wrede and Rothhaas, *ibid.*, **215**, 67 (1933); **219**, 267 (1933); Fischer and Gangl, *ibid.*, **267**, 201 (1941).



prodigiosin (provisional)

Tetrapyrrylethanes and Tetrapyrrylethylenes. Tetrapyrrylethylenes are of historical interest because of the fact that Willstätter proposed that porphyrins might be tetrapyrrylethylenes.[161] These substances are, in general, readily prepared from tetrapyrrylethanes. Their yellow color conclusively differentiates them from porphyrins, however.[162]



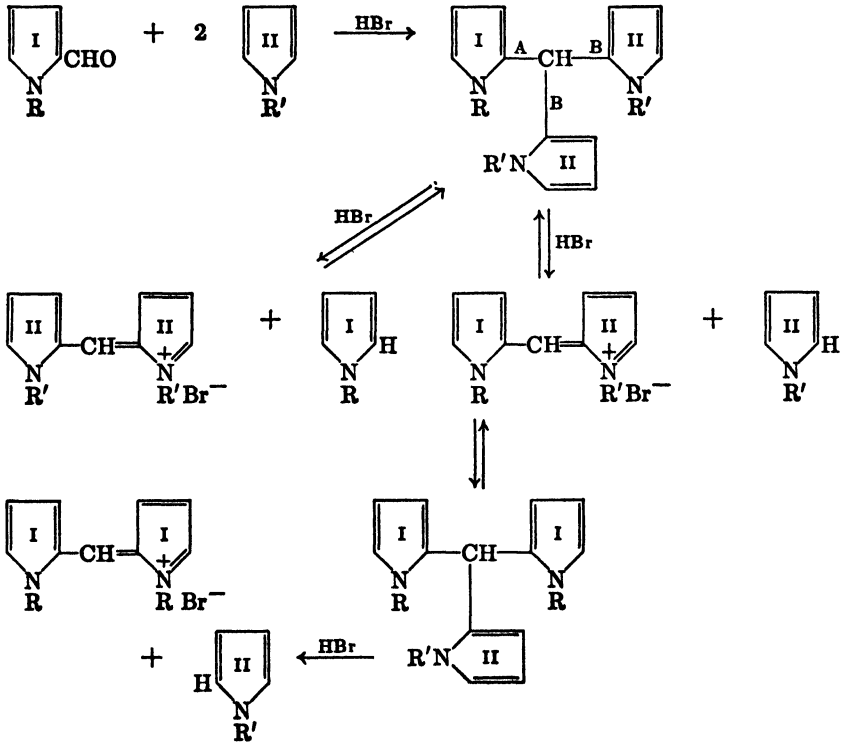
161 Willstätter and Stoll, *Untersuchungen über Chlorophyll*, J. Springer, Berlin, 1918, p. 39.

162 Fischer and Beller, *Ann.*, 444, 239 (1925).

When oxidized in acid media, tetrapyrrylethanes cleave to give dipyrrylmethenes.

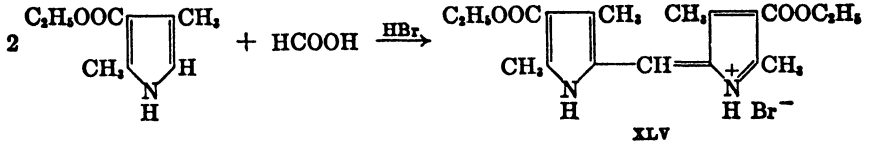
Dipyrrylmethenes. Because of their utility in the synthesis of porphyrins, the dipyrrylmethenes are the most important of the simple condensation products of the pyrroles. Two methods for producing them have already been mentioned. These are the synthesis with pyrryl aldehydes and the condensation of α-methylpyrroles with bromine.

In the aldehyde synthesis, discovered by Piloty, Krannich, and Will,[158] three different methenes are possible as products of the reaction, and at least one case is known in which all three possibilities have been realized.[157,158] The course of the reaction is given schematically below. For brevity, the pyrrole rings with different substituents in the 1, 2, 3, and 4 positions are numbered I and II, respectively.



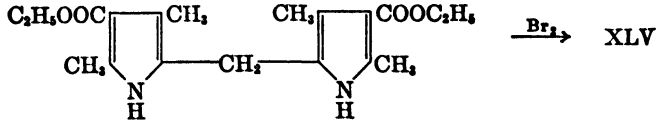
In the great majority of such condensations, the expected unsymmetrical product is obtained. An abnormal product is to be expected only when some influence slows down the condensation. Substituents which could act in this manner would be any that would slow down sufficiently the recombination of pyrrole I after cleavage at bond A. Such substituents would be strongly electron-attracting groups on ring I or a group on N which would slow the recombination by its steric influence. Similarly, groups on ring II which would strongly hinder the reactivity of pyrrole II should slow down the recombination after cleavage at bond B. If pyrrole I were sufficiently reactive, formation of the second tripyrrylmethane, I–I–II, would occur. Cleavage to methene I–I and pyrrole II would then take place, but the reverse combination would be hindered by the lack of reactivity on the part of pyrrole II. Thus, the methene I–I would be the final product. Tripyrrylmethanes which undergo all these cleavages are known.[157,158]

In spite of the possibilities for abnormal reaction, the aldehyde synthesis has been most useful in producing unsymmetrical methenes for porphyrin synthesis. The coupling of pyrroles with formic acid to give symmetrical methenes, a reaction discovered by Fischer and Zerweck,[163] may be considered as a special case of this synthesis, since a pyrryl aldehyde may be the intermediate in this condensation.



XLV

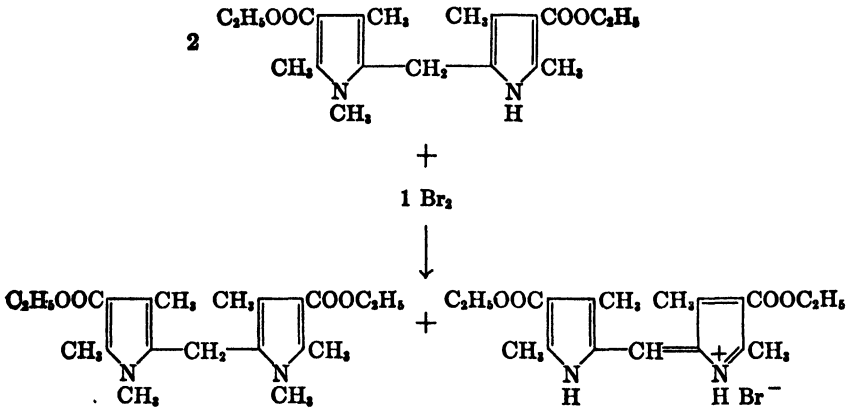
Still another method for producing symmetrical methenes is the oxidation of symmetrical methanes, a reaction also discovered by



Piloty, Krannich, and Will.[158] It should be noted that even this apparently straightforward reaction may be complicated when the methene is not symmetrical.[150,164]

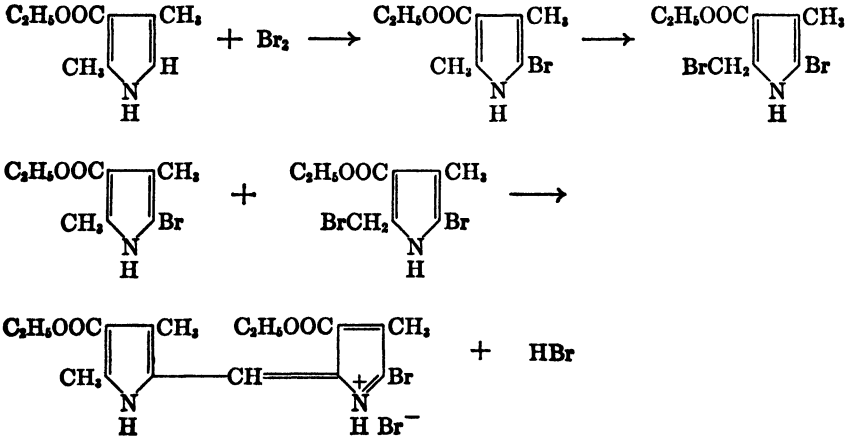
[163] Fischer and Zerweck, *Ber.*, **55**, 1942 (1922).

[164] Brunings and Corwin, *J. Am. Chem. Soc.*, **66**, 337 (1944).



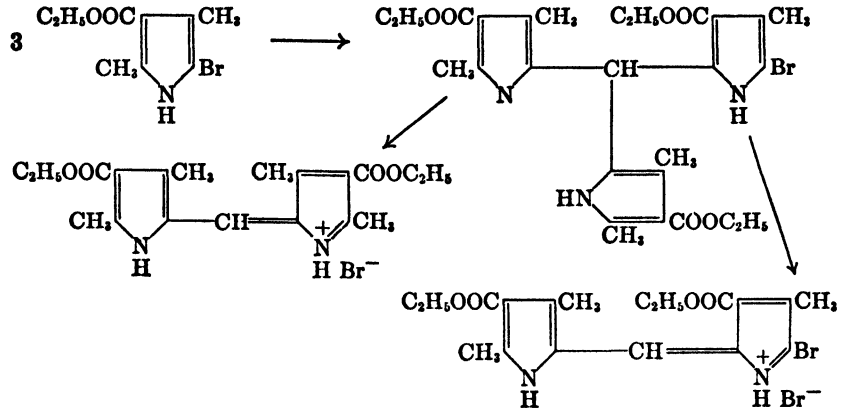
Since few unsymmetrical methenes have been prepared by this process, the limits of reliability of the oxidation reaction are not known. It is apparent, however, that the lability of the linkages between pyrrole rings must be taken into account when dipyrrylmethenes are being prepared by any process.

The Fischer synthesis of methenes by means of the bromination of α-methylpyrroles [106] is most extraordinary. The sequence of reactions involved is given below.[165]



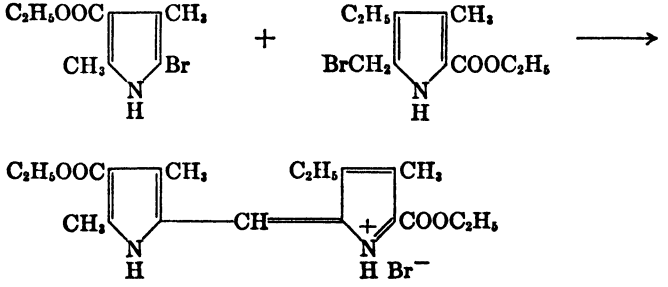
In this reaction, quantitative yields are not obtained. An investigation of the by-reactions shows that the monobromopyrrole, formed as the first intermediate, is capable of undergoing still another re-

[165] Corwin and Viohl, *J. Am. Chem. Soc.*, **66**, 1137 (1944).



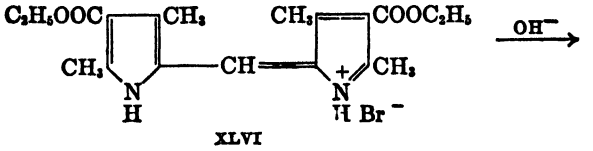
action.[165] Both possible methenes have been isolated from this condensation. Under normal conditions, the bromination of the Fischer synthesis proceeds much more rapidly than the self-condensation by-reaction, so that the amount of symmetrical methene formed by this reaction is not sufficient to account for the low yield of the unsymmetrical bromomethene actually obtained. It is evident that still further side reactions exist which have not yet been characterized.

The last step in the Fischer synthesis, the condensation of a bromomethylpyrrole with an α-bromopyrrole to yield a methene, is capable of extension to give other unsymmetrical methenes.[165]

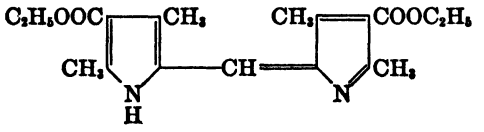


One property of the dipyrrylmethenes differentiates them from most triphenylmethane dyes. This is the ready formation of colored anhydro bases. In the triphenylmethane dyes, colorless carbinol bases are the rule. The variations in structure of dipyrrylmethenes which are readily available make this series ideal for the investigation of this peculiarity. The formation of an anhydro base can be blocked by complete substitution on each pyrrole ring.[164]

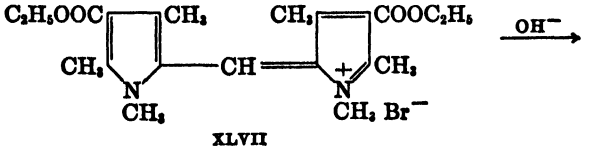
A model of dipyrrylmethene (XLVII) shows that the planar, ionic, resonating halide must be substantially distorted to exist. Such distortion would detract from the energy of stabilization of the planar



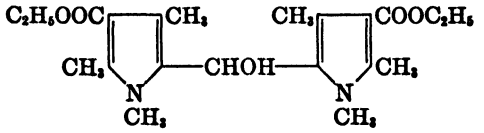
XLVI



anhydro base



XLVII

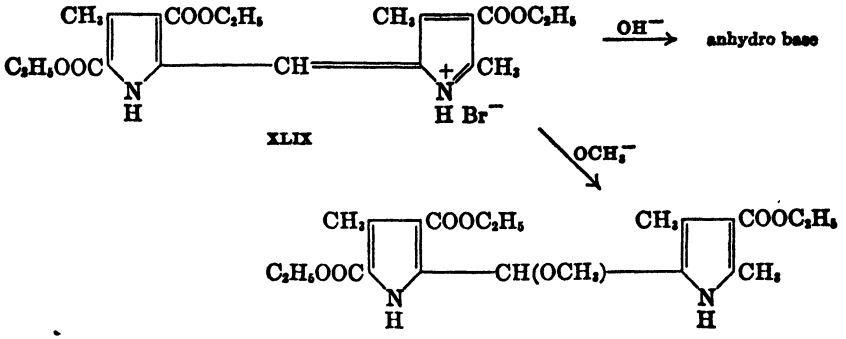


carbinol base

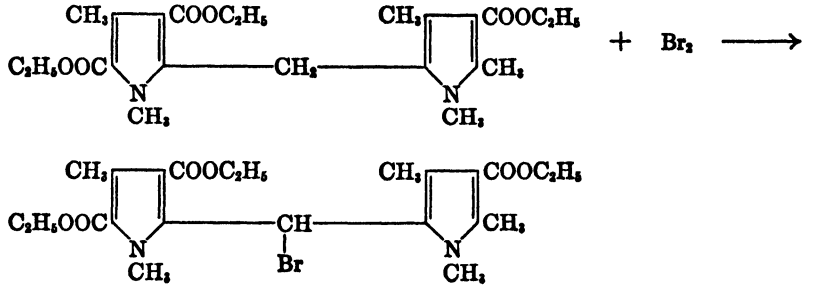
XLVIII

form without interfering seriously with a covalent form of the type of the carbinol base (XLVIII). Thus, any influence which would strengthen covalent bond formation would tend toward the stabilization of a non-coplanar, covalent halide rather than the ionized form (XLVII) found in the preceding illustration. As might be predicted, electron-attracting groups, such as carbethoxy, increase the attraction of the organic cation for negatively charged ions in solution. This is illustrated with a tricarbethoxymethene (XLIX) instead of the dicarbethoxymethene (XLVI).

Whereas the dicarbethoxymethene (XLVI) yields only an anhydro base when treated with methoxide ion, the tricarbethoxymethene (XLIX) has sufficiently increased attraction for the methoxide ion to yield a carbinol ether. The attraction is not sufficient for the weaker base, hydroxide ion, to form a carbinol, however. If the additional



effect of steric interference with coplanarity is now added to the effect of the electron-attracting groups, combination with even so weak a base as the bromide ion is favored.



In this case it is possible to prepare the organic cation with stannic chloride in a manner similar to the preparation of the cation of triphenylmethyl bromide.

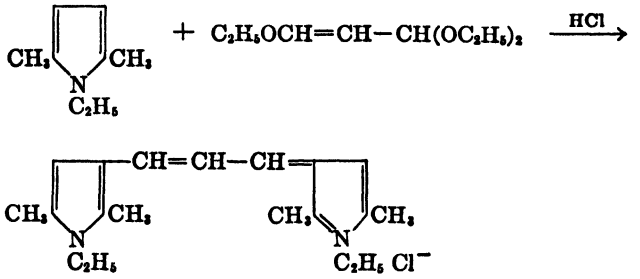
It thus can be concluded that the presence of electron-attracting groups and of interferences with planarity of organic cations are both influences which will increase the tendency to form covalent structures instead of the usual ionic dyes.

Models of triphenylmethane dyes show that these substances are constrained from complete planarity by interferences between hydrogen atoms in the *o* positions to the central carbon linkage. This effect is exactly the same as that which increases the tendency toward covalent bond formation with the central carbon in the dipyrrylmethenes. We may conclude that this interference is responsible for carbinol formation in the triphenylmethane dye series and makes *o* substituents larger than hydrogen unacceptable in the formulation of dyes. This concept has been elaborated by Lewis, Magel, and Lipkin,[166] who have

166 Lewis, Magel, and Lipkin, *J. Am. Chem. Soc.*, **64**, 1774 (1942).

suggested that such deviations from coplanarity give rise to isomerism in the triphenylmethane dyes.

The effect of the crowding caused by the N-methyl groups in deepening the color of the dipyrrylmethenes has also been pointed out.[150,166] This subject has been greatly extended and reviewed by Brooker and his collaborators.[167] These investigators regard the dipyrrylmethenes as pyrrolocyanines and have prepared higher cyanines of this series by condensation with β-ethoxyacrolein acetal.[168,169]



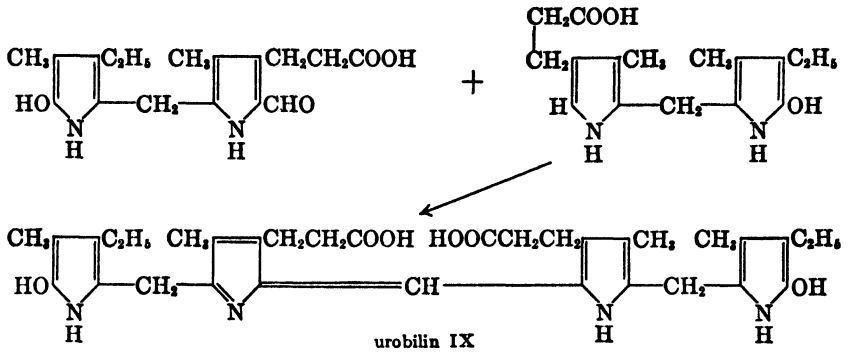
By means of this series, the concept of steric interference in N-methyl methenes has been strengthened. With a bridge consisting of a single carbon, the substitution of methyl for hydrogen reverses the usual effect and causes a shift of absorption to longer wavelengths. With a bridge length of three carbons, the possibility of steric interference is greatly reduced and the usual effect of a shift to shorter wavelengths is observed when methyl is substituted for hydrogen. This emphasizes the peculiarity of the system in which crowding is pronounced.

Synthetic Analogs of the Bile Pigments. Many of the syntheses of dipyrrylmethanes and methenes have been extended to produce substances related to the bile pigments. In general, these substances consist of four pyrrole rings joined by three single carbon bridges, either of the methane or the methene type. An example of each type of substance will be given. It should be noted that many of the syntheses given as examples yield symmetrical substances but that the naturally occurring pigments are all believed to be unsymmetrical substances, corresponding to the materials which would be obtained by the cleavage of hemin at a single bridge.

Urobilin and Urobilinogen. The urobilin type of compound consists of two methane linkages, symmetrically disposed, and a central

167 Brooker et al., *Chem. Revs.*, **41**, 325 (1947).
168 Brooker and Sprague, *J. Am. Chem. Soc.*, **67**, 1869 (1945).
169 Brooker et al., *J. Am. Chem. Soc.*, **67**, 1875 (1945).

methene linkage. A product identical with the urobilin obtained by the oxidation of mesobilirubinogen has been obtained by synthesis.[170] This has not been definitely identified with the natural urobilin obtained in extremely small yields from pathological urine. Although it resembles the natural substance, it has a higher melting point.[171]



It will be noted that this molecule is not symmetrical. This synthesis has been performed in reverse fashion, with the aldehyde group and the free hydrogen interchanged on the methanes.[170] The products of the two syntheses are identical, showing that the central methene linkage is a resonating structure and that the disposition of the double bonds in such a dye system is arbitrary.

Urobilin-like materials have also been prepared by symmetrical condensations by condensation of 2 moles of the same methane with formic acid to form the methene bridge.

The leuco compounds of these dyes have been obtained by reduction with sodium amalgam and, in some cases, by catalytic hydrogenation.[172]

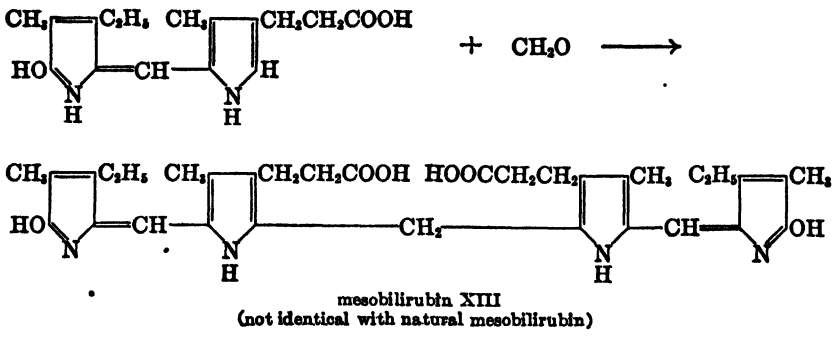
Mesobilirubin and Dihydromesobilirubin Types. Mesobilirubin contains two methene linkages, symmetrically disposed, and a central methane linkage. Synthetic mesobilirubin has not been separated because of technical difficulties, but many substances of this general type have been prepared.[173]

170 Siedel, *Z. physiol. Chem.*, **237**, 19 (1935); Siedel and Meier, *ibid.*, **242**, 101 (1936).

171 Watson, *Z. physiol. Chem.*, **221**, 149 (1933); *J. Biol. Chem.*, **114**, 47 (1936); Watson and Schwartz, *Proc. Soc. Exptl. Biol. Med.*, **49**, 636 (1942); Schwartz and Watson, *ibid.*, **641** (1942).

172 Siedel and Meier, *Z. physiol. Chem.*, **242**, 129 (1936).

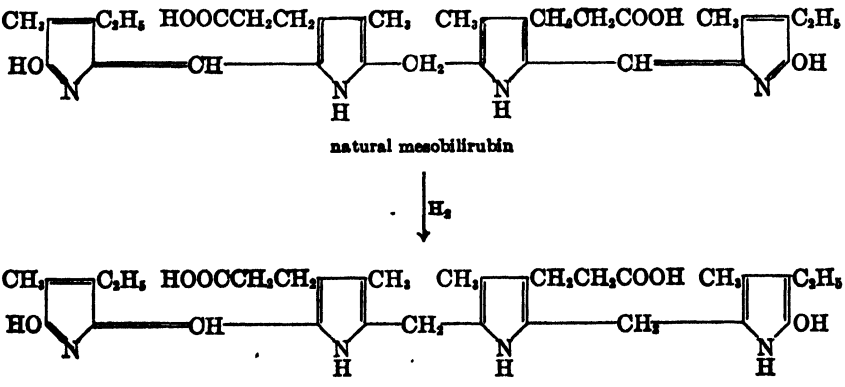
173 Fischer and Adler, *Z. physiol. Chem.*, **200**, 211 (1931); Siedel and Fischer, *ibid.*, **214**, 154 (1933).



mesobilirubin XIII
(not identical with natural mesobilirubin)

The hydrolytic cleavage and condensation of bromomethylpyrroles to yield formaldehyde and dipyrrylmethanes has been paralleled in this series. The central methane linkage can be formed from bromomethylmethenes.[178,174] In view of the course of the reaction with the simpler dipyrrylmethane formation, Fischer's formulation of this reaction as the elimination of methyl bromide seems hardly tenable. It is interesting that in the case of methenes with one hydroxyl group and all the remaining nuclear positions alkylated, the reaction leads to a series of colored compounds which can be separated and which are presumed to result from further oxidation of the initial condensation product.[174] Exhaustive structural investigations of these substances have not been completed.

When bilirubin is hydrogenated catalytically, mesobilirubin is obtained. In the mother liquor from this reduction, some dihydromeso-



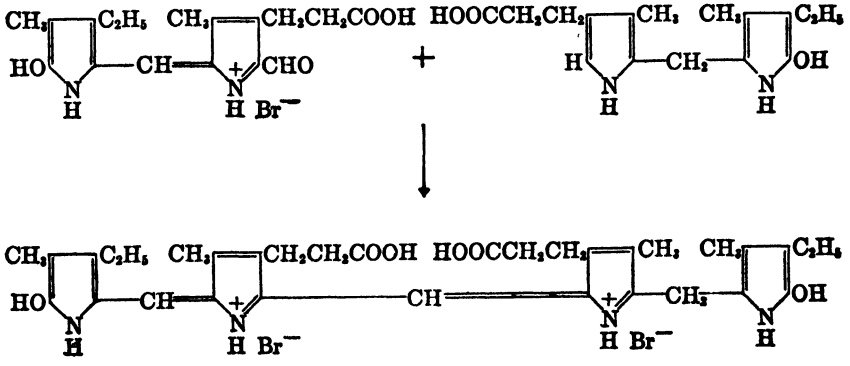
dihydro mesobilirubin (provisional)

174 Fischer and Adler, *Z. physiol. Chem.*, **206**, 188 (1932).

bilirubin can be found.[175] In this substance, only one of the methene linkages has been hydrogenated.

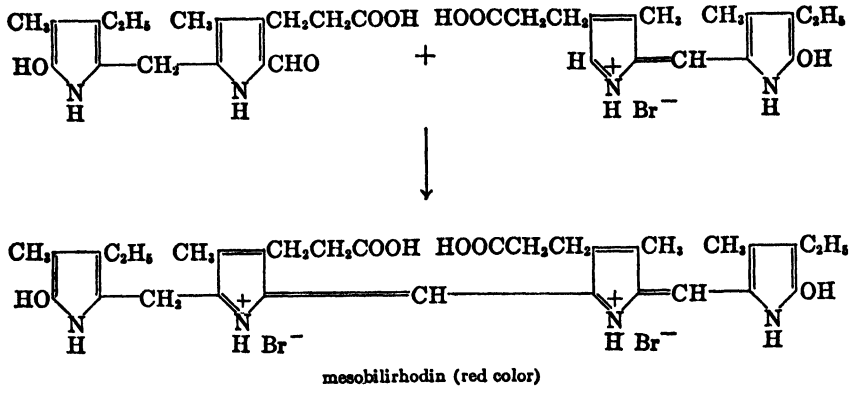
Which one of the two methene linkages has been hydrogenated in this reaction has not been established. This substance is an isomer of urobilin, differing from it in the position of the methene linkage. This difference leads to alterations in the chemistry of the substances, particularly the partial oxidation reaction, which permit easy distinction between the isomers. The characteristic fluorescence of zinc complexes observed in the urobilin-like compounds is absent in the dihydromesobilirubin series. The typical color play with nitric acid, the Gmelin test, is also absent in this series. The two groups can also be distinguished by their reactions to ferric chloride, the urobilin series giving a characteristic green reaction, the mesobilirubin series a red reaction. The details of these color plays have not been completely elucidated.

Mesobiliviolin and Mesobilirhodin. When urobilinogen or mesobilirubinogen is oxidized with ferric chloride, a violet oxidation product, mesobiliviolin, is obtained.[176] As a result of his studies on the pigments of red algae, Lemberg[177] suggested that this was a mixture of substances. In 1935, Siedel[178] demonstrated the correctness of this hypothesis by separating the mixture and synthesizing the individual components. One of these proved to be a red pigment which was named mesobilirhodin. The synthetic method employed indicates that both of these substances are isomers of mesobilirubin.



mesobiliviolin (violet color)

175 Fischer, Baumgartner, and Hess, *Z. physiol. Chem.*, **216**, 260 (1933).
176 Fischer and Niemann, *Z. physiol. Chem.*, **137**, 297 (1924).
177 Lemberg, *Ann.*, **505**, 158 (1933); *Chemistry & Industry*, **53**, 1024 (1934).
178 Siedel, *Z. physiol. Chem.*, **237**, 20 (1935).



mesobilirhodin (red color)

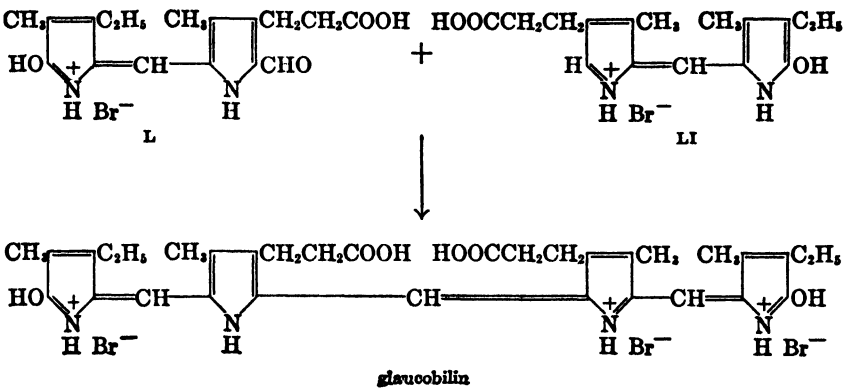
It seems most probable that the formulation of the second compound, mesobilirhodin, is incorrect. The simple interchange of β-methyl and β-ethyl groups should not cause a profound change in color. The chromophoric groups in the two compounds are identical, consisting of a system of three linked pyrrole rings resonating as a unit. Siedel attempted to explain the observed differences by the assumption of fixed bonds in each compound. A more reasonable explanation would be that one of the known anomalies in methene synthesis had occurred in the second condensation, which proceeds much more slowly than the first.

The isomerism between mesobiliviolin and mesobilirubin, however, should and does cause a profound alteration in color. The mesobilirubin series consists of two methene systems isolated by a methane linkage. Thus, the color should be twice the intensity but of the same type as that of the methenes. This conclusion is substantiated by examination of the material. In mesobiliviolin, the chromophoric system contains three rings resonating as a unit instead of two and should, therefore, possess a deeper color. This is also borne out by the appearance of the material. Detailed spectrophotometric studies and interpretations should add a useful chapter to our knowledge of the theory of color.

Glaucobilin. When mesobilirubin is treated with nitric and nitrous acids, with lead dioxide, or with any of several other oxidizing agents under suitable conditions, a blue pigment, glaucobilin, is formed.[179] This has the property of forming a stable iron complex, ferrobilin, and was first obtained by the removal of iron from ferrobilin, after

[179] Fischer and Haberland, *Z. physiol. Chem.*, **232**, 254 (1935).

oxidation of mesobilirubin with ferric chloride.[180] Synthetically, the material may be prepared by the aldehyde condensation of methenes L and LI.[178]



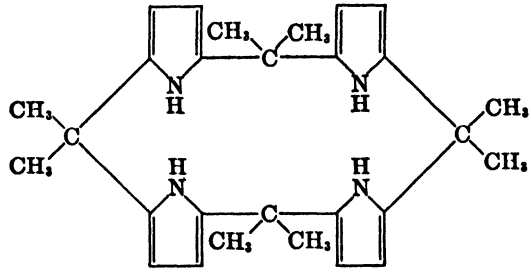
Glaucobilin is of special interest because of its close relationship to the colored part of the algae pigment, phycocyanine or phycocyan, studied by Lemberg.[177,181] It is also probably closely related to biliverdin, the green pigment of the bile, and to uteroverdin, a green pigment obtained from canine placentas.[182] Fischer has stated that the green and blue pigments may be related as an enol is to a ketone because of the fact that the oxidation of the enol ethers stops at the green phase whereas the free enols go on to the characteristic blue of glaucobilin.[178,174,180]

Porphyrin Condensations. The simple condensations of pyrroles which have been outlined have been extended to the production of porphyrins. Each condensation of a pyrrole to a dipyrrylmethane or a dipyrrylmethene can be paralleled by a similar condensation of a suitable pyrrole to a porphyrin or by the condensation of suitable sets of dipyrryl systems to porphyrins.

The first condensation discovered which led to a substance now known to be porphyrin-like was the formation of acetone pyrrole by the reaction of pyrrole with acetone in the presence of hydrochloric acid.[183] The constitution of this substance was investigated by Denn-

180 Fischer, Baumgartner, and Hess, *Z. physiol. Chem.*, **206**, 200 (1932).
181 Lemberg, *Ann.*, **461**, 56 (1928); **477**, 195 (1930).
182 Lemberg, *Ann.*, **499**, 25 (1933); *Biochem. J.*, **29**, 978 (1934).
183 Baeyer, *Ber.*, **19**, 2184 (1886).

stedt and Zimmermann [184] and later by Chelintzev and Tronov.[185] It is represented as octamethyl porphyrinogen (LII).



LII

Other porphyrinogens have been prepared by Fischer and his collaborators by the reduction of porphyrins.[186] These substances are distinguished by the ease with which they are reoxidized to porphyrins, the process taking place spontaneously by exposure of the solid crystals of the leuco compound to air. In acetone pyrrole, this oxidation is blocked by the bridge methyl groups. Because of the ease of this oxidation in normal porphyrinogens, it is to be expected that any condensation formulated to yield porphyrinogens would be found to give porphyrins instead, unless drastic precautions to prevent oxidation were taken.

The condensation of pyrrole with formaldehyde takes such a course. This reaction has been investigated by Rothemund,[187] who found among the reaction products not only porphyrin itself but other substances at first believed to be isomeric. The structure of these substances has been reinvestigated by Calvin, Ball, and Aronoff,[188] who conclude that they are chlorins, that is, β-dihydroporphyrins.

Fischer, Sturm, and Friedrich [189] have investigated the condensation of 3-methyl-4-ethylpyrrole (opsopyrrole) with formic acid. They obtained a mixture of isomeric etioporphyrins which was not separated. The condensation with formic acid, which couples pyrroles to methenes,

184 Dennstedt and Zimmermann, *Ber.*, **19**, 2189 (1886); **20**, 2449 (1887); **23**, 1370 (1890).

185 Chelintzev and Tronov, *J. Russ. Phys. Chem. Soc.*, **48**, 105, 127, 1197 (1916).

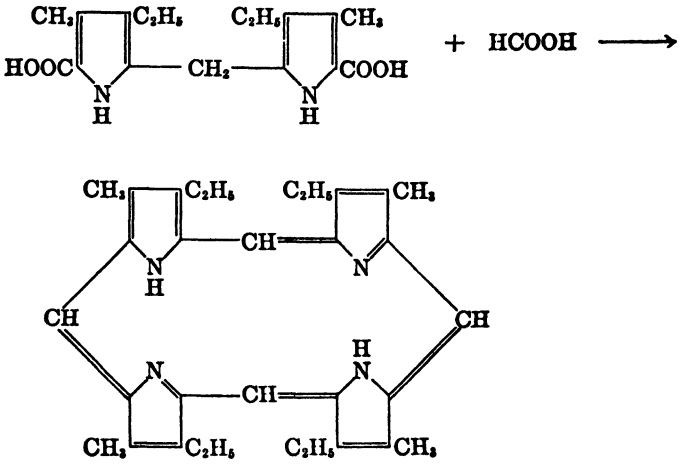
186 Fischer, Bartholomäus, and Röse, *Z. physiol. Chem.*, **84**, 270 (1913); Fischer and Zerweck, *ibid.*, **137**, 242 (1924). Cf. Seidel and Winkler, *Ann.*, **554**, 162 (1943)

187 Rothemund, *J. Am. Chem. Soc.*, **61**, 2912 (1939).

188 Calvin, Ball, and Aronoff, *J. Am. Chem. Soc.*, **65**, 2259 (1943).

189 Fischer, Sturm, and Friedrich, *Ann.*, **461**, 261 (1928).

has been exploited by Fischer and his collaborators [190] in the preparation of etioporphyrin II in 50% yield.



etioporphyrin II

Without experimental evidence in support of their views, Fischer and Orth [191] formulate this reaction as involving the intermediate formation of a diketoporphyrinogen by interaction of the carboxyl groups, followed by reduction of the keto groups by the formic acid. A much more straightforward assumption would be that the usual easy decarboxylation of the dipyrrylmethane takes place, followed by condensation of the methane with two free nuclear positions with formic acid to give the dihydroporphyrin. This is then readily oxidized to the porphyrin, as was pointed out above.

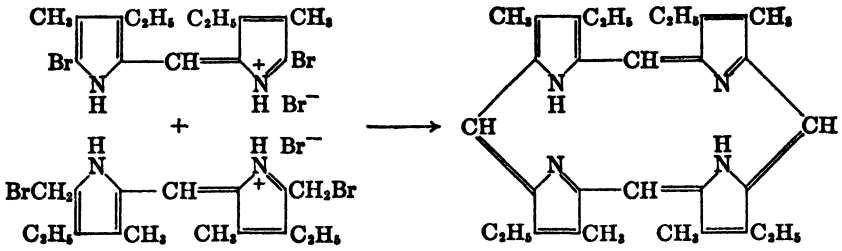
The most productive porphyrin syntheses have been based on an extension of the Fischer methene synthesis. In the methene synthesis, it has been shown that a bromomethylpyrrole condenses with an α-bromopyrrole to yield a dipyrrylmethene. If for pyrroles we substitute methenes, we have the first porphyrin synthesis, discovered by Fischer and Klarer, which is summarized on p. 316.[142]

In the Fischer and Klarer synthesis the ring bromo- and α-bromomethyl groups are on the same methene. When they are on different

190 Fischer and Halbig, *Ann.*, **448**, 200 (1926); **450**, 158 (1926); Fischer and Stangler, *Ann.*, **459**, 86 (1927).

191 Fischer and Orth, *Die Chemie des Pyrrols*, Bd. II. Akademische Verlagsgesellschaft, Leipzig, 1937, pp. 1, 165.

methenes, a greater variety of synthetic possibilities arises, even though the process is essentially similar.[192]



etioporphyrin IV

Although we know much about the processes for synthesizing porphyrins, we know relatively little about the reactions of the porphyrin ring. It is known that the porphyrins form salts with strong bases [89] and with dilute mineral acids [193] and that they form complexes with many metals.[194] Also free nuclear positions in the ring may be brominated.[195] Iron complexes of porphyrins undergo the Friedel-Crafts reaction,[196] permitting the introduction of acetyl groups. Porphyrins can also be reduced to porphyrinogens,[186] which are hexahydroporphyrins, and to the chlorins,[197] which are dihydroporphyrins hydrogenated on two adjacent β-carbons. Lead dioxide attacks porphyrins with the formation of xanthoporphyrinogens,[198] oxygen-containing substances of unknown structure, and halogens may attack the ring system under certain conditions.[199] Porphyrins can also be N-methylated with methyl iodide.[200]

Of the foregoing reactions, those of hydrogenation deserve special mention. From the drastic conditions necessary to produce hydrogenation of the porphyrin ring, the ring system apparently is a very stable one. This is also indicated by the ease with which the porphyrinogens revert to porphyrins. It may appear contradictory, then, that the chlorins, which are dihydroporphyrins, are stable substances.

192 Fischer, Halbig, and Walach, *Ann.*, **452**, 286 (1927). See also Fischer and Stangler, *Ann.*, **452**, 53 (1927); **462**, 251 (1928).

193 Willstätter and Mieg, *Ann.*, **350**, 1 (1906).

194 Willstätter and Pfannenstiel, *Ann.*, **358**, 205, 249 (1907).

195 Fischer and Lindner, *Z. physiol. Chem.*, **161**, 31 (1927).

196 Fischer and Zeile, *Ann.*, **468**, 98 (1929).

197 Fischer, Treibs, and Helberger, *Ann.*, **466**, 243 (1928); Treibs and Wiedemann, *Ann.*, **471**, 146 (1929).

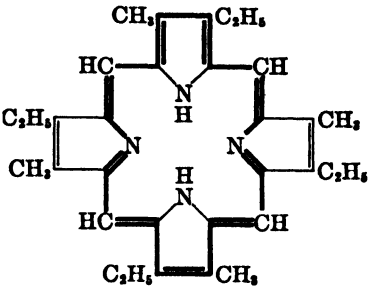
198 Fischer and Treibs, *Ann.*, **457**, 209 (1927).

199 Fischer and Röse, *Ber.*, **46**, 2461 (1913).

200 McEwen, *J. Am. Chem. Soc.*, **68**, 711 (1946); Ellingson and Corwin, *ibid.*, **68**, 1112 (1946).

This apparent contradiction is resolved by a further consideration of the details of porphyrin structure.

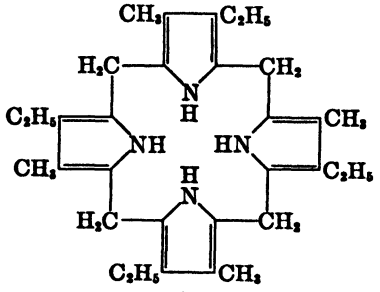
Etioporphyrin I, as formally represented, contains a large eighteen-membered ring with alternate single and double bonds. This is represented by heavy bonds in formula LIII.



etioporphyrin I

LIII

It is probable that the great stability of the porphyrin system is accounted for by resonance between the Kekulé forms of the main conjugation, since in this system each single bond can be replaced by a double bond and each double bond by a single bond.



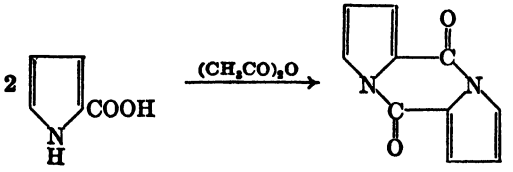
etioporphyrinogen

Hydrogenation of the cross-conjugated double bonds, on the other hand, would give rise to chromophoric systems in which the main conjugation is still intact and therefore stabilized by resonance. The dihydroporphyrins of this type are the chlorins,[197] which are the pigments of the chlorophyll series. Tetrahydroporphyrins, hydrogenated on both the β bonds, have not been found in nature.

Pyrocolls. A reaction of the pyrrole system which forms an exception to the general rule that substitution on nitrogen does not take place except under alkaline conditions is that of pyrocoll formation.

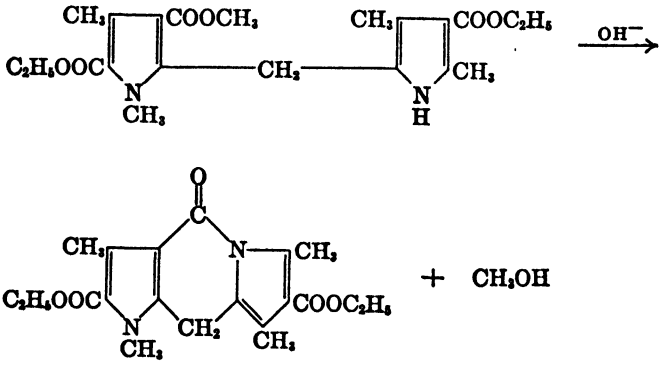
Pyrocolls are bimolecular anhydrides of pyrrole α-carboxylic acids, formed by heating them with acetic anhydride.[201]

Pyrocoll (LIV) was first isolated from the products of dry distillation of glue by Weidel and Ciamician.[202]



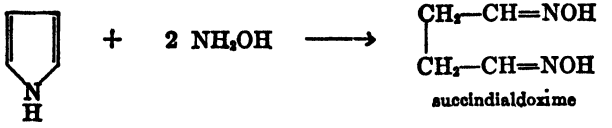
LIV

Dipyrrolopyridones. A reaction which limits synthesis with dipyrrylmethanes is the condensation to form dipyrrolopyridones. This reaction takes place upon attempted alkaline hydrolysis of 2,2′-dipyrrylmethanes with a carbalkoxy group in the 3 position and a hydrogen in the 1′ position.[148, 203]



REACTIONS DESTROYING THE PYRROLE RING

The five-membered ring of pyrrole can be opened by refluxing with an alcoholic solution of hydroxylamine,[204] a reaction which may be re-



succindialdoxime

201 Ciamician and Silber, *Ber.*, **17**, 103 (1884).
202 Weidel and Ciamician, *Monatsh.*, **1**, 279 (1880).
203 Corwin and Buc, *J. Am. Chem. Soc.*, **66**, 1151 (1944).
204 Ciamician and Zanetti, *Ber.*, **22**, 1968 (1889).

garded as reversing the Harries synthesis. This method has served for the preparation of succindialdehyde.[205]

It has already been noted that the Reimer-Tiemann synthesis when applied to pyrrole leads to some abnormal reaction products, among which are pyridine derivatives. For example, potassium pyrrole on treatment with chloroform and sodium ethoxide yields β-chloropyridine.[206]

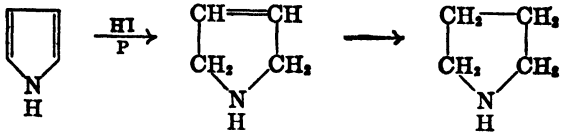
On treatment with acid, pyrrole condenses to form tripyrrole [207] and pyrrole red.[208] When heated to 300°, tripyrrole decomposes to give pyrrole, indole, and ammonia.[207] Structural investigations on tripyrrole are not complete.[209]

Substituted pyrroles with adjacent free α and β positions can dimerize. The structure of these bipyrroles has been investigated.[210]

THE REDUCED PYRROLES

In addition to the hydropyrrole pigments, the chlorins, mentioned above, and stercobilin,[211] the reduced pyrroles are found widely distributed in nature in alkaloidal systems. It is not the purpose of this summary to deal with these systems, but, instead, the direct relationships between the pyrroles and the reduced pyrroles will be treated.

Pyrrolines. Direct reduction of pyrrole might lead to either Δ^2-pyrroline or Δ^3-pyrroline. In fact, however, only the latter is obtained.[212]



Δ^3-pyrroline pyrrolidine

205 Willstätter and Heubner, *Ber.*, **40**, 3871 (1907).

206 Ciamician and Dennstedt, *Ber.*, **15**, 1172 (1881).

207 Dennstedt and Zimmermann, *Ber.*, **21**, 1478 (1888); Dennstedt and Voigtländer, *Ber.*, **27**, 476 (1894).

208 Anderson, *Ann.*, **105**, 70 (1858); Weidel and Ciamician, *Ber.*, **13**, 65 (1880).

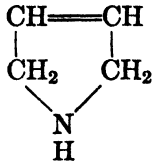
209 Pieroni and Moggi, *Gazz. chim. ital.*, **53**, 120 (1924); Tronov and Popov, *J. Russ. Phys. Chem. Soc.*, **58**, 745 (1926).

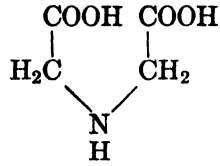
210 Allen, Gilbert, and Young, *J. Org. Chem.*, **2**, 227 (1937); Allen, Young, and Gilbert, *ibid.*, **235** (1937).

211 Watson, *Z. physiol. Chem.*, **204**, 57 (1932); **208**, 101 (1932); **221**, 145 (1933); **233**, 89 (1935); *J. Biol. Chem.*, **105**, 469 (1934); Watson, Sborov, and Schwartz, *Proc Soc. Exptl. Biol. Med.*, **49**, 647 (1942); Fischer and Halbach, *Z. physiol. Chem.*, **238**, 59 (1936); Fischer and Libowitzky, *ibid.*, **258**, 255 (1939).

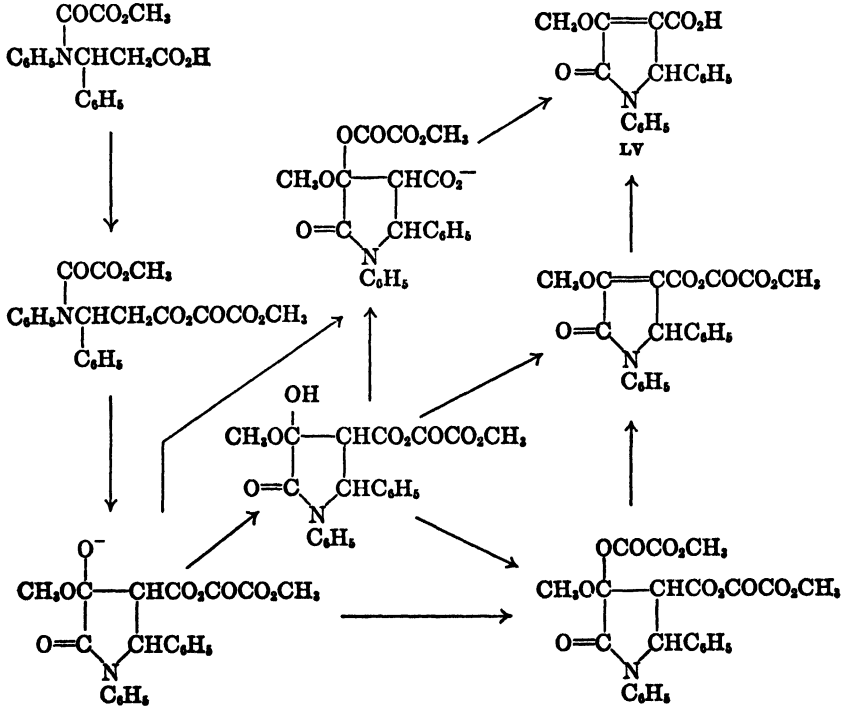
212 Ciamician and Dennstedt, *Ber.*, **16**, 1536 (1883); Anderlini, *Ber.*, **22**, 2512 (1889); Knorr and Rabe, *Ber.*, **34**, 3497 (1901); Ciamician, *Ber.*, **34**, 3952 (1901); Langheld, *Ber.*, **42**, 2973 (1909).

The method of Ciamician and Dennstedt leads mainly to pyrrolidine, together with *n*-butylamine, ammonia, and, presumably, butane. A better yield of pyrroline can be secured with zinc and hydrochloric acid. The structure of this substance has been established by ozonolysis, followed by oxidation of the initial product with hydrogen peroxide.[213]





An unusual reaction leading to derivatives of Δ^3-pyrroline is that resulting from the action of methoxalyl chloride on β-anilino-β-phenylpropionic acid in the presence of pyridine.[214] The interesting internal condensation by which water is eliminated from an α-methylene group of a carboxylic acid and an ester rather than alkoxide ion as in the usual Dieckmann type reaction is formulated as a variation of the Perkin reaction involving an intermediate mixed anhydride by one or the other of the following tentative routes.

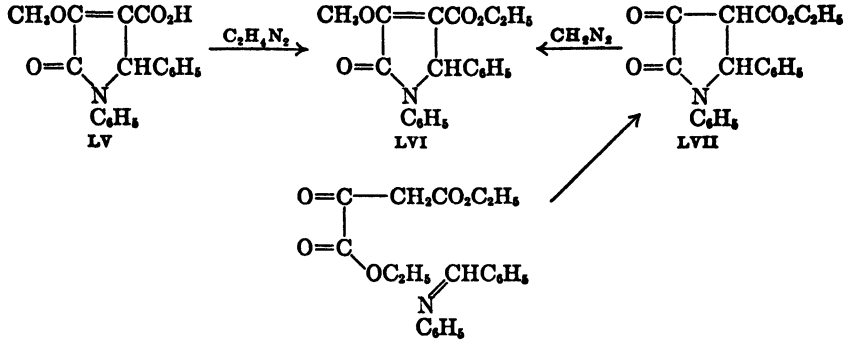


LV

213 Treibs and Dinelli, *Ann.*, **517**, 170 (1935).

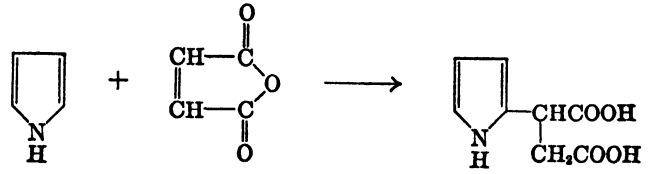
214 Southwick and Seivard, *J. Am. Chem Soc.*, **71**, 2532 (1949).

The structure of the final product, LV, was suggested by its conversion to LVI. LVII was prepared from benzalaniline and ethyl oxalacetate according to Schiff and Bertini.[215] A rigid degradation

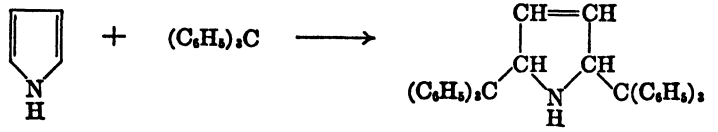


study of these substances would be most welcome in view of some uncertainties still involved in the structures assigned to them.

That the diene system of pyrrole is not analogous to butadiene has been demonstrated by Diels and Alder,[216] who showed that ordinary diene reagents, such as maleic anhydride, do not add to pyrrole derivatives but substitute instead.



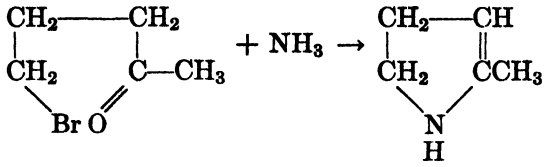
One typical diene reaction of pyrrole has been discovered by Conant and Chow, however, in the addition of triphenylmethyl to give a substituted pyrroline derivative.[217] For comparative reactions of furan, see p. 139.



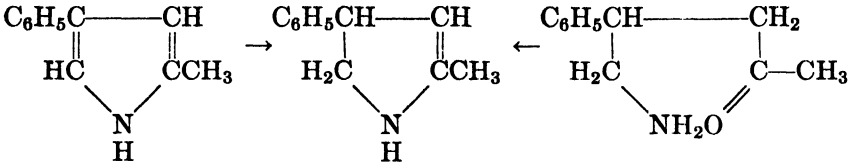
Unlike pyrrole, the pyrrolines are basic, forming hydrochlorides and other salts which can be isolated for identification.

215 Schiff and Bertini, *Ber.*, **30**, 602 (1897).
216 Diels and Alder, *Ann.*, **490**, 267 (1931).
217 Conant and Chow, *J. Am. Chem. Soc.*, **55**, 3475 (1933).

Δ^2-Pyrrolines are prepared, in general, by ring closure rather than by hydrogenation of pyrroles.[218]



One exception to this rule is found in 2-methyl-4-phenylpyrrole, which can be reduced to a Δ^2-pyrroline.[219]



Numerous pyrroline derivatives have been prepared and are presumed to be Δ^3 derivatives, but the fact that the reduction can proceed in the other manner raises a question as to the structures of these substances, unless they are established by independent synthesis.

Pyrrolidines. Pyrrolidines can be prepared by the reduction of pyrrole by means of phosphorus and hydrogen iodide [220] or by catalytic hydrogenation.[221] They have also been prepared by electrolytic reduction of substituted succinimides.[222] A very convenient method for obtaining certain pyrrolidines involves reaction of the commercially available 1,4-dibromobutane or 1,4-dibromopentane with ammonia or a primary amine.[223]

The pyrrolidines differ strongly from pyrrole in their basic properties. They possess ammoniacal odors and readily form salts which serve for identification.

The contrasting basic properties of the pyrrolines and pyrrolidines on the one hand, and the pyrroles on the other, lend further support to the concept advanced in the initial part of this discussion that the resonance of pyrrole suppresses its basic properties and accentuates its acidic character.

218 Hielscher, *Ber.*, **31**, 277 (1898).
219 Sonn, *Ber.*, **68**, 148 (1935).
220 Ciamician and Magnaghi, *Ber.*, **18**, 2079 (1885).
221 Willstätter and Hatt, *Ber.*, **45**, 1471 (1912); Andrews and McElvain, *J. Am. Chem. Soc.*, **51**, 887 (1929).
222 Späth and Breusch, *Monatsh.*, **50**, 349 (1928).
223 Elderfield and Hageman, *J. Org. Chem.*, **14**, 605 (1949).

CHAPTER 7

MONOCYCLIC PYRANS, PYRONES, THIAPYRANS, AND THIAPYRONES

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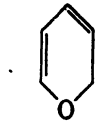
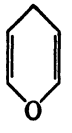
CONTENTS

NOMENCLATURE

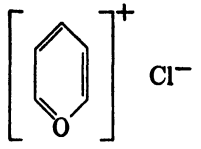
This chapter deals with the monocyclic pyrans, pyrones, and pyrylium salts and their partially and fully hydrogenated derivatives. The basic ring system from which these substances are derived is that of pyran, which contains a doubly unsaturated six-membered ring with a single oxygen as hetero atom. The two double bonds may be conjugated as in α- or 1,2-pyran or isolated as in γ- or 1,4-pyran.



α- or 1,2-pyran

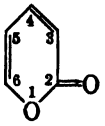


γ- or 1,4-pyran



pyrylium chloride

Aromatization of the pyran ring, involving the removal of a proton and two electrons, leads to the positively charged pyrylium nucleus, which forms the cation in the stable, colored phenylpyrylium salts. Replacement of the methylene group of the pyrans by a carbonyl group leads to the α- or 1,2- and γ- or 1,4-pyrones, which rank first in importance among the derivatives to be discussed. As a result of the conjugation



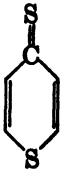
α-pyrone

γ-pyrone

of the carbonyl group with the nuclear double bonds, the α- and particularly the γ-pyrones possess properties not encountered in similar non-cyclic systems.

The nomenclature of the thiapyrans follows that of their oxygen isologs.

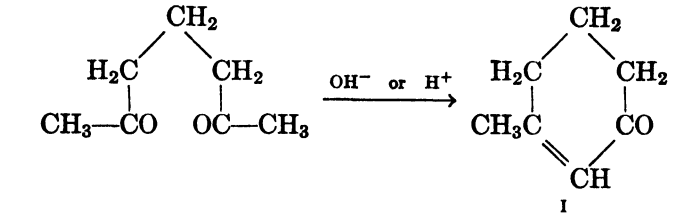
1,4-thiapyrone



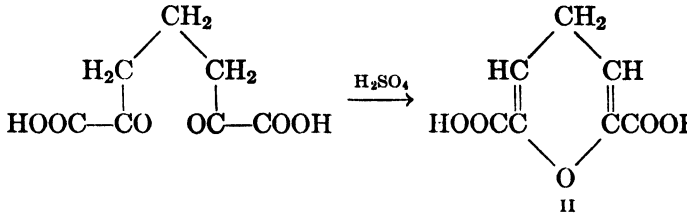
4-thio-1,4-thiapyrone

PYRANS AND PYRYLIUM SALTS

The failure to prepare simple alkyl-substituted 1,2- or 1,4-pyrans may be attributed primarily to the instability to be expected of such dienolic ethers. Another reason may be found in the extreme ease with which aliphatic δ-diketones under the influence of both acids and bases cyclize to cyclohexenones (I), rather than to 1,4-pyrans.[1] Blaise and



I



II

Gault[2] have prepared γ-pyran-2,6-dicarboxylic acid (II) by cyclization of α,α′-diketopimelic acid, but all attempts to prepare the unsubstituted pyran by decarboxylation of II have resulted in deep-seated decomposition of II.

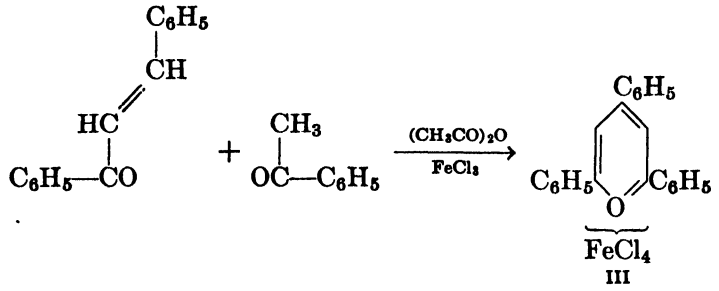
A high degree of stabilization of the pyran nucleus is achieved by substituting phenyl groups in the 2 and 6 and preferably also in the 4 positions. Such phenyl-substituted pyrans are readily oxidized by mild oxidizing agents to the corresponding pyrylium salts (III) in which the pyran nucleus has become stabilized by aromatization. The phenylpyrylium salts are colored, strongly fluorescing substances, the chemistry of which closely parallels that of the naturally occurring anthocyanins. Our present concepts of the structure of the latter compounds have been greatly influenced by the observations of Dilthey[3]

1 Knoevenagel and Klages, *Ann.*, **281**, 97 (1894); Fargher and Perkin, *J. Chem. Soc.*, **105**, 1353 (1914).

2 Blaise and Gault, *Bull. soc. chim. France*, [4] **1**, 129 (1907).

3 Dilthey, (*a*) *J. prakt. Chem.*, [2] **94**, 53 (1916); (*b*) [2] **95**, 107 (1917); (*c*) *Ber.*, **50**, 1008 (1917); (*d*) **52**, 1195 (1919); (*e*) **53**, 252 (1920).

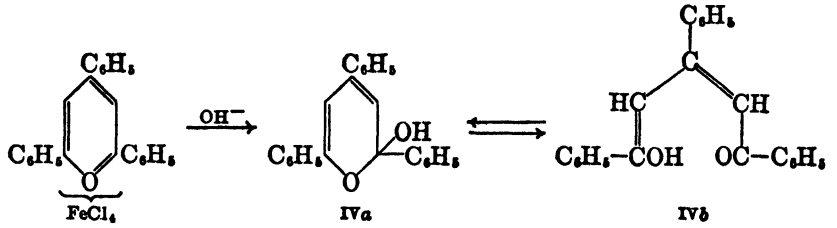
and Schneider [4] on these relatively simple and readily accessible substances. Several methods have been devised for their preparation, of which the reaction typified by the condensation of benzylideneacetophenone with acetophenone in the presence of acetic anhydride and ferric chloride has been most frequently used.[3a,b] Two reactions



III

which have accidentally been found to produce pyrylium salts are of interest because of their simplicity. Davis and Armstrong,[5] attempting to synthesize trianisylbenzene by the action of sulfuric acid and potassium pyrosulfate on *p*-methoxyacetophenone, found that half of the product formed consisted of 2,4,6-trianisylpyrylium sulfate. Similarly, Dovey and Robinson [6] isolated 2,4,6-triphenylpyrylium fluoroborate in 26% yield from the reaction products of acetophenone and boron trifluoride. In both reactions, a methyl group was eliminated during the reaction, the fate of which neither the American nor the British investigators have been able to ascertain.

The pyrylium salts are stable in acid solution, and those possessing phenolic ether groups may be hydrolyzed to the corresponding phenols without difficulty. With aqueous ammonia they readily form the corresponding substituted pyridines, and with alkali the ether-soluble, colorless pseudobases which probably exist as tautomeric mixtures of the open (IV*b*) and ring (IV*a*) forms. 2-*p*-Hydroxyphenyl-4,6-di-



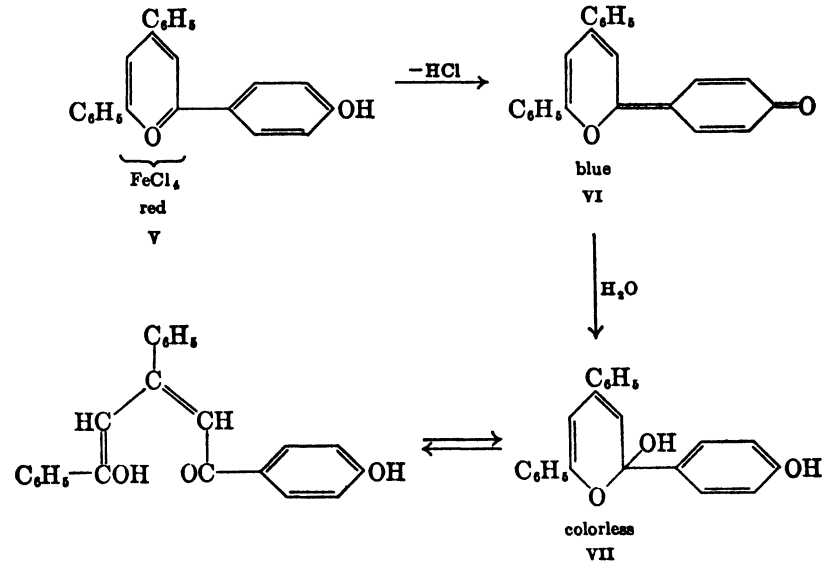
IVa IVb

[4] Schneider et al., *Ber.*, **54**, 1484, 2285 (1921); **55**, 2775 (1922); *Ann.*, **432**, 297 (1923); *Ber.*, **74**, 1252 (1941).

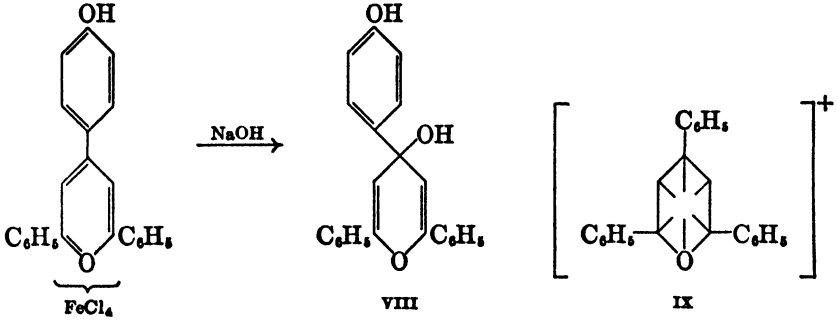
[5] Davis and Armstrong, *J. Am. Chem. Soc.*, **57**, 1583 (1935).

[6] Dovey and Robinson, *J. Chem. Soc.*, 1389 (1935).

phenylpyrylium ferric chloride was prepared by Dilthey,[3d,e] and the color changes produced by gradual alkalinization of its acid solution were found to parallel the characteristic changes observed with the anthocyanidins. The red color of the salt (V) passed through purple at neutrality to the pure blue of the anhydrobase (VI), which eventually became hydrated to the pseudobase (VII). Similarly, 4-*p*-hy-



droxyphenyl-2,6-diphenylpyrylium ferric chloride formed a pseudobase (VIII) in which the hydroxyl group was assumed to occupy the 4 position.

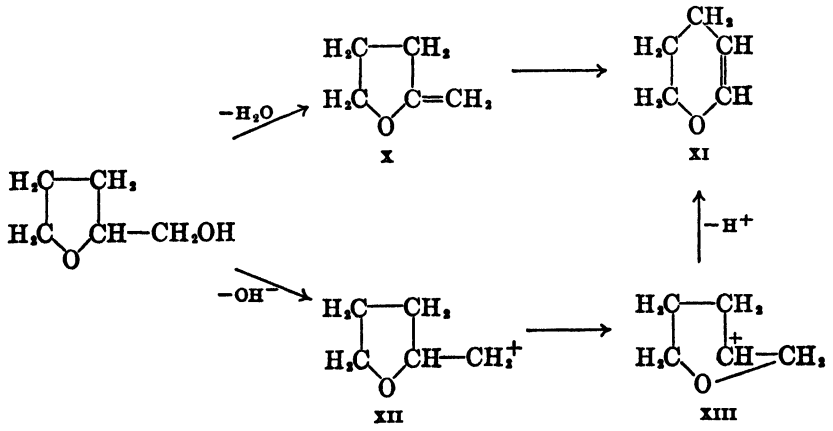


From these observations, Dilthey[3e] concluded that the positive charge of the pyrylium ion was not associated exclusively with the ring oxygen, as the proponents of the oxonium theory maintained, nor

with any particular one of the carbon atoms, but rather was distributed equally throughout the ring. For this reason, he favored the centric formula IX, which had previously been postulated by Werner for the xanthylium salts. From the point of view of the electronic theory, the pyrylium nucleus is visualized as resonating among all the possible oxonium and carbonium structures (p. 374), no single one of which is able to explain all the properties, and particularly the extraordinary degree of stability, of the pyrylium salts. Convincing experimental evidence for such a view has been adduced by Shriner and Moffett [7] for the closely related flavylium salts.

DIHYDROPYRANS

Preparation and Reactions of Dihydropyran. In contrast to the alkyl pyrans, dihydropyran and its derivatives have become a group of easily available and well-explored substances, largely through the researches of Paul,[8] who noted that, when tetrahydrofurfuryl alcohol is passed over activated alumina at temperatures between 300 and 350°, it is dehydrated and rearranged to dihydropyran (XI). The reaction is strongly exothermic and may proceed via the unsaturated furan derivative (X), which has been shown to yield dihydropyran under the above conditions or directly by ring enlargement of the carbonium ion (XII), followed by elimination of a proton from XIII and equalization of the charges by double-bond formation. A number of dehy-

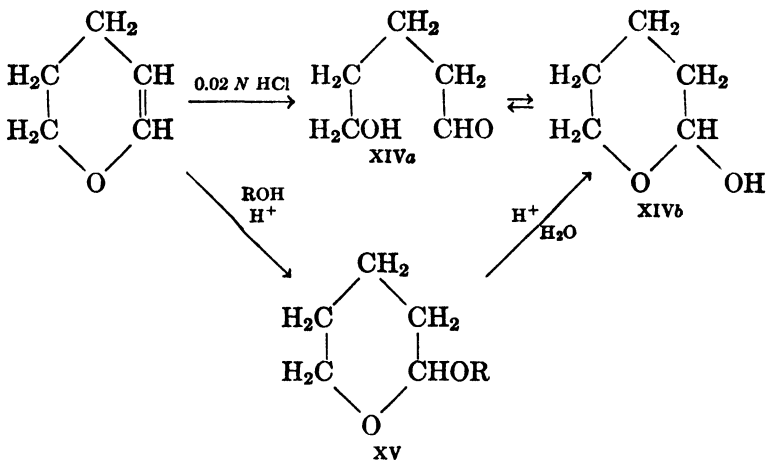


[7] Shriner and Moffett, *J. Am. Chem. Soc.*, **61**, 1474 (1939); **62**, 2711 (1940); **63**, 1694 (1941).

[8] Paul, *Bull. soc. chim. France:* (*a*) [4] **53**, 1489 (1933); (*b*) [5] **1**, 971 (1934); (*c*) [5] **2**, 311, 2220 (1935).

dration reactions have been shown to take an analogous course.[9] A thorough study of the reaction conditions has resulted in substantial improvements in the yield,[10] and it is now possible to prepare dihydropyran in the laboratory in about 85–90% yield. If the dehydration reaction is conducted over a less active catalyst, such as alumina-silica, at 450°, the reaction products are acrolein and ethylene [11] formed by further cracking of dihydropyran.

As a cyclic vinyl ether, dihydropyran is a very reactive substance. It is hydrolyzed by 0.02 *N* acid to 5-hydroxypentanal (XIV*a*) [8,10a] which, according to absorption spectra measurements,[10c] appears to exist to the extent of 95% in the tautomeric hemiacetal form XIV*b*. Under the influence of catalytic amounts of hydrogen chloride, dihydropyran adds alcohols and forms inner cyclic acetals (XV) [8,10c,12]



of the type known as glycopyranosides in carbohydrate chemistry. At low temperatures, it adds chlorine [13] and bromine [8,14] and forms dihalides (XVI) in which the difference in reactivity between the two halogen atoms is most striking. Thus, 2,3 dichlorotetrahydropyran (XVI, X = Cl) reacts readily with Grignard reagents and forms 2-

9 Paul, *Bull. soc. chim. France,* [4] **53**, 1491 (1933).

10 (*a*) Kline and Turkevich, *J. Am. Chem. Soc.*, **67**, 498 (1945); (*b*) Sawyer and Andrus, *Org. Syntheses*, **23**, 25 (1943); (c) Schniepp and Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946).

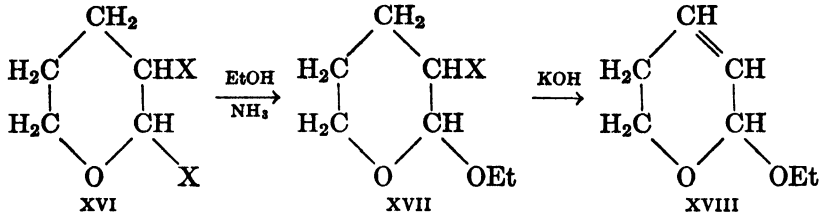
11 (*a*) Wilson, *J. Am. Chem. Soc.*, **69**, 3004 (1947); (*b*) Bremer, Jones, and Beaumont, *J. Chem. Soc.*, 1018 (1946).

12 Woods and Kramer, *J. Am. Chem. Soc.*, **69**, 2246 (1947).

13 Paul, *Compt. rend.*, **218**, 122 (1944).

14 Woods and Sanders, *J. Am. Chem. Soc.*, **68**, 2483 (1946).

alkyl(aryl)-3-chlorotetrahydropyrans.[13] Similarly, the dibromo derivative (XVI) (X = Br) reacts with alcoholic ammonia to form the



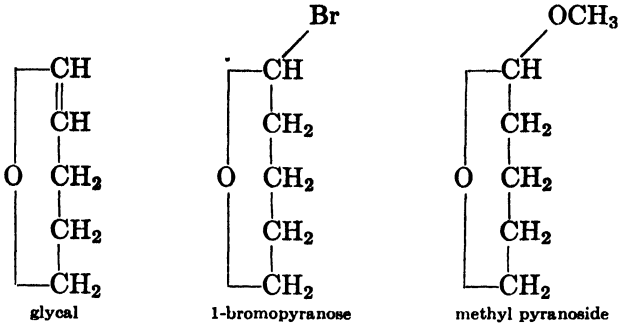
XVI XVII XVIII

2-ethoxy derivative (XVII) (X = Br),[14] from which the second bromine atom is eliminated by more drastic treatment with hot alcoholic potassium hydroxide. The resulting 2-ethoxy-Δ^3-dihydropyran (XVIII) on acid hydrolysis does not form the expected 5-hydroxy-Δ^2-pentenal but instead yields pentadienal in 55% yield.[14,15] The addition of hydrogen bromide to dihydropyran affords 2-bromotetrahydropyran, from which a number of 2-alkyltetrahydropyrans have been prepared by means of the Grignard reagent.[8c]

Dihydropyran and its derivatives are of importance in synthetic chemistry because of their ready conversion in good yield into 1,5-disubstituted alkanes, either by catalytic hydrogenation of 5-hydroxypentanal [10c] or by cleavage of the tetrahydropyran nucleus by means of hydrogen bromide in an inert solvent, which leads to the dibromides. Two methods, which should prove useful where different substituents are desired at either end of the chain, have been described. Wilson [16] obtained 1-bromo-5-acetoxypentane by the prolonged action of hydrogen bromide in acetic anhydride on tetrahydropyran, and Snyerholm [17] prepared the corresponding chloride in 85% yield by the reaction of tetrahydropyran with acetyl chloride and anhydrous zinc chloride.

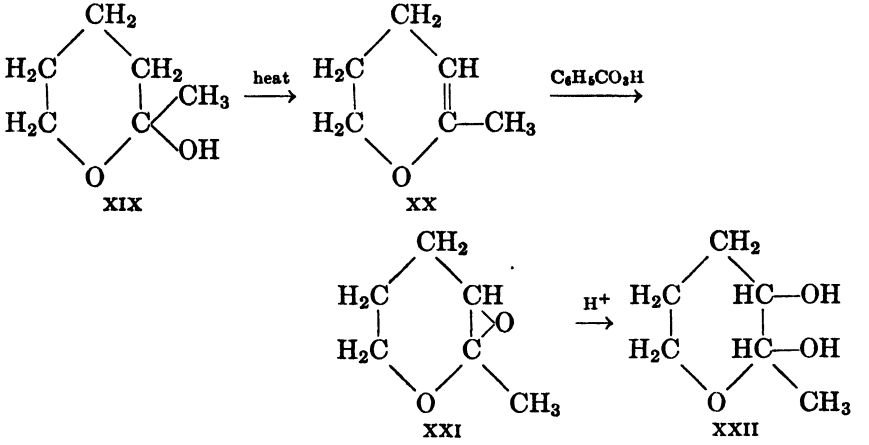
Dihydropyrans as Models in Carbohydrate Chemistry. The dihydropyrans are of interest also from the point of view of the carbohydrate chemist. If the formulas for dihydropyran and its derivatives are written in the form customary in sugar chemistry, the relationship of these simple derivatives to the carbohydrates is more clearly emphasized.

[15] Woods and Sanders, *J. Am. Chem. Soc.*, **69**, 2926 (1947).
[16] Wilson, *J. Chem. Soc.*, **48** (1945).
[17] Snyerholm, *J. Am. Chem. Soc.*, **69**, 2581 (1947).



glycal 1-bromopyranose methyl pyranoside

The study of the properties of the pyranoside ring system in its simplest form, devoid of the influence of hydroxyl groups and asymmetric carbon atoms, has attracted several groups of workers interested in the carbohydrate field.[18,19] The reactions carried out by Bergmann and Miekeley [19] with the "ketose," 4-hydroxybutyl methyl ketone (XIX),[20] are described here in some detail to illustrate the use of simple dihydropyran derivatives as model substances in carbohydrate chemistry.



XIX XX XXI XXII

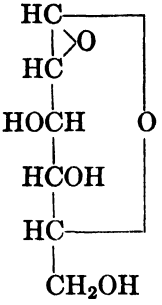
In methanolic solution containing 0.002% of hydrogen chloride, XIX yields a cyclic methyl acetal which can be hydrolyzed back to the original material by the same concentration of aqueous acid. Distillation of XIX yields 2-methyl-Δ^2-dihydropyran (XX), which reacts

18 Helferich et al., *Ber.*, **55**, 702, 3348 (1922).

19 Bergmann and Miekeley, *Ber.*, **55**, 1390 (1922); **56**, 2255 (1923); *Ann.*, **432**, 319 (1923).

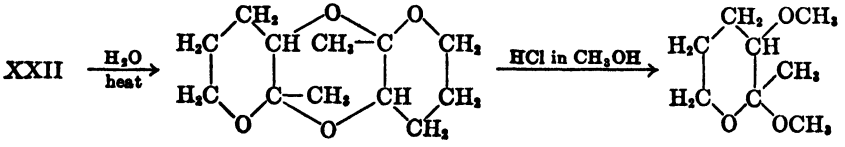
20 Lipp, *Ber.*, **18**, 3280 (1885); *Ann.*, **289**, 181 (1896).

with perbenzoic acid in absolute ether to give the oxide (XXI). This simple 1,2-glycosan is stable towards hot alcohol and resists hydrolysis by water at 130°. In this respect, it resembles the α-glucosan (XXIII) of Pictet and Castan [21] obtained by heating glucose under reduced pressure, rather than the epoxide prepared by Brigl [22] by the elimination of hydrogen chloride from 1-chloro-3,4,6-triacetylglucose. This latter epoxide readily forms a methyl glycoside when dissolved in cold methanol. Hydrolysis of XXI occurs readily in dilute acid



XXIII

solution, and a new ketose, 1,4-dihydroxybutyl methyl ketone (XXII), is formed. XXII dimerizes in hot aqueous solution to the anhydride (XXIV), the structure of which follows from its hydrolytic cleavage to the monomer and from the formation of the dimethoxy compound



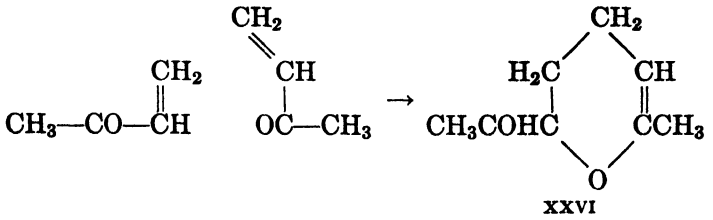
XXIV XXV

(XXV) by methanolysis. The rate of hydrolysis of the dimer (XXIV) differs radically from that of the simple cyclic methyl acetals, 1 *N* acid at 100° being required to effect complete hydrolysis. Difructopyranose anhydride [23] possesses a similar stability towards hydrolytic agents.

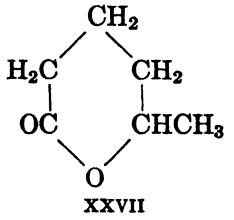
Dihydropyrans from α,β-Unsaturated Aldehydes and Ketones. When methyl vinyl ketone is autoclaved in the presence of a small amount of hydroquinone in order to prevent chain polymerization, a

21 Pictet and Castan, *Helv. Chim. Acta*, **3**, 649 (1920).
22 Brigl, *Z. physiol. Chem.*, **122**, 245 (1922).
23 Schlubach and Behre, *Ann.*, **508**, 16 (1934).

dimeric substance [24] is formed in good yield, the structure of which has been found to be that of 2-methyl-6-acetyl-Δ^2-dihydropyran (XXVI).[25] The presence of the pyran ring in this substance and the



XXVI



XXVII

position of the two substituents were shown by oxidation of its dihydro derivative to the lactone of δ-hydroxycaproic acid (XXVII). Oxidation of the substance before hydrogenation furnished succinic acid. This result, taken in conjunction with the fact that XXVI does not possess the properties of an α,β-unsaturated ketone, limits the double bond to the 2,3 position. The formation of XXVI may be pictured as a 1,4 addition of 1 molecule of the unsaturated ketone to the double bond of a second unsaturated ketone molecule. Other α,β-unsaturated aldehydes [25,26] and ketones [27] have been found to dimerize according to the same scheme, provided that the β-carbon atom carries no substituents. In special cases, as with α-methylenecyclohexanone,[28] dimerization proceeds with such rapidity that it is difficult to isolate the monomer.

A different type of dimerization of an α,β-unsaturated aldehyde has been described by Delépine,[29a] who obtained the dihydropyran derivative (XXVIII) on treatment of crotonaldehyde with dilute acid.

24 Merling, *Chem. Zentr.*, **1910**, II, 1421.

25 Alder, Offermanns, and Rüden, *Ber.*, **74**, 905 (1941).

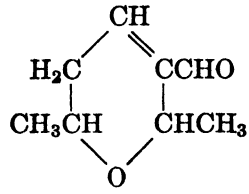
26 Scherlin et al., *J. Gen. Chem.* (*U.S.S.R.*), **8**, 22 (1938).

27 Pummerer and Cherbuliez, *Ber.*, **52**, 1392 (1919); Fries and Brandes, *Ann.*, **542**, 48 (1939).

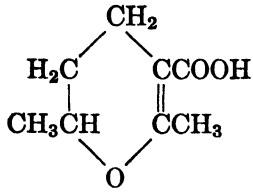
28 Mannich, *Ber.*, **74**, 557 (1941).

29 (*a*) Delépine, *Compt. rend.*, **150**, 394, 535 (1910); (*b*) Delépine and Horeau, *Bull. soc. chim. France*, [5] **5**, 339 (1938).

Proof for this structure has been adduced by Delépine and Horeau [29b] in the following manner. On oxidation, XXVIII yielded an acid, which



XXVIII

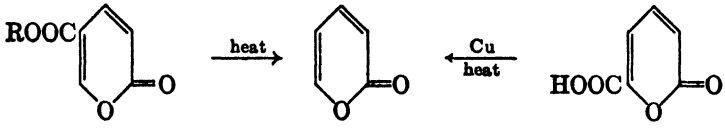


XXIX

in the presence of Raney nickel and hydrogen was not reduced to the expected saturated acid but instead formed an isomeric acid. The latter was found to be identical with 2,6-dimethyl-Δ^2-dihydropyran-3-carboxylic acid (XXIX), the structure of which had been securely established by Fargher and Perkin.[1]

α-PYRONES

α-Pyrone. The simplest representative of this group, α-pyrone (II) or coumalin, has been prepared [30] by dry distillation of the mercurous salt of coumalic acid (I, R = Hg) in an atmosphere of hydrogen. It

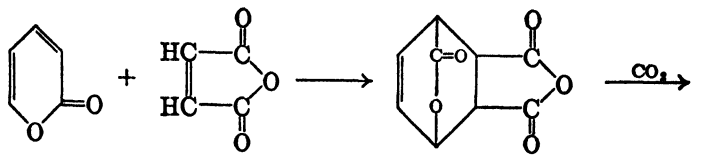


I II III

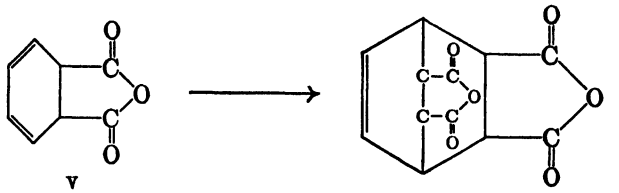
is difficult to separate the α-pyrone obtained by this method from the accompanying impurities, and it has been found that a cleaner product is obtained by decarboxylation of α-pyrone-6-carboxylic acid (III) in the presence of copper powder.[31] The properties of α-pyrone are in the main those expected of an unsaturated aldo-enol lactone, little stabilization of the ring system being achieved by resonance. As an enol lactone, it is readily saponified by dilute alkali and on catalytic hydrogenation furnishes a mixture of δ-valerolactone and valeric acid,[31] a behavior characteristic of most enol lactones.[32] With other derivatives of α-pyrone, it shares its reactivity towards maleic anhydride [33] and in this respect behaves as a true diene. The addition of maleic anhydride to α-pyrone proceeds in two steps: (1) 1,4 addition leading to

30 v. Pechmann, *Ann.*, **264**, 305 (1891).
31 Fried and Elderfield, *J. Org. Chem.*, **6**, 566 (1941).
32 Jacobs and Scott, *J. Biol. Chem.*, **87**, 601 (1930); **93**, 139 (1931).
33 Diels and Alder, *Ann.*, **490**, 257 (1931).

the tricyclic product (IV), which loses carbon dioxide and forms 1,2-dihydrophthalic anhydride (V), and (2) 1,4 addition of a second mole



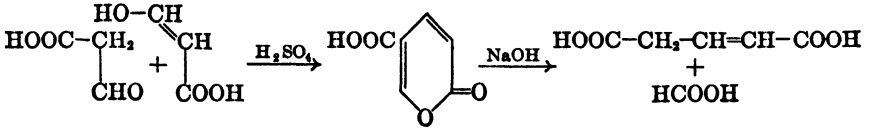
IV



V VI

of maleic anhydride to V to form the final product (VI), which can also be obtained by the addition of maleic anhydride to authentic 1,2-dihydrophthalic anhydride, thus proving its structure. When allowed to remain at room temperature for several days, α-pyrone polymerizes to a viscous gum and gradually loses its odor of new-mown hay. Its homologs show a similar tendency to polymerize. However, stabilization of the α-pyrone nucleus is achieved by the introduction of phenyl or carboxyl groups, especially in the 6 position.

Coumalic Acid. Coumalic acid (I) and its simple esters have been prepared by v. Pechmann [30] by the action of concentrated sulfuric acid on malic acid. Carbon monoxide is evolved, and 2 molecules of the resulting formylacetic acid combine to form I. The methyl or



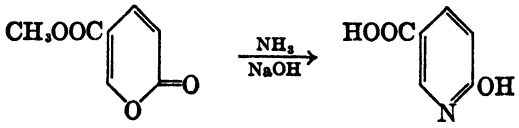
I

ethyl esters may be prepared directly by adding the appropriate alcohol to the crude reaction mixture.[30] On treatment with hot alkali, coumalic acid is cleaved into glutaconic and formic acids, a reaction which is characteristic also of substituted α-pyrone-5-carboxylic acids and which is of importance for the preparation of some substituted glutaconic acids.[34,35]

34 Goss, Ingold, and Thorpe, *J. Chem. Soc.*, **123**, 348 (1923).

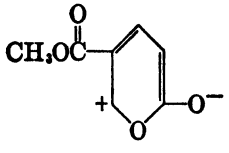
35 Ruhemann, *J. Chem. Soc.*, **75**, 245 (1899).

A reaction of equal significance for both α- and γ-pyrones is the replacement of their ring oxygen by nitrogen, leading to α- and γ-pyridones, respectively. This reaction is usually carried out by warming the pyrone derivative in aqueous solution with ammonia or with a primary amine or, if the substance is resistant to such action, by heating it with ammonium acetate in glacial acetic acid.[36,31] Thus, methyl coumalate, if treated with aqueous ammonia and then boiled with dilute sodium hydroxide, forms 2-hydroxypyridine-5-carboxylic acid (VII).[37]

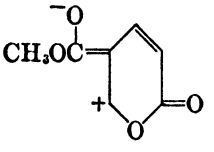


VII

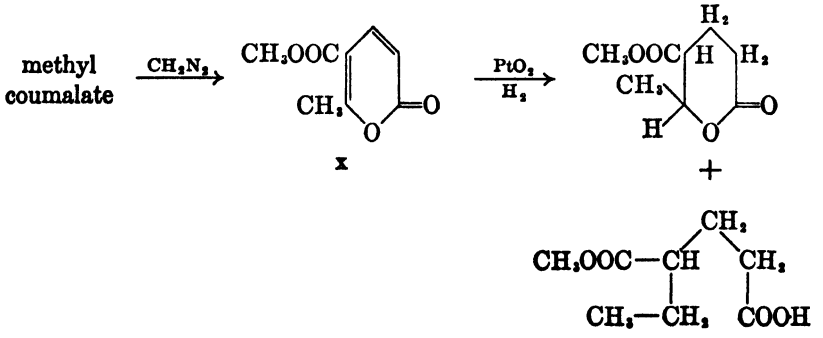
An interesting example of C methylation was observed with methyl coumalate[38] when its methanolic solution was treated with ethereal diazomethane. As to the location of the methyl group, it was reasoned that the carbon atom in position 6 of the pyrone ring was the most likely one to react with the nucleophilic diazomethane, since resonance forms VIII and IX possessing a residual positive charge on that carbon atom are highly probable among the possible resonating struc-



VIII



IX

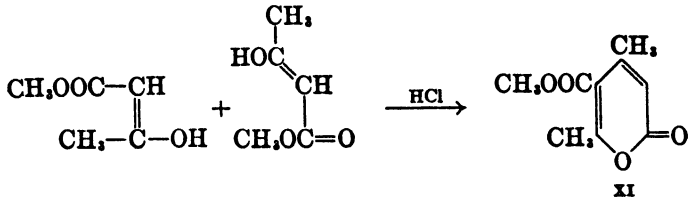


X

[36] Leben, *Ber.*, **29**, 1673 (1896).
[37] v. Pechmann and Welsh, *Ber.*, **17**, 2391 (1884).
[38] Fried and Elderfield, *J. Org. Chem.*, **6**, 577 (1941).

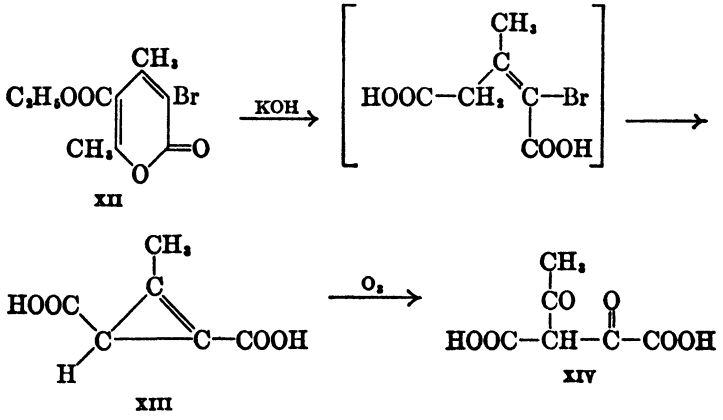
tures. That the reaction product was actually the expected methyl 6-methyl coumalate (X) was shown by its catalytic reduction to a neutral and an acidic product, followed by hydrolysis of the remaining ester group in the acidic product with hydrochloric acid to a dicarboxylic acid which was identified as α-ethylglutaric acid. The presence of a carbonyl group in position 5 is a necessary prerequisite for this reaction, since 5-methyl-α-pyrone is not attacked by diazomethane.

Isodehydracetic Acid. The esters of this well-known α-pyrone derivative (XI) are formed from acetoacetic esters under the influence of concentrated sulfuric acid [39] or, better, of dry hydrogen chloride.[34]



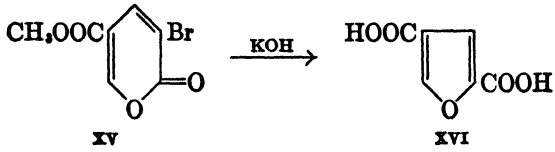
When heated at 160° in concentrated sulfuric acid, isodehydracetic acid loses carbon dioxide and forms 4,6-dimethyl-α-pyrone or mesiten lactone.[39,40] By a similar procedure, benzoylacetic ester is converted into 4,6-diphenylcoumalin [41] which, on treatment with phosphorus pentasulfide, yields 4,6-diphenyl-2-thio-α-pyrone as an orange-red stable substance, the only 2-thio-α-pyrone on record.

Ethyl isodehydracetate is readily brominated in carbon disulfide or chloroform solutions to the 3-bromo ester (XII),[40] which by the action



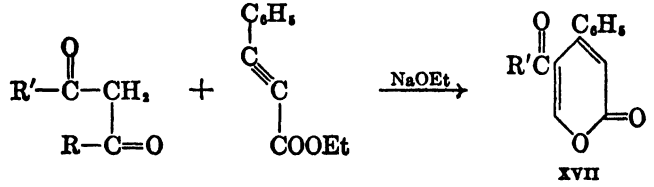
39 Hantzsch, *Ann.*, **222**, 9 (1893).
40 Anschütz, Bendix, and Kerp, *Ann.*, **259**, 154 (1890).
41 Arndt and Eistert, *Ber.*, **58**, 2318 (1925).

of hot alkali is transformed into 1-methylcyclopropene-2,3-dicarboxylic acid (XIII).[35,42] The structure of this acid apparently has been established and is based, among other data, on its cleavage by ozonolysis to acetyl oxaloacetic acid (XIV).[43] Under similar conditions the analogous methyl 3-bromocoumalate (XV) [37] is converted into furan-2,4-dicarboxylic acid (XVI),[44] which proves the position of the bromine atom in XV (cf. p. 136).



XV XVI

Syntheses of Polysubstituted α-Pyrones. Among the reactions leading to substituted α-pyrones, only those possessing a certain general applicability will be discussed here.[45] Ruhemann [46] condensed phenylpropiolic ester with an acylacetic ester or acylacetone in the presence of sodium ethoxide and obtained α-pyrones of the general type (XVII).



XVII

Products of this type are available also by a procedure discovered by Buchner and Schröder,[47] who in a typical experiment condensed benzylideneacetoacetic ester with diazoacetic ester to the pyrazoline ester (XVIII), which when heated lost nitrogen and cyclized to ethyl 4-phenyl-6-methyl coumalate (XIX).

A variation of Ruhemann's procedure is the condensation of an alkyl acylacetylene of the general formula XX with diethyl malonate,[48]

42 Feist, *Ber.*, **26**, 747 (1893).

43 Goss, Ingold, and Thorpe, *J. Chem. Soc.*, **123**, 3342 (1923).

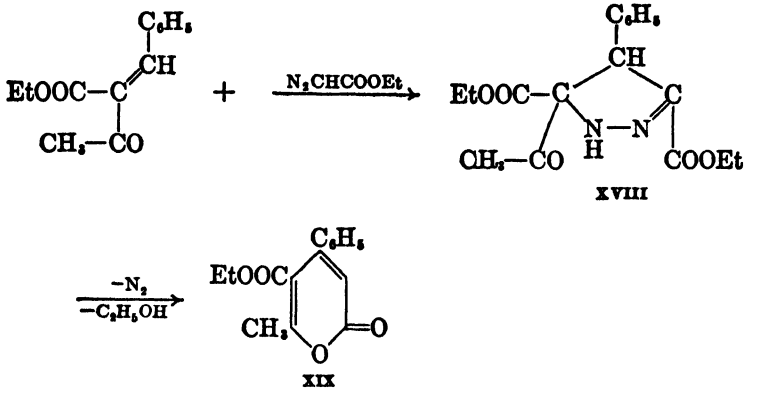
44 Feist, *Ber.*, **34**, 1992 (1901).

45 For a review on α- and γ-pyrones which also includes some reactions of occasional interest, see Cavalieri, *Chem. Revs.*, **41**, 525 (1947).

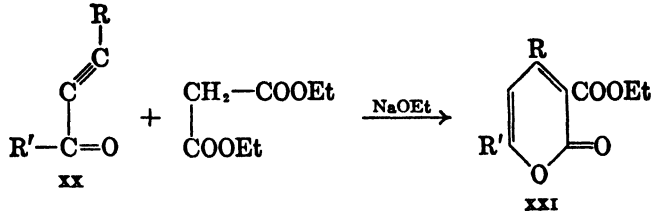
46 Ruhemann, *J. Chem. Soc.*, **75**, 245 (1899).

47 Buchner and Schröder, *Ber.*, **35**, 782 (1902).

48 (*a*) Kohler, *J. Am. Chem. Soc.*, **44**, 379 (1922); (*b*) *ibid.*, **46**, 747 (1924); (*c*) Anker and Cook, *J. Chem. Soc.*, 311 (1945).



which leads to 3-carboxylic acids of α-pyrones (XXI). These acids are characterized by unusual stability of the pyrone ring in alkaline

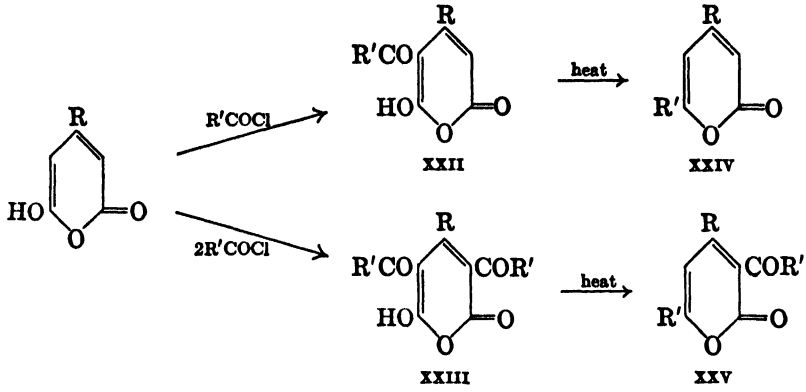


solution under conditions which readily lead to hydrolytic cleavage of the isomeric 5-carboxylic acids. If an alkyl substituent is desired in the 3 position, a substituted cyanoacetic ester may be used in the above condensation reaction. Ring closure and elimination of the nitrile group take place under the alkaline conditions of the Michael condensation, and a 3,4,6-trialkyl-substituted α-pyrone results.[48b]

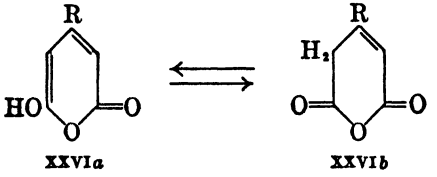
A synthetic method, which should prove to be of general applicability, has been described by Gogte.[49] It is based on the fact that β-substituted glutaconic anhydrides react readily in the presence of pyridine with 1 or 2 moles of an acyl chloride to form the C-acylation products XXII or XXIII. These in turn when heated above their melting points lose carbon dioxide and form the α-pyrone derivatives XXIV and XXV in good yield. The starting materials for the above reaction, the glutaconic anhydrides, have been termed hydroxy anhydrides[50] in view of their tendency to exist as 6-hydroxy-α-pyrones

[49] Gogte, *Proc. Indian Acad. Sci.*, **7A**, 214 (1938); *J. Univ. Bombay*, **8**, Pt. 3, 208 (1939); **9**, Pt. 3, 127 (1940).

[50] Bland and Thorpe, *J. Chem. Soc.*, **101**, 856 (1912).

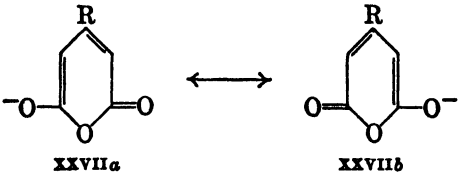


(XXVI*a*) rather than as the tautomeric form (XXVI*b*). They are formed by the action of acetyl chloride on the corresponding acids,



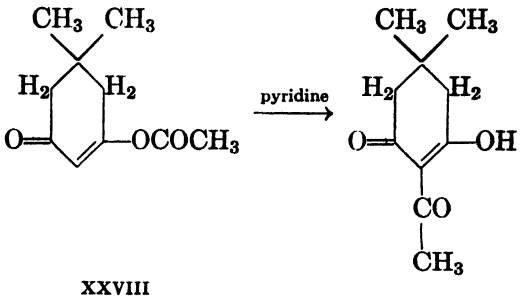
and they exhibit the properties of strong acids. They dissolve in alkali carbonate solutions with effervescence and form stable salts, from which the anhydrides can be recovered unchanged upon acidification of their aqueous solutions. The less water-soluble glutaconic anhydrides can be recrystallized from hot water without decomposition and are hydrolyzed to the parent acids only if heated with excess alkali. As enolic substances, their aqueous solutions produce strong colorations with ferric chloride.

The remarkable tendency of the glutaconic anhydrides to ionize may be ascribed to the fact that, for the ion, the two extreme resonance forms XXVII*a* and XXVII*b* are equivalent and have the same energy.



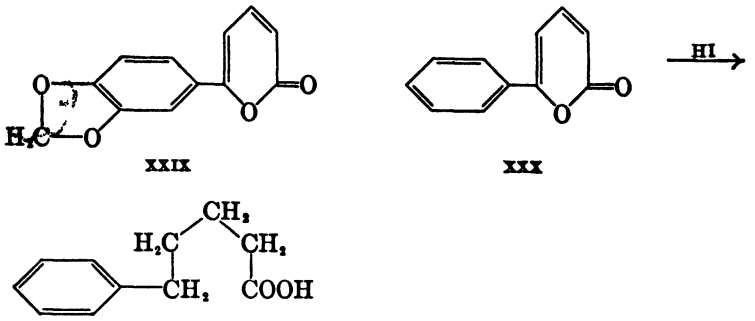
This is an ideal condition for resonance resulting in a stabilization of the symmetrical ionic form. In view of the acidic properties of the glutaconic anhydrides, it appears likely that the acylation reaction described above proceeds via the O-acyl derivatives, which under the

influence of pyridine rearrange into the C-acyl derivatives. This recalls the behavior of the O-acyl derivatives of dimethyldihydroresorcinol (XXVIII), which are rearranged to the C-acyl compounds when warmed with pyridine.[51]



XXVIII

Paracotoin and Phenylcoumalin. In 1879 Jobst and Hesse[52] isolated from coto bark, the bark of an unidentified tree indigenous to Bolivia and Brazil, a substance which they named paracotoin and for which Ciamician and Silber[53] later suggested the structure of 6-piperonylcoumalin (XXIX), on the basis of its transformation by strong alkali into piperonylic acid and acetopiperone and because of the similarity of its properties to those of 4,6-dimethylcoumalin. A closely

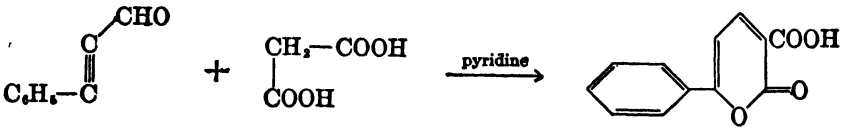


XXIX XXX

related substance was isolated by these authors[53] from the same source, for which the analogous formula (XXX) was proposed on similar grounds. Exact proof for the α-pyrone nature of XXX was presented by Leben,[36] who reduced it to δ-phenyl valeric acid by means of hydroiodic acid and was able to overcome the difficulties previously encountered by Ciamician and Silber in replacing the ring oxygen by nitrogen. The resulting 6-phenylpyridone-2 on zinc dust distillation gave 2-phenylpyridine, the structure of which was established by oxi-

51 Dieckmann and Stein, *Ber.*, **37**, 3370 (1904).
52 Jobst and Hesse, *Ann.*, **199**, 31 (1879).
53 Ciamician and Silber, *Ber.*, **27**, 841 (1894).

dation to picolinic and benzoic acids by acid and neutral permanganate, respectively.[54] The synthesis of phenylcoumalin has been achieved by Kalff[55] by condensation of phenylpropargyl aldehyde with malonic acid in pyridine, followed by decarboxylation of the resulting 6-phenyl-α-pyrone-3-carboxylic acid (XXXI) by boiling it with 50% sulfuric acid.



XXXI

Squill Glycosides and Toad Venoms. A number of physiologically highly active substances possessing the α-pyrone nucleus have been isolated from the poisonous secretions of a variety of toads and from the fleshy bulbs of the white and red squills (*Scilla maritima*). Both the toad venoms and the active principles of the squill form part of a larger group of drugs, which is characterized by a specific action on the heart muscle, and which for that reason comprises a number of valuable therapeutic agents. Scilliroside, the active principle of the red squill, is also a powerful rodenticidal agent.

Chemically, this group of substances consists of the steroid cyclopentanophenanthrene ring system, carrying the α-pyrone ring as a side chain in the 17 position. Whereas the active principles of the squill occur in the plant as glycosides, the toad venoms are found as the free genins or in conjugation with suberylarginine. The elucidation of the structure of the squill glycosides is due to Stoll and his collaborators.[56] Structural studies on the toad venoms have attracted several workers.[57–60] Only the structural studies concerned with the

[54] Chichibabin, *Ber.*, **37**, 1373 (1904).

[55] Kalff, *Rec. trav. chim.*, **46**, 594 (1927).

[56] Stoll et al., Scillaren A: (*a*) *Helv. Chim. Acta*, **16**, 703 (1933); (*b*) *Z. Physiol. Chem.*, **222**, 24 (1933); (*c*) *Helv. Chim. Acta*, **17**, 641 (1934); (*d*) **17**, 1334 (1934); (*e*) **18**, 82 (1935); (*f*) **18**, 401 (1935); (*g*) **18**, 644 (1935); (*h*) **18**, 1247 (1935); (*i*) **24**, 1380 (1941); Scilliroside; (*j*) *ibid.*, **25**, 43, (1942); (*k*) **25**, 377 (1942); (*l*) **26**, 648 (1943).

[57] Wieland et al., (*a*) *Ber.*, **46**, 3315 (1913); (*b*) *Sitzber. math. naturw. Abt. bayer. Akad. Wiss. München*, **1920**, 329; (*c*) *Ber.*, **55**, 1789 (1922); (*d*) *Ann.*, **481**, 215 (1930); (*e*) **493**, 272 (1932); (*f*) **517**, 22 (1935); (*g*) **524**, 203 (1936).

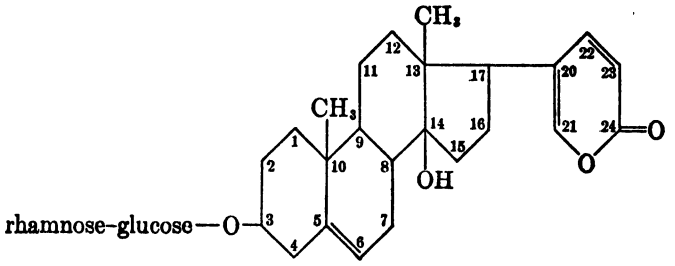
[58] Kotake et al., *Ann.*, **465**, 1, 11 (1928); *Sci. Papers Inst. Phys. Chem. Research Tokyo*, **9**, 233 (1928); **24**, 39 (1934); **32**, 1, 79 (1937); **34**, 824 (1938); **35**, 419 (1939); **36**, 106 (1939).

[59] Kondo et al., *J. Pharm. Soc. Japan*, **53**, 1, 62 (1933); **54**, 22 (1934); **55**, 49, 144 (1935); **58**, 15, 102, 282, 235 (1938); **59**, 186 (1939).

[60] Tschesche and Offe, *Ber.*, **68**, 1998 (1935); **69**, 2361 (1936).

α-pyrone ring, its reactions, and its properties will be described here. For a discussion of the steroid portion, the reader is referred to reviews on that subject.[61,62]

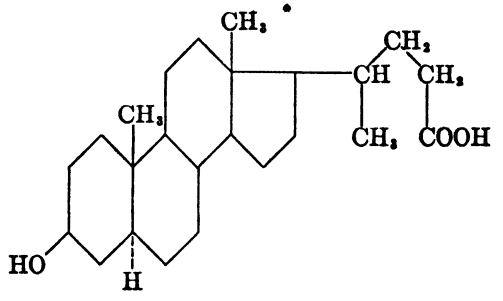
One of the most illuminating series of reactions dealing with the structure of scillaren A (XXXII), the crystalline active principle of the white squill, is its conversion by catalytic hydrogenation into a



XXXII

scillaren A

3 steps



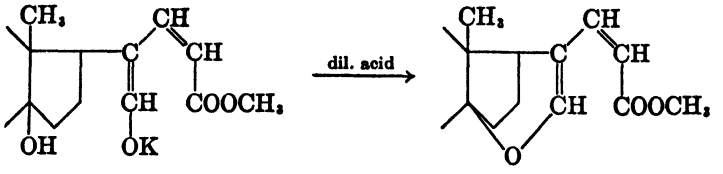
XXXIII

hexahydrodesoxy acid, which after removal of the sugar moieties and the tertiary hydroxyl group in the 14 position by means of methanolic hydrogen chloride followed by catalytic hydrogenation of the resulting anhydro compound, yielded the known 3(β)-hydroxyallocholanic acid (XXXIII).[56i] This sequence of reactions not only demonstrated the presence of the steroid nucleus and the arrangement of the carbon atoms of the side chain in scillaren A but also suggested that this side chain was present as an unsaturated lactone ring (see p. 185). When scil-

61 Strain, "The Steroids," *Organic Chemistry*, edited by Gilman, John Wiley & Sons, New York, 1943.

62 Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed. Reinhold, 1949.

laren A is treated with methanolic potassium hydroxide, the lactone ring is opened and the methyl ester potassium salt of scillarenic acid (XXXIV) is formed, which on treatment with dilute acid forms the methyl ester of isoscillarenic acid (XXXV) by ring closure of the

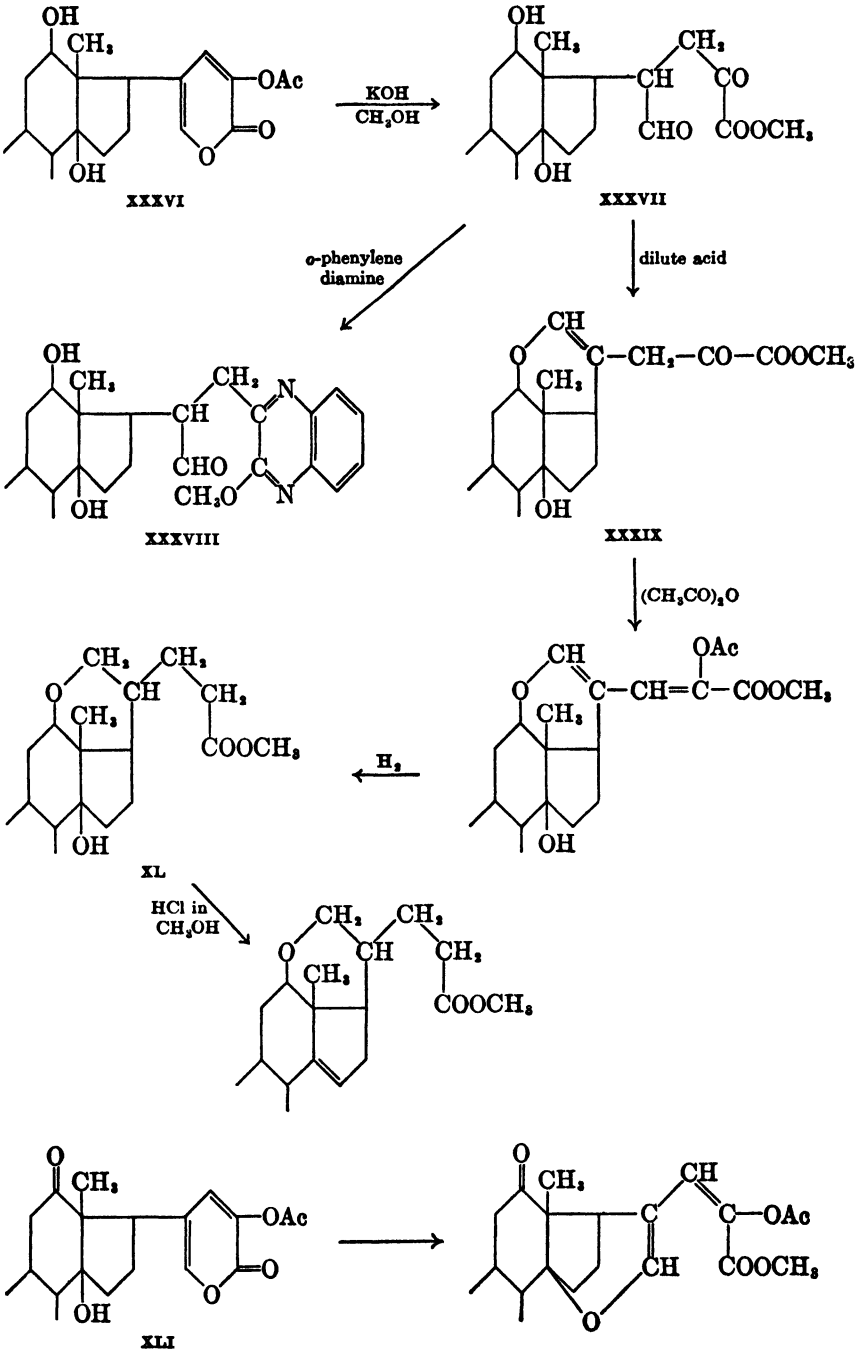


XXXIV XXXV

enolic hydroxyl group of the side chain with the tertiary hydroxyl group at C 14. The formation of an enolic substance upon saponification of scillaren A is best explained by the assumption of a doubly unsaturated lactone ring in that substance. The identity of the absorption spectra of scillaren A with those of simple alkyl-substituted α-pyrones [56f,31] is in harmony with the α-pyrone structure (XXXII). On the basis of similar evidence, Wieland and Hesse [57] and Tschesche and Offe [60] concluded that the α-pyrone ring was present in bufotalin, the venom isolated from the parotid glands of *Bufa vulgaris* and in cinobufagin from Chan Su, the dried secretions of a Chinese toad.

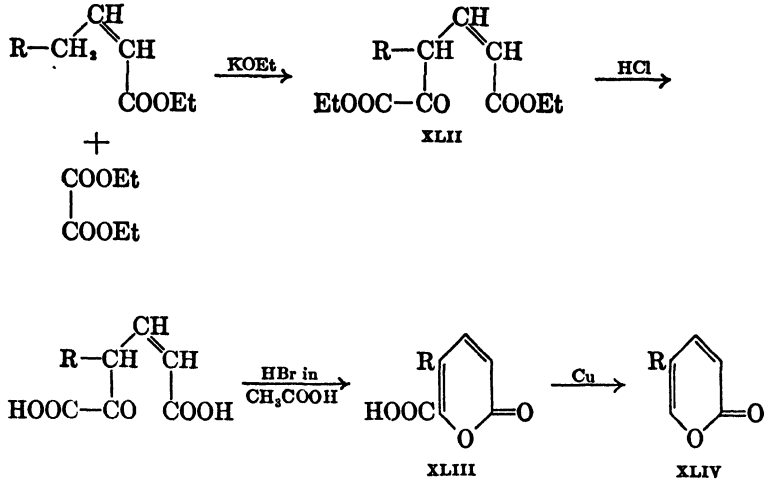
In contrast to the active substances described above, in which the α-pyrone ring contains but one substituent in the 5 position, scilliroside (XXXVI), the active principle of the red squill, contains in addition an acetoxy group. The location of this group in the 3 position of the α-pyrone ring was proved in the following manner.[56j-l] On treatment with methanolic potassium hydroxide, scilliroside yielded acetic acid and an α-keto ester (XXXVII), which upon reaction with *o*-phenylenediamine gave a quinoxaline derivative (XXXVIII), and, after saponification of the ester group, yielded 1 mole of carbon dioxide upon oxidation with hydrogen peroxide.

Treatment of XXXVII with dilute acid led to XXXIX in which formation of an oxide ring had taken place, involving the secondary hydroxyl group attached to C 12 rather than the tertiary hydroxyl group at C 14. That this latter group had not entered into ring formation followed from its ready elimination by dehydration of XL, which was derived from the oxide (XXXIX) by acetylation and subsequent hydrogenation. If the secondary hydroxyl group at C 12 is not available for oxide formation as in tetraacetyldehydroscilliroside (XLI), cyclization takes place in the conventional manner involving C 14.



XXXVI XXXVII XXXVIII XXXIX XL XLI

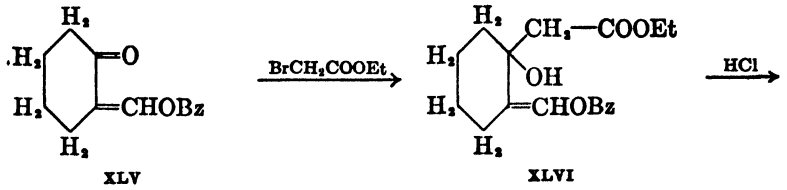
The interest in this group of physiologically active substances has prompted several investigators to take up the question of the synthesis of 5-substituted α-pyrones, in the hope of preparing such derivatives for pharmacological study. Fried and Elderfield,[31] utilizing a condensation reaction discovered by Lapworth,[63] prepared 5-methyl- and 5-ethyl-α-pyrones (XLIV) by condensing ethyl $\Delta^{\alpha,\beta}$-pentenoate and ethyl $\Delta^{\alpha,\beta}$-hexenoate with ethyl oxalate in the presence of potassium ethoxide. The resulting esters (XLII) on acid hydrolysis yielded the corresponding acids, which were cyclized to the pyrone acids (XLIII)



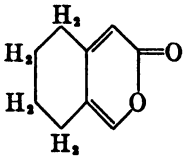
by heating them in sealed tubes with hydrogen bromide in glacial acetic acid. Decarboxylation of the pyrone acids proceeded smoothly when heated with copper powder above their melting points. Attempts to prepare 5-cyclohexyl-α-pyrone [64] by this procedure were unsuccessful since γ-cyclohexylcrotonic ester yielded the α-oxalyl derivative instead of the required γ-substitution product.

A synthesis leading to 4,5-disubstituted α-pyrones has been reported by Plattner, Treadwell, and Scholz,[65] who subjected α-benzoxymethylenecyclohexanone (XLV) to a Reformatsky reaction with ethyl bromoacetate and converted the resulting hydroxy ester (XLVI) into the α-pyrone derivative XLVII by dehydration and simultaneous ring closure with hydrochloric acid.

[63] Lapworth, *J. Chem. Soc.*, **79**, 1265 (1901).
[64] Blout, Fried, and Elderfield, *J. Org. Chem.*, **8**, 37 (1943).
[65] Plattner, Treadwell, and Scholz, *Helv. Chim. Acta*, **28**, 771 (1945).

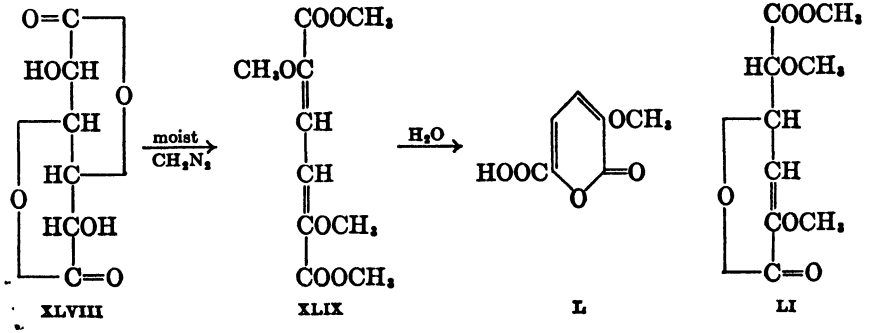


XLV XLVI



XLVII

α-Pyrones from Sugars and Sugar Acids. The dehydration of sugars and sugar acids by heat or strong acids leads mainly to furan derivatives (cf. p. 121). The formation of α-pyrones from carbohydrates has been observed in few instances only and appears to depend greatly on the stereo configuration of the substance undergoing dehydration and on rather specialized reaction conditions. Characteristic of this type of reaction is the conversion of mannosaccharic acid dilactone (XLVIII) by moist diazomethane into 2,5-dimethoxymuconic acid (XLIX) which lactonizes when boiled with water to yield



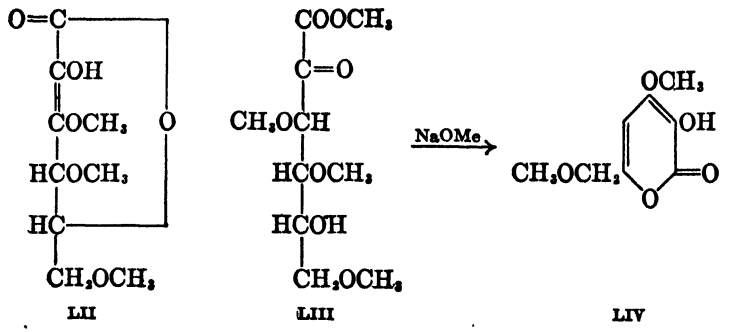
XLVIII XLIX L LI

3-methoxy-α-pyrone-6-carboxylic acid (L).[66] The influence of the stereo configuration on the course of this reaction is obvious, since the isomeric saccharic acid dilactone forms the mono-unsaturated ester LI.[67]

Attempts to prepare the ascorbic acid analog (LII) from 3,4,6-trimethyl-2-ketogluconic acid methyl ester (LIII) by means of sodium

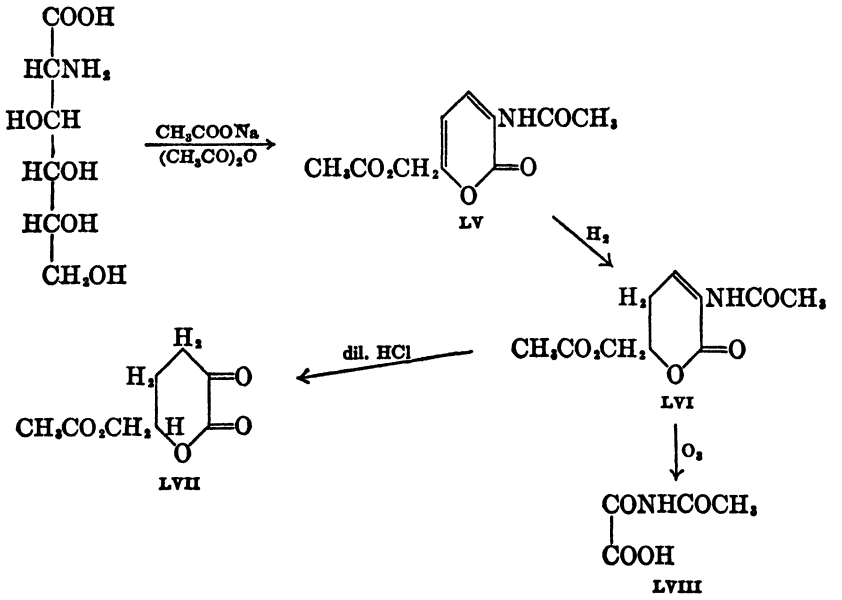
[66] Schmidt and Kraft, *Ber.*, **74**, 33 (1941).
[67] Schmidt, Zeiser, and Dippold, *Ber.*, **70**, 2402 (1937).

methoxide resulted instead in the formation of 3-hydroxy-4-methoxy-6-methoxymethyl-α-pyrone (LIV) by elimination of methyl alcohol



between carbon atoms 4 and 5 of LII.[68] The pyrone nature of this substance was inferred from the formation of glyoxylic acid upon ozonization and from absorption spectra measurements.

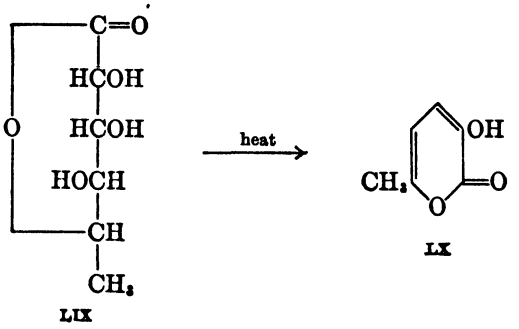
On treatment of glucosaminic acid with acetic anhydride and sodium acetate under normal acetylation conditions, Neuberg[69] obtained a neutral, optically inactive product, which was recognized by Bergmann, Zervas, and Silberkweit[70] as 3-acetamido-6-acetoxymethyl-α-pyrone (LV). On catalytic hydrogenation the substance absorbed



68 Haworth, Hirst, and Jones, *J. Chem. Soc.*, 710 (1938).
69 Neuberg, *Ber.*, **35**, 4014 (1902).
70 Bergmann, Zervas, and Silberkweit, *Ber.*, **64**, 2428 (1931).

2 moles of hydrogen, and two isomeric lactones were formed. The absorption of the second mole of hydrogen was found to be sluggish, and it was possible to isolate the $\Delta^{3,4}$-dihydropyrone derivative (LVI), the structure of which follows from its conversion by dilute acid into the α-ketolactone (LVII) and from the isolation of N-oxalyl acetamide (LVIII) following ozonolysis. It is interesting to note that the O-acetyl group in LV is readily exchanged for chlorine by cold concentrated hydrochloric acid.

6-Methyl-3-hydroxy-α-pyrone (LX) has been prepared in about 30% yield by Votoček and Malachta [71] by dry distillation of rhamnonolactone (LIX) and of other 6-desoxyhexonolactones. Similarly,



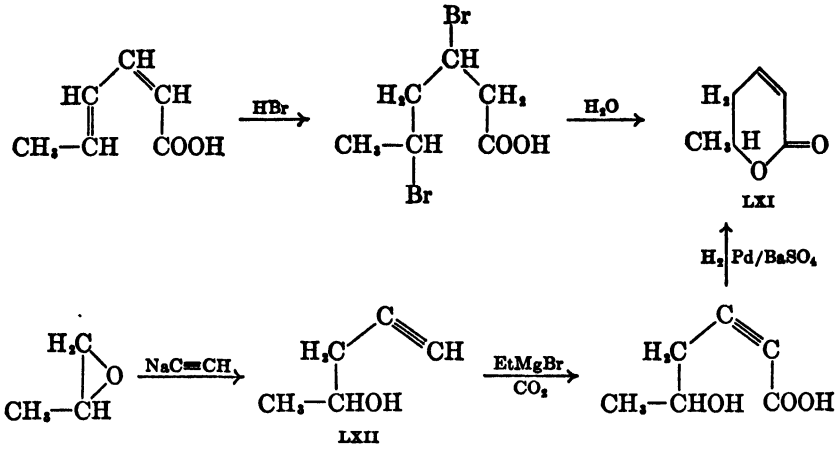
LIX LX

arabonolactone was dehydrated to 3-hydroxy-α-pyrone (isopyromucic acid).[72] Both LX and isopyromucic acid give strong colorations with ferric chloride, indicating that they exist largely in the enolic forms.

Parasorbic Acid. The *d* form of this substance has long been known to occur in the red berries of the mountain ash.[73] Since the discovery of its function as a differential cell growth inhibitor,[74,75] its chemistry has been reinvestigated and it has been shown to possess the structure of 6-methyl-Δ^3-dihydro-α-pyrone.[76] Two practical syntheses have been described which lead, of course, to the *dl* form. Kuhn and Jerchel [76] obtained an over-all yield of 25%, starting from sorbic acid and proceeding via 3,5-dibromocaproic acid, and more recently Haynes and Jones [77] obtained an over-all yield of 33% by condensation of propylene oxide with sodium acetylide in liquid ammonia, followed by

71 Votoček and Malachta, *Collection Czechoslov. Chem. Communs.*, **8**, 66 (1936).
72 Chavanne, *Ann. chim. phys.*, [8] **3**, 507 (1904).
73 Hofmann, *Ann.*, **110**, 129 (1859).
74 Medawar, Robinson, and Robinson, *Nature*, **151**, 195 (1943).
75 Kuhn et al., *Naturwiss.*, **31**, 468 (1943).
76 Kuhn and Jerchel, *Ber.*, **76**, 413 (1943).
77 Haynes and Jones, *Nature*, **155**, 780 (1945).

carbonation of the magnesium bromide salt of the resulting acetylene derivative (LXII), and finally catalytic reduction to LXI (cf. p. 187).



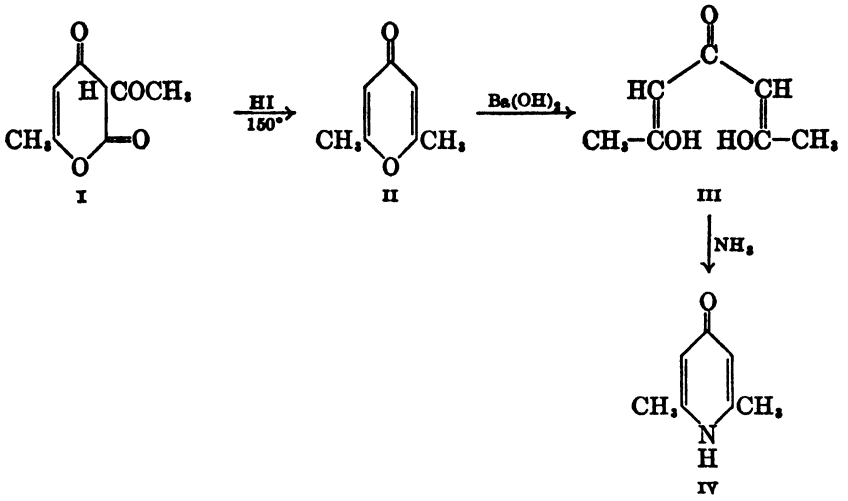
γ-PYRONES

Structure of γ-Pyrones. The problem of the "fine structure" of the γ-pyrone nucleus arose when it was discovered early in the twentieth century that the conventional formulas established on the basis of degradation and synthesis were unable to account for all the properties of γ-pyrones. This question has since attracted many prominent workers in the field of structural chemistry who have advanced numerous formulas to explain the unusual behavior of γ-pyrones. A short historical outline may lead to a better appreciation of the problem and the solution offered by modern theory.

The substance which has been most widely studied in connection with structural problems is 2,6-dimethyl-γ-pyrone. It was discovered by Feist,[78] who prepared it from dehydracetic acid (I) by treatment with hot mineral acid and assigned to it structure II, mainly on the basis of its conversion via the crystalline diacetylacetone (III) into 2,6-dimethyl-4-pyridone (IV). Concerning the properties of II, Feist remarked that it did not form a phenylhydrazone and that its double bonds were not reduced by zinc and glacial acetic acid, observations which have since been confirmed with a number of γ-pyrones. He also noted that its aqueous solution is neutral. It was surprising, therefore, when Collie and Tickle [79] were able to isolate well-defined, crystalline addition products of dimethyl-γ-pyrone with a large number

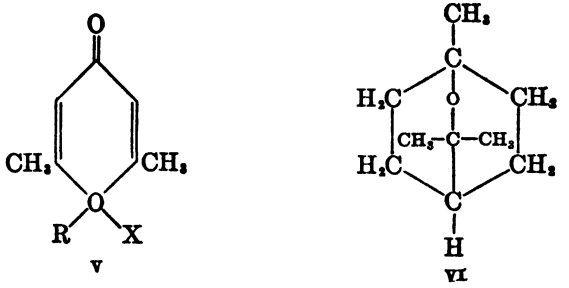
[78] Feist, *Ann.*, **257**, 253 (1890).

[79] Collie and Tickle, *J. Chem. Soc.*, **75**, 710 (1899).



I II III IV

of inorganic and organic acids, in which 1 mole of the pyrone was combined with 1 equivalent of the acid. The authors assumed these adducts to be true salts [80] and formulated them as oxonium salts (V, R = H) in analogy to the salts of γ-pyridone. The concept of tetravalent oxygen was new at the time, but enough examples could be cited from the literature in which it was necessary to assume that the oxygen was tetravalent, such as the hydrochloride of dimethyl ether which Friedel had described [81] and the hydrochloride and hydrobromide of cineol (VI).[82] Baeyer and Villiger [83] reasoned that if the



V VI

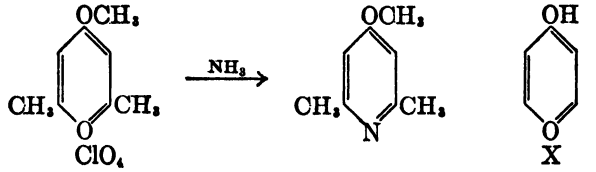
80 The fact that in these addition products the ions pyrone-H^+ and Cl^- are present was proved by Roerdam [*J. Am. Chem. Soc.*, **37**, 557 (1915)], who compared the conductivities of an aqueous solution of dimethylpyrone hydrochloride with that of aqueous hydrochloric acid having an equal concentration of Cl^-. The solution containing the less mobile pyrylium ion has a smaller conductivity and approaches that of hydrochloric acid at infinite dilution (complete hydrolysis). The K_B for 2,6-dimethylpyrone was calculated from these data to be 1.9×10^{-14}.

81 Friedel, *Bull. soc. chim. France*, [2] **24**, 166, 241 (1875).

82 Wallach, *Ann.*, **246**, 281 (1888).

83 Baeyer and Villiger, *Ber.*, **34**, 2679 (1901).

ring oxygen in dimethylpyrone was basic enough it might be methylated by dimethyl sulfate in the way that dialkyl sulfides are alkylated to sulfonium salts. The methylation of dimethylpyrone resulted in a yellow syrup from which Kehrmann and Duttenhoefer [84] later succeeded in isolating a crystalline iodide of the composition $C_8H_{11}O_2I$, which undoubtedly represented a methiodide of 2,6-dimethylpyrone. They considered its existence proof that the ring oxygen in pyrones had basic properties and formulated the salt according to V(R = CH_3). This view became untenable, however, when Baeyer [85] succeeded in isolating 2,6-dimethyl-4-methoxypyridine (VIII) from the reaction of the crystalline methoperchlorate of dimethylpyrone with ammonium carbonate. He proposed the benzene-like structure VII for the metho-



VII VIII IX

perchlorate and favored an analogous structure (IX) for γ-pyrone salts in general.[86] A structure (X) patterned after the Baeyer-Armstrong formula for benzene and having essentially the same meaning as formula IX had been suggested by Werner [87] as a result of his experiences with xanthylium and chromylium salts. Hantzsch [88] measured the ultraviolet absorption spectra of dimethylpyrone in alcohol and in concentrated sulfuric acid, and of 2,6-dimethyl-4-methoxypyrylium perchlorate, and found that the three absorption curves were similar with the exception that the γ-pyrone base showed the characteristic ketone absorption band of low intensity at 280 mμ. He there-

84 Kehrmann and Duttenhoefer, *Ber.*, **39**, 1299 (1906).

85 Baeyer, *Ber.*, **43**, 2338 (1910).

86 Baeyer introduced the terms pyroxonium and pyrothionium chloride for the hypothetical salt:  and its sulfur isolog. Decker and Fellenberg [*Ann.*, **356**, 286 (1907)] had previously used the terms pyrylium and thiopyrylium chloride for the same ring system. In view of the widespread use of this latter nomenclature in connection with the anthocyanins and other substances, it will be used here. VII is therefore 2,6-dimethyl-4-methoxypyrylium perchlorate.

87 Werner, *Ber.*, **34**, 3309 (1901).

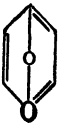
88 Hantzsch, *Ber.*, **52**, 1535 (1919).

fore accepted Baeyer's concept of a benzene-like structure for the salts and the conventional unsaturated ketone structure for the base.

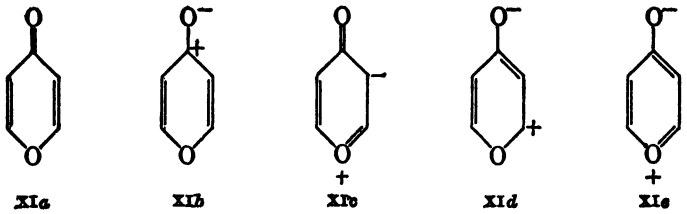
X

Arndt and co-workers [89] were the first to consider the structure of γ-pyrones from the point of view of the electronic theory and in the light of the concepts of quantum mechanics. They explained the lack of reactivity of the carbonyl group and of the double bonds by assuming interaction between the unshared electrons of the ring oxygen and those of the carbon-oxygen double bond through the two nuclear double bonds. The tendency of the carbonyl group to form the dipole $>C^+—O^-$ initiates a shift of the electrons of the nuclear double bonds towards the γ-carbon atom, which in turn causes the ring oxygen to share one of its lone electron pairs with an α-carbon atom. The dipole formula XI*e* [90] picturing this electronic shift expresses the failure of γ-pyrones to behave as unsaturated ketones and likewise explains the tendency of the carbonyl oxygen to bind protons and other electrophilic groups. According to Arndt, the displacement of electrons does not occur to the extent pictured in formula XI*e*. Instead, the electrons occupy levels between those indicated by formula XI*e* and the conventional γ-pyrone formula (XI*a*), the actual "intermediate" state of the molecule depending on the character of the substituents attached to the nucleus. The same idea is expressed in more precise form by stating that the molecule resonates [91] among the structures XI*a*–XI*e* (and symmetrical structures) and that its stability is greater than that

89 Arndt et al., *Ber.*, (*a*) **57**, 1903 (1924); (*b*) **58**, 1640 (1925); (*c*) **63**, 3121 (1930).

90 Collie [*J. Chem. Soc.*, **85**, 971 (1904); **95**, 144 (1909)] had previously proposed the betaine-like structure  in order to account for the non-reactivity of γ-pyrones towards carbonyl reagents and reducing agents. The two poles of the dipole are connected by a bond according to the general usage of that time.

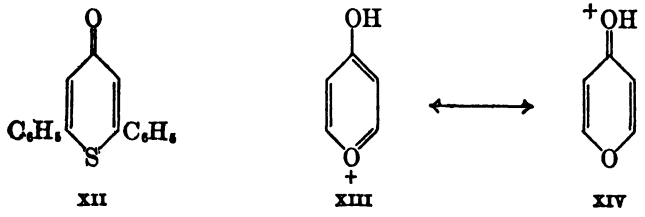
91 Pauling, *Fortschritte der Chemie Organischer Naturstoffe*, **III**, 219 (1939).



XIa XIb XIc XId XIe

indicated by any of the individual formulas. The extent to which the pyrone nucleus is stabilized, that is, its resonance energy, has been determined for 2,6-diphenyl-1,4-thiapyrone (XII) and found to be 32.7 kcal./mole.[92] Measurements of the dipole moments [92b,93] of a number of pyrones and thiapyrones indicate that the diolefin ketone structure (XI*a*) makes the most significant contribution to the normal state of the pyrone molecule. Thus, 2,6-dimethylpyrone possesses a moment of 4.05 *D*, which is closer to that calculated for structure XI*a* (1.75 *D*) than to that calculated for the extreme dipole structure XI*e* (22 *D*). This is to be expected since dipole structures, even though otherwise favored, become increasingly unstable the further their charges are separated.

The separation of charges which reduces the probability of structures XI*b*–XI*e* for the pyrone bases is no longer present in their salts, since the addition of a proton to any of these resonance forms neutralizes their negative charges and produces non-dipole cationic structures



XII XIII XIV

(XIII), which are in resonance with structure XIV. The increased importance of the phenol-like structure (XIII) for the salts of γ-pyrones follows from a comparison of the Raman spectra [94] of dimethyl-

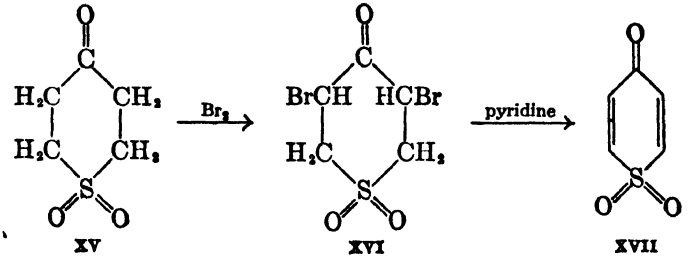
92 (*a*) Lorenz and Sternitzke, *Z. Elektrochem.*, **40**, 501 (1934); (*b*) Arndt, Martin, and Partington, *J. Chem. Soc.*, 602 (1935); (*c*) Eistert, *Tautomerie und Mesomerie*, Ferdinand Enke, Stuttgart, 1938, p. 64.

93 (*a*) Hunter and Partington, *J. Chem. Soc.*, 87 (1933); (*b*) Rau, *Proc. Indian Acad. Sci.*, **A4**, 687 (1936); (*c*) Le Fèvre and Le Fèvre, *J. Chem. Soc.*, 1088 (1937); (*d*) Wassiliew and Syrkin, *Acta Physicochim. U.R.S.S.*, **6**, 639 (1937).

94 (*a*) Wolkenstein and Syrkin, *Acta Physicochim. U.R.S.S.*, **10**, 677 (1939); (*b*) Kahovec and Kohlrausch, *Ber.*, **75**, 627 (1942).

pyrone and its hydrochloride, in which the latter not only displays the expected shift of the carbonyl band but also shows a lowering of the C=C frequency, indicating a change in the character of the ring system as a whole in the direction of the aromatic structure (XIII).

Purely chemical evidence to show that resonance within the γ-pyrone nucleus involves the unshared electrons of the hetero atom has been adduced by Arndt and Bekir,[95] who synthesized 1,4-thiapyrone and tested its behavior towards oxidizing agents. Whereas the action of hydrogen peroxide in glacial acetic acid on tetrahydro-1,4-thiapyrone readily yielded the sulfone (XV), no oxidation took place with 1,4-thiapyrone under identical conditions. More rigorous treatment led to the destruction of the thiapyrone nucleus. The desired sulfone

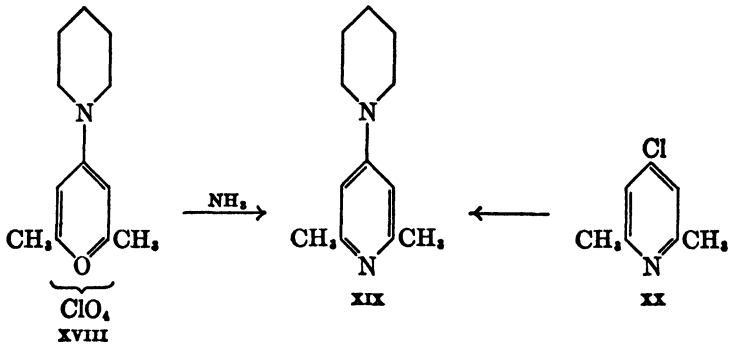


XV XVI XVII

(XVII) was obtained by bromination (XVI) and subsequent dehydrobromination of its tetrahydro derivative, and it exhibited the properties characteristic of doubly unsaturated ketones. In the sulfone (XVII), the two unshared electron pairs of the sulfur are occupied and cannot participate in the pyrone resonance, with a resulting loss of the aromatic character of the nucleus.

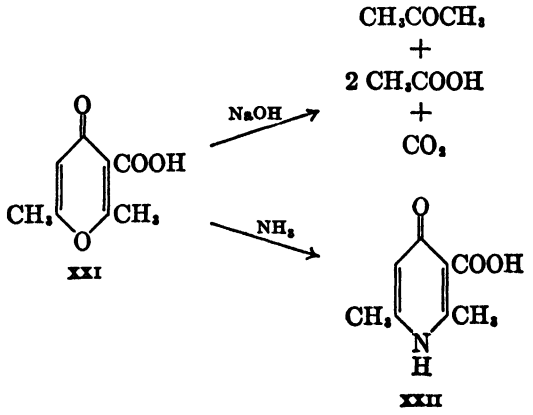
The need of expressing the properties of γ-pyrone and its salts by a group of formulas holds true also for 2,6-dimethyl-4-methoxypyrylium perchlorate. Thus, from Baeyer's formula (VII) for that salt, it would be expected that the methoxyl group has the stability of an aromatic ether group. This, however, is not true, as was shown by the ready exchange of that group for ethoxyl during recrystallization of the salt from ethyl alcohol [96] and by its replacement by primary and secondary amines. Thus, the action of piperidine on VII produced 4-(N-piperidyl)-2,6-dimethylpyrylium perchlorate,[96] which was shown to have structure XVIII by its conversion into the pyridine derivative (XIX), obtained also by synthesis from 2,6-dimethyl-4-

[95] Arndt and Bekir, *Ber.*, **63**, 2393 (1930).
[96] Anker and Cook, *J. Chem. Soc.*, 117 (1946).



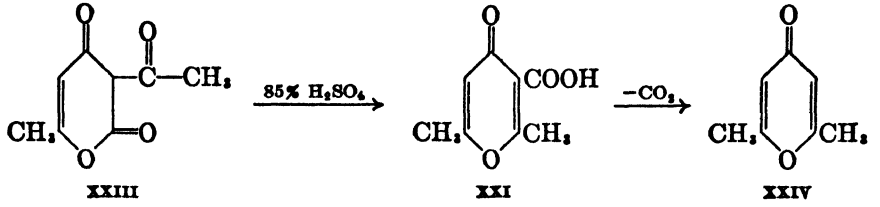
chloropyridine (XX) and piperidine. In these reactions, the pyrone nucleus reacts in the form of structure XI*b*, the ethoxyl group or the amine being attracted by the residual positive charge at position 4.

Dehydracetic Acid. One of the best-explored derivatives of γ-pyrone is dehydracetic acid, $C_7H_6O_4$, which was discovered by Geuther in 1866[97] among the products of pyrolysis of acetoacetic ester. Its preparation was improved by Oppenheim and Precht,[98] and, as a result of a study of its constitution by Haitinger[99] and Perkin,[100] formula XXI was proposed mainly because of its cleavage in alkaline medium into acetone, acetic acid, and carbon dioxide and because of the formation of a lutidone carboxylic acid by the action of ammonia, the structure of which was assumed to be XXII. It was soon recognized, however, that the low acidity of dehydracetic acid was not in

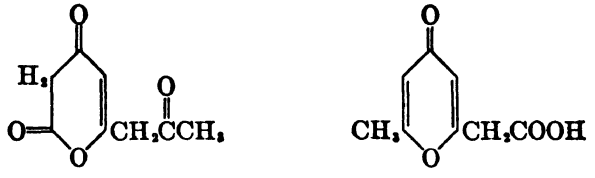


97 Geuther, *Chem. Zentr.*, **11**, 801 (1866).
98 Oppenheim and Precht, *Ber.*, **9**, 324 (1876).
99 Haitinger, *Monatsh.*, **6**, 103 (1885).
100 Perkin, *J. Chem. Soc.*, **51**, 484 (1887).

line with formula XXI. Feist [78] succeeded in preparing the carboxylic acid of that formula by isomerization of dehydracetic acid and proposed formula XXIII for dehydracetic acid. In contrast to dehydracetic acid, the isomeric acid (XXI) readily lost carbon dioxide when heated and formed 2,6-dimethylpyrone (XXIV). Soon after, Collie [101] proposed the alternative formulas XXV and XXVI for dehydracetic



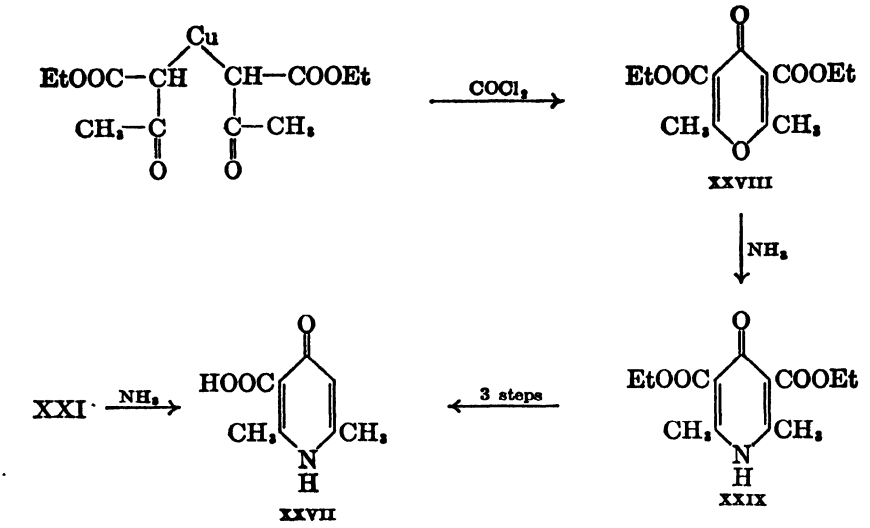
XXIII XXI XXIV



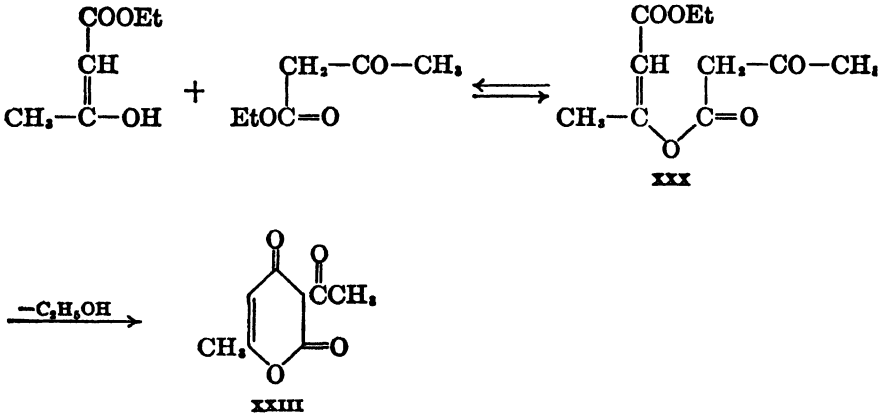
XXV XXVI

acid and Feist's carboxylic acid (XXI), respectively. These structures were likewise capable of explaining all the reactions known at the time. In the ensuing discussion concerning the merits of the two formulas for dehydracetic acid, Feist's formula (XXIII) was generally favored, but it was not until 1924 that Rassweiler and Adams [102] proved its correctness. These authors reasoned that, if structure XXI could be proved for the isomeric carboxylic acid, dehydracetic acid would have to possess Feist's formula (XXIII). This was indeed shown to be so by conversion of the carboxylic acid into a pyridone acid, the structure of which was proved by synthesis to be that of 2,6-dimethyl-γ-pyridone-3-carboxylic acid (XXVII). For the synthesis of XXVII, ethyl 2,6-dimethyl-γ-pyridone-3,5-dicarboxylate (XXIX) was prepared by condensation of copper acetoacetic ester with phosgene,[103] followed by treatment of the resulting γ-pyrone ester (XXVIII) with ammonia. XXIX on selective saponification followed by decarboxylation yielded the ethyl ester of XXVII, which was readily saponified to the desired acid.

101 Collie, *J. Chem. Soc.*, **59**, 179 (1891).
102 Rassweiler and Adams, *J. Am. Chem. Soc.*, **46**, 2758 (1924).
103 Conrad and Guthzeit, *Ber.*, **20**, 155 (1887).

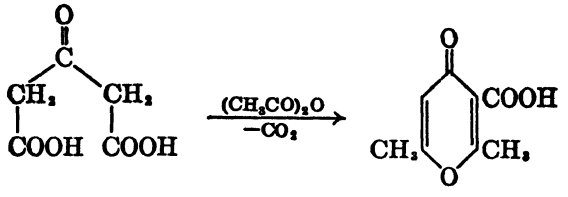


Dehydracetic acid is of importance in synthetic work, and a simple procedure for its preparation in good yield is desirable. The best method [104] is the self-condensation of acetoacetic ester in the presence of a small amount of sodium bicarbonate,[105] which, according to Arndt and Nachtwey,[104,105] proceeds by elimination of one molecule of ethyl alcohol between two molecules of ethyl acetoacetate, followed by a base-catalyzed internal Claisen condensation of the primary product (XXX). The first step is reversible and requires the continuous removal of the ethanol formed. This synthesis makes available dehy-



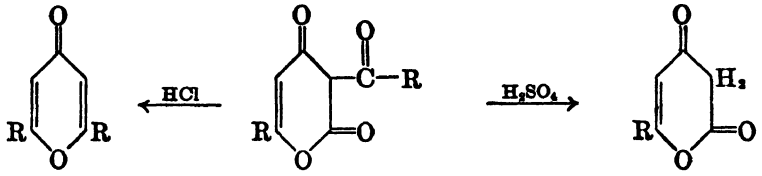
104 Arndt and Nachtwey, *Ber.*, **57**, 1489 (1924).
105 Arndt et al., *Ber.*, **69**, 2373 (1936).

dracetic acids of the general type (XXXI) from the appropriate acylacetic esters $RCOCH_2COOEt$. Before the development of the above method by Arndt et al., dehydracetic acid and dimethylpyrone were usually prepared by v. Pechmann's method,[106] in which acetonedicarboxylic acid was condensed with acetic anhydride in the presence of sulfuric acid to 2,6-dimethyl-γ-pyrone 3-carboxylic acid and the latter was rearranged to dehydracetic acid.



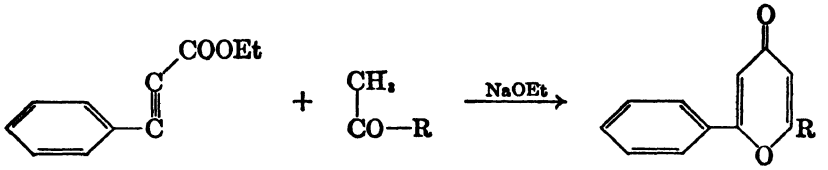
XXI

Dehydracetic acids are rearranged and decarboxylated to the symmetrical 2,6-dialkyl- and 2,6-diaryl-γ-pyrones (XXXII) when boiled with concentrated hydrochloric acid.[105,107] The action of 90% sulfuric acid leads to the so-called pyrononones (XXXIII).[105,107]



XXXII XXXI XXXIII

Syntheses and Properties of Alkyl- and Aryl-Substituted γ-Pyrones. In addition to the procedures outlined in the previous paragraphs, 2,6-disubstituted pyrones have been synthesized by various other methods. Ruhemann [108] prepared 2-phenyl-6-alkylpyrones (XXXIV) by con-



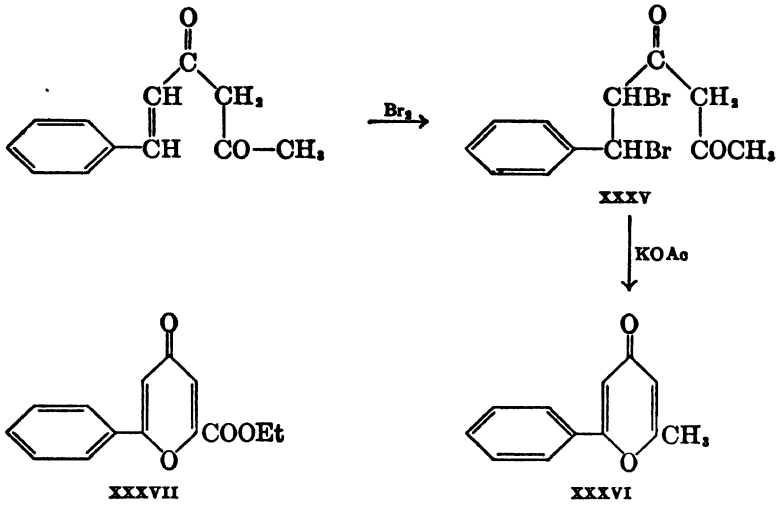
XXXIV

106 v. Pechmann, *Ber.*, **24**, 3600 (1891); *Ann.*, **273**, 194 (1893); Willstätter and Pfannenstiehl, *Ann.*, **422**, 7 (1920).

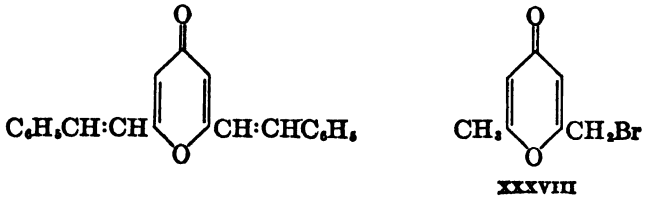
107 Collie, *J. Chem. Soc.*, **59**, 607, 617 (1891); Deshapande, *J. Indian Chem. Soc.*, **9**, 303 (1932); Schöttle and Petrenko-Kritschenko, *Ber.*, **45**, 3230 (1912).

108 Ruhemann, *J. Chem. Soc.*, **93**, 431 (1908); Barger and Starling, *ibid.*, **107**, 418 (1915).

densation of phenylpropiolic ester with ketones of the general formula CH_3COR in the presence of sodium ethoxide, whereas Borsche and Peter [109] obtained such derivatives by a procedure for which the following steps are typical: cinnamoylacetone was converted to the dibromo derivative (XXXV), which when warmed with potassium acetate in alcohol yielded 2-phenyl-6-methyl-γ-pyrone (XXXVI). The use of ethyl cinnamoylpyruvate in this reaction led to the γ-pyrone ester (XXXVII), which, after hydrolysis and decarboxylation, gave 2-phenyl-γ-pyrone.



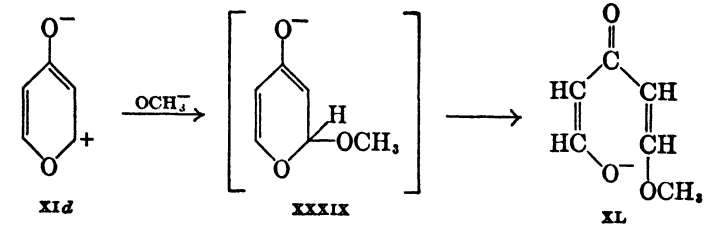
Methyl groups located in the 2 or 6 positions of the pyrone nucleus are activated and condense readily with aromatic aldehydes.[110] Bromination of 2,6-dimethyl-γ-pyrone with N-bromosuccinimide [111] leads to the monobromo derivative (XXXVIII).

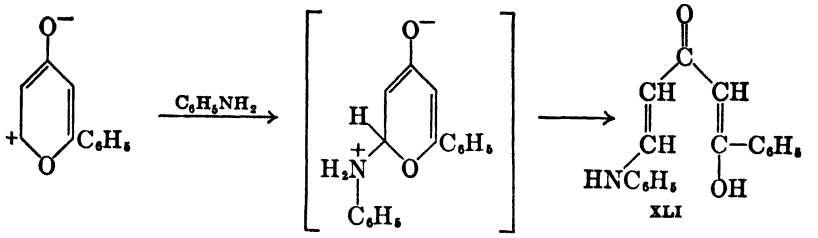


109 Borsche and Peter, *Ann.*, **453**, 148 (1927).
110 Boon, McKenzie, and Trotter, *Proc. Chem. Soc.*, **30**, 206 (1914).
111 Buu-Hoï and Lecocq, *Compt. rend.*, **222**, 1441 (1946).

The tendency of γ-pyrones to form salts has already been discussed (p. 370). In addition to the simple salts, double salts with zinc chloride,[112] mercuric chloride,[113] and others have been prepared. The basic strength of a number of substituted γ-pyrones has been determined [114] and found to decrease in the following order: 2,6-dimethylpyrone > 2-phenyl-6-methylpyrone > 2,6-diphenylpyrone. The dipole moments of these substances decrease in the same order (p. 374).

In contrast to their stability in acid media, γ-pyrones are very susceptible to alkaline reagents. In its reactions with bases, the pyrone nucleus reacts according to formula XI*d* (p. 374). Thus, the action of methoxide ion on γ-pyrone leads presumably to the intermediate anion (XXXIX) in which the pyrone resonance is disrupted. XL results from XXXIX by a shift of the negative charge from the carbonyl to the ring oxygen. The reaction of 2-phenyl-γ-pyrone with aniline acetate follows a similar pattern.[105,109]

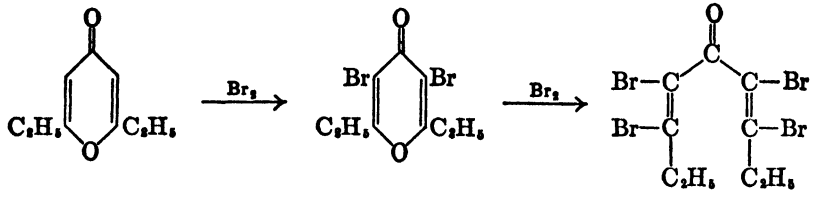




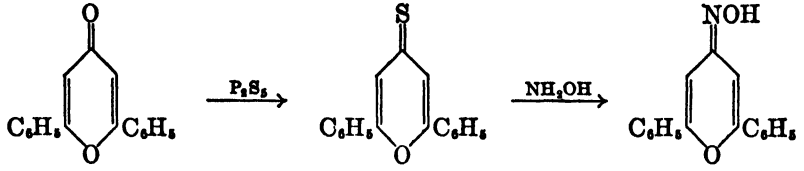
The aromatic character of the γ-pyrones is evident from their behavior towards bromine.[115] In the presence of ferric chloride or iodine, substitution takes place with moderate ease and 3,5-disubstituted pyrones are formed, together with smaller amounts of monobromo products. In these derivatives, the bromine is firmly bound and cannot be

112 Gomberg and Cone, *Ann.*, **376**, 226 (1910).
113 Werner, *Ann.*, **322**, 300 (1902).
114 Johnson and Partington, *J. Chem. Soc.*, 86 (1931).
115 Feist and Baum, *Ber.*, **38**, 3562 (1905).

removed by boiling with strong barium hydroxide solution or with sodamide.[116] The prolonged action of bromine leads to ring cleavage.[116]

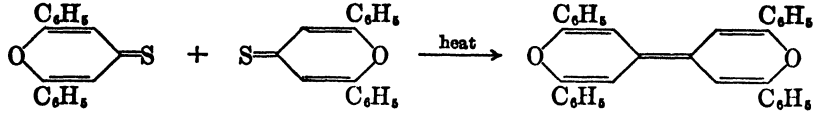


Interesting differences in the aromatic character have been observed with 4-thiopyrones, which are readily prepared by the action of phosphorus pentasulfide on the corresponding pyrones.[92] Thus, whereas 4-thiopyrone and 2,6-dimethyl-4-thiopyrone are of light yellow color and are inert towards carbonyl reagents, 2,6-diphenyl- (XLII) and



XLII

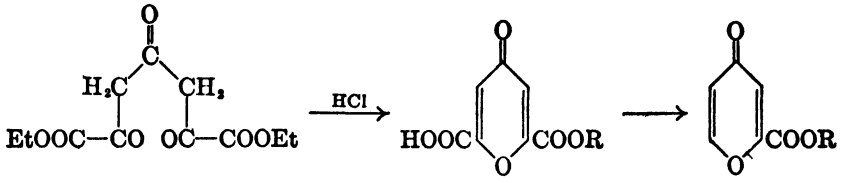
2,6-dicarbethoxy-4-thiopyrones are highly colored, are converted into oximes and semicarbazones by hydroxylamine and semicarbazide, respectively, and give the dipyrylene reaction which is characteristic of thioketones.[92]



Chelidonic Acid. Chelidonic acid was first isolated by Probst[117] from *Chelidonium majus*. It has since been found in a number of papaveraceous and liliaceous plants. Its structure has been determined by Haitinger and Lieben.[118] On the basis of its hydrolytic cleavage into 1 mole of acetone and 2 moles of oxalic acid and of the formation of γ-pyridone-2,6-dicarboxylic acid from its reaction with

[116] Maheshwari, Kaushal, and Deshapande, *J. Indian Chem. Soc.*, **23**, 24 (1946).
[117] Probst, *Ann.*, **29**, 116 (1839).
[118] Haitinger and Lieben, *Monatsh.*, **5**, 339 (1884); **6**, 279 (1885).

ammonia, formula XLIII for chelidonic acid was proposed. This was confirmed by Claisen's synthesis [119] from diethoxalylacetone. Cheli-

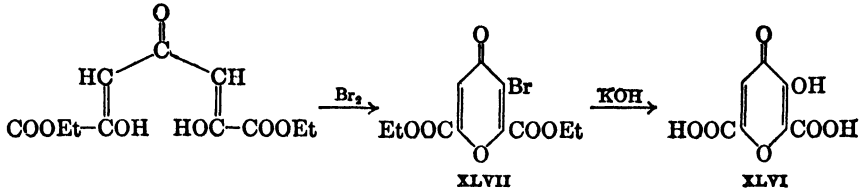


XLV

XLIII, R = H
XLIV, R = C_2H_5

donic acid readily forms a monoethyl ester (XLIV) [118,120] which loses carbon dioxide when heated and forms ethyl comanate (XLV). [118,120] Complete decarboxylation [118,121] of chelidonic acid, preferably over copper powder, yields γ-pyrone.

Meconic Acid. Meconic acid was first isolated by Séguin [122] from opium, in which it occurs to the extent of 3–5%. Peratoner [123] prepared its diethyl ester monoethyl ether and obtained from it by hydrolytic cleavage with hot barium hydroxide 2 moles of oxalic acid and 1 mole of ethoxyacetone. Since Ost [124] had previously demonstrated the presence of the γ-pyrone nucleus in meconic acid by its conversion into comanic acid (XLV), Peratoner suggested formula XLVI for meconic acid. Its synthesis [125] from diethoxalylacetone by bromination and simultaneous ring closure to diethyl bromochelidonate (XLVII) followed by hydrolytic removal of the bromine atom firmly



XLVII XLVI

establishes formula XLVI for meconic acid. When boiled with concentrated hydrochloric acid, meconic acid loses 1 mole of carbon di-

119 Claisen, *Ber.*, **24**, 111 (1891).

120 Attenburrow et al., *J. Chem. Soc.*, 571 (1945).

121 Willstätter and Pummerer, *Ber.*, **37**, 3740 (1904); **38**, 1461 (1905); Cornubert and Robinet, *Bull. soc. chim. France*, [4] **53**, 565 (1933).

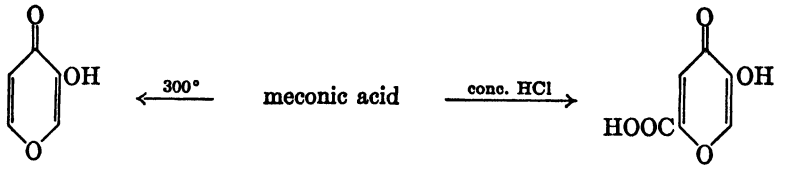
122 Séguin, *Ann. chim.*, [1] **92**, 225 (1814).

123 Peratoner, *Chem. Ztg.*, **21**, 40 (1897).

124 Ost, *J. prakt. Chem.*, [2] **29**, 62 (1884).

125 Thoms and Pietrulla, *Ber. deut. pharm. Ges.*, **31**, 4 (1921); Wibaut and Kleipool, *Rec. trav. chim.*, **66**, 24 (1947).

oxide and forms comenic acid (XLVIII);[126,127] heating it at 300° in a stream of carbon dioxide produces pyromeconic acid (XLIX). The

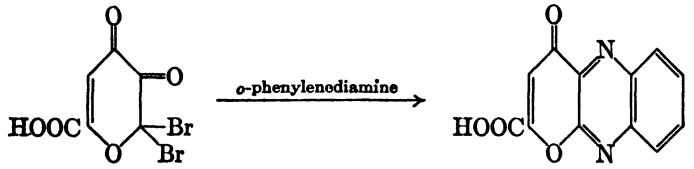


XLIX
pyromeconic acid

XLVIII
comenic acid

structure of pyromeconic acid rests on its formation from meconic acid by elimination of 2 moles of carbon dioxide and is confirmed by the hydrolytic cleavage of its methyl ether into methoxyacetone and 2 moles of formic acid.[128] It has been synthesized[129] in small yield by oxidation of γ-pyrone with ferrous sulfate and hydrogen peroxide.

For the structure of comenic acid, formula XLVIII and a formula having the hydroxyl and the carboxyl groups in the *o* position to each other have to be considered. On the basis of conductivity measurements[130] and of the formation of a quinoxaline derivative (LI)[131] from dibromocomenic acid (L), structure XLVIII is generally considered to be the correct one.

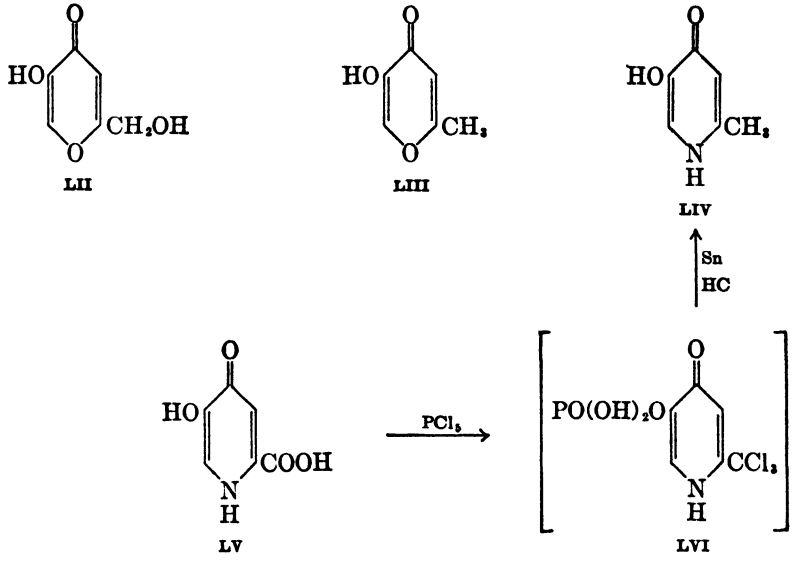


L LI

Kojic Acid.[132] Kojic acid was first isolated by Saito[133] as a by-product of the fermentation of steamed rice by *Aspergillus orizae*. It has since been found to be produced by a large number of molds, mostly of the genus *Aspergillus*, and by bacteria of the species *acetobacter*. It has been reported to possess weak antibiotic activity

126 Robiquet, *Ann. chim. phys.*, [2] **51**, 246 (1832); **53**, 428 (1833).
127 Meyer, *Monatsh.*, **26**, 1328 (1905).
128 Peratoner and Spallino, *Chem. Zentr.*, **1905**, II, 678.
129 Peratoner, *Gazz. chim. ital.*, **41**, II, 686 (1912).
130 Peratoner and Palazzo, *Chem. Zentr.*, **1905**, II, 678.
131 Peratoner and d'Angelo, *Gazz. chim. ital.*, **41**, II, 619 (1912).
132 Review on kojic acid: Barham and Smits, *Trans. Kansas Acad. Sci.*, **37**, 91 (1934).
133 Saito, *Botan. Mag. Tokyo*, **21**, 7 (1907).

against many Gram-positive and Gram-negative organisms [134] and also against yeasts and fungi.[135] Its chemical constitution was elucidated by Yabuta [136] who assigned structure LII to it. His proof was based on the comparison of derivatives of kojic acid with appropriate derivatives of comenic acid (XLVIII). Treatment of kojic acid with thionyl chloride at room temperature yielded 2-chloromethyl-5-hydroxy-γ-pyrone, which after reduction with zinc dust and acetic acid yielded 2-methyl-5-hydroxy-γ-pyrone (allomaltol) (LIII). The



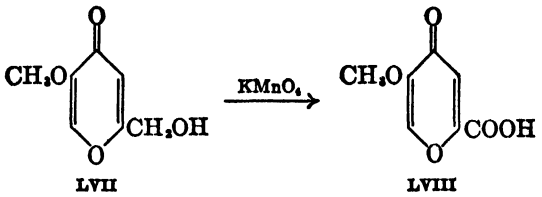
methyl ether of LIII was converted into the corresponding pyridone, and the methyl ether group was removed again by hydrolysis. The resulting product (LIV) was found to be identical with a substance which Ost [137] had obtained from comenamic acid (LV) by reducing the product of the reaction of that acid with phosphorus pentachloride (LVI) by means of tin and hydrochloric acid. The oxidation of 5-methylkojic acid (LVII) to 5-methylcomenic acid (LVIII) by means of permanganate in acetone [136b] provides further proof for structure LII for kojic acid.

134 Morton et al., *J. Bact.*, **50**, 579 (1945).

135 Yabuta, *J. Chem. Soc. Japan*, **37**, 1185 (1916).

136 Yabuta, (*a*) *J. Chem. Soc.*, **125**, 575 (1924); (*b*) *J. Agr. Chem. Soc. Japan*, **6**, 516 (1930).

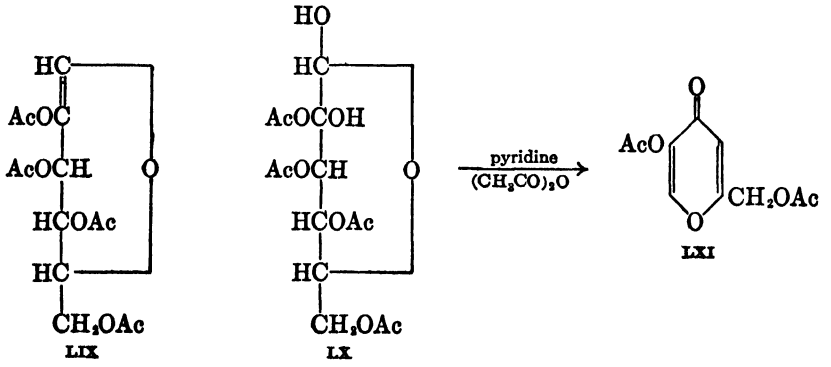
137 (*a*) Ost, *J. prakt. Chem.*, [2] **27**, 266 (1883); (*b*) Bellmann, *ibid.*, [2] **29**, 14 (1884).



LVII LVIII

Like other hydroxylated γ-pyrones, kojic acid gives an intense coloration with ferric chloride. Its 6 position is very reactive, as shown by the facts that it couples with diazonium salts,[138] condenses with aromatic aldehydes [139] and with Schiff bases,[140] and forms Mannich bases.[141] With maltol (LXII), in which the 6 position is blocked by a methyl group, this reactivity is lacking.

The mechanism of the biosynthesis of kojic acid from carbohydrate precursors has interested several workers. Haworth's suggestion [142] that kojic acid arises directly from glucose by oxidation and dehydration does not take into consideration that pentoses and trioses produce equally high yields as glucose. Challenger, Klein, and Walker [143] proposed that dihydroxyacetone or glyceraldehyde were the most likely intermediates, on the basis of observed high yields with dihydroxyacetone as the carbohydrate source. This conclusion was also reached by Katagin and Kitahore.[144]



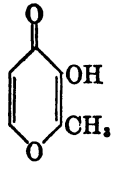
LIX LX LXI

138 Quilico and Musante, *Gazz. chim. ital.*, **74**, 26 (1944).
139 Barham and Reed, *J. Am. Chem. Soc.*, **60**, 1541 (1938).
140 Barchielli, *Ann. chim. applicata*, **30**, 473 (1940).
141 Woods, *J. Am. Chem. Soc.*, **68**, 2744 (1946).
142 Haworth, *Constitution of Sugars*, Longmans, Green and Co., New York, 1929.
143 Challenger, Klein, and Walker, *J. Chem. Soc.*, 16 (1931).
144 Katagin and Kitahore, *Mem. Coll. Agr. Kyoto Imp. Univ.*, **26**, 1 (1933).

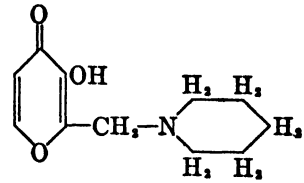
Kojic acid has been synthesized by Maurer [145] from both glucose and galactose. 2,3,4,6-Tetraacetyl-2-hydroxyglucal (LIX) [146] was converted into tetraacetylglucosone hydrate (LX) by chlorination and subsequent hydrolytic removal of the chlorine atoms by means of silver carbonate. LX on treatment with pyridine and acetic anhydride formed diacetyl kojic acid (LXI) in good yield.

Maltol. Maltol has been isolated from the bark of the larch tree [147] and from the needles of the silver fir.[148] It is also present in the products of destructive distillation of a number of carbohydrate-containing materials.[149]

Its structure (LXII) has been determined by Peratoner and Tamburello,[150] who hydrolyzed its methyl ether to methoxyacetone, formic acid, and acetic acid and also converted it into a pyridone derivative.



LXII



LXIII

This leaves structures LIII and LXII for maltol, of which LIII is eliminated, since it represents allomaltol (p. 385). Maltol has been synthetically produced [151] in small yield by converting pyromeconic acid into the Mannich base 3-hydroxy-2-piperidinomethyl-γ-pyrone (LXIII) and removing the piperidino group by catalytic hydrogenation.

Maltol is also formed by the action of weak alkali on the antibiotics, streptomycin (LXIV) [152] and mannosidostreptomycin.[153] This reaction may be interpreted as a "pinacolic change" [154] involving carbon

145 Maurer, *Ber.*, **63**, 25, 2069 (1930); **64**, 2358 (1931).

146 Maurer and Mahn, *Ber.*, **60**, 1316 (1927).

147 Stenhouse, *Ann.*, **123**, 191 (1862).

148 Feuerstein, *Ber.*, **34**, 1804 (1901).

149 Brand, *Ber.*, **27**, 806 (1894); Kiliani and Bazlen, *Ber.*, **27**, 3115 (1894); Erdmann and Schaefer, *Ber.*, **43**, 2398 (1910); Reichstein and Beitter, *Ber.*, **63**, 824 (1930).

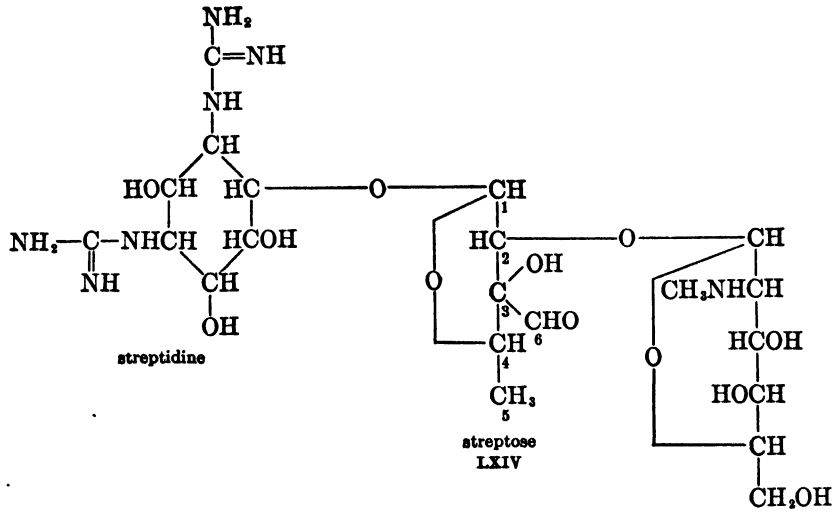
150 Peratoner and Tamburello, *Chem. Zentr.*, **1905**, II, 680.

151 Spielman and Freifelder, *J. Am. Chem. Soc.*, **69**, 2908 (1947).

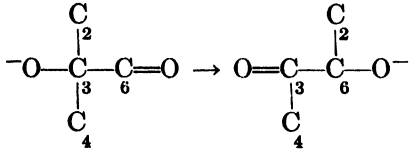
152 Schenck and Spielman, *J. Am. Chem. Soc.*, **67**, 2276 (1945).

153 Fried and Titus, *J. Biol. Chem.*, **168**, 391 (1947).

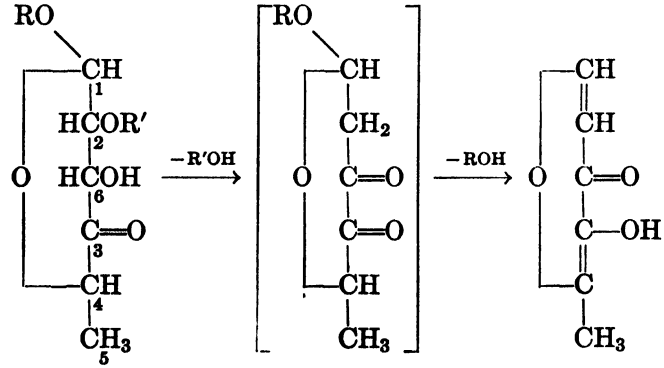
154 Shoppee and Ingold, *J. Chem. Soc.*, 365 (1928).



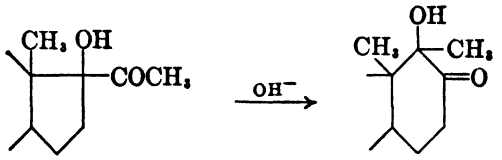
atoms 2, 3, and 6 of the streptose moiety, which under the influence of a proton acceptor, rearranges according to the scheme



and forms the isomeric pyranoside LXV. The latter, under the influence of the newly formed keto group, splits off N-methylglucosa-

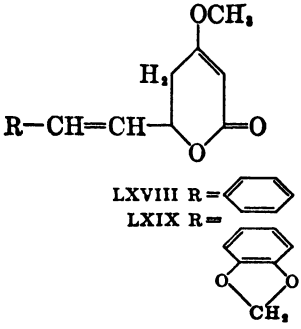


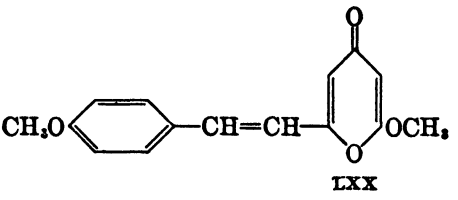
mine and finally streptidine, and forms maltol. A rearrangement resembling the first stage of the maltol reaction is the formation of homoandrostane derivatives (LXVII) from 17-hydroxy-20-ketosteroids (LXVI) by enlargement of ring D, which is promoted by basic catalysts, and may occur during chromatography over alumina which has not been washed with acid.[155]



LXVI LXVII

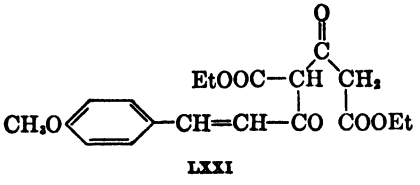
Constituents of the Kava Root. The roots of the kava shrub (*Piper methysticum*), which is indigenous to many of the South Sea Islands and from which the natives prepare an intoxicating drink known as kavakava, contain a number of pyrone and dihydropyrone derivatives, the most important of which are kavain (LXVIII), methysticin (LXIX), and yangonin (LXX). Their chemistry has been elucidated



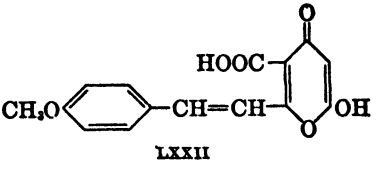


LXX

mainly by Borsche and his collaborators,[156] who have also described a synthesis for yangonin. Diethyl acetonedicarboxylate was condensed with *p*-methoxycinnamoyl chloride, and the resulting diester (LXXI)



LXXI



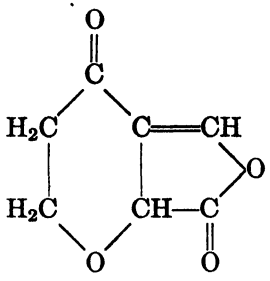
LXXII

155 Stavely, *J. Am. Chem. Soc.*, **63**, 3127 (1941).

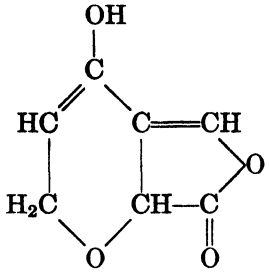
156 Borsche et al., Yangonin: *Ber.*, **47**, 2902 (1914); **62**, 2515 (1929); **65**, 820 (1932); Kavain: *Ber.*, **63**, 2414 (1930); Methysticin: *Ber.*, **60**, 2113 (1927).

was treated with acetic anhydride, causing cyclization and simultaneous acetylation of the enolic hydroxyl group in the 2 position of the pyrone nucleus. Careful saponification of the acetyl and carbethoxy groups yielded yangonalactone-5-carboxylic acid (LXXII), which was converted into yangonin (LXX) by decarboxylation and subsequent methylation with diazomethane.

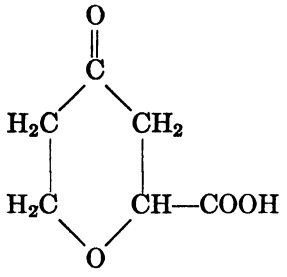
Clavacin. Clavacin has been isolated from the culture filtrates of a number of molds,[157] mostly of the genus *Aspergillus* and *Penicillium*, and found to be the substance responsible for the antibiotic action of such filtrates towards a large variety of Gram-positive and Gram-negative microörganisms. Structure LXXIII [158] has been assigned to it mainly because of its cleavage by hot dilute sulfuric acid into formic



LXXIII



LXXIIIa



LXXIV

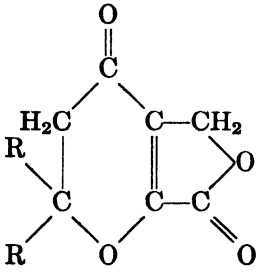
acid and tetrahydro-γ-pyrone-2-carboxylic acid (LXXIV) and of the isolation of β-*n*-propyl-γ-butyrolactone following reductive degradation. There are, however, some observations with which formula LXXIII is not in agreement. Clavacin shows an absorption maximum in the ultraviolet at 276 mμ (ϵ = 16,600), whereas an α,β-unsaturated ketone of structure LXXIII would be expected to show maximum absorption at 239 mμ ± 5.[159] Furthermore, clavacin yields 1 mole of methane in the Zerewitinoff determination and forms a monoacetate whose absorption spectrum is identical with that of the unacetylated substance. To explain the formation of this acetyl derivative, Bergel and his collaborators assumed an equilibrium for clavacin between the tautomeric forms LXXIII and LXXIII*a*. Since clavacin is a neutral substance and does not give a coloration with ferric chloride, it would be assumed to exist mainly in the ketonic form (LXXIII), whereas its acetate

157 Clavacin: Hooper et al., *Science*, **99**, 16 (1944); Clavatin: Bergel et al., *Nature*, **152**, 750 (1943); Patulin: Raistrick et al., *Lancet*, **245**, 625 (1943); Claviformin: Chain, Florey, and Jennings, *Brit. J. Exptl. Path.*, **23**, 202 (1942).

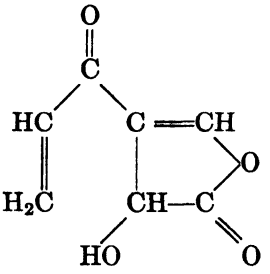
158 Raistrick et al., *Lancet*, **245**, 625 (1943); Bergel et al., *J. Chem. Soc.*, 415 (1944).

159 Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

would have to be derived from the enol form (LXXIIIa). Contrary to these conclusions based on Raistrick's and Bergel's formulas, clavacin and its acetate possess identical absorption spectra, indicating that both contain the same chromophoric system. The failures [160] to isomerize the synthetic product (LXXV) to clavacin and to prepare an acetyl

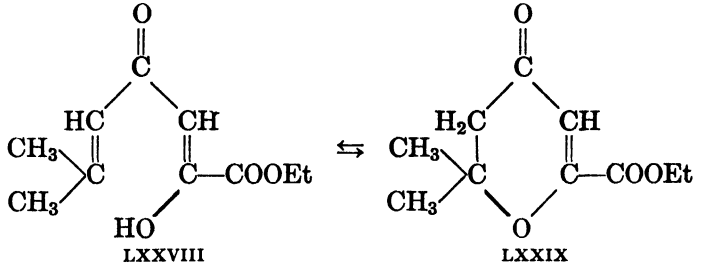


LXXV R = H
LXXVI R = CH_3



LXXVII

derivative from LXXVI further emphasize the fact that additional data are necessary to establish with certainty the structure of this antibiotic. Among the possible formulas for clavacin, LXXVII may be considered because it not only explains the above-mentioned discrepancies but is likewise in agreement with the numerous other data that have been cited in support of formula LXXIII. Thus, the formation of tetrahydro-γ-pyrone-2-carboxylic acid, the only authentic pyrone derivative obtained from clavacin, would be analogous to the cyclization of mesityloxideoxalic ester (LXXVIII) to the dihydropyrone (LXXIX).[161]



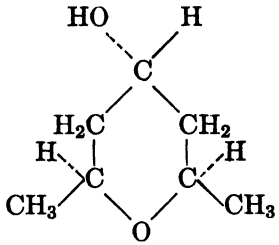
LXXVIII LXXIX

Tetrahydro-γ-Pyrones. Reduction of the γ-pyrone nucleus by chemical means is not suitable for the preparation of tetrahydropyrone, since most reducing agents are either without effect (p. 370) or lead to ring

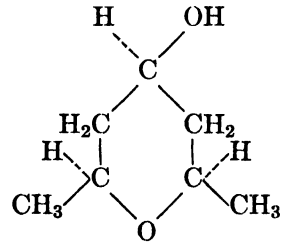
160 Puetzer, Nield, and Barry, *J. Am. Chem. Soc.*, **67**, 834 (1945).

161 Dieckmann, *Ber.*, **53**, 1772 (1920); v. Auwers and Dieckmann, *Ber.*, **56**, 1527 (1923).

opening.[118] It is possible, however, to effect reduction of the pyrone nucleus by catalytic hydrogenation. Borsche [162] succeeded in selectively hydrogenating the two carbon-carbon double bonds by means of a colloidal palladium catalyst, and similar results were later obtained with palladized strontium carbonate.[163] Attenburrow et al.[164] studied the hydrogenation of a number of γ-pyrone derivatives with different supported palladium catalysts and found that, if the hydrogenation was allowed to go to completion, reduction to the tetrahydro-γ-pyranols occurred. By interrupting the reaction at the 1- and 2-mole stages, they were able to obtain dihydro- and tetrahydropyrones in small yield. High-pressure hydrogenation of γ-pyrone in the presence of copper chromite [165] yielded 50% of 4-hydroxytetrahydropyran and 23% of tetrahydro-γ-pyrone, whereas Raney nickel at moderate pressure [166] yielded only the former. Raney nickel activated by chloroplatinic acid and a trace of alkali leads to partial opening of the ring by hydrogenolysis, the chief products from dimethylpyrone being two isomeric 2,6-dimethyl-4-hydroxytetrahydropyrans (LXXX*a*, *b*) and heptanediol-(2,4).[167] The two isomers differ from each other by epimerism of the hydroxyl group, since both yield the



LXXX*a*



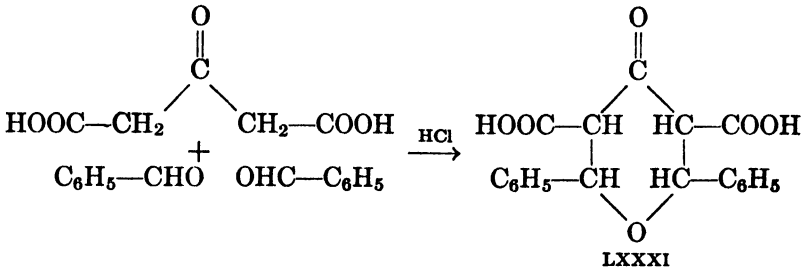
LXXX*b*

same 2,6-dimethyltetrahydropyrone on oxidation with chromic acid.

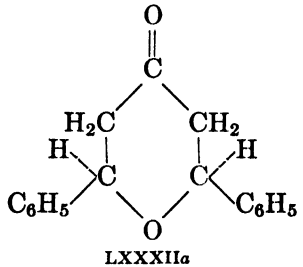
Tetrahydropyrones have also been obtained by condensation of open-chain [168–170] and cyclic ketones [171] with aldehydes in the presence of dry hydrogen chloride. Typical of this reaction is the condensation of acetonedicarboxylic acid with benzaldehyde, which leads to the

162 Borsche, *Ber.*, **48**, 682 (1915); **56**, 2012, 2132 (1923); **59**, 237 (1926).
163 Cawley and Plant, *J. Chem. Soc.*, 1214 (1938).
164 Attenburrow et al., *J. Chem. Soc.*, 571 (1945).
165 Mozingo and Adkins, *J. Am. Chem. Soc.*, **60**, 669 (1938).
166 Blanchard and Paul, *Compt. rend.*, **200**, 1414 (1935).
167 De Vrieze, *Rec. trav. chim.*, **66**, 486 (1947).
168 Petrenko-Kritschenko and Plotnikoff, *Ber.*, **30**, 2801 (1897).
169 Petrenko-Kritschenko and Stanischewsky, *Ber.*, **29**, 994 (1896).
170 Vorländer and Hobohm, *Ber.*, **29**, 1352 (1896).
171 Cornubert and Robinet, *Bull. soc. chim. France*, [4] **53**, 620 (1933).

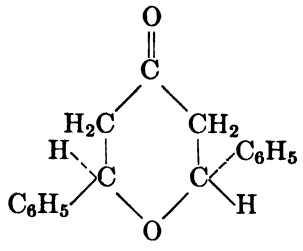
tetrahydropyronedicarboxylic acid (LXXXI). Decarboxylation of the crude acid produces two isomeric 2,6-diphenyltetrahydropyrones,



LXXXI



LXXXIIa

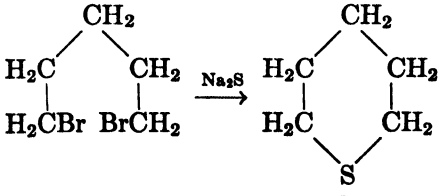


LXXXIIb

a *meso* form (LXXXII*a*) in which the phenyl groups are in *cis* position and a racemic form (LXXXII*b*) in which they are in *trans* position to each other.[172] Both isomers yield dibenzylideneacetone when heated with alcoholic hydrogen chloride.

THIAPYRANS AND THIAPYRONES

Tetrahydrothiapyrans and Pyrones. Whereas no representative of the thiapyrans has yet been described, the synthesis of their tetrahydro derivatives has received some attention. Tetrahydrothiapyran (I) and its 2-methyl derivative have been obtained by the action of sodium sulfide on the appropriate dihalides.[173,174] The chloro derivatives have



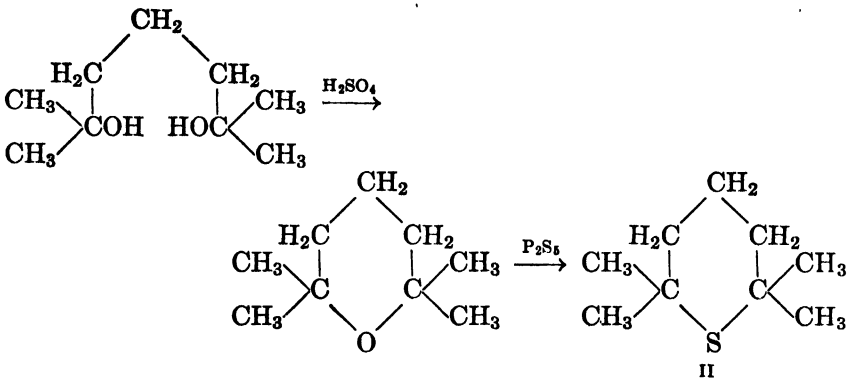
I

172 Cornubert and Robinet, *Bull. soc. chim. France*, [5] 1, 90 (1934).

173 Clarke, *J. Chem. Soc.*, 101, 1805 (1912).

174 Grischkewitsch-Trochimowski, *J. Russ. Phys. Chem. Soc.*, 48, 928 (1916) [*C. A.*, 11, 786 (1917)].

been reported to be superior to other dihalides for this purpose.[175] For the preparation of cyclic sulfides of type II, the above method is not applicable since the halogen atoms are replaced by ethoxyl if alcohol is used as a solvent or are eliminated as hydrogen halides if no solvent is present. 2,2,6,6-Tetramethyltetrahydrothiapyran (II) has been obtained in small yield by heating the corresponding tetrahydropyran derivative [176] with phosphorus pentasulfide.[177] Unlike tetrahydrothiapyran (I), which forms a stable methyl sulfonium salt when warmed

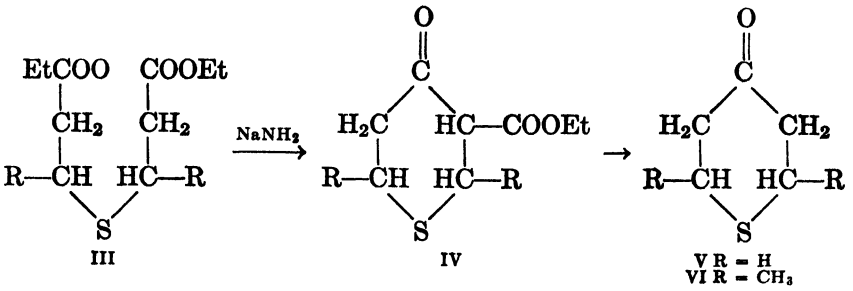


II

with methyl iodide, the tetra-substituted compounds of type II are cleaved by this reagent with the formation of trimethylsulfonium iodide.

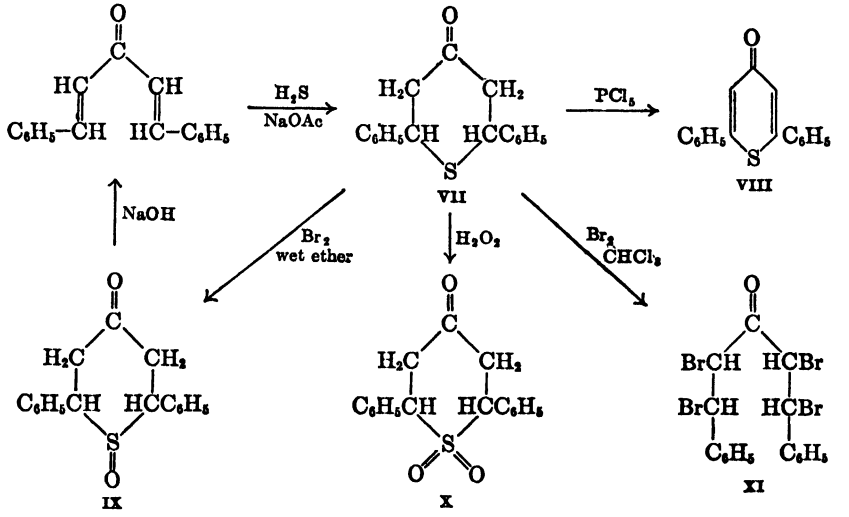
Tetrahydro-1,4-thiapyrone (penthianone) (V) [178] and its 2,6-dimethyl derivative (VI) [95] have been synthesized by internal Claisen condensation of the appropriate thiodihydracrylic acid diethyl esters (III) followed by hydrolysis and decarboxylation of the cyclic keto esters (IV) by hot dilute acid. The odor of the homologous penthianones is of interest. In contrast to penthianone (V), which has the unpleasant odor characteristic of many sulfur compounds, 2,2,6,6-tetramethylpenthianone (from phorone and hydrogen sulfide) possesses a pure camphor-like odor. The condensation of dibenzylideneacetone with hydrogen sulfide under carefully controlled, weakly alkaline conditions [89b] produces two isomeric 2,6-diphenyltetrahydrothiapyrones (VII), which must be *cis-trans* isomers since their dehydrogenation

175 Bost and Conn, *Oil Gas J.*, **32**, No. 3, 17 (1933).
176 Bruylants, *Rec. trav. chim.*, **29**, 130 (1910).
177 Naylor, *J. Chem. Soc.*, 1106 (1947).
178 Bennet and Scorah, *J. Chem. Soc.*, 194 (1927).



leads to the same diphenyl-1,4-thiapyrone (VIII). This method has been successfully applied to other diolefin ketones.[179]

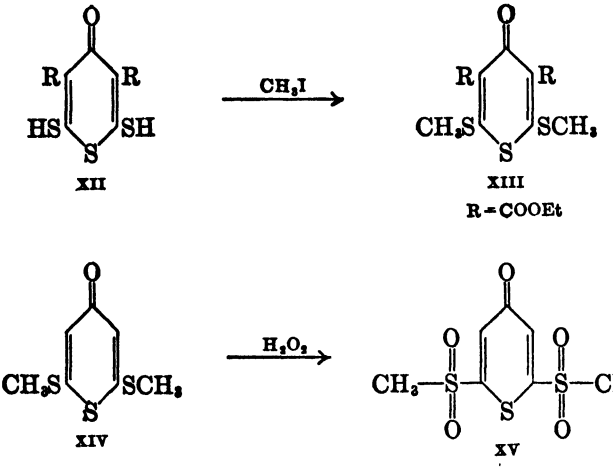
The tetrahydrothiapyrans and pyrones are stable towards acids and bases but are very susceptible to oxidizing agents, including atmos-



pheric oxygen. The action of bromine in wet ether or in glacial acetic acid containing pyridine leads to sulfoxides,[95] whereas bromine in dry chloroform may cause ring cleavage as typified by the isomeric 2,6-diphenylpenthianones which yield dibenzylideneacetone tetrabromide (XI) and sulfur bromide. Stronger oxidizing agents such as permanganate [174] or hydrogen peroxide in glacial acetic acid [89b,95] produce sulfones. *Cis-* and *trans*-diphenylpenthianones yield two corresponding stereoisomeric sulfoxides (IX) and two sulfones (X), respectively, from which the sulfur is readily eliminated by mild alkali, with the formation of dibenzylideneacetone.[89b]

179 Arndt and Pusch, *Ber.*, 58, 1648 (1925).

1,4-Thiapyrones. Derivatives of 1,4-thiapyrone were first synthesized by Apitzsch,[180] who prepared the 2,6-dithiols (XII) by the action of carbon disulfide and alkali on ketones of the general formula, $RCH_2—CO—CH_2R$. The two sulfhydryl groups in XII can be alky-



XII XIII

R = COOEt

XIV XV

lated and acylated and are readily oxidized to sulfonic acid groups. The diethyl ester (XIII) is hydrolyzed by concentrated hydrochloric acid to the corresponding dicarboxylic acid, which loses carbon dioxide at its melting point and forms 2,6-dithiomethyl-1,4-thiapyrone (XIV).[95]

The preparation of alkyl- and aryl-substituted 1,4-thiapyrones and of 1,4-thiapyrone itself has been accomplished by dehydrogenation of the corresponding tetrahydrothiapyrones by means of phosphorus pentachloride.[89b,95] On treatment with phosphorus pentasulfide in benzene solution, the oxygen atom of the 1,4-thiapyrones is replaced by sulfur and the 4-thio-1,4-thiapyrones are formed.[181] 1,4-Thiapyrones show the basicity and the lack of reactivity of the carbonyl group and of the double bonds characteristic of γ-pyrones in general. Their aromatic character is furthermore evident from the inertia of the sulfur atom towards oxidizing agents (see p. 375). This is well illustrated by the behavior of XIV which on oxidation yields the disulfone (XV) rather than a trisulfone.

180 Apitzsch, *Ber.*, **37**, 1599 (1904); **38**, 2888 (1905); **41**, 4028 (1908).
181 Arndt, Nachtwey, and Pusch, *Ber.*, **58**, 1644 (1925).

CHAPTER 8

THE CHEMISTRY OF THE PYRIDINES

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CONTENTS

INTRODUCTION

General

Pyridine is the parent substance of all the heterocyclic compounds that have one nitrogen atom in a six-membered ring and a double-bond system analogous to that of benzene. Since almost every type of known benzene compound has its analog in the pyridine series, the number and types of pyridine derivatives are potentially as extensive as those in the benzene system. In fact, the possible number of derivatives is even greater in the pyridine system because of the unsym-

metrical nature of the nitrogen-containing ring. For instance, there is only one monomethylbenzene, but there are three monomethylpyridines (picolines). There are three dimethylbenzenes (xylenes) but six dimethylpyridines (lutidines), and there are three trimethylbenzenes but six trimethylpyridines (collidines), etc. In all, there are some nineteen possible methyl-substituted pyridines, compared with thirteen methylbenzenes. Whereas all these benzene derivatives are known, three of the corresponding pyridine compounds have not yet been described with certainty. As a further example, there is only one possible biphenyl, whereas there are six bipyridyls known. In addition, there is a whole series of *pyridinium* derivatives possible in the heterocyclic series which has no counterpart in the benzene series and which greatly multiplies the number of possible pyridine compounds.

Although the number of known benzene derivatives far exceeds the number of pyridine compounds, there is still a large volume of chemical literature in the pyridine field. This literature has been increasing at an astonishing rate. Obviously, it is neither possible nor desirable to deal extensively with so large a field in the following pages, for much would then merely be a repetition of aromatic chemistry which can better be studied elsewhere; rather, an effort will be made to present and explain, when possible, the unique chemistry in the pyridine series and at the same time to indicate the other reactions which have their analogies in the benzene series.

This is, therefore, not a comprehensive review, and the references to the original literature which are cited constitute only those of particular interest. Several other reviews [1-8] of pyridine chemistry are available, and the reader is referred to these for special purposes. In

1 Maier-Bode and Altpeter, *Das Pyridin und seine Derivate,* Wilhelm Knappe Halle, Saale, 1934. Photo-lithoprint reproduction by Edwards Brothers, Inc., Ann Arbor, Michigan.

2 Bergstrom, "Heterocyclic Nitrogen Compounds, Part IIA, Pyridine, Quinoline, and Isoquinoline," *Chem. Revs.,* **35,** 79 (1944).

3 Calm and v. Buchka, *Die Chemie des Pyridins und seiner Derivate,* Friedrich Vieweg und Sohn, Braunschweig, 1889–1891.

4 Morton, *The Chemistry of Heterocyclic Compounds,* McGraw-Hill, New York, 1946, Chapter VIII, pp. 185–228.

5 Hollins, *Synthesis of Nitrogen Ring Compounds,* Von Nostrand Co., London, 1924, Chapter VII, pp. 182–242.

6 Richter, *The Chemistry of the Carbon Compounds,* Vol. IV, *Heterocyclic Compounds,* translated into English by Mee and Darkin, Elsevier Publishing Co., Inc., New York, 1947.

7 Meyer and Jacobsen, *Lehrbuch der organischen Chemie,* Vol. III, *Heterocyclishe Verbindungen,* Walter de Gruyter and Co., Berlin and Leipzig, 1923.

8 Taylor and Baker, *Sidgwick's Organic Chemistry of Nitrogen,* Oxford Press, London, 1937, Chapter XVIII, pp. 516–541.

particular, the book by Maier-Bode and Altpeter [1] is an excellent source for almost all references on pyridine chemistry prior to 1934. This is an additional reason why complete literature references have not been included here; any compound in the succeeding pages which is not accompanied with a reference can be found in reference 1. The review by Bergstrom [2] is also recommended for its treatment from the standpoint of the ammonia system of compounds, and those in Taylor and Baker's *Sidgwick* [3] and by Morton [4] include brief reviews of the field.

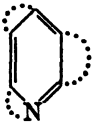
Structure of the Pyridine Ring

The same problem arises with respect to the structure of pyridine that exists for benzene.[9] Although pyridine was first separated, characterized, and analyzed by Anderson [10] in 1849 and its empirical formula was established as C_5H_5N, it was not until 1869 that Korner and Dewar [11] recognized its cyclic nature and proposed that its structure be represented by alternate single and double bonds (I), just as Kekule had represented benzene five years earlier. Two years later, Reidel [12] suggested the diagonal formula (II), and the centric formula (III) of Armstrong [13] and Baeyer [14] was later applied to pyridine by


I


II


III


IV

Bamberger.[15] Thiele's partial valence formula (IV) also was considered. From this it is apparent that the problem concerning the structure of pyridine closely paralleled that of the famous controversy concerning the benzene structure.

The representations (II, III, IV) were postulated in an attempt to explain, first, the saturated nature of pyridine where the original Baeyer formula (I) would indicate an unsaturated compound, and,

9 For a complete discussion of the subject of the structure of benzene, see Gilman, *Organic Chemistry*, John Wiley & Sons, New York, 1943, Chapter 3 by Fieser. Ref. 3 (pp. 23–36), has a complete discussion of the earlier proposed structures for pyridine.

10 Anderson, *Trans. Roy. Soc. Edinburgh*, **16**, 123 (1849).

11 See Dobbin, *J. Chem. Ed.*, **11**, 596–600 (1934) for an interesting account of the historical background of this observation.

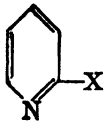
12 Reidel, *Ber.*, **16**, 1612 (1883).

13 Armstrong, *J. Chem. Soc.*, **51**, 264 (1887).

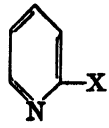
14 Baeyer, *Ann.*, **245**, 121 (1888); **251**, 285 (1889); **269**, 188 (1892).

15 Bamberger, *Ber.*, **24**, 1758 (1891); *Ann.*, **273**, 373 (1893).

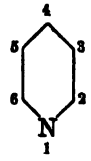
second, the existence of only one known isomer of any α-substituted pyridine derivative where the Baeyer formula (I) would predict two such isomers (V and VI). These apparent discrepancies have now

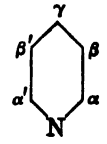


V



VI





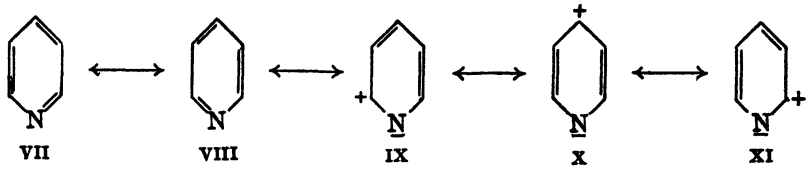
numbering system in the pyridine ring

been satisfactorily resolved by the application of the resonance theory,[16] according to which the α-substituted pyridine derivative is neither structure (V) nor (VI) but is a resonance hybrid of these two states in which no difference between the nitrogen-carbon bonds exists.

In addition to the two properties of the pyridine ring just mentioned, any theory concerning the structure of the pyridine nucleus must also successfully account for a variety of other more or less unique properties: (1) the great inertness towards nitration, sulfonation, and halogenation, (2) the susceptibility to attack by such reagents as sodium amide, (3) 3 or β substitution when attacked by nitric acid, sulfuric acid, or halogens, and 2 or α substitution when attacked by sodium amide, (4) the weakly basic nature of pyridine, (5) the reactivity of the 2- and 4-halogen derivatives as contrasted with the inert 3-halogen derivatives, (6) the normal aromatic diazotization reaction of the 3-aminopyridines, but the abnormal reaction of the 2 and 4 isomers, (7) the presence of active hydrogens in the methyl groups of the 2- and 4-picolines, but not in 3-picoline, (8) many related phenomena such as the carbonyl characteristics shown by 2- and 4-hydroxypyridines, and (9) the ease of decarboxylation of 2- and 4-pyridine carboxylic acids (picolinic and isonicotinic acids). These nine properties can be conveniently summarized as the typical "aromatic" nature of the 3 or β position in pyridine and the "anomalous" nature of the 2 and 4 or α and γ positions.

The above properties are all in harmony with modern organic chemical theory if we consider pyridine as a resonating system with VII and VIII the major contributing states and IX, X, and XI activated states whose contributions are significant in the reactions of pyridine by virtue of the electron attraction of the nitrogen atom.

16 Wheland, *The Theory of Resonance*, John Wiley & Sons, New York, 1945.



VII VIII IX X XI

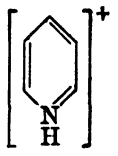
The evidence in favor of such a structure is completely analogous to the similar evidence in the benzene series and need not be discussed at length here. It is sufficient to point out that the resonance energy of pyridine has been determined from its heat of combustion,[17] and the results show that pyridine has the same order of resonance stability as is manifested by benzene and that quantitatively the resonance stability of pyridine is slightly greater than that of benzene. The high resonance energies of both pyridine and benzene likewise have been indicated by the shortened C—C bond distances in these compounds, as calculated from electron diffraction measurements.[18] Daudel [19] has attempted to assign quantitative values to the relative contributions of the various resonance forms of pyridine.

REACTIONS OF THE PYRIDINE NUCLEUS

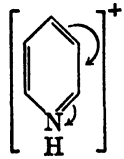
Substitution Reactions

Nitration. Certainly the slightly greater resonance energy of pyridine cannot alone account for the much more vigorous conditions necessary for the nitration of pyridine compared to the nitration of benzene. Whereas sulfuric and nitric acid mixture readily nitrates benzene at 40°, pyridine can be nitrated only with difficulty and in poor yield. Typical conditions are the reaction of pyridine with potassium nitrate in fuming sulfuric acid at approximately 300°. Such inert character can be explained by assuming that the natural electron attraction of the nitrogen atom in the pyridine ring is enormously enhanced in acid solution where the pyridine exists as the positively charged pyridinium ion (I). The effect of this positive ion can be represented according to the designation of the English school as II, which indicates that the electron attraction of the positively charged nitrogen atom will reduce the electron density in the 2 and 4 positions and therefore will enhance the polarizations indicated by the resonance states IX, X, and XI.

17 Ref. 16, p. 70.
18 Schomaker and Pauling, *J. Am. Chem. Soc.*, **61**, 1769 (1939).
19 Daudel, *Compt. rend.*, **222**, 791 (1946).



I



II

Since it has been well established that nitration in sulfuric acid proceeds via the NO_2^+ radical,[1] it is obvious that nitration of the already positively charged pyridinium ion will be difficult and that, when it does occur, it will not attack the 2 and 4 positions of low electron density but will attack the position which is relatively unaffected by the quaternary ring nitrogen atom, namely, the 3 position. The same considerations apply to other positive or electrophilic reagents, for example, in sulfonation, in bromination, or in the Friedel-Crafts reaction.

Friedel-Crafts Reaction. The extent to which the electron attraction of the ring nitrogen atom deactivates the ring for substitution by positive reagents is well illustrated by the fact that no case has yet been reported of the pyridine molecule's being attacked in a Friedel-Crafts type of reaction.

Bromination. The bromination of pyridine at approximately 300° gives predominantly 3-bromo- and 3,5-dibromo-pyridine. These are the expected products if bromination occurs via a "positive bromine," and the same considerations apply here as in the nitration of pyridine. On the other hand, when the bromination is conducted at 500°, the products are substituted primarily in the 2 and 2,6 positions. Quite apparently, under these conditions the mechanism is different and a positive bromine or its equivalent is no longer the brominating agent, but instead the increased temperature has probably resulted in the dissociation of the bromine molecules followed by an attack on the pyridine nucleus through a free radical mechanism.[2]

Radical Substitution. A clearer example of a radical mechanism is given by the Gomberg-Bachmann coupling reaction of phenyldiazonium chloride and pyridine as studied by Haworth, Heilbron, and Hey.[3] The product is predominantly 2-phenylpyridine, but 3- and 4-phenylpyridines are also formed. It is not clear why a radical reaction should show preference in attacking the 2 position.

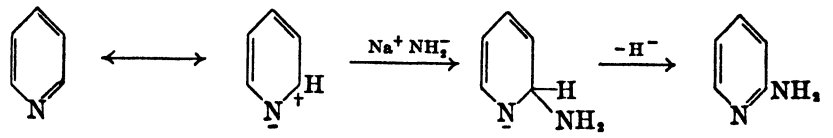
[1] Westheimer and Kharasch, *J. Am. Chem. Soc.*, **68**, 1871 (1946).

[2] Wheland, *The Theory of Resonance*, John Wiley & Sons, New York, 1945, pp. 260–262.

[3] (*a*) Haworth, Heilbron, and Hey, *J. Chem. Soc.*, 349, 372 (1940); (*b*) Elks and Hey, *ibid.*, 441 (1943); (*c*) Heilbron, Hey, and Lambert, *ibid.*, 1279 (1940).

Amination. The low electron density in the 2 and 4 positions as shown in the activated resonance states, IX, X, and XI (p. 403), affords a relatively easy point of attack for negative or nucleophilic reagents, as illustrated by the reaction of alkali amides. Thus, sodium amide and pyridine react with relative ease and, after hydrolysis, 2-aminopyridine results in good yield.[4]

The most probable course of this reaction is indicated below where the negative amide ion attacks the positive α-carbon atom, forming the intermediate (IV) which is stabilized by the loss of hydrogen with its electrons to give the 2-aminopyridine (V). In actual practice, the sodium hydride resulting from this reaction reacts in turn with the 2-aminopyridine to give the sodium salt of the aminopyridine and hydrogen.



III IV V

This reaction has been considered as taking place by the initial addition of $NaNH_2$ across the carbon-nitrogen double bond to give an unstable addition product which loses sodium hydride to give 2-aminopyridine. The fact that an unstable addition product has actually been obtained in the related case of sodium amide and quinoline does not necessarily indicate that this addition compound is the intermediate. The situation in certain respects is comparable to the problem concerning the mode of substitution of bromine in the benzene ring. A review of the evidence in favor of the direct substitution of bromine by electrophilic attack as contrasted with the addition of bromine to the "double bond" of benzene followed by elimination of hydrogen bromide has been given by Price.[5] A kinetic study of the reaction of sodium amide and pyridine is desirable in order to decide definitely between these alternate mechanisms.

Mercuration. Pyridine and many pyridine derivatives readily undergo mercuration with mercuric acetate[6,7] to give 3-pyridylmercuriacetate and its derivatives. When mercuric acetate is added to pyridine at room temperature, an addition compound is formed which

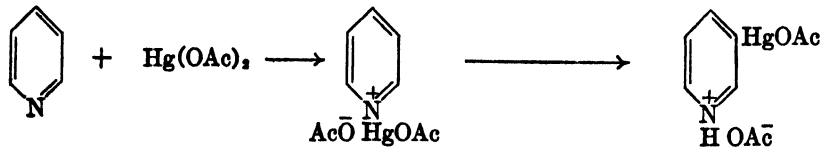
4 See Leffler, "The Amination of Heterocyclic Bases by Alkali Amides" in *Organic Reactions*, Vol. I, John Wiley & Sons, New York, 1942, Chapter 4.

5 Price, *Chem. Revs.*, **29**, 37 (1941). See also Price, *Reactions at Carbon-Carbon Double Bonds*, Interscience Publishers, Inc., New York, 1946, Chapter II.

6 Swany, Skeeters, and Shreve, *Ind. Eng. Chem.*, **32**, 360 (1940).

7 Kobe and Doumani, *Ind. Eng. Chem.*, **33**, 170 (1941).

is soluble in excess pyridine. If this is heated in the dry state [8] or, preferably, in the presence of water [6] at 155°, nuclear substitution takes place and a 35–50% yield of 3-pyridylmercuriacetate is obtained. The same type of reaction occurs at 100° with 2-aminopyri-



dine or at 150° with 2-picoline to give even better yields of the respective mercurated products. The fact that an amino group activates the substitution and that the only pure substitution product which has been isolated is the 3 isomer would indicate that this is an electrophilic substitution. This does not completely agree with the results on the mercuration of nitrobenzene, which at 150° is reported to give a 78% yield of mercurated products consisting of 52.6% *o*, 38.5% *m*, and 8.9% *p* isomers.[9]

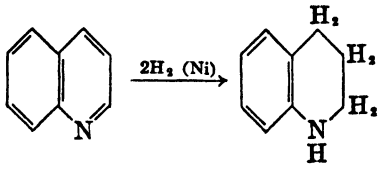
Grignard-Type Reactions. Just as treatment with sodium amide produces substitution in the α position in the pyridine nucleus (or in the γ position if both α positions are blocked), attack by nucleophilic reagents such as metalalkyls and alkali hydroxides results in products substituted in the 2 position. Thus, phenylmagnesium bromide and pyridine at 150° give 2- and 2,6-diphenylpyridine; butyllithium and pyridine at 100° give 2-butylpyridine; and phenyllithium reacts with pyridine in ether solution at room temperature to give as high as 50% yield of 2-phenylpyridine.[10]

Reduction. Pyridine is readily reduced by a variety of methods such as treatment with sodium in absolute alcohol or with hydrogen and a nickel catalyst, or electrolytically, in each case giving the hexahydro product, piperidine. The electrolytic method is the one employed commercially. Even under special conditions, it has not been possible to achieve the partial reduction of pyridine by direct methods. However, some pyridinecarboxylic acids have been reduced with aluminum amalgam in moist ether to dihydropyridinecarboxylic acids.[11] This reaction is accompanied by bimolecular reduction to a tetrahydrobipyridyl. The difficulty is not with any inherent instability of the dihy-

[8] McCleland and Wilson, *J. Chem. Soc.*, 1283 (1932).
[9] Ingold, *Ann. Repts., Progress Chem.* (*Chem. Soc. London*), **23**, 129 (1926).
[10] Evans and Allen, *Org. Syntheses Coll. Vol.* **2**, 517 (1943).
[11] Mumm and Beth, *Ber.*, **54**, 1592 (1921).

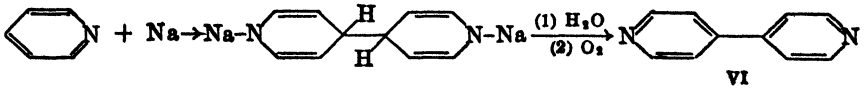
dropyridines since they can be obtained readily by the Hantzsch synthesis. Reduction of pyridine with hydriodic acid can result in cleavage of the ring with formation of pentane and ammonia. Similar hydrogenolysis constitutes an important side reaction in the catalytic reduction of pyridine with nickel catalyst when the temperature exceeds 150°.

The pyridine ring in quinoline is more readily hydrogenated than the benzene ring, and the only product which can be isolated is 1,2,3,4-tetrahydroquinoline. This indicates in general the greater



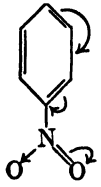
ease of reduction of pyridine compounds than of the corresponding benzene derivatives which is usually, but not invariably, the case. Similarly, the reduction of 2-phenylpyridine gives a good yield of 2-phenylpiperidine but not of 2-cyclohexylpyridine.

Alkali Metals. The alkali metals all react with pyridine, resulting in the formation of metal-substituted products of reduced bi- (and poly-) pyridyls. The structures of the metallo compounds are deduced from the tetrahydrobipyridyls which result on hydrolysis. These are very susceptible to oxidation even by atmospheric oxygen which converts them to bipyridyls. Accordingly, when sodium is added to dry pyridine at room temperature, a dirty, dark-green solution results from which the pyridine can be removed under vacuum, leaving a dark substance with the approximate composition $(C_5H_5N)_2Na$. This is apparently an addition compound of some sort, since, when it is warmed in vacuum, more pyridine is lost, leaving a dark substance that corresponds in composition to the sodium salt of the tetrahydrobipyridyl $(C_5H_5NNa)_2$. This dark substance on hydrolysis and air oxidation yields a mixture of 2,2′-bipyridyl and 4,4′-bipyridyl in which the 4,4′ compound predominates. When sodium is added to pyridine at the boiling point, a much more complex mixture results, containing, in addition, the 2,3′, 3,3′, and 3,4′ isomers. These reactions are indicated below for the 4,4′ isomer (VI).

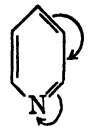


VI

Analogy with Nitrobenzene. A striking similarity between the substitution reactions of pyridine and nitrobenzene has been pointed out by Sidgwick.[12] This chemical resemblance is explained when we consider their respective formulas (VII and VIII). In VII, the strong



VII



VIII

attraction of the nitro group for electrons so displaces the electrons on the carbon atom to which it is attached that displacement of electrons from the *o* and *p* positions results; in VIII, the direct attraction of the ring nitrogen atom for electrons results in a similar electron displacement from the corresponding 2 and 4 positions. Thus, a direct analogy may often be drawn between the substitution reactions in the pyridine series and in the corresponding nitrobenzene derivatives. For example, the bromination of nitrobenzene is very difficult, requiring a special catalyst and temperatures of about 150°. This corresponds to the difficulty of bromination of pyridine, which requires a minimum of 300° and likewise gives a "*m* product" (substitution on the 3 position). Nitration and sulfonation of both nitrobenzene and pyridine are qualitatively similar. Nitrobenzene is attacked by finely pulverized, dry potassium hydroxide at 60–70° [13] to give predominantly the potassium salt of *o*-nitrophenol (45% yield), just as pyridine at 300° with sodium hydroxide gives the sodium salt of 2-hydroxypyridine.[14,15] As will be discussed a little later, the halogens in both *o*- and *p*-chloronitrobenzene on the one hand and 2- and 4-chloropyridine on the other hand are reactive and readily hydrolyze, as contrasted with chlorobenzene, *m*-chloronitrobenzene, or 3-chloropyridine. Neither nitrobenzene nor pyridine is known to take part in a Friedel-Crafts reaction.

The simple analogy between corresponding nitrobenzene and pyridine derivatives is a very useful additional criterion for predicting properties and reactions of the pyridine series. Of course, this analogy

[12] Taylor and Baker, *Sidgwick's Organic Chemistry of Nitrogen*, Oxford Press, London, 1942, p. 523.

[13] Wohl, *Ber.*, **32**, 3486 (1899).

[14] Chichibabin, *Ber.*, **50**, 1879 (1923).

[15] Barth and Schreder, *Ber.*, **12**, 417, 503 (1879).

TABLE 1

SUMMARY OF THE SUBSTITUTION REACTIONS OF NITROBENZENE AND PYRIDINE

Reaction	Product and percentage of yield from	
	Nitrobenzene	Pyridine
1. Nitration $HNO_3 + H_2SO_4$	*m*-Dinitrobenzene (83%) *o*-Dinitrobenzene (5%) *p*-Dinitrobenzene (3%) Fuming nitric acid, 95°	3-Nitropyridine (20%) Fuming sulfuric acid and KNO_3, 300°
2. Sulfonation $H_2SO_4 \cdot SO_3$	*p*-Nitrobenzene sulfonic acid (2%), Fuming sulfuric acid, 60–70°	Pyridine-3-sulfonic acid (70%), 230°, with $HgSO_4$ catalyst
3. Bromination Br_2	*m*-Bromonitrobenzene (60–75%), 135°, with reduced iron catalyst	3-Bromopyridine (35–40%) Pyridine hydrochloride at 300°
4. Mercuration $Hg(OAc)_2$	*o*-Nitrophenylmercuriacetate (53%) *p*-Nitrophenylmercuriacetate (9%) *m*-Nitrophenylmercuriacetate (38%), 150°	3-Pyridylmercuriacetate (50%), 155°
5. Amination $NaNH_2$	Only a small amount of sodium benzene diazotate	2-Aminopyridine (85%), 115° in dimethylaniline
6. Friedel-Crafts reaction $RX + AlCl_3$	No reaction	No reaction
7. Gomberg- Bachmann coupling $C_6H_5N_2ONa$	*p*-Nitrobiphenyl	2-Phenylpyridine (22%) 3-Phenylpyridine (9%) 4-Phenylpyridine (9%)
8. Hydroxylation KOH	*o*-Nitrophenol (45%), 70°	2-Hydroxypyridine, 300°
9. Lithiumphenyl	.....	2-Phenylpyridine (40–50%)

will not hold if the reaction involves the ring nitrogen atom, either in ring opening or in formation of pyridinium compounds. The analogy is not complete, furthermore, as shown by Bergstrom,[16] who has reported unsuccessful attempts to obtain *o*-nitroaniline from nitrobenzene and sodium amide.

Substitution Reactions of Pyridine Derivatives. Some broad generalizations are possible for the nuclear substitution reactions of pyridine derivatives. *o,p*-Directing groups such as amino, hydroxyl, and methoxyl greatly facilitate substitution in nitration, sulfonation, and halogenation reactions. There seems to be no exception to the *o,p*-directing influence of these groups, regardless of their position in the pyridine ring. On the other hand, the deactivating effect of such groups as nitro, sulfonic acid, and carboxyl for substitution by electrophilic reagents is such that, in the pyridine ring which is already resistant to such substitution, a second group cannot be introduced unless an activating radical is also present. Thus, it has been impossible to obtain a dinitro compound such as 3,5-dinitropyridine or a nitrocarboxylic acid such as 5-nitronicotinic acid by direct nitration. However, 2-amino-5-nitropyridine can be further nitrated under vigorous conditions to give 2-amino-3,5-dinitropyridine. The entering group always takes the position *ortho* or *para* to the activating group, and thus for most practical purposes the orientation influence of the *m*-directing groups is never apparent.

Addition Reactions of the Nitrogen Atom

The nitrogen atom in the pyridine ring has the structure typical of a tertiary amine; thus, three of the nitrogen's five valence electrons are shared by carbon, and the remaining two are present as an unshared pair. As a result, pyridine and its derivatives show most of the characteristic reactions of tertiary amines, the most important of which can be divided into four groups: (1) characteristic salt formation with acids, (2) complex formation, (3) oxidation by reagents such as persulfuric acid and benzoyl peroxide to give the amine oxide, and (4) formation of N-alkyl- and N-aryl-pyridinium compounds. In all these reactions, the unshared pair of electrons has become shared, resulting in a tetracovalent nitrogen.

Pyridine, a tertiary amine, is unaffected by nitrous acid, mild oxidizing agents such as dichromate, and acid anhydrides in the cold; it does combine with acid chlorides to give more or less unstable addition compounds. In this connection, it is interesting to note that pyri-

[16] Bergstrom and Buehler, *J. Am. Chem. Soc.*, **64**, 19 (1942).

dine itself is only slowly attacked by warm permanganate or dichromate solution, and because of this property it has been used as a solvent for various oxidations.

Salt Formation. Pyridine is a relatively weak base ($K_b = 2.3 \times 10^{-9}$) compared with triethylamine ($K_b = 4.4 \times 10^{-4}$) and ammonia ($K_b = 1.8 \times 10^{-5}$), but, in spite of this, it forms stable crystalline salts with all strong acids. Although a characteristic reaction of the tertiary amine hydrochlorides is the loss of an alkyl halide with the formation of a secondary amine on dry distillation,

$$R_3N \cdot HCl \rightarrow RCl + R_2NH$$

pyridine and pyridine derivatives cannot take part in such a reaction without opening of the very stable pyridine ring. As a consequence, the hydrochlorides of pyridine and the alkylpyridines are completely stable, even to distillation. The inert properties of the pyridine ring coupled with the ability to form stable salts account for the wide use of pyridine in chemical reactions as a proton acceptor. Thus, in the conversion of alcohols (especially an alcohol which has a branch on the carbon atom adjacent to the carbinol group) to the corresponding alkyl halides by treatment with thionyl chloride, the presence of acid can easily lead to rearrangements. If the reaction is conducted in the presence of pyridine, the sulfur dioxide and hydrogen chloride which are liberated react with the pyridine as they are formed, thereby reducing rearrangements to the minimum. Treatment of isobutyl alcohol with hot hydrochloric acid results in a mixture of the expected isobutyl chloride and the rearranged *t*-butyl chloride, but treatment with thionyl chloride in the presence of pyridine by the Darzens method gives essentially pure isobutyl chloride. In addition, pyridine or a similar base such as quinoline has often been employed for the removal of HX from a halogen-substituted ester or similar compound under anhydrous conditions. For example, removal of hydrogen bromide from ethyl *d*-bromosuccinate by dry powdered sodium hydroxide is accompanied by hydrolysis of the ester by the water formed in the reaction between hydrogen bromide and sodium hydroxide. When pyridine is the base, no hydrolysis can occur.

$$C_2H_5OOCCHBrCH_2COOC_2H_5 + C_5H_5N \rightarrow$$
$$C_2H_5OOCCH{=}CHCOOC_2H_5 + C_5H_5N \cdot HBr$$

The pyridine salts (with the exception of the chloroaurate, chloroplatinate, and mercurichloride) all show the characteristic water solubility expected.

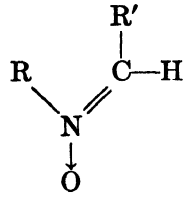
Complex Formation. Pyridine and pyridine derivatives form a large number and variety of addition compounds with both organic and inorganic substances. These addition compounds will be considered in greater detail in connection with the many reactions of pyridine. It will be sufficient for the present to point out a few examples. Perhaps the simplest of the pyridine addition compounds is the hydrate ($C_5H_5N \cdot 3H_2O$) which boils at 92–93°. Pyridine forms stable addition compounds with many inorganic salts. A well-known example is tetrapyridine ferrous chloride (IX) [17] which crystallizes di-

$$FeCl_2 + 4C_5H_5N \rightarrow \left[\begin{matrix} & NC_5H_5 & \\ C_5H_5N: & \ddot{Fe} & :NC_5H_5 \\ & \ddot{N}C_5H_5 & \end{matrix} \right]^{++} 2Cl^-$$

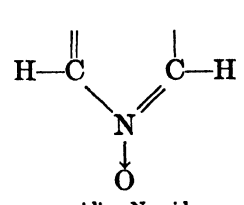
IX

rectly when a saturated ferrous chloride solution is mixed with the theoretical quantity of pyridine. The most extensively studied group of addition compounds with organic substances is that comprising the pyridine-phenol complexes. These complexes are, as a rule, difficultly soluble and have been used to separate phenols from solution. This property has added greatly to the difficulty of separating the phenols and pyridine bases in coal tar oils.[18]

Amine Oxides. When pyridine is treated with a peroxide oxidizing agent, pyridine N-oxide ($C_5H_5N \rightarrow O$) (XI) with tetracovalent nitrogen is formed. The usual oxidizing agents are perdisulfuric acid ($H_2S_2O_8$), permonosulfuric acid (Caro's acid, H_2SO_5), perbenzoic acid (C_6H_5COOOH), or monoperphthalic acid [o-$C_6H_4(COOH)(COOOH)$]. Pyridine N-oxide is a water-soluble white crystalline substance which is easily isolated as its picrate and behaves as a typical tertiary amine oxide in its reactions.[19] The structural and chemical



aldonitrone
X



pyridine N-oxide
XI

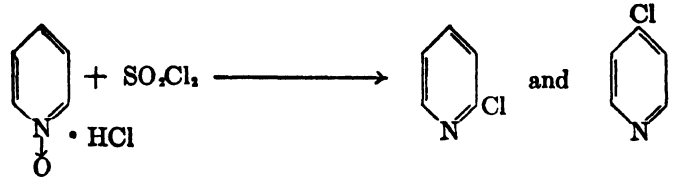
[17] Baudisch and Hartung, *Inorganic Syntheses*, Vol. I, McGraw-Hill Book Co., New York, 1939, p. 184.

[18] Wille, *Brennstoff-Chem.*, **23**, 271 (1942) [*C. A.*, **37**, 3757 (1943)].

[19] Meisenheimer, *Ber.*, **59**, 1848 (1926).

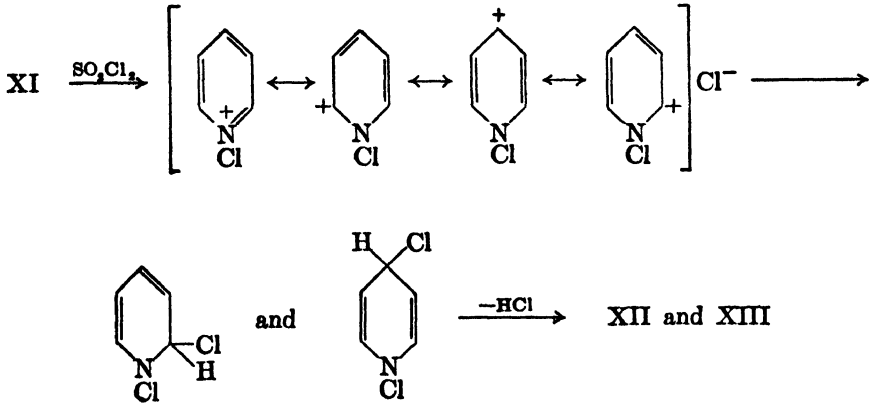
relationship existing between pyridine N-oxide (XI) and the aldonitrones (X) has been discussed by Colonna.[20] Although many interesting products are obtained by the pyrolysis of the aliphatic and aromatic amine oxides,[21,22] the thermal decomposition of pyridine N-oxides seems not to have been studied. Pyridine N-oxide reacts readily with phenylmagnesium bromide, and the product isolated on hydrolysis is 2-phenylpyridine.

The action of phosphorus oxychloride on the N-oxides of quinoline and its derivatives has been studied extensively as a method of synthesis for the corresponding 2- and 4-chloroquinolines,[23] but the reaction in the pyridine series [24] proceeds only after heating the reactants in a sealed tube at 120°. The two products (XII and XIII) are



XI XII XIII

obtained in the ratio of 43 to 57 and can be separated by fractional crystallization of the mercuric chloride addition compounds. This reaction has been only of theoretical importance, since the resultant products, 2- and 4-chloropyridine (XII and XIII), are obtained more



20 Colonna, *Boll. sci. facoltà chim. ind. univ. Bologna*, **1940**, No. 4, 134 [*C. A.*, **34**, 7290 (1940)].

21 Bamberger and Leyden, *Ber.*, **34**, 12 (1901).

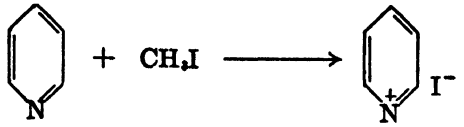
22 Meisenheimer, *Ber.*, **52**, 1667 (1919).

23 Bachman and Cooper, *J. Org. Chem.*, **9**, 302 (1944).

24 (*a*) Bobranski, Kochanska, and Kowalowska, *Ber.*, **71**, 2385 (1938); (*b*) Wibaut and Broekma, *Rec. trav. chim.*, **60**, 207 (1941) [*C. A.*, **35**, 5112 (1941)].

readily by other methods. It can be considered to take place through the mechanism shown above.

Alkyl- and Aryl-pyridinium Compounds. *Pyridinium Salts.* An important group of addition compounds comprises the quaternary alkyl- and aryl-pyridinium salts. When methyl iodide is added to pyridine, the mixture must be cooled in order to control the vigorous reaction which ensues. The reaction is usually conducted in an inert solvent such as benzene from which the N-methylpyridinium iodide (XIV)



XIV

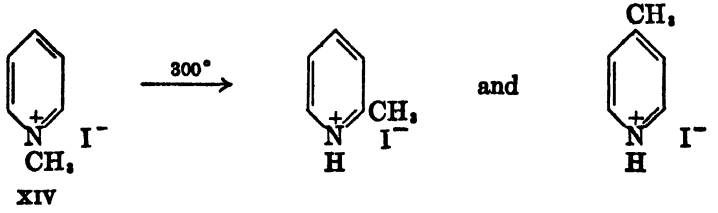
(often referred to as pyridine "methiodide") separates as a white crystalline material in nearly quantitative yields. In a similar manner, dimethyl sulfate reacts to give N-methylpyridinium methyl sulfate (or pyridine "methosulfate"), which differs only in the nature of the

$$C_5H_5N + (CH_3)_2SO_4 \rightarrow C_5H_5\overset{+}{N}—CH_3 \cdot CH_3SO_4^-$$

anion. These quaternary ammonium salts are crystalline solids, easily soluble in water, and give strongly conducting solutions. Although many of the typical tetraalkylammonium halides decompose

$$R_4NX \rightarrow R_3N + RX$$

instead of melting, yielding a tertiary amine and an alkyl halide, the simpler pyridinium halides in general are more stable and have well-defined melting points. When the pyridinium halides are heated above 300° in a sealed tube, however, rearrangement takes place, resulting in nuclear alkylation. This is the well-known Ladenburg synthesis [25] of alkylpyridines. The mechanism of this rearrangement is uncertain.



XIV

[25] (*a*) Ladenburg, *Ber.*, **16**, 1410, 2059 (1883); **32**, 42 (1899); (*b*) Ladenburg and Schrader, *Ann.*, **247**, 22 (1888); (*c*) Chichibabin and Rjumschin, *J. Russ. Phys. Chem. Soc.*, **47**, 1297 (1915); *Chem. Zentr.*, **1916**, II, 146.

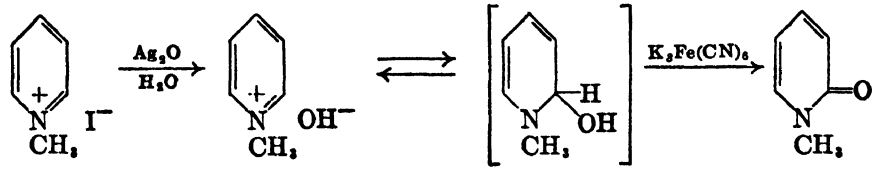
Instead of being a true rearrangement, it has been considered [26] to be a dissociation into methyl iodide and pyridine, followed by nuclear alkylation in a manner similar to the Hofmann-Martius migration which occurs when the salts of N-alkylanilines are heated above 250°. This interpretation is open to the objection that the entering methyl group in such a reaction should prefer the β position, whereas in actual practice a mixture of α- and γ-picolines is obtained; no definite conclusions can be drawn until further evidence is available. The reaction is of little interest in the pyridine series, since the resulting alkylpyridines are usually more readily available from other sources.

The N-alkylpyridinium iodides and methosulfates are readily converted into the corresponding chlorides by treatment with a suspension of silver chloride. Alternatively, N-methylpyridinium chloride may be obtained by the direct action of methyl chloride on pyridine in a sealed vessel at 70° or by heating a mixture of pyridine hydrochloride in methanol to 230°.

Pyridinium Hydroxides. In a similar manner, treatment of an N-alkylpyridinium halide with moist silver oxide gives rise to an N-alkylpyridinium hydroxide (XV).

These products have not been isolated in pure crystalline form but are obtained as syrups when their aqueous solutions are evaporated to dryness. The reactions of the pyridinium hydroxides described later are reactions performed on a solution of the N-alkylpyridinium halide which has been made basic.

Pseudobases. A characteristic reaction of the N-alkylpyridinium hydroxides is illustrated by the oxidation of N-methylpyridinium hydroxide (XV) to N-methyl-2-pyridone (XVI), with potassium ferricyanide. Principally on the basis of this evidence, it has been postu-



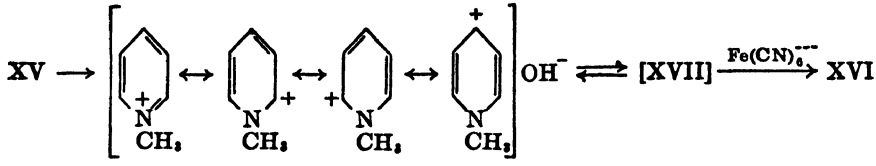
XIV XV XVII XVI

lated that the N-methylpyridinium hydroxide (XV) rearranges to the 1-methyl-2-hydroxy-1,2-dihydropyridine (XVII), which belongs to the class of compounds known as pseudobases or carbinol bases.[22,23] This postulate readily lends itself to experimental verification, since

[26] Taylor and Baker, *Sidgwick's Organic Chemistry of Nitrogen*, Oxford Press, London, 1942, p. 524.

the properties of the quaternary ammonium hydroxide (XV) (which is a strong base and an electrolyte) differ widely from those of the carbinol base (XVII) (which is a tertiary amine and a relatively weak base). Hantzsch and Kalb [27] were able to test this theory by measuring the conductivity of a solution of N-methylpyridinium iodide immediately after neutralization by alkali. There was no decrease in conductivity with time, as would be expected if the conversion of XV to XVII took place, and accordingly there is no justification for considering the pyridinium hydroxides mainly in the pseudobase form (XVII). This must not be taken as a generalization for other heterocyclic quaternary hydroxides, since the existence of true carbinol bases in other ring systems such as acridine and dihydropyrazine is well established.

The fact that N-methyl-2-pyridone (XVI) is obtained upon oxidation of the basic solution from N-methylpyridinium iodide indicates that a substance such as XVII or its precursor is potentially present in solution. The pyridinium hydroxide (XV) undoubtedly exists as a resonating ion in which the state XVIII makes an important but minor contribution. It can react in this state with hydroxyl ion to give the carbinol base (XVII) by an equilibrium reaction, but, irreversible removal of the carbinol base (XVII) from the equilibrium by oxidation to the pyridone (XVI) allows a shift in the equilibrium to the right and eventually results in the conversion of all the N-methylpyridinium



XVIII

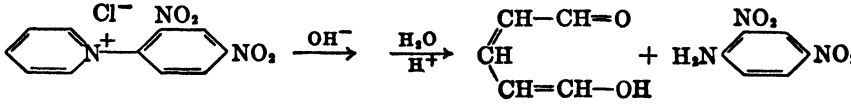
hydroxide (XV) to the N-methylpyridone (XVI). It is possible that XVII has no real existence, but that the mechanism of oxidation is such that the reaction can proceed directly from the resonating ion (XVIII) to the pyridone (XVI).

It would be expected that the completely conjugated structure of N-methylpyridinium hydroxide (XV) would be much more stable than that of the carbinol base, 1-methyl-2-hydroxy-1,2-dihydropyridine (XVII). The evidence supports this conclusion, and both Hantzsch and Kalb [27] and Aston and Lasselle [28] have concluded from their studies that very little, if any, of the carbinol base exists in solution.

[27] Hantzsch and Kalb, *Ber.*, **32**, 3109 (1899).

[28] Aston and Lasselle, *J. Am. Chem. Soc.*, **56**, 426 (1934).

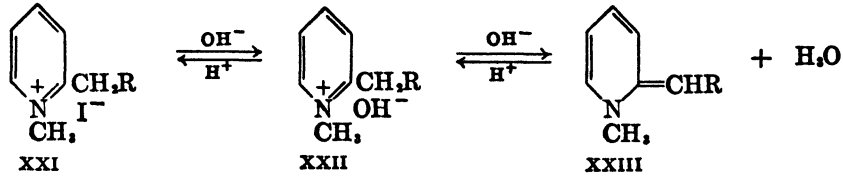
The presence of the carbinol base or its precursor in equilibrium with the quaternary hydroxide even in small amounts should render the alkylpyridinium hydroxides susceptible to alkaline hydrolytic ring cleavage. Although little work seems to have been published along this line, Decker and Kaufmann [29] have reported the very slow liberation of methylamine when N-methylpyridinium iodide is boiled with 10% sodium hydroxide. When, instead of a simple alkyl substituent on the ring nitrogen, there is a strongly negative group such as 2,4-dinitrophenyl or cyano, this hydrolysis occurs readily. Many examples have been extensively studied. Probably the best known is that of N-(2,4-dinitrophenyl)pyridinium chloride (XIX), which gives glutaconic aldehyde (XX) and 2,4-dinitroaniline on treatment first



XIX XX

with cold alkali and then with acid. This hydrolysis and the nature of the intermediates will be discussed in detail under the ring-opening reactions of pyridine (p. 425).

Methylene Bases. When the quaternary halide of a 2-alkylpyridine is treated with sodium hydroxide or moist silver oxide in the cold, neither the quaternary ammonium hydroxide nor a pseudobase is formed, but instead a product results which has lost the elements of water and which for this reason is sometimes called an anhydro base (methylene base) (XXIII). The anhydro bases (XXIII) are often



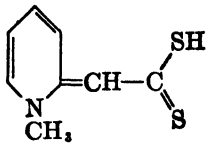
XXI XXII XXIII

obtained as analytically pure crystalline substances, and this, coupled with the fact that they are readily oxidized to the corresponding pyridones, leaves no doubt as to their structure. When a solution of 2-benzylpyridine methiodide (XXI, R = C_6H_5) is treated with strong sodium hydroxide, a product precipitates from the basic aqueous reaction mixture as a red-orange oil. When the substituent is *p*-nitrophenyl (XXIII, R = -*p*-$C_6H_4NO_2$), the product is a dark-blue crystal-

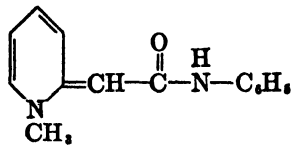
[29] Decker and Kaufmann, *J. prakt. Chem.*, [2] **84**, 229 (1911).

line precipitate. In this case, the methine group couples the conjugation of the phenyl ring with that of the dihydropyridine nucleus to form a stable, colored molecule.

If, on the other hand, the R group in XXI is hydrogen or an alkyl group as in 2-picoline, there is no precipitate.[30] The existence of the anhydro base in this case can be readily demonstrated. Such a base does not have the added stability that results from the coupled conjugation of an aromatic ring as illustrated by XXIII (R = C_6H_5) and, therefore, has been completely characterized only as certain addition derivatives, such as those with carbon disulfide or phenyl isocyanate (XXIV and XXV). Both methylene bases are recon-



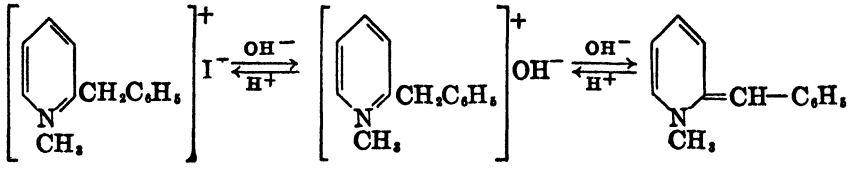
XXIV



XXV

verted to the quaternary iodides by treatment with hydriodic acid, and the equation (XXI–XXIII) must therefore be written as an equilibrium. As may be expected, the anhydro bases without a conjugated phenyl group revert to the quaternary salt (XXII) very readily, whereas those stabilized by conjugation (XXIII, R′ is aromatic) are reconverted much more slowly. The pyridinium iodide (XXI) is completely stable at ordinary temperatures, and there is no tendency for the loss of hydrogen iodide and formation of the anhydro base (XXIII) except in the presence of base.

When 1-methyl-2-benzylpyridinium iodide (XXVI) is treated with base, a definite equilibrium is established between the colorless

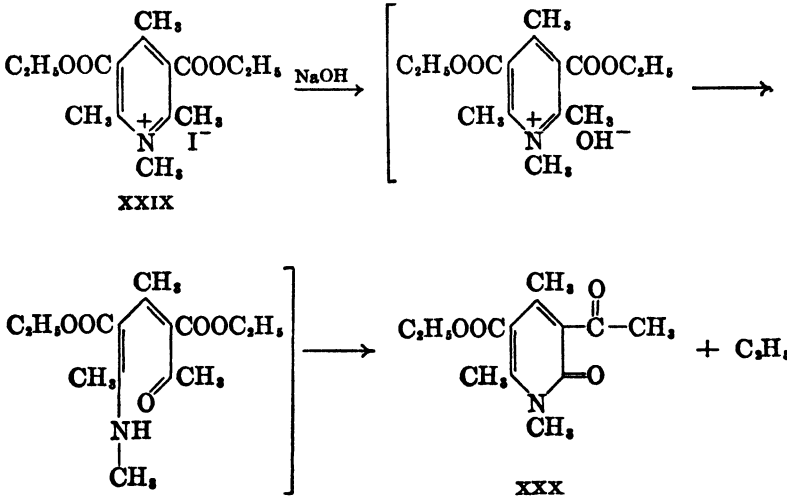


XXVI colorless XXVII yellow XXVIII

quaternary hydroxide (XXVII) and the methylene base (XXVIII), depending on the concentration of the sodium hydroxide solution. In the presence of solid sodium hydroxide, the 1-methyl-2-benzylidene-

[30] Hamer, Rathbone, and Winton, *J. Chem. Soc.*, 955 (1947).

1,2-dihydropyridine (XXVIII) separates as a yellow oil, which dissolves in water to give a colorless solution. This colorless solution, containing the quaternary hydroxide (XXVII), turns yellow if the sodium hydroxide concentration is raised to 20% or more, and the yellow oil which forms gives a crystalline phenyl isothiocyanate derivative. The formation of the methylene base is characteristic for many pyridine derivatives of a more complex nature, but the presence of other groups, such as in collidine-3,5-dicarboxylic ester, can lead to unexpected results. Hantzsch, and Mumm and Hingst [31] have studied the action of alkali upon the methiodide of collidine-3,5-dicarboxylic ester (XXIX) and have demonstrated the following conversions, which apparently involve hydrolysis with ring opening and subsequent ring closure in a different fashion to give N-methyl-4,6-dimethyl-3-acetyl-5-carbethoxy-2-pyridone (XXX).

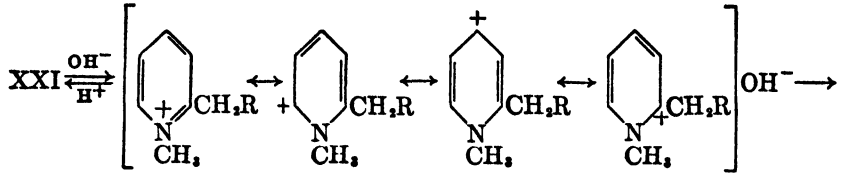


XXIX

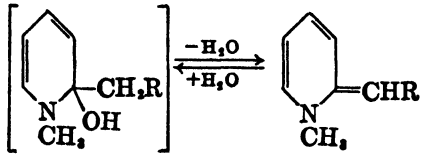
The mechanism for anhydro-base formation has been postulated to involve the formation of an intermediate pseudobase (XXXII) with subsequent loss of water to give the anhydro base (XXXIII). The situation is analogous to the oxidation of N-methylpyridinium hydroxide to N-methyl-2-pyridone with potassium ferricyanide. The quaternary iodide (XXI) on treatment with base is converted to the resonating ion (XXXI) and can theoretically rearrange to a hypothetical carbinol base (XXXII) which is unstable and immediately loses water to give the anhydro base (XXXIII). The formation of

[31] Mumm and Hingst, *Ber.*, **56**, 2301 (1923); *Ann.*, **443**, 278 (1925).

the carbinol base (XXXII) from the relatively stable resonating ion (XXXI) appears unlikely on grounds of energy involved, and it is



XXXI



XXXII XXXIII

more probable that the conversion of the resonating ion to the anhydro base takes place by a direct path involving stabilization merely by the expulsion of a proton, with the aid of basic ions which are present, from the methylene carbon atom. This course results in a compound which is quite stable, if the R group is aromatic; and, if the solubility conditions are favorable, the equilibrium will be forced essentially to completion in the direction of the methylene base (XXXIII).

Miscellaneous Addition Compounds. Pyridine is well known for its ability to form addition compounds with the halogens.[32] When bromine water is added to aqueous pyridine solution, a red crystalline substance of the formula $C_5H_5N \cdot Br_2$ precipitates. It can be obtained more readily in carbon tetrachloride. This addition compound reacts further with hydrogen bromide to form a crystalline salt, indicating

$$C_5H_5N \xrightarrow{Br_2} \underset{\text{XXXIV}}{C_5H_5N \cdot Br_2} \xrightarrow{HBr} C_5H_5N \cdot Br_2 \cdot HBr$$

that the unshared electron pair of the nitrogen atom is still available in the pyridine perbromide (XXXIV). The bromine in either of these addition compounds is only loosely bound since pyridine perbromide has been used as a mild brominating agent for organic compounds.[33] Even fluorine and pyridine will react to give a crystalline addition compound,[34] and chloroiodides or trichloroiodides likewise

[32] Williams, *J. Chem. Soc.*, 2783 (1931).

[33] Rosenmund and Kuhnhenn, *Ber.*, **56**, 1262 (1923).

[34] Simons and Herman, *Abstracts*, New York meeting of The American Chemical Society, 1947, p. 135.

form stable products.[35] Chlorine oxide gives a solid addition compound with pyridine which can replace chlorine oxide alone for many purposes.[36]

Sulfur dioxide reacts with pyridine to form a 1:1 addition compound ($C_5H_5N \cdot SO_2$).[37] The three picolines form similar compounds as well as two abnormal complexes $2(\alpha\text{-}CH_3C_5H_4N) \cdot 3SO_2$ and $\gamma\text{-}CH_3C_5H_4N \cdot 2SO_2$. The addition compound between sulfur trioxide and pyridine ($C_5H_5N \cdot SO_3$) and its use as a special mild sulfating agent will be taken up in the section on pyridine and its homologs (p. 481).

When acetyl chloride and pyridine are mixed, heat is evolved, and a stable salt, acetylpyridinium chloride, can be isolated by distillation.[38] Although a similar compound has not been isolated from the reaction mixture of benzoyl chloride and pyridine,[39] there seems to be little doubt that such a combination exists in solution, as will be indicated by some of the reactions of benzoyl chloride, pyridine, and ketones. These acylpyridinium derivatives appear to be much less stable than the corresponding alkyl and aryl derivatives. Their stability is such that both acetyl chloride in pyridine[40] and benzoyl chloride in pyridine[41] have been used for the acylation of alcohols and, particularly, enols.

Ring-Opening Reactions

Introduction. Another general reaction of the pyridine series which is without analogy in the chemistry of the benzene compounds involves the opening of the heterocyclic ring between the carbon and nitrogen atoms. In view of some of the reactions described in the preceding section which have been discussed in terms of the effect of a carbon-nitrogen double bond in the pyridine ring, it might be assumed that acid reagents would readily open the pyridine nucleus. The carbon-nitrogen double bond in aldimines and ketimines (I) is extremely vulnerable to attack by acid hydrolysis, and, if the static bond formula of pyridine is considered, it is apparent that a similar structure is present in pyridine. However, the corresponding hydrolysis of pyridine is not realized. Pyridine is completely stable in aqueous acid solution, even at 300°. This is further evidence that a true carbon-

35 Zappi and Fernandez, *Anales asoc. quim. argentina*, **27**, 102 (1939) [*C. A.*, **34**, 3741 (1941)].

36 Tang, U. S. pat. 2,210,268 (Aug. 6, 1941) [*C. A.*, **35**, 285 (1941)].

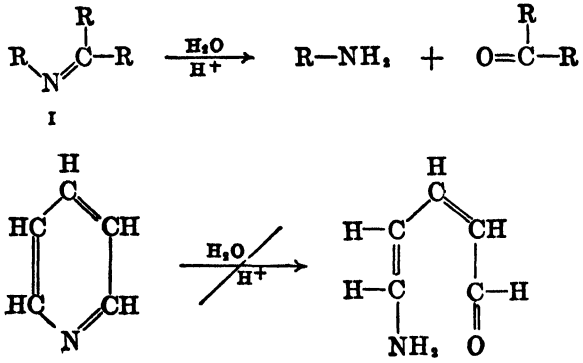
37 Hoffman and Vander Werf, *J. Am. Chem. Soc.*, **68**, 997 (1946).

38 Dennstedt and Zimmermann, *Ber.*, **19**, 75 (1886).

39 Prey, *Ber.*, **75**, 537 (1942).

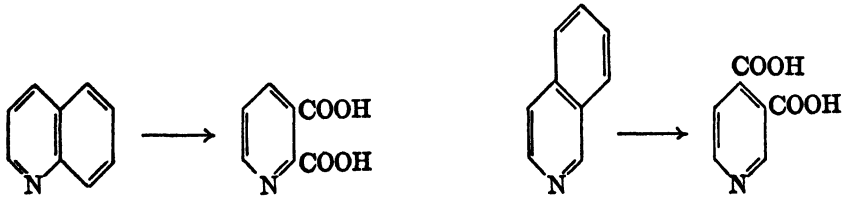
40 Claisen and Haase, *Ber.*, **33**, 1244 (1900).

41 McElvain and Kundiger, *J. Am. Chem. Soc.*, **64**, 254 (1942).



nitrogen double bond does not exist in the pyridine ring. If, on the other hand, we consider the "aromatic" character of the pyridine ring, it would be expected, from the well-known resistance of benzene to cleavage, that the corresponding opening of the pyridine ring would be equally difficult. In spite of the inert character of the pyridine ring with respect to splitting under most conditions, there are circumstances under which the ring is destroyed. In almost every such cleavage, this ring opening takes place at the nitrogen atom. The analogy that Kekule [1] drew in his early treatise is still pertinent. "Pyridine, like similar substances, is not really a ring, but a chain closed in a ring-shape by a lock. It appears as a ring, if the lock is treated as a member of the ring, but such a ring is always easier to open, and always at the lock, than a true ring containing equivalent members."

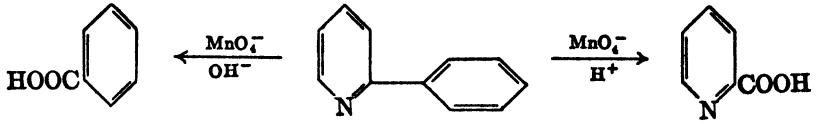
Oxidation. The resistance of the pyridine ring to rupture by oxidation is usually greater than that of benzene, as evidenced by the formation of pyridine-2,3-dicarboxylic acid (quinolinic acid) in good yields by the alkaline permanganate oxidation of quinoline, and also by the formation of pyridine-3,4-dicarboxylic acid (cinchomeronic acid) by the similar oxidation of isoquinoline. A study of the oxidation of 2-



quinoline — quinolinic acid — isoquinoline — cinchomeronic acid

1 Kekule, "Über die Konstitution des Pyridins," published in the biography *August Kekule* by Richard Anschutz, *Verlag Chemie, Berlin*, 1929, Vol. II, p. 768.

phenylpyridine under various conditions was conducted by Chichibabin. He found that the benzene ring was preferentially destroyed by oxidation with permanganate in acid solution, resulting in a 69% yield of picolinic acid, but that the pyridine ring was more readily attacked by basic permanganate oxidation, giving a 63% yield of benzoic acid. These results apparently conflict with those obtained



benzoic acid 2-phenylpyridine picolinic acid

above from the alkaline permanganate oxidation of quinoline and isoquinoline. A reinvestigation of Chichibabin's experiments [2] confirmed these findings, but additional experiments indicated that pyridine itself is much more stable to basic oxidation than it is to the action of oxidizing agents in acid solution. The resistance of pyridine to oxidation makes it a good solvent for the oxidation of substances which are relatively insoluble in aqueous solutions.

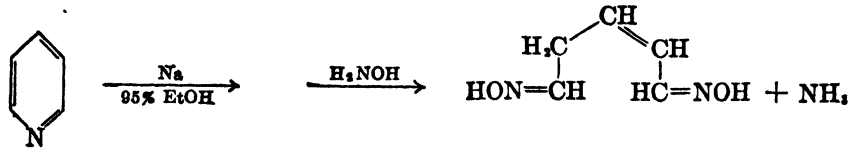
Reductive Cleavage. The non-aromatic reduced or partially reduced pyridine derivatives no longer retain the resistance to ring cleavage possessed by pyridine itself. Consequently, reduction under certain circumstances leads to fission of the six-membered ring. Of course, the reduction product, piperidine, can be subjected to special ring-opening reactions such as exhaustive methylation and the v. Braun degradation starting from N-benzoylpiperidine. A consideration of these reactions of piperidine will be taken up in the chapter on piperidine compounds. At present, it is sufficient to indicate some of the reductive methods which, when applied to pyridine, have led directly to opening of the ring. It is known, for instance, that the catalytic reduction of pyridine with nickel-type catalysts [3] gives *n*-amylamine, *n*-pentane, and ammonia, especially if the temperature is high. At approximately 140°, *n*-amylamine begins to appear as one of the products of reduction, and, above 200°, *n*-pentane and ammonia are the major by-products. These are probably formed by hydrogenolysis of the primary reduction product, piperidine.

$$C_5H_5N \xrightarrow[120°]{H_2(Ni)} C_5H_{10}NH \xrightarrow[140°]{H_2(Ni)} C_5H_{11}NH_2 \xrightarrow[200°]{H_2(Ni)} C_5H_{12} + NH_3$$

2 Tronov and Nikonova, *J. Russ. Phys. Chem. Soc.*, **61**, 541 (1929).
3 Sabatier and Mailhe, *Compt. rend.*, **144**, 784 (1907).

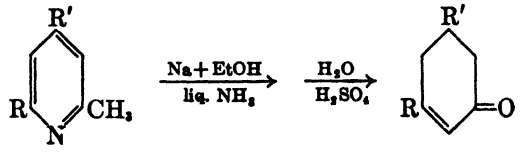
Treatment with concentrated hydriodic acid in a sealed container at 300° likewise reduces and cleaves pyridine into pentane and ammonium iodide.[4] Reduction of pyridine with cobalt sulfide catalyst results primarily in the formation of pentane,[5] and pyrolysis of pyridine cobaltic chloride complex and other similar addition compounds is reported to give a mixture of saturated hydrocarbons, hydrogen, nitrogen, alkylpyridines, 2-aminopyridine, and bipyridyl.[6]

It is indeed interesting that, when pyridine is reduced with sodium and 95% ethanol, only small amounts of piperidine are formed and the major product is either a non-distillable polymer[7] or glutaconic dialdehyde (27%), isolated as the dioxime. Apparently the aldehyde



groups are not free in the reduction mixture; otherwise, reduction would proceed to the alcohol stage. If the sodium reduction is conducted in absolute ethanol, however, good yields of piperidine are obtained.

Birch[8] has found that reduction of 2-picoline and its derivatives with sodium and alcohol in liquid ammonia gives cyclohexenone derivatives in yields from 12 to 30% (as high as 90% when the recovered picoline is considered). The reaction apparently involves a partial reduction of the pyridine ring followed by ammonolysis at the carbon-nitrogen bond and subsequent closure of the ring through the 2-methyl group.



R	R'	Yield (%)
—H	—H	12
—CH_3	—CH_3	30
—CH_3	—H	15
—H	—CH_3	17

Hydrolysis of Pyridinium Compounds. The pyridine ring does, however, offer a nitrogen atom with an unshared pair of electrons as

[4] Hofmann, *Ber.*, **16**, 590 (1883).

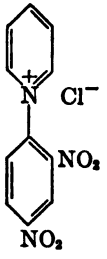
[5] Roberti, *Atti accad. naz. Lincei*, **13**, 527 (1931) [*C. A.*, **26**, 580 (1932)].

[6] Morgan and Burstall, *J. Indian Chem. Soc.*, Prafulla Chandra Ray Commemoration Vol., **1933**, 1 [*C. A.*, **27**, 5330 (1933)].

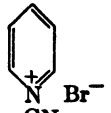
[7] Shaw, *J. Chem. Soc.*, **125**, 1930 (1924); **127**, 215 (1925); 300 (1937).

[8] Birch, *J. Chem. Soc.*, 1270 (1947).

a point of attack for possible ring-cleavage reactions. Some of the resulting pyridinium compounds have been discussed in the preceding sections in which it was stated that the quaternary salts such as N-methylpyridinium iodide were relatively stable to reactions that might open the ring. Boiling with strong base does seem to result in the slow evolution of methylamine, indicating a hydrolytic breakdown of the N-methylpyridinium hydroxide. With certain special pyridinium derivatives, this resistance to hydrolysis is completely lost. The pyridinium derivatives which have been studied most thoroughly from this standpoint are 2,4-dinitrophenylpyridinium chloride (II),[9,10] cyanopyridinium bromide (III),[11,12] pyridinium sulfonic acid (IV),[13] pyridinium chlorosulfonic acid,[14] and pyridylpyridinium chloride hydrochloride (V).[15]

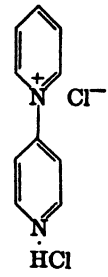


II



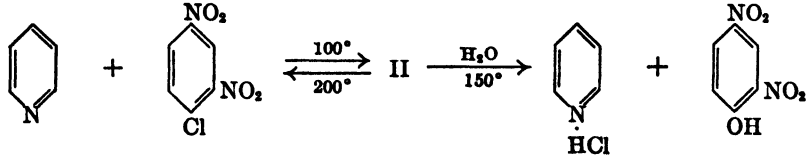
III

IV



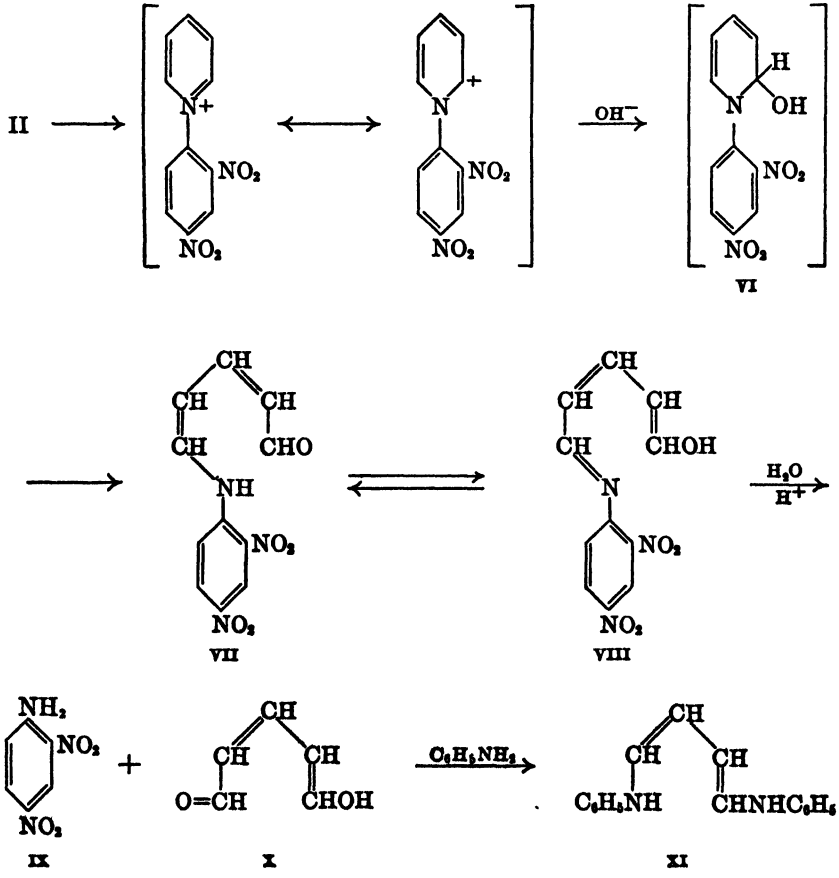
V

Probably the most studied and best known of these is Zincke's 2,4-dinitrophenylpyridinium chloride (II), which is formed in 89% yield by warming the two reactants on the steam bath.[16] It is an almost colorless, stable, crystalline compound which decomposes when heated to 200°, either dry or in a non-aqueous solvent, into pyridine and 2,4-dinitrochlorobenzene. If it is heated with water alone at 150°,



9 Zincke, *Ann.*, **330**, 367 (1904); Zincke and Wurker, *Ann.*, **338**, 107 (1905).
10 Zincke, Heuser, and Möller, *Ann.*, **333**, 296 (1904).
11 König, *J. prakt. Chem.*, [2] **69**, 105 (1904); [2] **70**, 19 (1904).
12 König and Becker, *J. prakt. Chem.*, [2] **85**, 353 (1912).
13 Baumgarten, *Ber.*, **59**, 1168 (1926).
14 Baumgarten, *Ber.*, **57**, 1624 (1924).
15 Koenigs and Greiner, *Ber.*, **64**, 1045 (1931); U. S. pat. 1,879,324 (Sept. 27, 1933) [*C. A.*, **27**, 313 (1933)].
16 Fisher and Hamer, *J. Chem. Soc.*, 189 (1933).

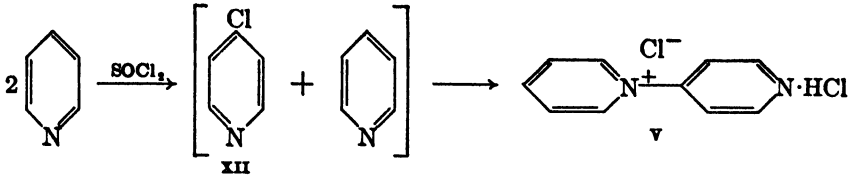
the products of hydrolysis are pyridine hydrochloride and 2,4-dinitrophenol, but if the quaternary salt is treated with a basic solution, even in the cold, a deep-red substance (m.p. ca. 180° dec.) is rapidly formed. The structure of this red compound was extensively investigated by Zincke. At first it was thought to be the carbinol base (VI), but there now seems to be little doubt that it has the open-chain structure of either VII or its tautomer (VIII). As yet, there has not been reported a well-founded case of the isolation of any substance corresponding to the carbinol-base structure (VI). The main evidence in favor of the open-chain structure (VII or VIII) is its color. Since II is almost colorless, VI, in which the conjugation of the pyridine has been destroyed, should, if anything, be less colored. On the other hand, the open-chain compound in the enol form, as represented by VIII, has a completely conjugated system and would therefore be ex-



pected to show strong absorption of visible light. Neither the pyridinium hydroxide nor the carbinol base (VI) has ever been isolated, but it seems likely that the reaction proceeds through these postulated intermediates, according to the sequence (II–VIII). Certainly the postulated pseudobase (VI), being a derivative of an aldimine, would be very susceptible to hydrolysis.

The red product resulting from treatment of II with base is very readily hydrolyzed by dilute acid into 2,4-dinitroaniline (IX) and glutaconic dialdehyde (X). X is not stable as such but is readily isolated in 70% yield as the dianil (XI) by addition of aniline. This series of reactions has been studied extensively and is the subject of several patents because of the brilliant color that the dianil (XI) and its derivatives impart to cotton.

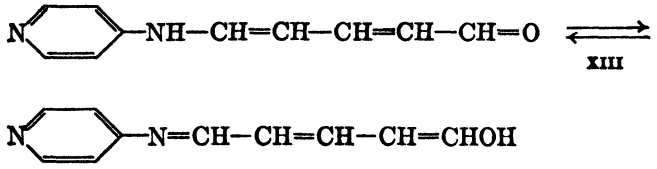
If we ascribe the ease of hydrolysis of pyridinium compounds to the presence of a strongly electron-attracting group on the nitrogen atom, then other similar compounds should be more or less susceptible to hydrolysis. In fact, there are many other examples of essentially the same type of ring-opening reaction in the pyridine series. A special variation uses N-(4-pyridyl)pyridinium chloride hydrochloride (V), which has been studied by Koenigs and Greiner.[15] If thionyl chloride is allowed to react with pyridine (3 days at room temperature or 5 hr. on the steam bath), N-(4-pyridyl)pyridinium chloride hydrochloride (V) is formed in fair yields, probably through the intermediate 4-chloropyridine (XII), as shown. This mechanism is substantiated by the



actual formation of V from 4-chloropyridine and pyridine under comparable conditions. The occurrence of nuclear substitution of chlorine by excess thionyl chloride is not uncommon in the pyridine series (p. 572). N-(4-Pyridyl)pyridinium chloride hydrochloride is analogous to N-(2,4-dinitrophenyl)pyridinium chloride (II), both in structure and in reactions. Koenigs and Greiner [15] report that, on hydrolysis with aqueous ammonia at 150° for 8 hr. in an autoclave, V gives a 60% yield of 4-aminopyridine. With water alone under the same conditions, the product is 4-hydroxypyridine (75% yield). Gluta-

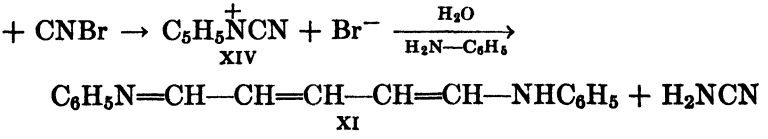
conic dialdehyde (IX) has also been isolated as its dianil (60% yield) and accounts for the second portion of the N-4-pyridylpyridinium ion.

If the hydrolysis is conducted in the presence of aniline, 4-phenylaminopyridine is formed; 4-phenoxypyridine is the product when potassium phenoxide solution is used. These hydrolysis products are readily explained by the same sequence of reactions outlined for the ring cleavage of N-(2,4-dinitrophenyl)pyridinium chloride. In this case, the electron attraction of the 4-pyridyl radical is not so great as that of the 2,4-dinitrophenyl group. As a result, the pyridinium ring is hydrolyzed with greater difficulty. The conditions necessary to bring about the hydrolysis are such that the intermediate XIII,



which is analogous to VII and VIII, is immediately converted to derivatives of glutaconic dialdehyde and 4-substituted pyridines. These reactions are sufficiently good to be of preparative value for 4-amino- and 4-hydroxypyridine.

In addition to the ring-opening reactions of N-(2,4-dinitrophenyl)-pyridinium chloride and N-(4-pyridyl)pyridinium chloride hydrochloride, there are several other reactions of a similar nature. Thus, cyanogen bromide reacts with pyridine to give N-cyanopyridinium bromide (XIV), from which the hydrobromide of glutaconic dialdehyde anil is readily obtained on treatment with aniline in aqueous solution. It

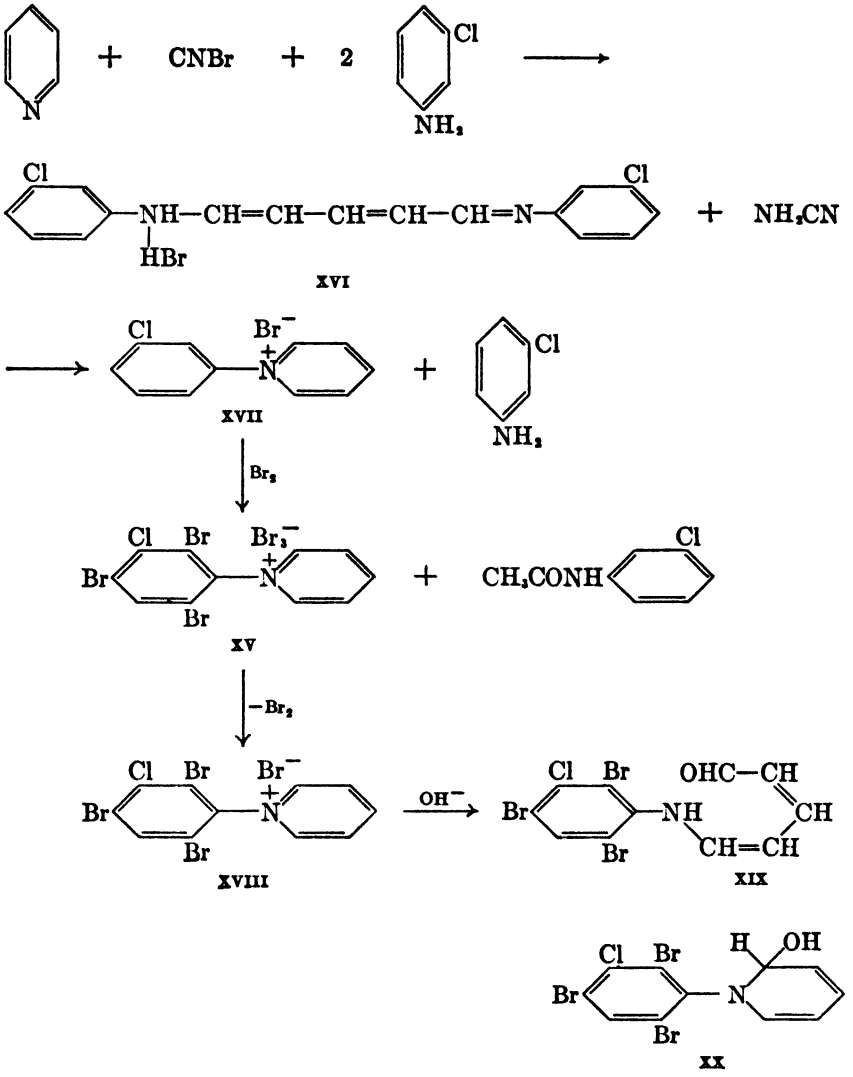


is not necessary to separate the N-cyanopyridinium bromide, which is difficult to obtain pure, but it is sufficient to treat the reaction mixture from pyridine and cyanogen bromide, as indicated in the reaction below, with *m*-chloroaniline.

König [17] studied the interesting case of 2,4,6-tribromo-3-chlorophenylpyridinium bromide (XVIII) and its hydrolysis. The di-*m*-chloro-

[17] König, *J. prakt. Chem.*, [2] **83**, 406 (1911).

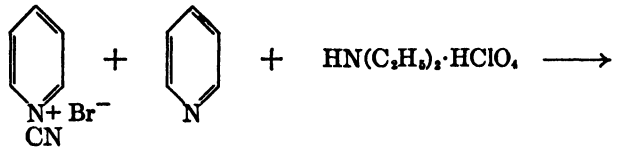
anil of glutaconic dialdehyde (XVI) was warmed in nitrobenzene, whereupon *m*-chloroaniline was split off and N-(*m*-chlorophenyl)pyri-



dinium bromide (XVII) was formed in 90% yield. When this product was treated with bromine in acetic acid solution, substitution on the phenyl ring took place, along with a certain amount of cleavage. On recrystallization from acetone, the perbromide (XV) lost a molecule of bromine to give the bromide (XVIII) as a white powder. When

XVIII was treated with cold basic solution or even with ammonium acetate, a yellow solution resulted from which could be isolated an unstable substance to which the open-chain structure XIX was assigned. Evidence for the glutaconic dialdehyde structure (XIX) instead of the carbinol base (XX) was found in the color as well as in the facility with which this product reacted with alcohol. On merely recrystallizing from ethanol, a molecule of solvent was taken up, giving a stable, crystalline ethyl alcoholate, presumably of semiacetal nature. Recrystallization from methanol resulted in an exchange to give the methyl alcoholate derivative. This behavior is similar to that of chloral and is circumstantial evidence in favor of the aldehyde representation (XIX).

Some remarkable reactions have been based on this opening of the pyridine ring by treatment with cyanogen bromide and subsequent hydrolysis. Schwarzenbach and Weber [18] have investigated the reactions of pyridine, cyanogen bromide, and various amines, for the purpose of making unusual polymethine derivatives. When an ethereal solution of cyanogen bromide and diethylamine perchlorate was added to pyridine, the perchlorate of a product was obtained (90% yield) which, from its properties, is undoubtedly correctly represented by XXI and which is formed according to the equation. On being warmed

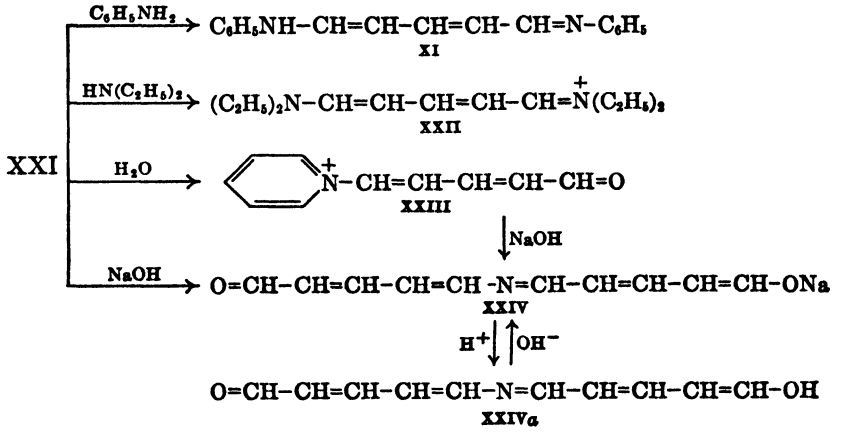


XXI

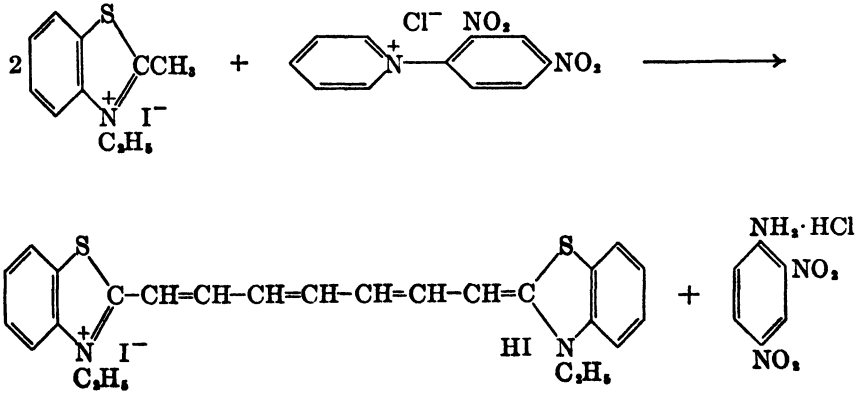
with aniline, this product was converted into 2 moles of the well-characterized dianil of glutaconic dialdehyde (XI). This could occur only by hydrolysis of a second pyridine ring and was the major evidence on which structure XXI was based. Treatment of XXI with diethylamine gave the diethylamino derivative (XXII) of glutaconic dialdehyde as the perchlorate, and warming with water gave the 5-pyridinium glutaconic dialdehyde (XXIII) as the almost colorless perchlorate salt. Treatment of either XXI or XXIII with ice-cold 2 *N* sodium hydroxide gave an intensely red-colored solution from which black

[18] Schwarzenbach and Weber, *Helv. Chim. Acta*, **25**, 1628 (1942).

crystals of the sodium enolate (XXIV) separated. On acidification with cold acetic acid, fine ochre-colored crystals of the dye (XXIV*a*) were formed.



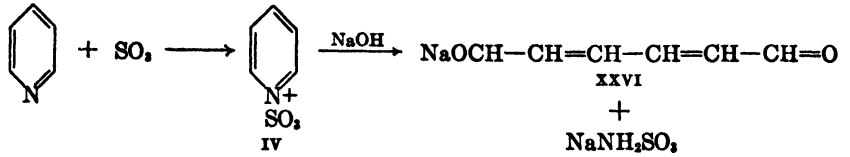
The cleavage of the pyridine ring by cyanogen bromide has also been employed for the formation of other polymethine compounds by Knunyantz and Kefeli [19] and by Fisher and Hamer,[16] who made a similar use of Zincke's N-(2,4-dinitrophenyl)pyridinium chloride. In the latter case, 2-methylbenzothiazole ethiodide (which possesses an active methylene group similar to that in 2-picoline) was treated with N-2,4-dinitrophenylpyridinium chloride in slightly basic solution with the formation of a polymethine cyanine type of dye (XXV).



XXV

[19] Knunyantz and Kefeli, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 628 (1945) [*C. A.*, **40**, 6079 (1946)].

Pyridine reacts with sulfur trioxide in an inert solvent in the cold to give N-pyridinium sulfonic acid (IV).[18] The same substance may be obtained by treating pyridine with either chlorosulfonic acid or ethyl chlorosulfate.[14] When IV is mixed with cold 20% sodium hydroxide, it is converted into the sodium salt of glutaconic dialdehyde (XXVI) and sodium sulfamate.

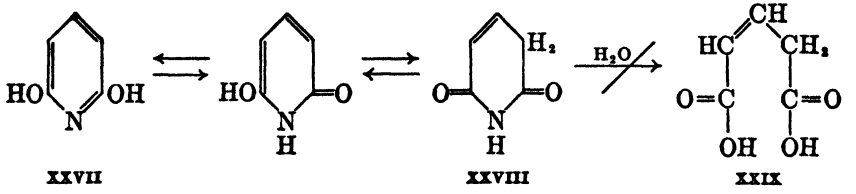


Another series of reagents, such as phosphorus pentachloride, phosphorus oxychloride, phosgene, and benzanilidimidochloride, forms quaternary pyridinium compounds in which the pyridine ring is opened by treatment with base.[20–22]

Other Ring-Opening Reactions. Pyridine reacts with sodium bisulfite solution to give a white crystalline addition compound containing 3 moles of bisulfite. This is reported to be decomposed by strong base into ammonia, sodium sulfite, water, and glutaconic aldehyde.[20,23]

It has been demonstrated that pyridine itself is slowly converted into open-chain products by exposure to ultraviolet light. Among the products are primary amines and glutaconic aldehyde or its derivatives.[24] This also applies to many pyridine derivatives and is one of the primary factors accounting for the yellowing of pyridine and pyridine compounds on standing.

It might be expected that a pyridine derivative such as 2,6-dihydroxypyridine (XXVII), which, in the carbonyl form, is commonly called glutaconicimide (XXVIII), would be readily hydrolyzed to the corresponding glutaconic acid (XXIX) (or acid amide), just as phthal-

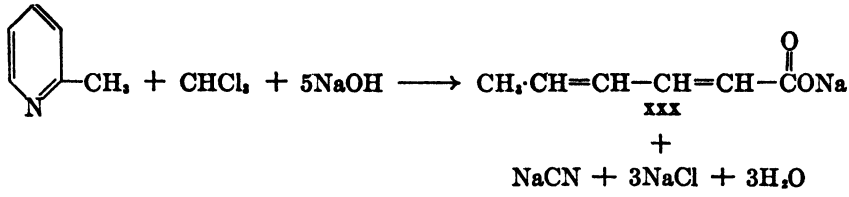


XXVII XXVIII XXIX

20 Reitzenstein and Breuning, *Ber.*, **43**, 2939 (1910).
21 König and Bayer, *J. prakt. Chem.*, [2] **83**, 325 (1911).
22 Treibs, *Ann.*, **497**, 297 (1932).
23 Schenkel, *Ber.*, **43**, 2597 (1910).
24 Freytag, *Ber.*, **67**, 1995 (1934); **69**, 32 (1936).

imide is hydrolyzed to phthalic acid. However, the majority of reports indicate that it is stable to hydrolysis under ordinary conditions, although it is susceptible to air oxidation.

It has been reported [17] that pyridine, chloroform, and sodium hydroxide form an unstable red dye solution on standing. After several months of standing, sodium cyanide and the sodium salt of β-vinyl-



acrylic acid were found in the solution. 2-Picoline in an analogous manner gives sorbic acid (XXX).

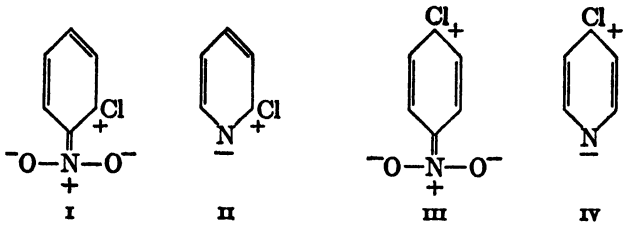
REACTIVITY OF PYRIDINE DERIVATIVES

Halopyridines

The halogens in 2- and 4-chloropyridines are easily hydrolyzed or replaced with amines, just as are the halogens in *o*- and *p*-chloronitrobenzene. Although chlorobenzene must be heated to approximately 350° with sodium carbonate and copper catalyst to achieve hydrolysis (Dow process), *o*-chloronitrobenzene is readily hydrolyzed by the same reagents at 100°, and 2-chloropyridine is reported [1] to undergo conversion to 2-hydroxypyridine in quantitative yield if heated to the boiling point (170°) with potassium hydroxide solution. This reactivity is not shared by 3-chloropyridine. The same reactivity of the 2-halopyridines is noted in the reaction of 2-bromopyridine with amines [2] and completely parallels the reactivity of *o*-bromonitrobenzene.[3]

The carbon atom which is substituted with a chlorine atom, by virtue of its relationship to either the nitro group in *o*-chloronitrobenzene or the ring nitrogen atom in 2-chloropyridine, has a lowered electron density because of resonance structures such as I and II and thus serves as an easy point of attack by a negative reagent.

1 Räth, Brit. pat. 288,629 (April 14, 1927) [*C. A.*, **23**, 670 (1929)].
2 Whitmore, Goldsmith, and Mosher, *J. Am. Chem. Soc.*, **67**, 393 (1945).
3 Adams, Weisel, and Mosher, *J. Am. Chem. Soc.*, **68**, 883 (1946).



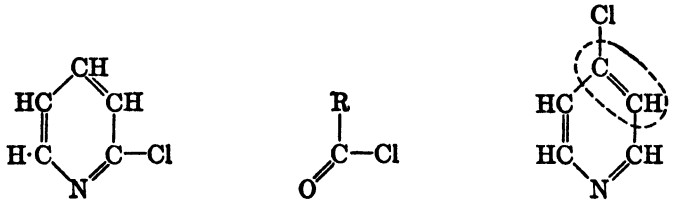
I II III IV

It is apparent that the effect of an acid on II (and on IV by analogy to III) should be to increase further the electron attraction of the ring nitrogen (see p. 404) and consequently should increase the vulnerability to attack on the α and γ positions by nucleophilic reagents. This fact has been demonstrated by Banks [4] in the acid-catalyzed reaction of α-haloheterocyclic compounds with aniline and substituted anilines.

It is also apparent, as indicated by formula IV, that this effect will be transmitted to the γ position in 4-chloropyridine. Of course, a chlorine atom in the *m* or β positions cannot be so activated.

There are many properties of pyridine and pyridine derivatives which have been explained on the basis of a carbon-nitrogen double bond in the ring. These are the properties of an ammono aldehyde ether (or an ammono keto ether) as designated by Franklin [5] and developed by Bergstrom.[6]

For example, the reactivity of 2-chloropyridine (V) can be compared to the reactivity of an acid chloride (VI), its closest analog in



V VI VII

the oxygen system of compounds. The similar reactivity of the 4-chloropyridines has been explained from this viewpoint on the basis of the principle of vinylogy,[7] according to which the effect of the carbon-nitrogen "double bond" will be transmitted across the vinyl group to the γ position, as indicated in VII. The chlorine atom shows a re-

[4] Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

[5] Franklin, *The Nitrogen System of Compounds*, A.C.S. Monograph Series, Reinhold Publishing Corp., New York, 1935.

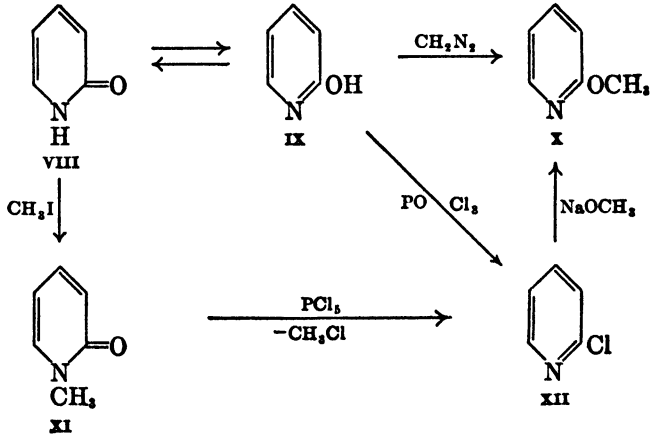
[6] Bergstrom, *Chem. Revs.*, **35**, 77 (1944).

[7] Fuson, *Chem. Revs.*, **16**, 1 (1935).

activity which would be expected if the vinyl group, encircled in VII, were not interposed between the chlorine atom and the nitrogen-carbon double bond. This, of course, does not explain why the halogen in 2- or 4-chloropyridine is reactive but only compares it to the more familiar acid chlorides. Actually, the reason for the reactivity in both the acid chloride and 2-chloropyridine is the same, namely, the carbon to which the halogen is attached has a lowered electron density by virtue of the fact that the adjacent oxygen or nitrogen atom has an even greater attraction for electrons. The resulting "positive" carbon atom is more readily attacked by reagents such as ammonia, water, sodium hydroxide, and sodium methoxide which can furnish electrons to the carbon atom.

Hydroxypyridines

The potential nitrogen-carbon double bond in pyridine allows a tautomerism between two distinct forms of certain pyridine derivatives such as 2-hydroxypyridine, 2-aminopyridine, and 2-methylpyridine, which leads to many reactions unique to such α-substituted pyridines or related heterocyclic nitrogen compounds. Accordingly, 2-hydroxypyridine shows reactions which lead to the conclusion that it has either structure VIII or IX. Treatment of 2-hydroxypyridine with phos-



phorus oxychloride or phosphorus pentachloride results in the formation of 2-chloropyridine in excellent yield. Likewise, treatment of 2-hydroxypyridine with diazomethane gives only 2-methoxypyridine (X). Since this same substance is obtained from 2-chloropyridine by treatment with sodium methoxide, there can be no doubt as to its

structure. On the other hand, treatment of 2-hydroxypyridine with methyl iodide results in the formation of N-methyl-2-pyridone (XI). Many other conditions leading to the formation of one or the other of these isomers will be given later under the specific discussion of the hydroxypyridines (p. 534). It should be emphasized that two

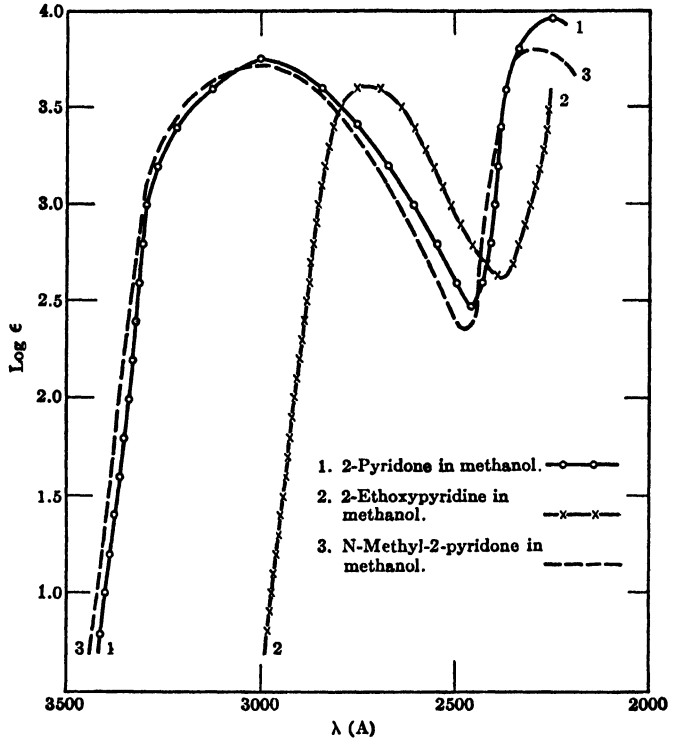


FIGURE 1

separate compounds corresponding to structures VIII and IX, which we commonly designate as 2-pyridone and 2-hydroxypyridine (or α-pyridone and α-hydroxypyridine), respectively, have never been isolated. Instead, only one substance is known to which two different names are applied, the name depending on the property that the author wishes to emphasize.

An analysis of the ultraviolet absorption spectra of these substances likewise leads to the conclusion that 2-hydroxypyridine exists in two different forms. The curves for 2-hydroxypyridine and N-methyl-2-pyridone in *neutral solution* are almost identical (Fig. 1, curves 1 and

3). Since there is no possibility of tautomerism with N-methyl-2-pyridone, it follows that in neutral solution 2-hydroxypyridine exists primarily in the pyridone form VIII.[8] The absorption spectra of 2-ethoxypyridine in *neutral solution* (Fig. 1, curve 2) differs consid-

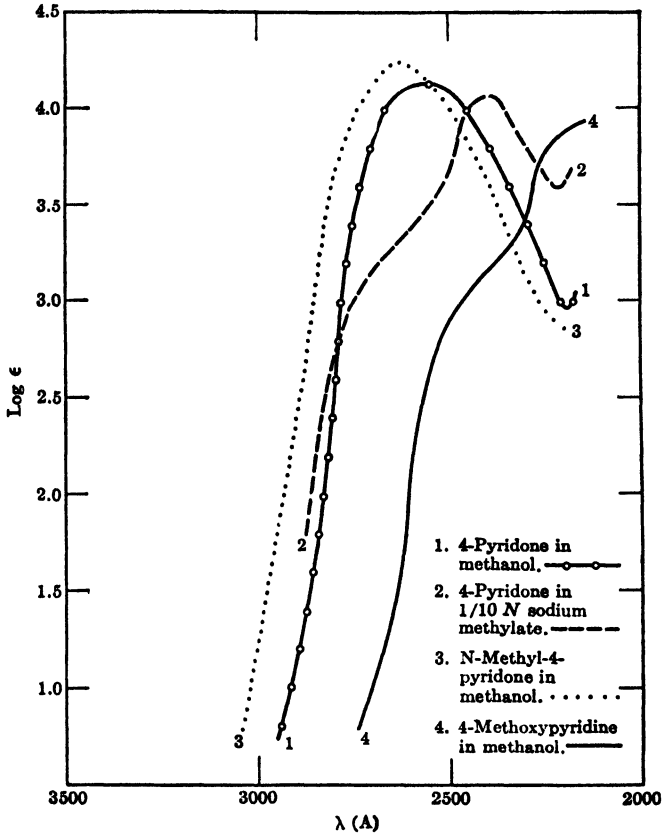


FIGURE 2

erably from that of either 2-hydroxypyridine or 2-pyridone. In *basic solution,* however, the absorption of 4-hydroxypyridine (Fig. 2, curve 2) differs greatly from that of N-methyl-4-pyridone (Fig. 2, curve 3), but it does have the same characteristic shape as that of 4-methoxypyridine (Fig. 3, curve 4), although it is shifted towards the longer wavelengths. Finally, the absorption curves for 4-hydroxypyridine, 4-methoxypyridine, and N-methyl-4-pyridone in hydrochloric acid

[8] Specker and Gawrasch, *Ber.*, 75, 1338 (1942).

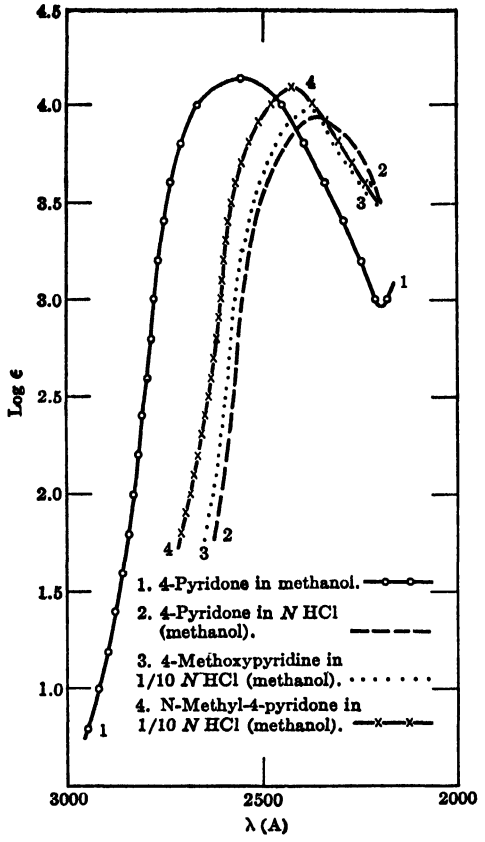
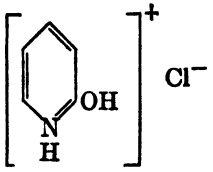
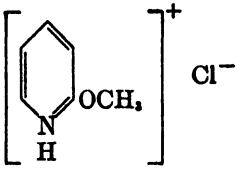


FIGURE 3

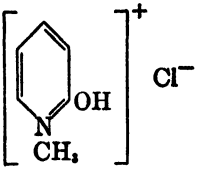
(Fig. 3) are all very closely related. This can best be explained by the following formulas for IX, X, and XI in acid solution. The facts



2-hydroxypyridine hydrochloride

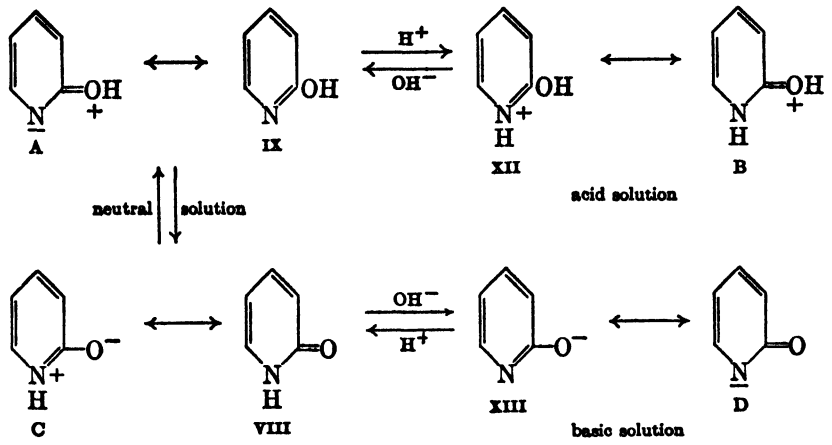


2-methoxypyridine hydrochloride



N-methyl-2-pyridone hydrochloride

are readily reconciled with the following representations for the ionic structures of the analogous 2-hydroxypyridine molecule in either acid or basic solution.



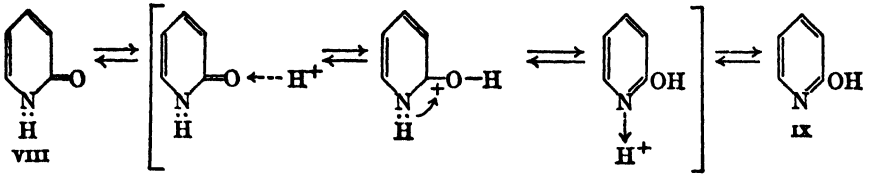
2-Hydroxypyridine is an amphoteric substance giving both a sodium salt in strong sodium hydroxide solution and a hydrochloride when dry hydrogen chloride is bubbled into its ether solution. Whether a specific reaction will give a derivative of 2-hydroxypyridine (IX) or of 2-pyridone (VIII) must depend on the acidic or basic conditions of the environment, the specific nature of the reagent, and the relative contributions of such forms as A and B or C and D, above. Assuming that we are concerned with a reaction in acid solution, then the determining factor is which form, XII or B, of the resonating state is assumed by the 2-hydroxypyridine molecule as the reacting reagent approaches. The physical evidence of absorption spectra seems to indicate definitely that in neutral solution 2-hydroxypyridine exists predominantly in the pyridone structure (VIII) with an appreciable contribution from its resonance form C. This conclusion is substantiated by evidence from the electric moments of pyridine derivatives.[9] Other resonance forms which are analogous to the known forms of phenol [10] may be written, but they are subordinate in importance. It should be pointed out that N-methyl-2-pyridone still retains the characteristic absorption of an aromatic ring.[8,11] This can only mean that such forms as C are relatively important in its structure.

In common with all tautomerisms, the change of VIII to IX does not take place by a direct shift of the hydrogen from the nitrogen atom to the oxygen atom, but instead it occurs through the approach of a proton from solution to the oxygen atom and the concomitant expulsion of the hydrogen without its electrons from the nitrogen atom.

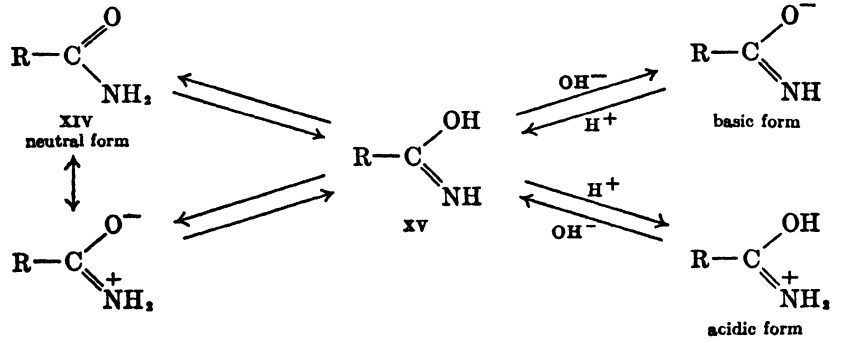
9 Leis and Curran, *J. Am. Chem. Soc.*, **67**, 79 (1945).

10 Wheland, *The Theory of Resonance*, John Wiley & Sons, New York, 1944, p. 72.

11 Arndt and Kalischek, *Ber.*, **63**, 587 (1930).



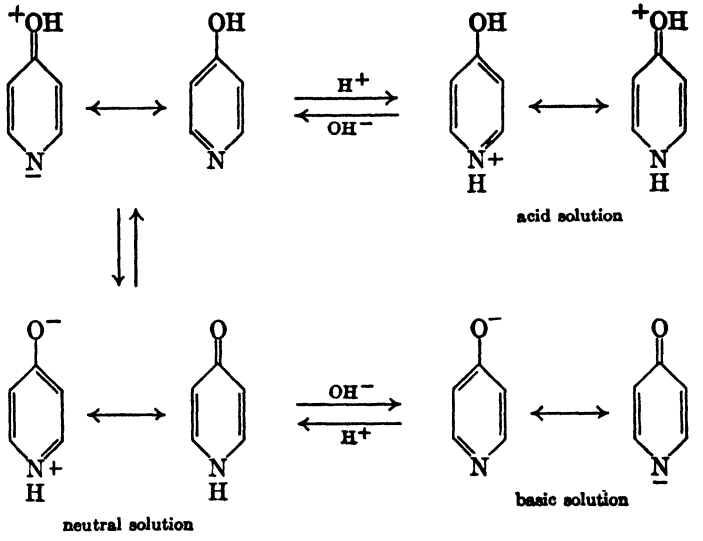
The proton is never free as represented but is either solvated or bound to some base. The base-catalyzed tautomerism takes place by an equivalent mechanism. It should also be stressed that, although 2-hydroxypyridine shows reactions of a true hydroxy compound, as 2-pyridone, it demonstrates almost none of the ketonic properties that its name might imply. Instead, 2-pyridone should be looked on more as an N-substituted amide which it resembles in some respects. Exceptions to this are the formation of the monoxime of 2,6-dihydroxypyridine and the reaction of 2,4,6-trihydroxypyridine with phenylhydrazine.[12] Although the structure of an amide is commonly written as XIV, the evidence [13] indicates that this simple representation is not adequate



and that the amide structure generally is more correctly represented by the hydroxyl structure XV (and its dipolar ion). The entire discussion of 2-hydroxypyridine can be directly applied to the analogous case of 4-hydroxypyridine. It has been considered a vinylog of 2-hydroxypyridine, and its reactions have been explained on this basis. It shows the properties of 4-hydroxypyridine in its conversion to 4-chloropyridine and is converted into N-methyl-4-pyridone by treatment with methyl iodide. The electron moment measurements of Leis and Curran [9] and the absorption spectra data of Specker and Gawrasch [8] indicate that 4-hydroxypyridine exists in neutral solution primarily in the pyridone form in resonance with the zwitterion. It

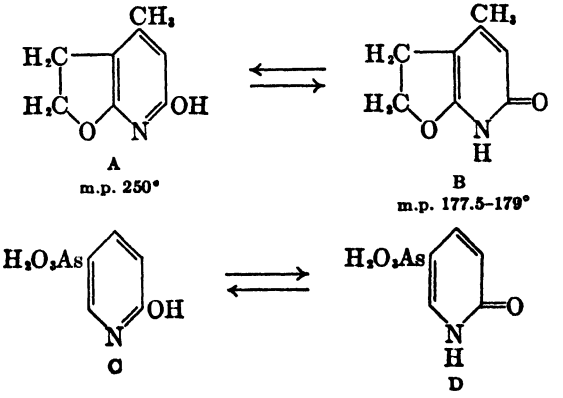
12 Arndt, *Ber.*, **63**, 2968 (1930).

13 Baker and Taylor, *Sidgwick's Organic Chemistry of Nitrogen*, Oxford University Press, London, 1942, pp. 143–144.



appears throughout that the structures containing the conjugated benzenoid ring are the more important; this is confirmed by the essentially aromatic absorption spectra of a substance such as N-methyl-4-pyridone.

There are two reported cases in which isomeric substances have been isolated and in which the isomerism can be explained on the basis of tautomeric hydroxypyridine and pyridone forms. These are 2,3-(2′,3′-dihydrofurano)-4-methyl-6-hydroxypyridine (A and B)[14] (see p. 471 for its synthesis) and 2-hydroxypyridine-5-arsenilic acid (C and D).[15] Of the two cases, the evidence for the former is much more



14 Stevens, Beutel, and Chamberlin, *J. Am. Chem. Soc.*, **64**, 1093 (1942).
15 Binz, Rath, and Maier-Bode, *Ann.*, **478**, 22 (1930).

complete. B, the lower melting form, gives no ferric chloride coloration and is very soluble in ethyl acetate, whereas A gives a positive ferric chloride test and is insoluble in ethyl acetate. Samples of the purified solids show no interconversion when stored, but by heating them in concentrated hydrochloric acid at 150° or by dissolving them

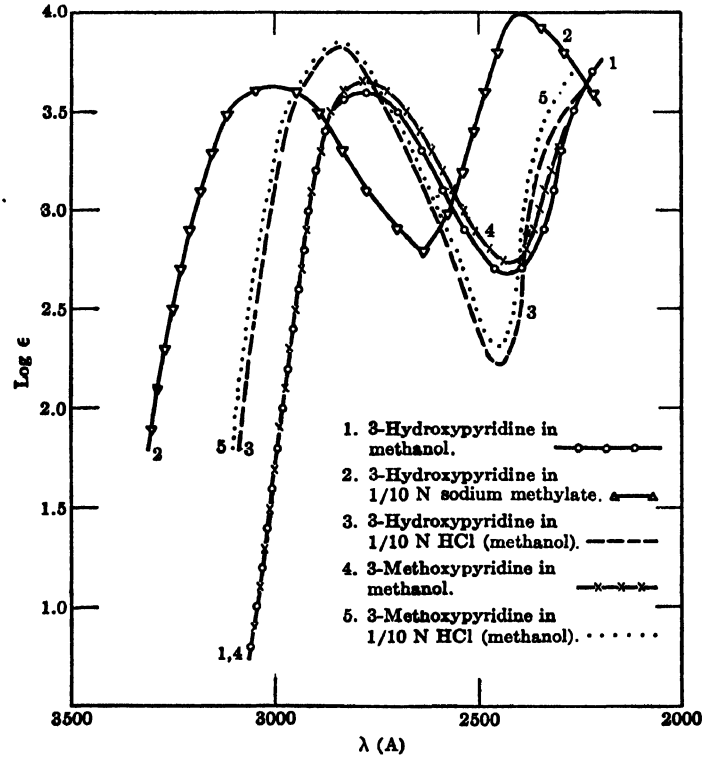


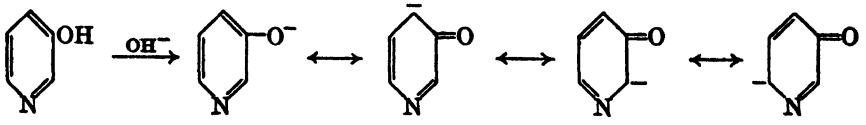
FIGURE 4

in 10% alkali an equilibrium mixture is established. The ultraviolet absorption spectra of A and B substantiate these conclusions.

The 2- and 4-hydroxypyridines in general show subdued phenolic character. They give faint but definite colorations with ferric chloride, readily undergo electrophilic substitution, and couple with diazonium salts to give azo dyes.

On the other hand, 3-hydroxypyridine, as would be expected, is a typical phenolic substance and shows the properties to be expected of a phenol, conditioned, of course, by the conditions imposed by the pyridine ring. It gives a purple ferric chloride test, condenses with formaldehyde, participates in the Mannich condensation, and readily

undergoes halogenation. The ultraviolet absorption spectra of 3-hydroxypyridine and 3-methoxypyridine are almost identical in *neutral* and *acid* solutions as expected [8] (Fig. 4); in *basic* media the spectrum of 3-hydroxypyridine differs greatly from that of 3-methoxypyridine but is similar to that of phenol. The anion of 3-hydroxypyridine undoubtedly exists, as indicated, in resonance with certain activated states just as does that of phenol,[10] but with these resonance forms playing a minor role because of the inherent attraction of the ring nitrogen atom for electrons.

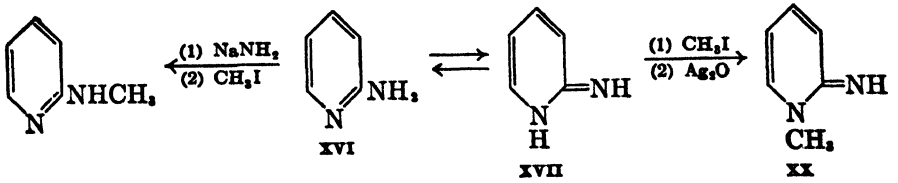


Aminopyridines

A similar situation exists with respect to 2- and 4-aminopyridine. Only one substance of this composition is known, yet the reactions of 2-aminopyridine can be sharply divided into two classes: those based on the structure of an amine group (XVI and XVIII) and those based

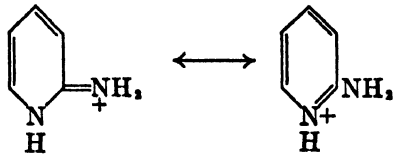
XVI XVII XVIII XIX

on that of an imino group (XVII and XIX). A tautomerism completely parallel to that discussed above for 2-hydroxypyridine can exist here. Treatment of 2-aminopyridine with sodium amide followed by methyl iodide results in the formation of 2-methylaminopyridine, identical with that obtained from methylamine and 2-chloropyridine. The direct treatment of 2-aminopyridine with methyl iodide followed by treatment with silver oxide leads to N-methyl-2-pyridonimine (XX).



XVI XVII XX

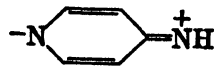
In acid solution, 2-aminopyridine must exist as the hybrid of the two structures, and as such it shows complete analogy with the amidines.[16]



The properties of the NH_2 group in 2-aminopyridine should be looked upon not so much as those of an aromatic amine as those of an NH_2 group as commonly written in an ordinary amide or, better yet, in an amidine. Only a few reactions of 2-aminopyridine will be cited to substantiate this point, but many others will be found under the specific discussion of 2- and 4-aminopyridines. It might be expected that 2-aminopyridine would form a dihydrochloride, but, in line with its characteristic amide (or amidine) properties, only a monohydrochloride is formed under ordinary conditions. The same is true for 4-aminopyridine, but 3-aminopyridine shows the properties of a more or less typical aromatic amine and forms a dihydrochloride. This amide property of 2-aminopyridine is again evidenced in its reactions towards nitrous acid, which produces 2-hydroxypyridine just as the action of nitrous acid on an acid amide results in the production of an acid by replacement of the NH_2 group with an OH group. This is in contrast to 3-aminopyridine, which yields 3-pyridyldiazonium chloride under these same conditions.

As will be pointed out later, it is possible to replace the NH_2 group in 2-aminopyridine with a halogen. In the synthesis of 2-bromopyridine, 2-aminopyridine is treated in concentrated hydrobromic acid first with bromine and then with sodium nitrite, but this reaction differs greatly from the typical diazotization reaction. On the other hand, 3-aminopyridine reacts in most respects like an aromatic amine and participates normally in the Sandmeyer reaction.

A similar tautomerism is shown by 4-aminopyridine and its derivatives. The relatively high dipole moment of 4-aminopyridine [9] would indicate that a dipolar ion such as XXI makes a major contribution to its structure.



XXI

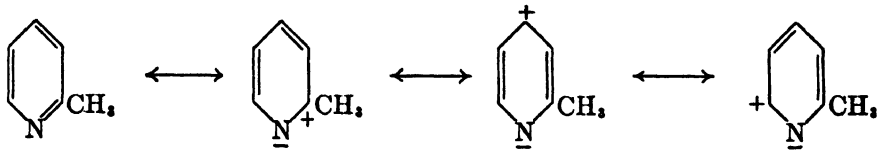
[16] Ref. 13, pp. 155–156; ref. 10, pp. 180–181.

Picolines

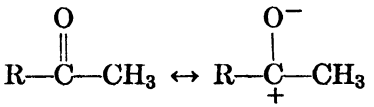
Finally, consideration will be given to the 2- and 4-alkylpyridines; for the present, the discussion will be limited to the simplest of such derivatives, the methylpyridines or picolines.

Many reactions of 2- and 4-picoline have been interpreted in the light of static bonds in the pyridine nucleus. Thus, in the formula of 2-picoline the methyl group is attached to a carbon atom which in turn possesses a double bond to the nitrogen. On this basis, 2-picoline should show many of the properties of a methyl ketone of the ammonia system. This is in fact so, and the analogy between 2-picoline and a methyl ketone is of value in predicting the reactions of the latter. Fundamentally, however, the interpretation on the basis of static bonds in pyridine is hardly justified.

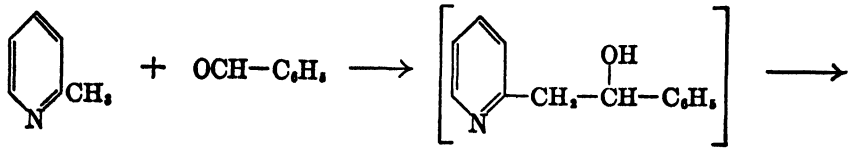
The same conclusions, however, can be drawn by consideration of resonance states of the pyridine ring as given on p. 403. The inherent

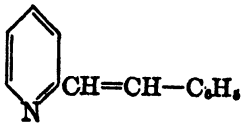


electron-attracting nature of the ring nitrogen atom imparts a positive character to the α-carbon atom. This situation is, of course, the same that exists in a methyl ketone



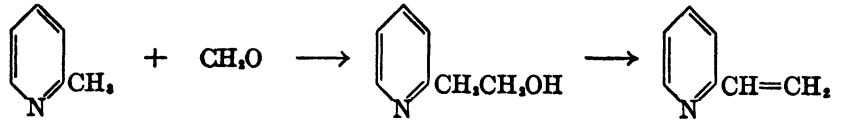
which allows attack by basic catalysts to give the reactive anion (conjugate base) which can then take part in aldol-type condensations. Consequently, 2-picoline undergoes typical aldol-type condensation reactions. For instance, just as acetophenone reacts with benzaldehyde to give benzalacetophenone, 2-picoline condenses with benzaldehyde by refluxing in acetic anhydride to give the analogous compound in the pyridine series known as stilbazole (XXII). A further example of the aldol-type condensation of picoline is found in its reaction





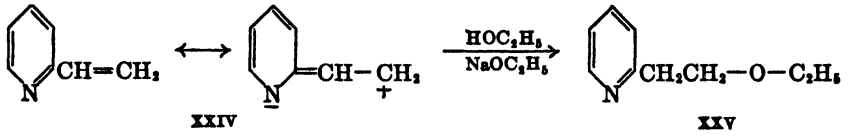
XXII

with formaldehyde to give first 2-(β-hydroxyethyl)pyridine (XXIII), which readily dehydrates to the commercially available 2-vinylpyri-

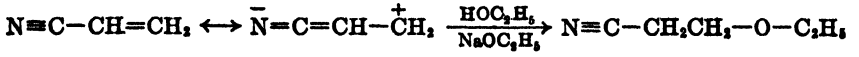


XXIII XXIV

dine (XXIV). XXIV is a remarkable compound, not only because it shows properties comparable to styrene in polymerization reactions with butadiene and acrylonitrile but also because it shows the addition reactions characteristic of a substance such as acrylonitrile.[17] The lowered electron density at the 2- (and 4-) carbon atoms, which results from the electron attraction of the ring nitrogen, is extended through the vinyl group in 2-vinylpyridine (and 4-vinylpyridine) and thus greatly facilitates attack at the end of the side chain by electrophilic reagents. A typical case is the reaction with alcohol in the presence of sodium ethoxide to give 2-(β-ethoxyethyl)pyridine (XXV)



XXIV XXV



in 65% yield. The analogy with the similar reaction of acrylonitrile [18-20] is quite apparent. Other examples, including the addition of

17 Doering and Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

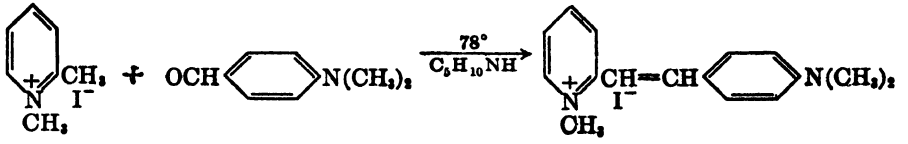
18 Bruson, *J. Am. Chem. Soc.*, **64**, 2457 (1942).

19 Bruson and Reiner, *J. Am. Chem. Soc.*, **64**, 2850 (1942); **65**, 18, 23 (1943); **66**, 56 (1944).

20 Bruson et al., *J. Am. Chem. Soc.*, **67**, 601 (1945).

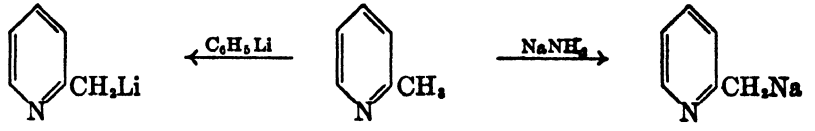
hydrogen cyanide, diethylamine, and sodiomalonic ester, are considered on p. 599.

It follows that N-methyl-2-picolinium iodide (XXVI), in which the electron-attractive nature of the nitrogen atom has been enhanced by the presence of a formal charge, should condense with even greater ease. This is illustrated by the condensation with a substance such as *p*-dimethylaminobenzaldehyde which takes place when the reactants



XXVI

are refluxed in alcohol with a small amount of piperidine as catalyst.[21-23] According to such an interpretation, it is unnecessary to assume a reactive intermediate methylene base as postulated by Mills et al.[24,25] These reactions indicate the presence of active hydrogens on the methyl group of 2-picoline. This is also demonstrated by the reaction of 2-picoline with sodium amide to give a sodium salt or with



lithium phenyl to give 2-picolyllithium. The resultant alkali metal salts give the expected reactions with alkyl halides, carbon dioxide, benzaldehyde, and benzoyl chloride (pp. 488, 592, and 594). The question of the reactivity of the hydrogens in the α position of alkyl groups in the 2 and 4 positions of analogous heterocycles is discussed further in Volume 2 of this series.

Although the effect of a potential carbon-nitrogen double bond in the pyridine ring on the reactions of certain pyridine derivatives has been indicated in the preceding discussion, it should be reemphasized that this is merely a convenient scheme for interpreting these reactions and that pyridine itself is completely lacking in the most characteristic

21 Clemo and Swan, *J. Chem. Soc.*, 1454 (1938).
22 Cocker and Turner, *J. Chem. Soc.*, 57 (1940).
23 Phillips, *J. Org. Chem.*, 12, 333 (1947).
24 Mills and Smith, *J. Chem. Soc.*, 121, 2724 (1922).
25 Mills and Raper, *J. Chem. Soc.*, 127, 2466 (1925).

reaction which would be expected of a carbon-nitrogen double bond, namely, hydrolytic cleavage of the ring in acid solution.

SYNTHESIS OF PYRIDINE COMPOUNDS

Introduction

The natural occurrence of the pyridine compounds is not very extensive. The best-known instance is the alkaloid nicotine which gives nicotinic acid (pyridine-3-carboxylic acid) on oxidation. With this one exception, naturally occurring pyridine compounds are of little value for synthetic purposes. Pyridine and pyridine homologs obtained from coal tar, bone oil, petroleum, etc., cannot be considered as naturally occurring since these products are undoubtedly produced in the pyrolytic treatment of the coal, bone, and petroleum from which they are obtained.

Syntheses in the pyridine series divide themselves naturally into two broad groups: first, those methods which construct the pyridine ring from simpler aliphatic components, and second, those reactions which start with the pyridine ring already present and accomplish the alteration of the parent compound by the processes of substitution, addition, oxidation, reduction, condensation, and other well-established organic preparative methods.

The first group of reactions is to a large extent unique to the pyridine series and is for the most part without analogy in the chemistry of benzene.[1] The second group of reactions is merely the pyridine counterpart of reactions utilized in the benzene series for replacing the hydrogens on the aromatic ring with various groups and for modifying these groups once they have been introduced.

The number of starting materials available for the synthesis of pyridine compounds from aliphatic substances is very large. All these reactions in one sense or another can be considered those of an unsaturated or potentially unsaturated compound with ammonia or a nitrogen-containing compound, the reaction taking place in such a manner that a six-membered ring is formed.

Pyrolytic Methods

The first group of reactions to be discussed in connection with the actual elaboration of the pyridine ring will be the pyrolytic reactions,

[1] This does not apply to the formation of both pyridine and benzene, along with their homologs, in the coking process. The formation of both these series of compounds in this process must take place by analogous mechanisms.

the most important of which is the coking of coal. The actual method of formation of the nitrogen bases in this process is unknown and can only be surmised. Coal is a complex material which varies considerably in composition. Anthracite may have as high as 88% carbon, whereas the bituminous coal which is employed predominantly in the by-product coking process contains approximately 75–80% carbon, 6% hydrogen, 3–5% oxygen, 5–7% ash, and 1–2%, each, of nitrogen and sulfur. The carbon, as well as the other elements, is not present in the free state but in polymeric combination. When coal is subjected to temperatures of 1000–1300°, decomposition results and most of the oxygen is lost as carbon monoxide and carbon dioxide, the hydrogen as free hydrogen, and the nitrogen either as ammonia or in combination with carbon and hydrogen as nitrogen bases and in the slightly acidic nitrogenous substances, indole and carbazole. Other aromatic compounds such as benzene, naphthalene, and thiophene, etc., are produced. The fact that the low-temperature coking process (600–700°) produces a much larger percentage of aliphatic and alicyclic compounds indicates that one of the final steps in the formation of these aromatic substances is dehydrogenation. In any event, it seems most probable that pyridine and its homologs arise from the reforming of unsaturated aliphatic compounds in the presence of ammonia, to give the very stable cyclic nitrogen bases.

Further evidence for the mechanism of formation of pyridine is afforded by studies on the production of pyridine bases by the dry distillation of bones.[2] It has been shown [2] that the bones must still contain their natural fats in order to yield any pyridine bases on dry distillation, since dry distillation of bones which have been previously treated by a saponification process does not yield any pyridine (although pyrrole is still formed). This strongly suggests that the fats furnish glycerol, which at the high temperature dehydrates to acrolein; the acrolein then reacts with ammonia to give pyridine bases such as

$$2CH_2OHCHOHCH_2OH \xrightarrow{-H_2O} 2CH_2{=}CH{-}CHO \xrightarrow[-H_2O]{NH_3} C_6H_7N$$

the picolines. Of historical interest only is the earliest synthesis of pyridine by Baeyer,[3] who reasoned that the production of pyridine by the distillation of animal tar is a result of the combination of acrolein and ammonia. He therefore passed acrolein into aqueous ammonia

2 For an excellent review of the pyridine bases from bone oil and the original discoveries of pyridine from this source, see Calm and v. Buchka, *Die Chemie des Pyridins und seiner Derivate*, Friedrich Vieweg und Sohn, Braunschweig, 1889–1891, pp. 7–18.

3 Baeyer, *Ber.*, **2**, 398 (1869); *Ann.*, **155**, 281, 294 (1870).

and, after evaporation to dryness, distilled the residue from a retort. From the small amount of basic material, a chloroplatinate was obtained and identified as the β-picoline derivative.

Pyridine bases have likewise been found in the kerosene fraction from petroleum distillates. Here again there is no evidence that these products are present in the native petroleum itself, and it is assumed that they are formed in the distillation and cracking processes from nitrogenous substances present in the crude petroleum. The low-temperature pyrolysis of cottonseed meal produces a very small amount of a basic fraction from which pyridine and pyridine derivatives have been separated.[4]

The potential percentage of pyridine bases present in coal is extremely small, being only about one part in thirty thousand; approximately 3% of mined coal is converted to coal tar in the high-temperature pyrolysis of bituminous coal, and of this 3% only about 0.1% constitutes pyridine bases. Approximately 750 million gal. of coal tar are produced in the United States each year, and from this slightly less than 0.1% (some 600,000 gal.) constitutes crude and refined pyridine bases. Approximately one-third of this (200,000 gal.) is obtained as purified pyridine, with lesser amounts of 2-picoline (50,000 gal.) and mixed 3- and 4-picolines (35,000 gal.).[5]

In spite of this potentially large source of pyridine bases, the supply is not sufficient to serve as the basis of a really large industry. When it appeared that 2-vinylpyridine might produce a superior rubber when substituted for styrene in copolymerization with acrylonitrile, it was apparent that there was insufficient 2-picoline (from which 2-vinylpyridine is prepared) from coal tar sources to make enough synthetic rubber tires to take care of even a small portion of the total demand. Situations such as these have led to various studies on the synthesis of pyridine and pyridine compounds from more abundant starting materials, such as acetylene (see p. 455).

The pyridine bases are obtained from coal tar by washing the light oil (b.p. up to 160°) and middle oil (b.p. 160–230°) fractions with dilute sulfuric acid. The bases are recovered from the acid solution by neutralization and distillation. Separation of the pyridine bases contained in the light oil fractions demands use of very efficient fractionation equipment. As a result, pyridine and 2-picoline, which comprise the lower fractions of the light oil, have been available commer-

[4] Parker, Gutzeit, Bratton, and Bailey, *J. Am. Chem. Soc.*, **58**, 1097 (1936).

[5] Chemical Facts and Figures, 2nd ed., 1946, p. 53, Manufacturing Chemists Association of the United States, Washington, D. C.

cially in pure form only recently. The next higher fraction boiling at 144°, the so-called "commercial β-picoline," cannot be separated into its three components, 3-picoline, 4-picoline, and 2,6-lutidine, even by efficient fractionation. The discovery that nicotinamide (which can readily be prepared from 3-picoline) was a member of the vitamin B complex made it imperative to find a method of resolving the "commercial β-picoline" mixture into its components by some practical method.[6] Many older methods which depend on the difference in chemical reactivity of methyl groups in the 2 and 4 positions over those in the methyl group in the 3 position have been described. Thus, the treatment of the crude "commercial β-picoline" fraction with phthalic anhydride forms the insoluble phthalone (see p. 497) of 4-picoline and 2,6-lutidine but leaves the 3-picoline unchanged. The purified 3-picoline can thus be recovered from the reaction mixture. In a similar manner, separations have been developed, based on the selective reactivity with benzaldehyde,[7] selenium dioxide,[8] and air at high temperatures. In the latter method developed by Cislak and Wheeler,[9] the vapors of the mixture are passed with air over a vanadium pentoxide catalyst at 350°, under which conditions the 4-picoline and 2,6-lutidine are destroyed by oxidation, and the 3-picoline is for the most part unchanged. Although these methods do obtain the desired 3-picoline, they are very wasteful as well as uneconomical and must therefore be considered unsatisfactory.

Fractional crystallization has served repeatedly in research work for the separation of the pyridine bases. Various derivatives such as picrates, hydrochlorides, mercurichloride hydrates, oxalates, or zincichlorides have been employed successfully. In contrast to 3- and 4-picolines, lutidine forms an insoluble addition compound with urea and can be readily separated as this derivative and then regenerated by heat. With the possible exception of the urea method, the processes based upon crystallization cannot be considered acceptable for separating large amounts of materials.

Whereas 3- and 4-picoline boil within a fraction of a degree of each other, the respective hydrochlorides boil some 5 deg. apart at 200-mm. pressure, which is ample to permit fairly good separation in efficient fractionating equipment. The extremely corrosive action of the pyridine hydrochlorides is such that it requires the use of all-glass appa-

[6] Coulson and Jones, *J. Soc. Chem. Ind.*, **65**, 169 (1946).
[7] Schwarz, *Ber.*, **24**, 1676 (1891).
[8] Henze and Henze, Ger. pat. 697,759 (Sept. 26, 1940) [*C. A.*, **35**, 6270 (1941)].
[9] Cislak and Wheeler, U. S. pat. 2,300,741 (Nov. 3, 1943) [*C. A.*, **37**, 2019 (1943)].

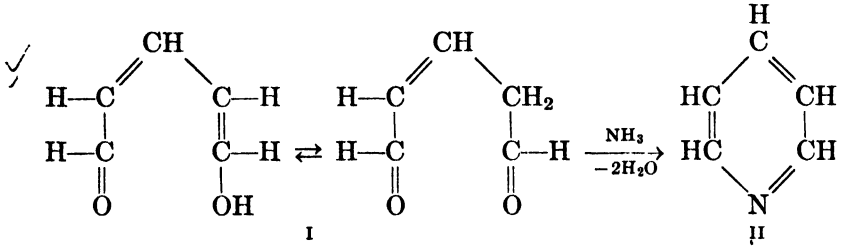
ratus; therefore, this process is not well adapted to large-scale work. In addition, the high melting point of the 4 isomer makes its distillation difficult.

Coulson and Jones,[6] however, describe in detail an azeotropic distillation with acetic acid, and similar processes have been patented [10] for separating the "commercial 3-picoline" into its cogenors. The problem has been solved on a commercial scale by simple azeotropic distillation with water. Fractional freezing or melting of the crude 3-picoline mixture has also been patented as a satisfactory method of separation.[11]

Since the separation of the picolines by crystallization of the salts requires very critical and exacting work, many samples of so-called pure γ- or β-picoline used in the past were really impure mixtures. This difficulty is no longer encountered since the relatively pure individual picolines are now commercially available.

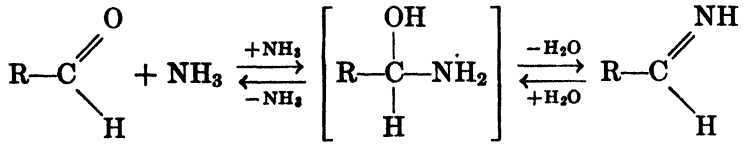
Synthesis from Aliphatic Compounds

Glutaconic Dialdehyde, Glutaconic Acid, and Derivatives. Glutaconic dialdehyde (I) reacts with ammonia to give pyridine (II).



I II

This synthesis is of theoretical importance not only because it lends convincing evidence to the structure of pyridine but also because it is fundamentally the simplest method of ring closure in the pyridine series and thus gives an insight into the mechanism of the many similar and related reactions. The tendency of an aldehyde such as III

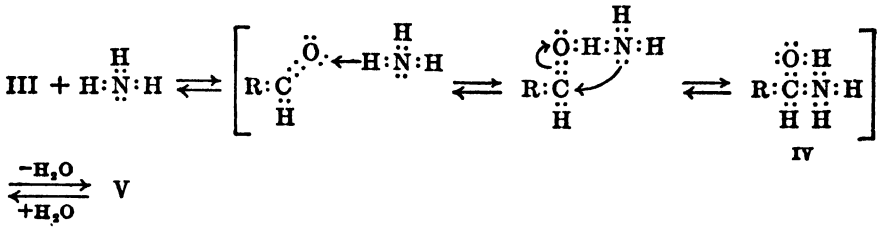


III IV V

[10] Cislak and Karnatz, Brit. pat. 580,048 (Aug. 26, 1946) [*C. A.*, 41, 2447 (1947)].

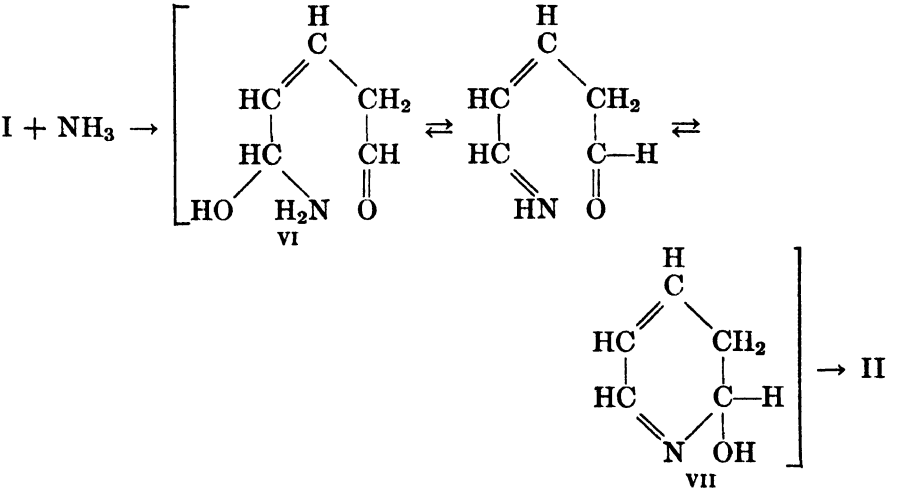
[11] Glowacki and Winans, U. S. pat. 2,402,158 (June 18, 1946) [*C. A.*, 40, 6102 (1946)].

to react with ammonia (or a primary alkyl- or aryl-amine) to form an imine such as V is well known and undoubtedly takes place via an initial addition reaction to form IV. The addition is initiated by an intermolecular hydrogen bond and may be represented as follows.



Only in special cases such as that of chloral is the addition product IV stable. Either it loses ammonia and gives back the starting materials, or it loses water which process then results in the formation of the imine (V).

These steps are characteristic not only of the initial condensation of the carbonyl compound (I) to give the imine (II) but also of the subsequent ring closure. If, as with glutaconic dialdehyde (I), the arrangement of the atoms is such that the elimination of water results in the formation of both a six-membered ring and a conjugated system, then these additional factors join forces and greatly facilitate the ring closure (VI–VII).

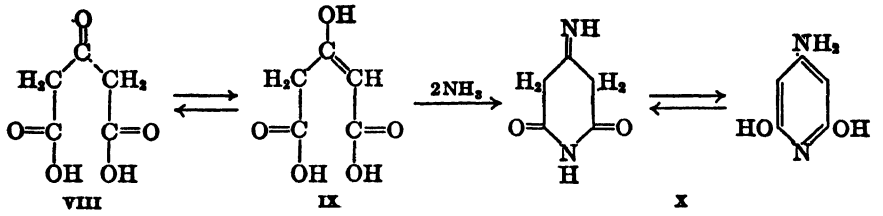


This conversion of glutaconic dialdehyde to pyridine [12] is reversible if the proper path is chosen (p. 426). In fact, the only practical

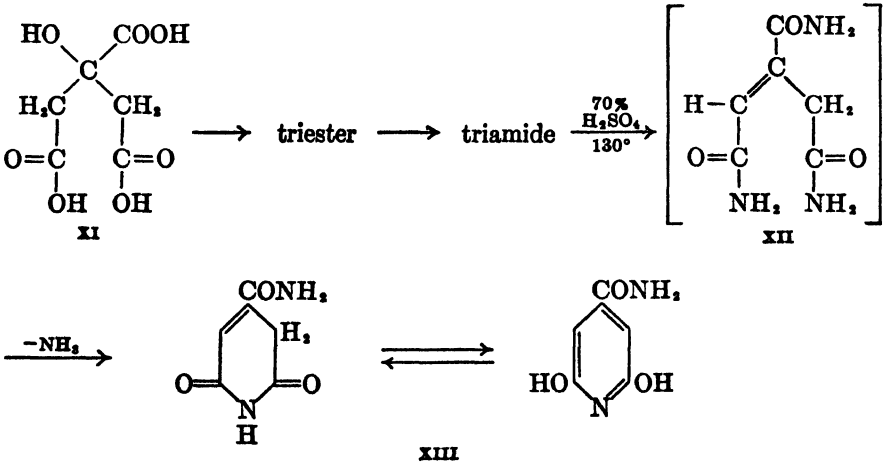
[12] Baumgarten, *Ber.*, **57**, 1622 (1924).

method available for the preparation of glutaconic dialdehyde is from pyridine, and, for this reason, the synthesis of pyridine by this ring closure is of no preparative value. If the dioxime of glutaconic dialdehyde is allowed to stand with concentrated hydrochloric acid, a 42% yield of pyridine N-oxide is obtained.[13]

Acetonedicarboxylic acid (VIII) may be considered in its enol form (IX) to be a hydroxy derivative of glutaconic acid, and as such it should undergo ring closure with ammonia to form 2,4,6-trihydroxypyridine. In actual practice, ammonia also adds to the keto group of VIII, and the end product is 2,6-dihydroxy-4-aminopyridine or glutazine (X).[14]



The conversion of citric acid (XI) to the amide and subsequent cyclization with sulfuric acid to 2,6-dihydroxyisonicotinic acid[15] undoubtedly proceeds through the intermediate aconitic triacid amide (XII), which may also be considered a derivative of glutaconic acid. Although the over-all yield on these conversions is reported to be only about 25%,[16] citric acid is relatively cheap and the steps involved



[13] Baumgarten, Merländer, and Olshausen, *Ber.*, **66**, 1802 (1933).
[14] Niementowski and Sucharda, *J. prakt. Chem.*, [2] **94**, 193 (1916).
[15] Levelt and Wibaut, *Rec. trav. chim.*, **48**, 466 (1929).
[16] Behrmann and Hofmann, *Ber.*, **17**, 2681 (1884).

are quite simple so that XIII may be considered an available starting material for laboratory syntheses.

Thorpe and co-workers [17] have studied the synthesis of various cyano- and methyl-substituted pyridines by ring closures of the corresponding glutaconic esters with ammonia.

Ammonia and Unsaturated Aliphatic Compounds. The prospect of augmenting the supply of pyridines and picolines from coal tar by synthetic methods which would give a more or less unlimited and possibly cheaper supply has prompted many investigations on the synthesis of pyridines by the catalytic reactions of such compounds as acetylene, acetaldehyde, and acrolein with ammonia or hydrogen cyanide. Kline and Turkevich [18] have reviewed the literature and the thermodynamics of such conversions and have reported several experiments in which small amounts of pyridine were obtained. Maier-Bode and Altpeter [19] have also reviewed the many references including patents on this phase of pyridine syntheses. Many reactions have been tried and have given small amounts of pyridine bases, among which the following will be mentioned.

When acetylene and hydrogen cyanide are passed through a hot tube, a mixture containing acetonitrile and some pyridine is formed.

$$2C_2H_2 + HCN \rightarrow C_5H_5N$$

Friedlina has claimed that a better yield is obtained by carrying out the reaction in the presence of mercuric chloride. Similarly, when ammonia and acetylene react at elevated temperatures, a mixture of acetonitrile and pyridine bases is obtained.

Ethanol, when heated at 30 atm. pressure with ammonia and hydrogen in contact with an oxide catalyst of thorium, zinc, aluminum, or silicon, gives a mixture of bases in which pyridine, the three picolines, lutidine, and collidines have been identified.[19] Although these reactions seem to have been studied extensively and many patents have been issued on various modifications, none have produced a good yield of a pure pyridine base, and in general it seems just as difficult to separate the pure components from the mixture of products obtained in any of these ways as from those obtained from coal tar itself.

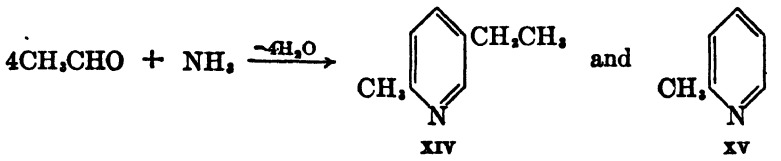
The reactions of aldehydes with ammonia have been studied extensively as a method of obtaining pyridine derivatives. The pioneer-

17 Thorpe, *J. Chem. Soc.*, 87, 1673 (1905) et seq.

18 Kline and Turkevich, *J. Am. Chem. Soc.*, 66, 1710 (1944).

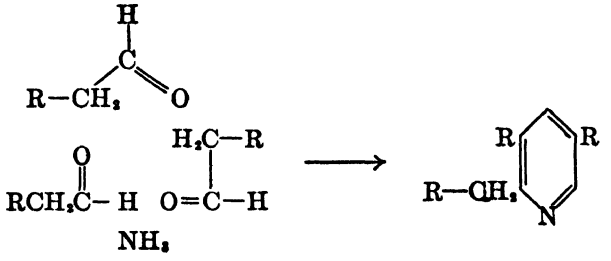
19 Maier-Bode and Altpeter, *Das Pyridin und seine Derivate*, Wilhelm Knappe Halle, Saale, 1934, pp. 6–10. Photo-lithoprint reproduction by Edwards Brothers, Inc., Ann Arbor, Michigan.

ing work of Dürkopf and Chichibabin [20] has indicated that the condensation can take several courses, depending on the aldehyde and the conditions. By carefully studying the conditions for the condensation of aqueous solutions of paraldehyde with ammonia, Frank et al.[21] were able to realize as high as 70% yield of 2-methyl-5-ethylpyridine (XIV) (called "aldehyde collidine"). In a typical run, 24 moles of paraldehyde were heated with 240 moles of ammonia (as concentrated ammonium hydroxide) in the presence of a small amount of ammonium acetate in an autoclave at temperatures of 200–250° for 1 hr. Aldehyde collidine (XIV), 52–57%, and 2-picoline (XV), 6%, were formed.

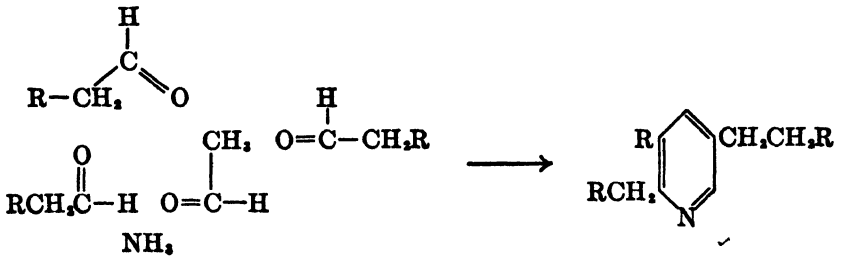


XIV XV

The condensation apparently takes place by two different schemes, which are indicated by the following general equations where R is hydrogen. In the reaction in aqueous solution, scheme 2 obviously predominates.



scheme 1



scheme 2

20 Hollins, *Synthesis of Nitrogen Ring Compounds*, Van Nostrand Co., London, 1924, pp. 217–221.

21 Frank et al., *J. Am. Chem. Soc.*, 68, 1368 (1946).

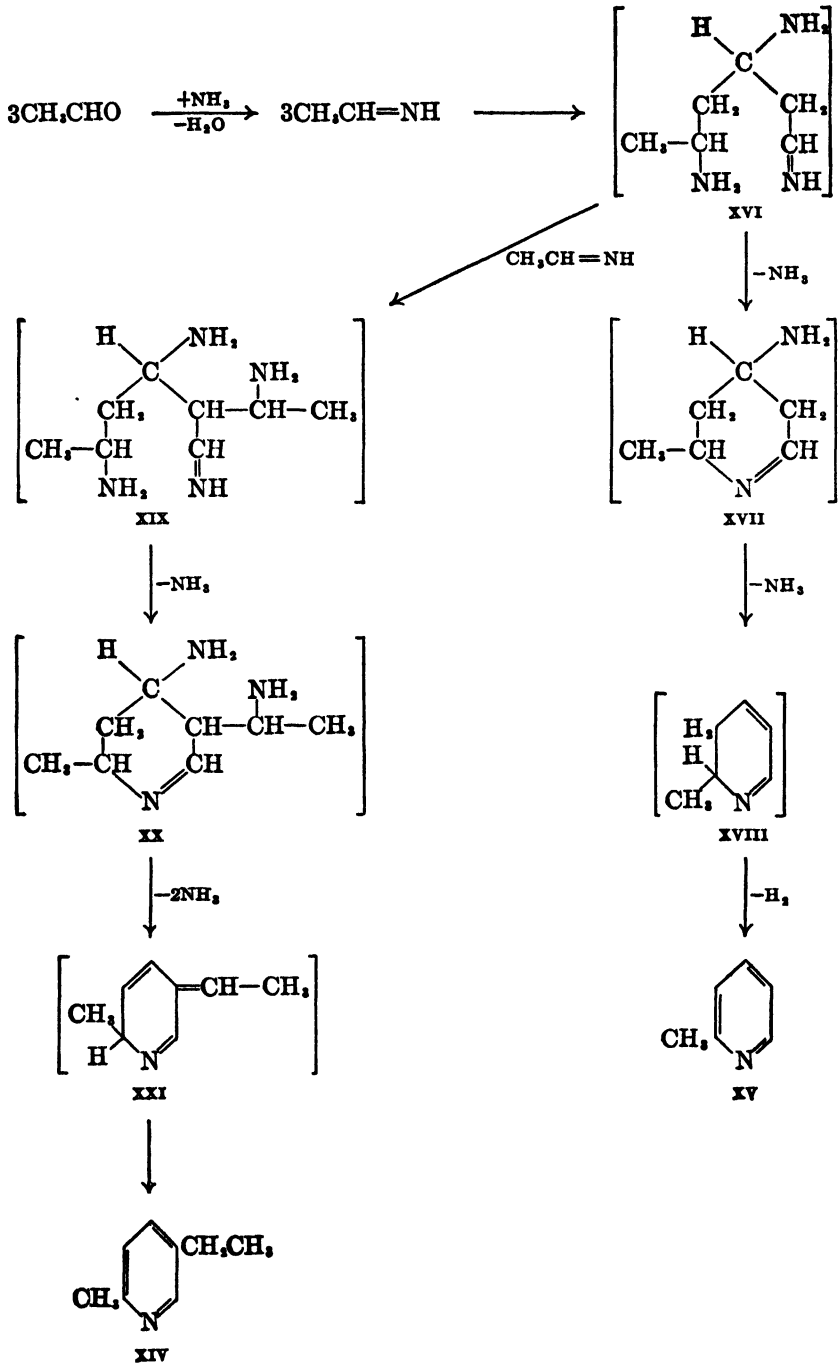
The mechanism of this condensation has been studied and discussed by Strain,[22] Alder,[23] and Chichibabin,[24,25] but its precise course is unknown, and sufficient evidence is available to make only a well-founded and logical guess. The initial step may be a condensation of the aldol type, involving 3 molecules of acetaldehyde, which in its simplest form would be as follows.

$$3CH_3CHO \rightarrow CH_3\overset{OH}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2CHO$$

It is unknown whether or not the initial reaction is the formation of the imine followed by condensation, but it seems unlikely that any large amount of the free aldehyde would remain in the presence of such an excess of ammonia at the temperature of the reaction. In support of this interpretation, it is known that aldehyde ammonia itself under approximately the same conditions gives aldehyde collidine (XII).[7,26,27] Under these circumstances, the aldol condensation probably takes place, at least in part, with the imine, and the above equation may be modified to lead to the intermediate imine (XVI), which may take part in several possible reactions. In order to explain the formation of 2-picoline (scheme 1), it may be assumed that ammonia is lost internally to form the cyclic intermediate (XVII), which then loses ammonia to give the conjugated diene (XVIII). This in turn can be oxidized (acetaldehyde serving as the hydrogen acceptor) to α-picoline (XV).

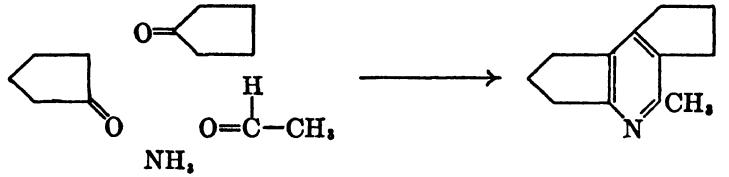
In order to explain the formation of 2-methyl-5-ethylpyridine (scheme 2), four molecules of acetaldehyde must condense in some manner. This may be accomplished by the condensation of another molecule of acetaldehyde or acetaldehyde ammonia with XVI or by some equivalent reaction. It is necessary to assume that the fourth molecule of acetaldehyde condenses in a non-linear fashion to give the desired intermediate (XIX). This intermediate can undergo ring closure, just as in the passages from XVI to XVII, to give the cyclic product XX, which loses ammonia and finally gives the completely conjugated pyridine derivative XIV. Many other sequences of reactions explain the products equally well, and it is impossible to state

22 Strain, *J. Am. Chem. Soc.*, **54**, 1221 (1932).
23 Alder et al., *Ber.*, **74**, 905, 920, 926 (1941).
24 Chichibabin, *Bull. soc. chim. France*, [5] **4**, 1826 (1937); [5] **6**, 522 (1939).
25 Chichibabin, *J. prakt. Chem.*, [2] **107**, 122 (1924).
26 Dürkopf et al., *Ber.*, **20**, 444 (1887).
27 Sprung, *Chem. Revs.*, **26**, 302 (1940).

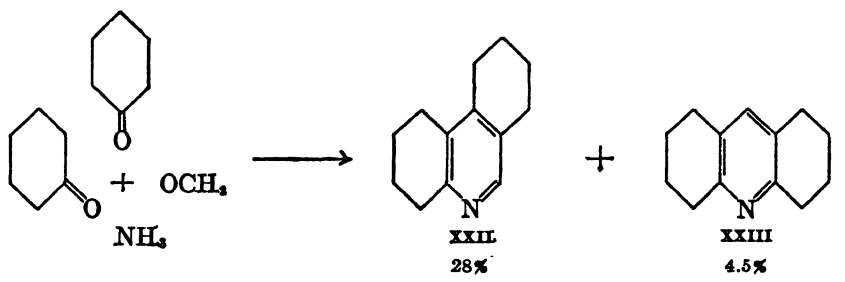

3CH3CHO
+NH3
-H2O
3CH3CH=NH
XVI
CH3CH=NH
-NH3
XIX
XVII
-NH3
-NH3
XX
XVIII
-2NH3
-H2
XXI
XV
XIV

whether olefin formation precedes ring closure, whether the actual condensations are between aldehydes or imines, or whether an oxygen-containing ring is first formed and converted to a pyridine ring in the final steps.[28] If all the possible reactions are considered, it is quite amazing that 2-methyl-5-ethylpyridine can be obtained in 70% yield from ammonia and acetaldehyde. This material is commercially available through the above process.

The products of the reaction of paraldehyde with ammonia in the presence of a ketone give information concerning the mode of condensation. Thus, cyclopentanone and paraldehyde condense with aqueous ammonia in the presence of a small amount of ammonium acetate to give 2-methyl-3,4,5,6-di(trimethylene)pyridine.[24] This is



obviously a modification of scheme 1. A similar condensation between formaldehyde and cyclohexanone gives the octahydrophenanthridine

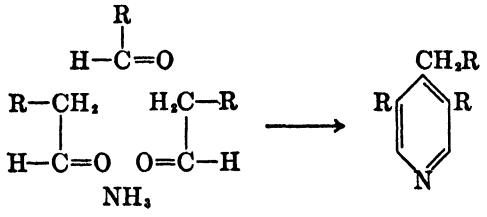


(XXII) and octahydroacridine (XXIII).[24] From the relative yields of the two products (XXII and XXIII) and from the cyclopentanone product, it appears that the predominant reaction is that in which the aldehyde first condenses with the ammonia.

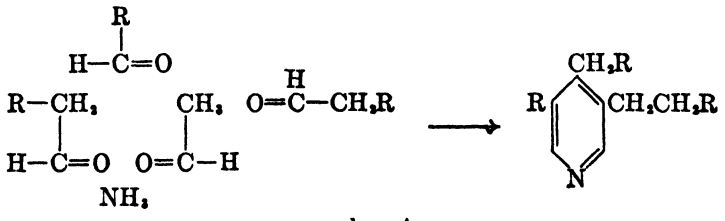
The condensation of aldehydes and ammonia may also be conducted in the vapor phase over various catalysts such as aluminum oxide. The reaction may take a course somewhat different from that indicated for the synthesis of aldehyde collidine in aqueous solution. A complex mixture of products results in all cases, and yields are often poor, but under the proper conditions a satisfactory yield of pyridine bases has

[28] Alder, Offermanns, and Ruden, *Ber.*, **74**, 905, 920, 926 (1941).

been reported. Thus, when acetaldehyde and ammonia were passed over an aluminum oxide catalyst at 330°,[29] a mixture of crude bases (60% yield) resulted which was reported to have the following composition: 2-picoline, 28%; 4-picoline, 30%; 2-methyl-5-ethylpyridine, 33%; and 4-methyl-3-ethylpyridine, 6%. The 2-picoline and 2-methyl-5-ethylpyridine are formed in both the aqueous and vapor phase reactions; in the aqueous reaction 2-methyl-5-ethylpyridine is the main product, but in the vapor phase reaction both compounds are formed in approximately equal amounts. The 4-picoline and the 4-methyl-3-ethylpyridine must have been formed by condensations represented by schemes 3 and 4 (R = H) which gives products isomeric with those of schemes 1 and 2. It should be noticed that in both schemes 2 and 4 one of the aldehyde molecules has been specifically designated



scheme 3



scheme 4

as acetaldehyde. The reaction of a higher aldehyde according to either of these schemes would require the elimination or rearrangement of an R group. Since this is very unlikely except where R is hydrogen, the products represented by these formulations would not be expected with the higher aldehydes. This is confirmed in the condensation of propionaldehyde with ammonia over aluminum oxide catalyst at 300°. Chichibabin [30] reported a 40% yield of crude bases from which was separated 60% of 2-ethyl-3,5-dimethylpyridine (parvoline), formed as indicated by scheme 1, and a small amount of the isomeric 4-ethyl-3,5-

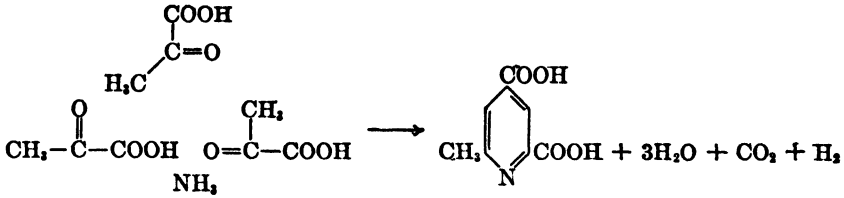
[29] Chichibabin, Moschkin, and Tjaschelowa, *J. Russ. Phys. Chem. Soc.*, **54**, 413 (1923) [*C. A.*, **18**, 2495 (1924)]; *J. prakt. Chem.*, [2] **107**, 132 (1924).

[30] Chichibabin and Oparina, *J. prakt. Chem.*, [2] **107**, 138, 145 (1924).

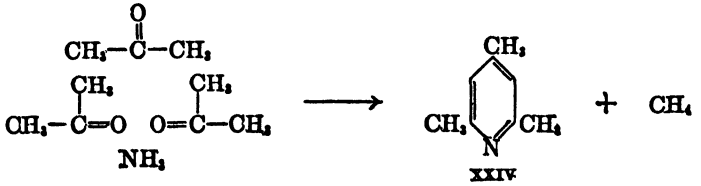
dimethylpyridine, formed as indicated by scheme 3. However, there was also obtained 18% of 3,5-dimethylpyridine, which is difficult to explain on the basis of any simple condensation.

Dürkopf,[31] who studied condensations with higher aldehydes with ammonia, found that propionaldehyde gave 2-ethyl-3,5-dimethylpyridine, butyraldehyde gave 2,6-diethyl-3-propylpyridine, and isovaleraldehyde gave 2-isobutyl-3,5-diisopropylpyridine. All these products can be explained on the basis of the generalized equation represented by scheme 1 [26,32] and are the products to be expected from a linear aldol-type condensation of three molecules of aldehyde. This therefore appears to be the most general course for the condensation of aldehydes and ammonia to give pyridine bases.

Mixtures of aliphatic aldehydes and ketones give mixtures of alkylpyridines when condensed with ammonia.[33] Acetaldehyde, benzaldehyde, and ammonia give predominantly 4-phenylpyridine, whereas benzaldehyde, acetone, and ammonia give 2,6-dimethyl-4-phenylpyridine.[34] A variation of this condensation is the reaction of pyruvic acid with alcoholic ammonia to give 6-methylpyridine-2,4-dicarboxylic acid, according to the following representation.



It is particularly interesting that acetone and ammonia give a small yield of 2,4,6-trimethylpyridine (*sym*-collidine) (XXIV) with the elimination of one carbon atom in the form of methane.



XXIV

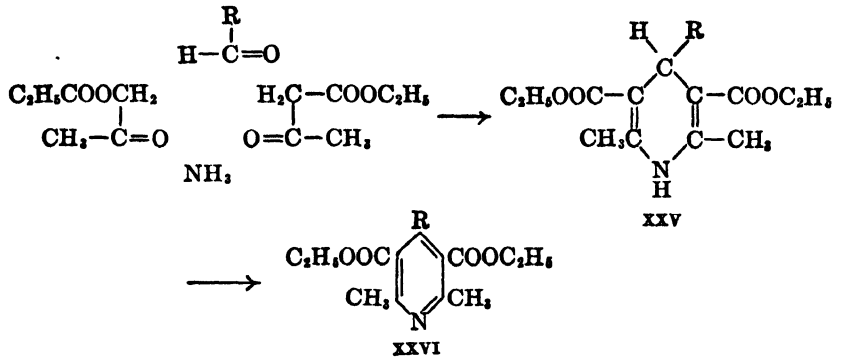
31 Dürkopf and Göttsch, *Ber.*, **23**, 1110 (1890).

32 Chichibabin, *Bull. soc. chim. France*, [5] **3**, 762 (1936).

33 Oparina, *Ber.*, **64**, 569 (1931).

34 Chichibabin and Orochko, *J. Russ. Phys. Chem. Soc.*, **62**, 1201 (1930) [*C. A.*, **25**, 2725 (1931)].

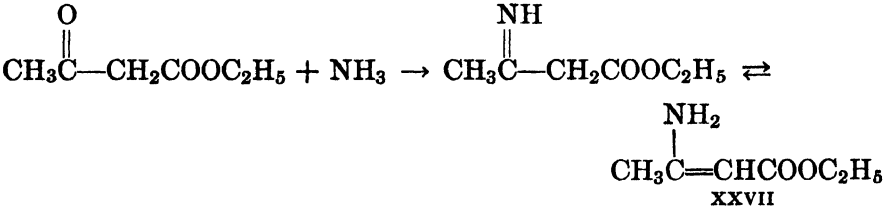
1,5-Diketones or Potential 1,5-Diketones. The most general and useful of the synthetic methods for the preparation of specific pyridine compounds utilizes as starting materials either 1,5-diketones, potential 1,5-diketones, or reactions that will give these compounds. The most widely used application of this general method is that due to Hantzsch,[35] in which a mixture of a β-keto ester such as acetoacetic ester is condensed with an aldehyde in the presence of ammonia, as indicated in the equation, to give a dihydropyridine which can readily be oxidized with nitric acid to the pyridine derivative XXVI. There



XXV

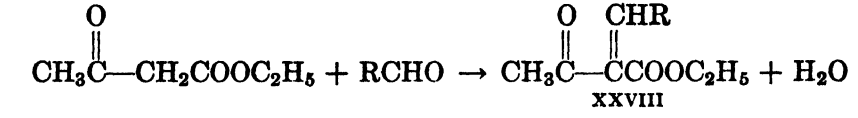
XXVI

are two plausible courses for the Hantzsch synthesis which differ only in the sequence of the steps. In the first, ammonia reacts with acetoacetic ester to give β-aminocrotonic ester (XXVII), and the aldehyde



XXVII

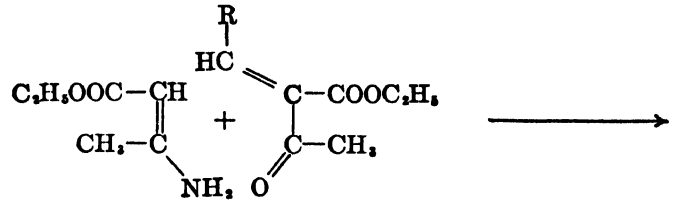
condenses with the other mole of acetoacetic ester in the presence of the basic catalyst, ammonia, in a typical Knoevenagel condensation to yield XXVIII. These two products may then join by a process of



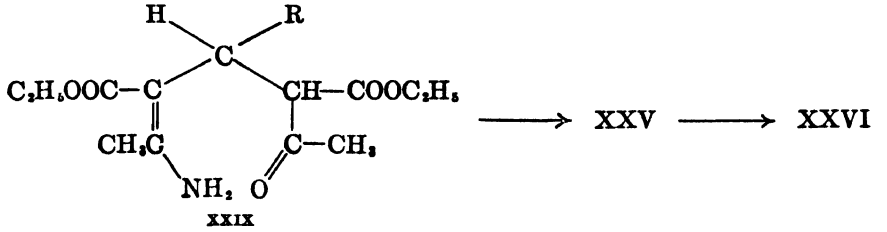
XXVIII

[35] Ref. 20, pp. 227–231.

addition of the ethyl β-aminocrotonate to the double bond of the alkyl- or aryl-idene acetoacetic ester to give XXIX. This latter reaction is an example of the well-known Michael condensation.

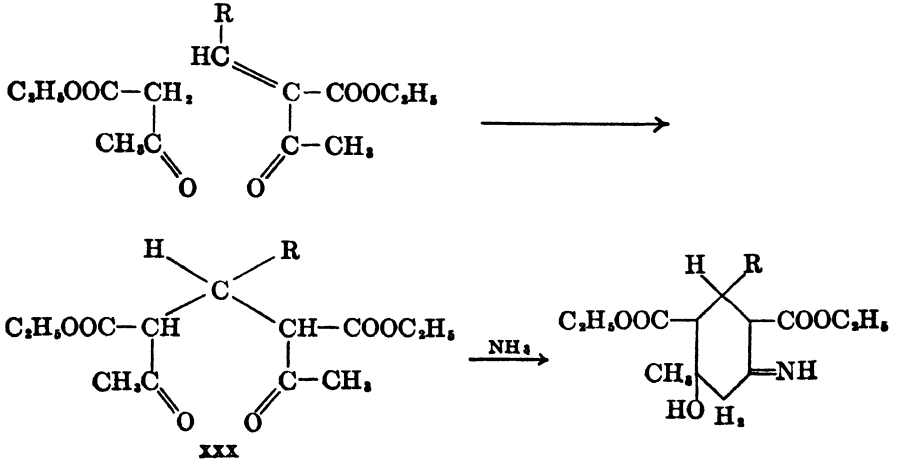


XXVII XXVIII



XXIX

On the other hand, it is not likely, under the conditions of the Hantzsch reaction, that the alkyl- or aryl-idene acetoacetic ester first undergoes a Michael condensation with a molecule of acetoacetic ester to give XXX, since Knoevenagel [36] has found that in this par-

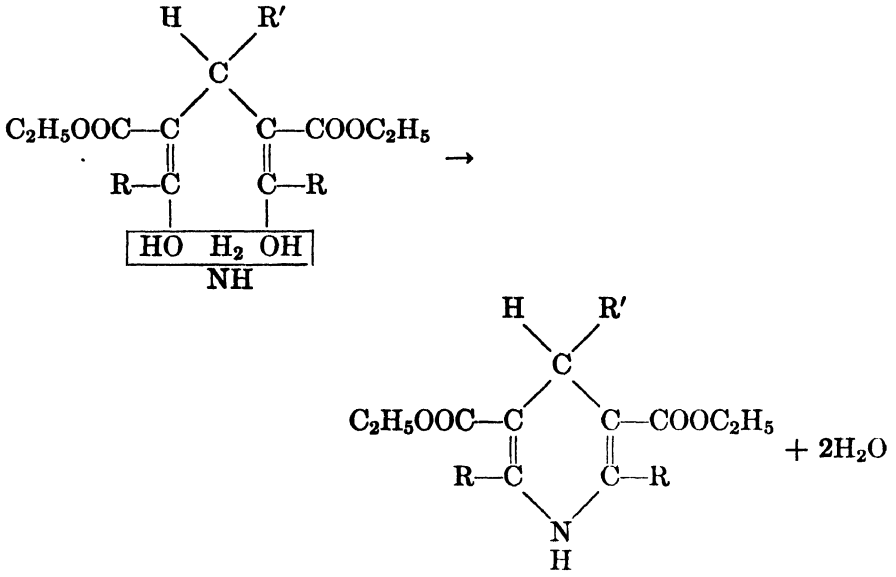


XXX

ticular case the 1,5-diketone (XXX) is converted into a cyclohexanolimine derivative as the primary reaction product. That the initial

[36] Knoevenagel, *Ann.*, **288**, 348 (1895); *Ber.*, **36**, 2180 (1903).

condensation in the Hantzsch reaction can occur in several ways is indicated by the fact that the reaction gives excellent yields when the intermediates are isolated and used in various combinations.[37] In any event, it seems logical that the ring closes in the final step. It is often convenient to represent the ring closure of a diketone such as XXX with ammonia, in the enolic form instead of the keto form.

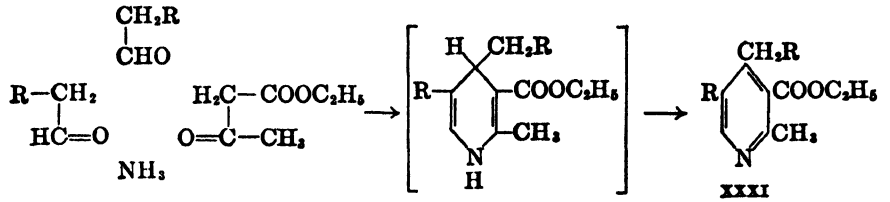


The mechanism of such a ring formation undoubtedly involves the initial addition of a molecule of ammonia to the carbonyl group as indicated on p. 453 for the ring closure with glutaconic dialdehyde and ammonia. Considered from the standpoint of this mechanism, the Hantzsch synthesis is just a special case of the glutaconic dialdehyde condensation.

Although the classical Hantzsch synthesis is conducted with 2 moles of a β-keto ester and 1 mole of aldehyde as indicated, to give a symmetrical derivative of 3,5-dicarbethoxypyridine, essentially the same type of reaction takes place when 1 mole of β-keto ester is condensed with 2 moles of aldehyde in the presence of ammonia. Instead of a dicarboxylic acid derivative of pyridine, a monocarboxylic acid derivative (XXXI) is formed. In this reaction, in which a molecule of aldehyde has replaced a molecule of acetoacetic ester, the yields are much poorer (20–30%), but the same wide variety of products

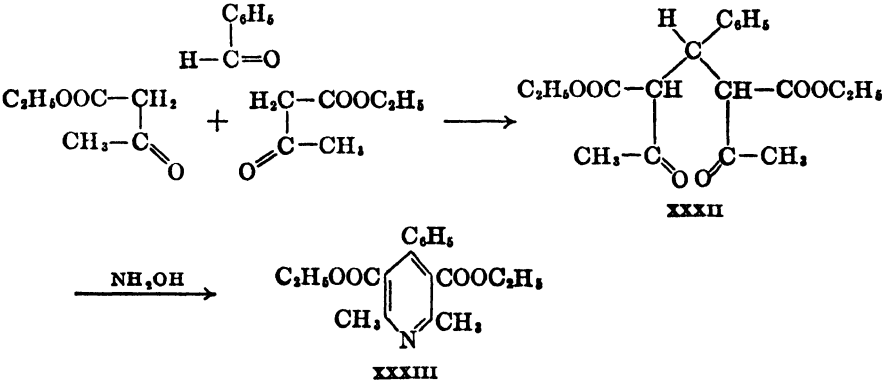
[37] Knoevenagel, *Ber.*, **31**, 738 (1898).

can be prepared.[38] The pyridine derivative itself (XXXI) and not the dihydro compound is obtained, since the excess aldehyde acts as an



XXXI

oxidizing agent. Knoevenagel[36,39] has introduced a modification of Hantzsch's original synthesis in which the intermediate condensation product (XXXII) of acetoacetic ester and the aldehyde is isolated and treated with hyroxylamine in water solution at 120°. Three molecules of water instead of two are split out, and the pyridine compound (XXXIII) results directly without oxidation. Thus, acetoacetic



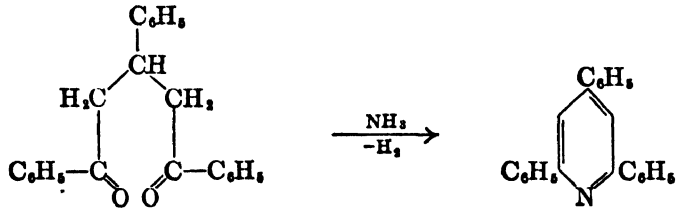
XXXII

XXXIII

ester and benzaldehyde in the presence of a little piperidine give the 1,5-diketone (XXXII) which reacts with hydroxylamine to form the pyridine derivative (XXXIII). The mechanism for the ring closure must differ only slightly from that for the Hantzsch synthesis. Hydroxylamine instead of ammonia adds to the keto groups. A wide variation is possible in the nature of the pyridine derivatives obtained by the Hantzsch synthesis or Knoevenagel modification by the proper choice of the β-keto ester (or 1,3-dicarbonyl compound) as well as the aldehyde. These reactions follow the same general pattern as the original Hantzsch synthesis and may conveniently be considered as modifications thereof.

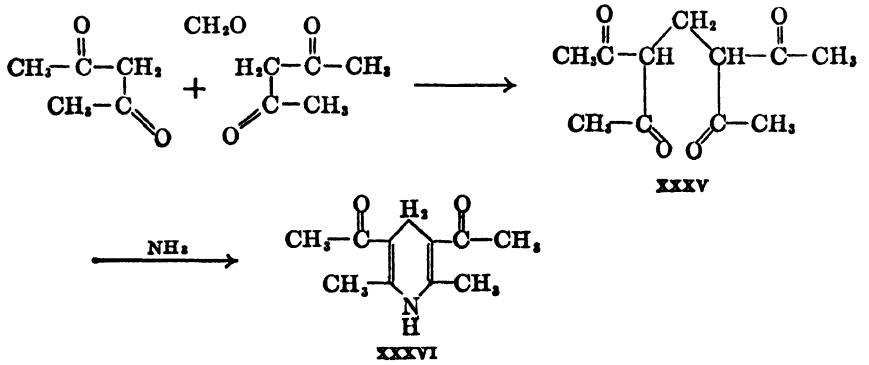
38 Michael, *Ber.*, **18**, 2020 (1885).
39 Knoevenagel, *Ann.*, **281**, 25 (1894).

For instance, ethyl benzoylacetate and benzaldehyde in the Knoevenagel modification give 2,4,6-triphenyl-3,5-dicarbethoxypyridine. This, of course, can be conveniently hydrolyzed and decarboxylated to give 2,4,6-triphenylpyridine. If benzaldiacetophenone (XXXIV), a 1,5-diketone, is treated with ammonia, 2,4,6-triphenylpyridine is formed directly.[40]



XXXIV

When the formaldehyde condensation product from acetylacetone (methylene bisacetylacetone) (XXXV) is treated with ammonia, the Hantzsch-type synthesis gives 2,6-dimethyl-3,5-diacetyldihydropyri-



XXXV

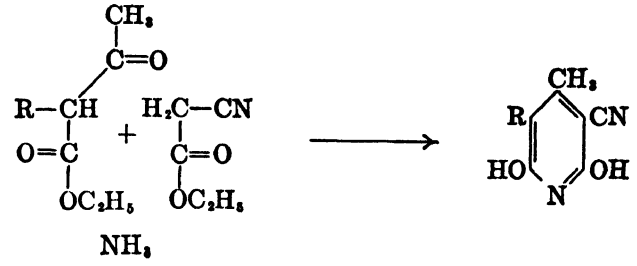
XXXVI

dine (XXXVI).[41] Claisen,[42,43] starting with the methenyl bisacetylacetone (—CH= instead of —CH_2— in formula XXXV), produced the pyridine compound directly.

The method known as the Guareschi or Guareschi and Thorpe synthesis is a modification of the Hantzsch reaction in which no aldehyde is added but, instead, the keto group of the β-keto ester takes its place. A typical example is the condensation of cyanoacetic ester and

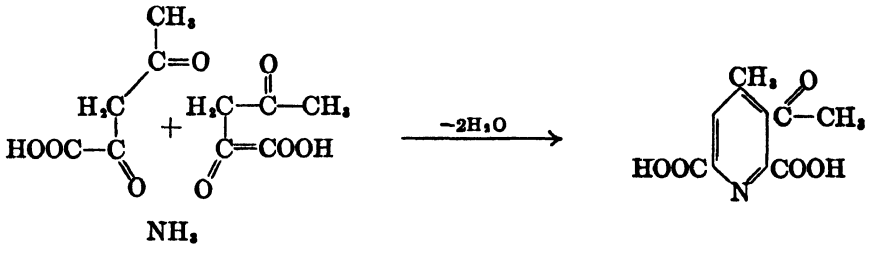
40 Merz and Richter, *Arch. Pharm*, **275**, 294 (1937).
41 Scholtz, *Ber.*, **30**, 2295 (1897).
42 Claisen, *Ann.*, **297**, 1 (1897); Ger. pat. 79,863, Jan. 21, 1895.
43 Mohr and Schneider, *J. prakt. Chem.*, [2] **69**, 245 (1904).

ethyl α-ethylacetoacetate (R = $-C_2H_5$) with ammonia to give an 85% yield of 2,6-dihydroxy-3-cyano-5-ethyl-4-methylpyridine.[44] The



reaction has been investigated for the normal and branched alkyl derivatives through butyl as well as for allyl, benzyl, and β-hydroxyethyl. Malonic ester cannot replace acetoacetic ester in these reactions, but acetoacetamide or cyanoacetamide may replace the cyanoacetic ester.[45]

If two molecules of acetylpyruvic acid (XXXVII) are treated with ammonia, the condensation takes place in the following sense to give 3-acetyl-4-methyl-2,6-pyridinedicarboxylic acid (XXXVIII).[45]



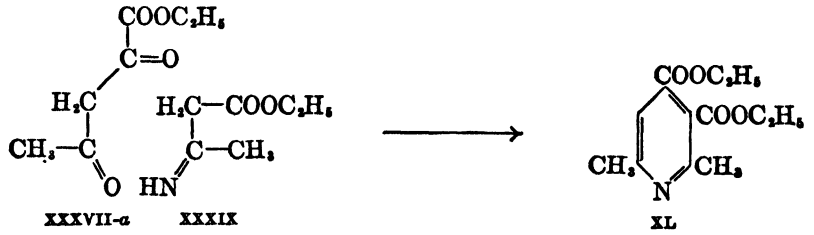
XXXVII XXXVIII

Nitrogen-Containing Aliphatic Compounds. The line of demarcation between the Hantzsch synthesis and the many very closely related reactions which employ aliphatic nitrogen-containing compounds such as β-aminocrotonic ester (XXXIX) is largely a matter of definition. As was indicated in the previous section, β-aminocrotonic ester is very likely an intermediate in the Hantzsch synthesis. Thus, if this material is separated and then treated with an aldehyde and another molecule of a β-keto ester, the result is equivalent to that obtained by conducting the Hantzsch synthesis in a stepwise manner. There are certain definite advantages in this stepwise type of reaction, the most

[44] Ruzicka and Fornasier, *Helv. Chim. Acta*, **12**, 343 (1919).
[45] Ref. 20, pp. 197–205.

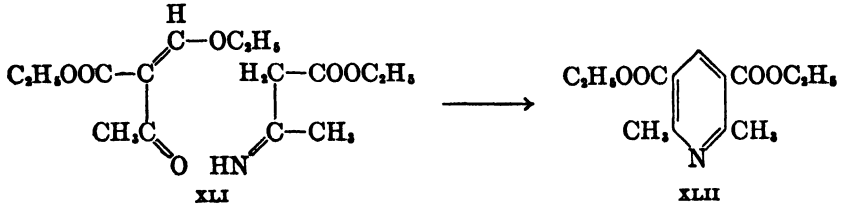
important of which is the possibility of using two different β-keto esters, thus forming an unsymmetrical pyridine derivative.

A special case in which it is unnecessary to add any aldehyde involves the condensation of acetylpyruvic ester and β-aminocrotonic ester. The reaction proceeds with great ease and in good yields to give 2,6-dimethyl-3,4-dicarbethoxypyridine (XL).[46] The analogy to



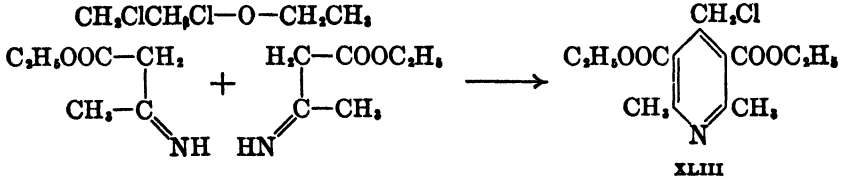
XXXVII-α XXXIX XL

the reaction of ammonia and acetylpyruvic acid is apparent. In this particular case, a pyridine derivative (XL) instead of a dihydropyridine derivative is formed. In another interesting variation, ethoxymethyleneacetoacetic ester (XLI) serves as β-keto ester and XLII is



XLI XLII

formed.[47] Benary [48] employed α,β-dichloroethyl ether as a source of chloroacetaldehyde, which, when condensed with β-aminocrotonic ester, gave a 54% yield of 2,6-dimethyl-4-chloromethyl-3,5-pyridine dicarboxylic acid ester (XLIII).

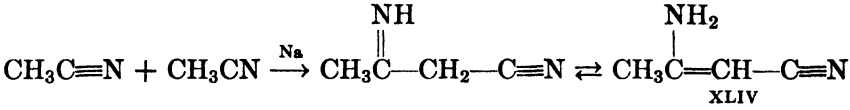


XLIII

Although it appears that many of the possibilities have not been explored, such compounds as ethoxymethylenemalonic ester, acetamido-

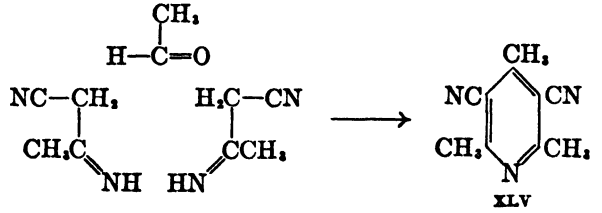
[46] Mumm et al., *Ber.*, **50**, 1573 (1917); **54**, 726 (1921).
[47] Claisen, *Ber.*, **26**, 2729 (1893).
[48] Benary, *Ber.*, **44**, 489 (1911); **51**, 567 (1918).

methylenemalonic ester, acetamidomethyleneacetoacetic ester, benzoylacetone, and acetonedicarboxylic acid should give normal reactions with β-aminocrotonic ester to form pyridine derivatives. Mumm and Böhme,[49] however, failed to obtain a pyridine compound in the condensations of β-aminocrotonic ester with acetylacetone, oxalacetic ester, or formylacetone. In addition, β-aminoacrylic ester or β-aminocinnamic ester should readily replace the β-aminocrotonic ester. Several reactions of importance proceeding from derivatives of β-aminoacrylonitrile have been described, but none with β-aminoacrylonitrile, itself. When acetonitrile is treated with sodium or sodium ethoxide under the right conditions, a dimer (XLIV) which belongs to the class of compounds known as "dinitriles" is formed. This substance, which is simply the nitrile of β-aminocrotonic ester, is formed according to the following equation, which is completely analogous to the formation of acetoacetic ester from ethyl acetate and sodium ethoxide.



XLIV

It reacts in a manner completely analogous to β-aminocrotonic ester and gives 2,4,6-trimethyl-3,5-dicyanopyridine on reaction with acetaldehyde. The intermediate dihydropyridine derivative is oxidized during the reaction to the true pyridine compound (XLV). If a ketone



XLV

such as acetone is substituted for an aldehyde, a dihydropyridine analogous to XLV but possessing two methyl groups in the 4 position is formed. It is remarkable that chromic acid oxidation removes one methyl group, giving a pyridine derivative.[50]

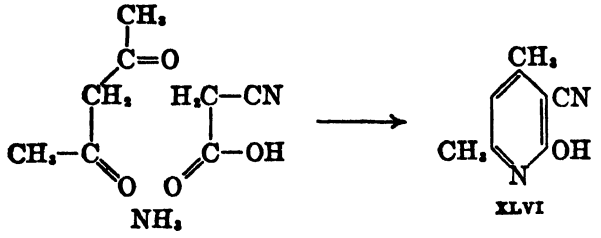
Cyanoacetic ester, cyanoacetic acid, or cyanoacetamide can replace acetoacetic ester in the Hantzsch-type synthesis.[51] The ester and the

[49] Mumm and Böhme, *Ber.*, **54**, 726 (1921).

[50] Meyer, *J. prakt. Chem.*, [2] **78**, 497 (1908); [2] **90**, 1 (1915); [2] **92**, 174 (1915).

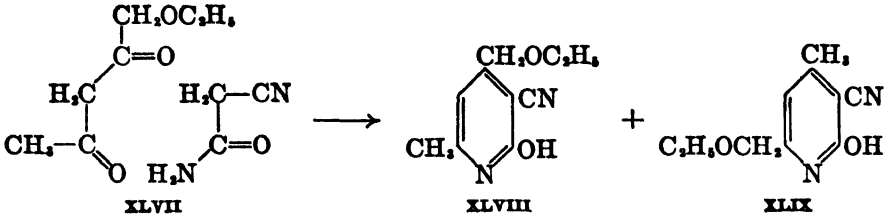
[51] Bardhan, *J. Chem. Soc.*, 2223 (1929).

acid require ammonia as an additional reactant, whereas reactions with cyanoacetamide proceed without ammonia in the presence of piperidine and, in general, give the best yields. As an example of the use of cyanoacetic acid, the formation of 4,6-dimethyl-3-cyano-2-hydroxypyridine (XLVI) may be given.[52] The production of XLVIII, a valu-



XLVI

able intermediate for the synthesis of vitamin B_6 (pyridoxine) [53] from XLVII, has been studied extensively by Wenner and Plati,[54] who found that two isomers were produced; the expected isomer (XLVIII) was formed in 75% yield along with about 15% of the isomeric 3-cyano-6-ethoxymethyl-4-methyl-2-hydroxypyridine (XLIX).

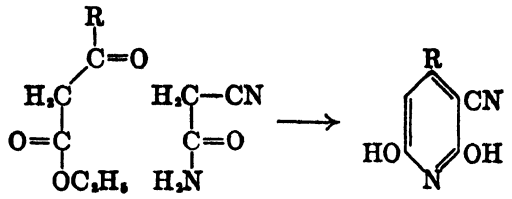


XLVII XLVIII XLIX

Bardhan [51] has studied this reaction, using oxaloacetic ester, benzoylacetone, benzoylmethyl ethyl ketone, and acetylmethyl ethyl ketone in order to determine the relative reactivities of the respective carbonyl groups. Except when there is a carbethoxy group so situated in the 1,3-diketone, as for instance in ethyl acetylpyruvate, that it greatly enhances the activity of one of the carbonyl groups, it appears that the carbonyl which is least hindered is the first to react with the methylene group of the acetoacetamide. The cyclization occurs, therefore, so that the predominant product has the larger group in the 2 position. Many types of 1,3-dicarbonyl compounds undergo this condensation. An unusual example which illustrates its versatility is the reaction of cy-

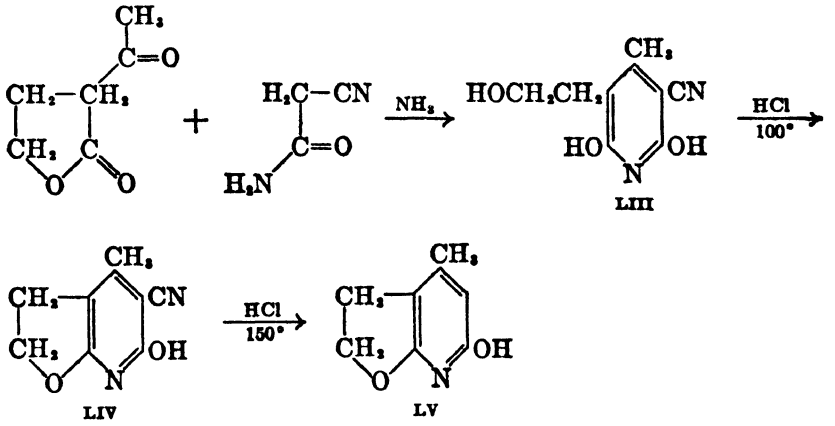
[52] Bergel and Cohen, Brit. pat. 4,553,097 (May 7, 1943) [*C. A.*, 38, 4271 (1944)].
[53] Harris, Stiller, and Folkers, *J. Am. Chem. Soc.*, 61, 1242 (1939).
[54] Wenner and Plati, *J. Org. Chem.*, 11, 751 (1946).

anoacetamide with acetonedicarboxylic ester (R = $-CH_2COOC_2H_5$) to give LI in 31% yield.[55] Ethyl oxaloacetate and diethyl β-ketoadi-



	R
L	$-COOC_2H_5$
LI	$-CH_2COOC_2H_5$
LII	$-CH_2CH_2COOC_2H_5$

pate both condense with cyanoacetamide in a similar manner to give the homologs L (R = $COOC_2H_5$) and LII (R = $CH_2CH_2COOC_2H_5$), respectively. Acetylpyruvic acid gives 2-methyl-3-hydroxy-4,5-pyridinedicarboxylic acid.[56] An exceptional example is the spontaneous condensation of cyanoacetamide with the commercially available α-acetylbutyrolactone in concentrated ammonium hydroxide to give a 52% yield of 2,6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanopyridine (LIII).[57] The lactone ring is hydrolyzed in the process but can be closed to give a tetrahydrofuranopyridine derivative (LIV)



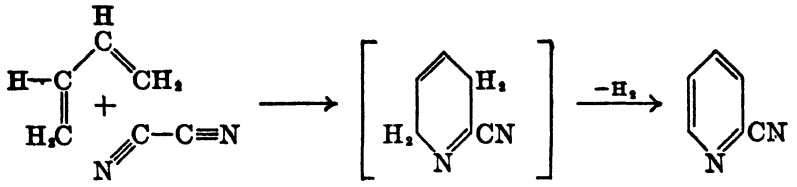
when refluxed in concentrated hydrochloric acid. It is quite surprising that the cyano group is not hydrolyzed by such treatment; if the hydrochloric acid treatment is continued at 150°, however, hydrolysis and decarboxylation result to give LV. The tautomerism of this product has been discussed (p. 441).

[55] Stevens and Beutel, *J. Am. Chem. Soc.*, **65**, 449 (1943).

[56] Itiba and Emoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **38**, 347 (1941) [*C. A.*, **35**, 6960 (1941)].

[57] Stevens, Beutel, and Chamberlin, *J. Am. Chem. Soc.*, **64**, 1093 (1942).

An isolated instance of the formation of pyridine as a by-product from a nitrogen-containing aliphatic compound has been observed in the peroxide-catalyzed polymerization of acrylonitrile.[58] 1-Cyano-1,3-butadiene is a chain isomer of pyridine, but pyridine has not been detected as a by-product in the polymerization of this diene.[59] It has been found [60,61] that 1,3-dienes will condense with cyanogen to give cyanopyridines. In the simplest case, 1,3-butadiene reacted with cyanogen in the vapor phase at 480° to give a 20% yield of 2-cyanopyridine. The reaction was formulated as a Diels-Alder synthesis in

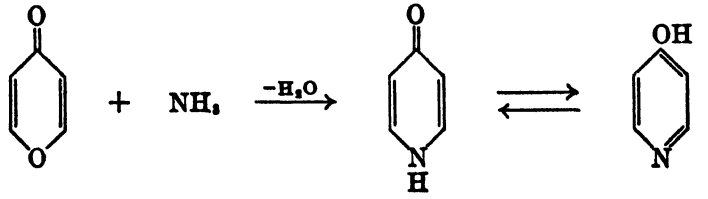


which the primary adduct underwent dehydrogenation to give the more stable pyridine. The reaction was extended to include isoprene, chloroprene, 2-methylpentadiene and hexachlorobutadiene, all of which gave a mixture of isomeric cyanopyridines.

Synthesis from Other Ring Compounds

Various other ring compounds such as the pyrones, the pyrroles, piperidines, or quinolines can be converted into pyridine derivatives; some of these reactions are of no preparative value, but others serve as sources of otherwise difficultly available compounds.

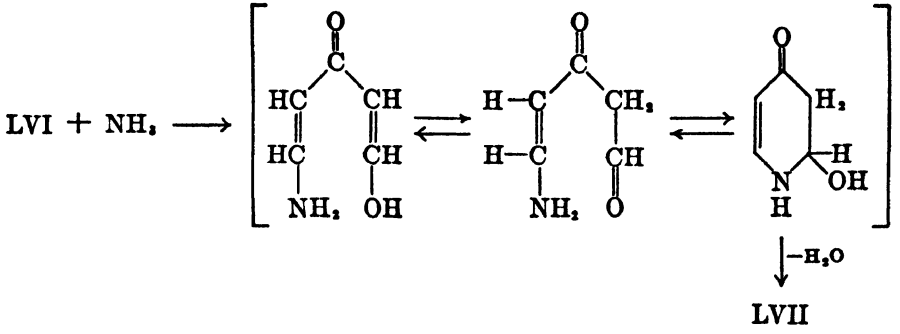
Pyrones (cf. Ch. 7). The pyrones are closely related to the pyridines, and they react readily with ammonia to replace the ring oxygen atom with an =NH group to give the corresponding pyridone. Thus γ-pyridone (LVII) may be made by treatment of γ-pyrone (LVI) with



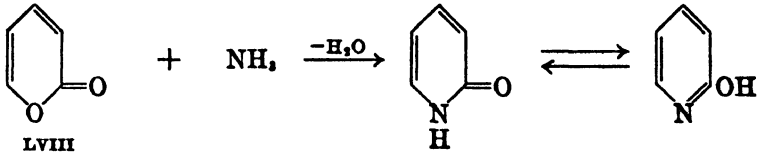
LVI LVII

58 Kern and Fernow, *J. prakt. Chem.*, [2] **160**, 281 (1942).
59 Unpublished work of Milton Frankel, Pennsylvania State College.
60 Janz, Ascah, and Keenan, *Can. J. Research*, **25**, 272 (1947).
61 Janz and Keenan, *Can. J. Research*, **25**, 283 (1947).

ammonia. In the ammonolysis, a ring opening must take place, with subsequent ring closure and loss of water. This reaction is in a sense another example of the formation of a pyridine ring from a derivative of glutaconic dialdehyde (p. 452).



The reason for the reaction of γ-pyrone with ammonia is not so apparent as the corresponding reaction of ammonia with α-pyrone (LVIII). This latter reaction is the ammonolysis of an inner ester,



and the reaction of ammonia with a lactone is well known. γ-Pyridone can be considered the vinylog of α-pyridone and, in accordance with the properties of vinylogous compounds,[62] would be expected to show similar reactions. The reverse reaction, hydrolysis of the α- or γ-pyridone to the α- or γ-pyrone, has not been reported. This is an indication of the greater stability of the pyridine ring.

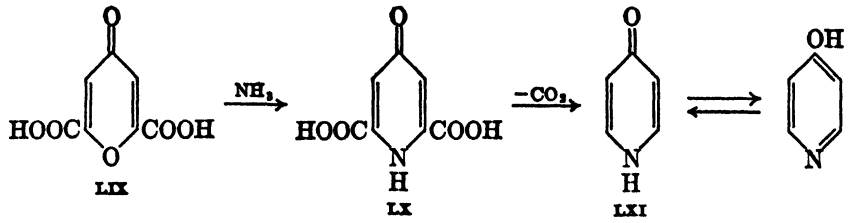
Although α-pyridone may be made much more readily by other methods, the preferred method [63] for the synthesis of γ-pyridone (LXI) is through chelidonic acid (LIX) (for the preparation of which see p. 382). LIX is converted into chelidamic acid (LX) which is decarboxylated to the product.[64,65] The reaction in which the ring oxygen of a

62 Fuson, *Chem. Revs.*, **16**, 1 (1935).

63 The other preparative method available for the synthesis of γ-pyridone is by the hydrolysis of pyridylpyridinium chloride hydrochloride (p. 529). When pressure equipment is available, this method may compete successfully or even be preferred to the one indicated here.

64 Robinson and Thornley, *J. Chem. Soc.*, 2169 (1924).

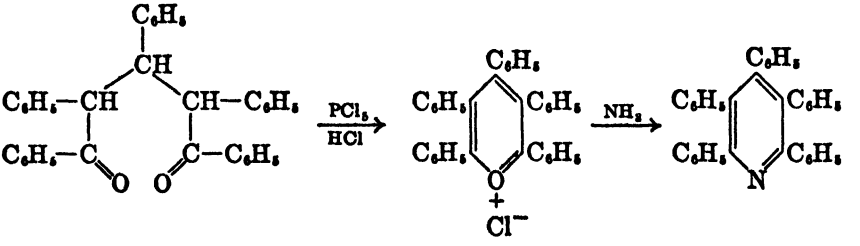
65 King and Ware, *J. Chem. Soc.*, 873 (1939).



LIX LX LXI

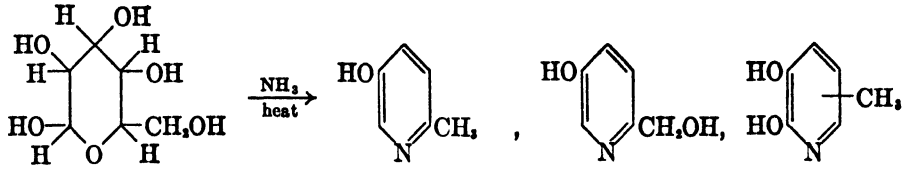
pyrone is replaced by nitrogen is accomplished by treatment with concentrated ammonium hydroxide and takes place with varying difficulty, depending on the starting pyrone. In general, α-pyrones are much more easily converted than γ-pyrones, and a carbethoxy group in the α position renders the γ-pyrone more reactive. Thus, to convert γ-pyrone to γ-pyridone, the former is heated with concentrated ammonium hydroxide at 120–140° for 8 hr. On the other hand, the conversion of chelidonic acid (LIX) to chelidamic acid (LX) requires only that it be warmed with concentrated ammonium hydroxide at 100° for 4 hr. Substantially all pyrones, the modes of synthesis of which are described in Chapter 7, may be converted to pyridones by this method. A refluxing mixture of ammonium acetate, acetic acid, and acetic anhydride has been found to be superior to ammonia for the conversion in many cases.[66,67]

Pyrylium Salts. In an analogous manner, the ammonolysis of pyrylium salts [68] results in pyridine compounds, as illustrated by the following example in which pentaphenylpyrylium chloride hydrochloride is warmed with ammonia and converted into the corresponding pentaphenylpyridine in almost quantitative yield.[65,68] This method is of very doubtful synthetic value because of the difficulty in obtaining large amounts of the pyrylium salts and because of the much better alternate methods of synthesis.



66 Leben, *Ber.*, **29**, 1673 (1896).
67 Fried and Elderfield, *J. Org. Chem.*, **6**, 566 (1941).
68 Ref. 20, pp. 189–192.

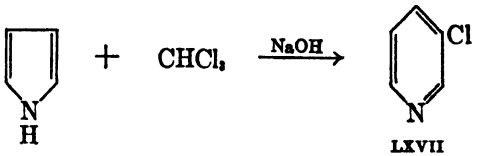
A special but very interesting example of the formation of a pyridine compound was reported by Aso.[69] Aqueous solutions of glucose (LXII) or sucrose, when heated for from 1 to 3 hr. at 155–165° with ammonium salts such as ammonium sulfate, chloride, or oxalate, gave



LXII LXIII LXIV LXV

various pyridine derivatives such as 5-hydroxy-2-methylpyridine (LXIII), 5-hydroxy-2-hydroxymethylpyridine (LXIV), and a 2,3-dihydroxy-5-methyl- or 2,3-dihydroxy-6-methyl-pyridine (LXV). The reported yields are not good, but the abundance of the starting material adds greatly to the interest in this and similar reactions as possible sources for new or difficultly available pyridine compounds.

Pyrroles. The conversion of pyrrole (LXVI) to 3-chloropyridine (LXVII) by treatment with chloroform in basic solution[70] was discovered very early, and several additional examples of this reaction have been observed (cf. p. 309).



LXVI LXVII

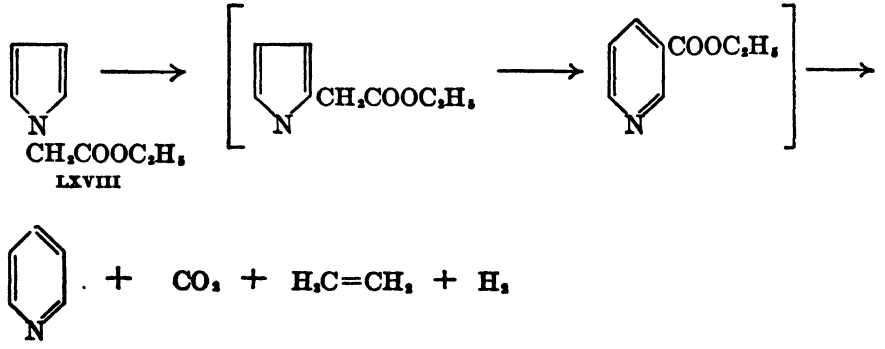
Other halogen derivatives such as bromoform, benzal chloride, and methylene iodide react in an analogous manner, the new carbon atom always becoming the 3 carbon in the pyridine ring. The mechanism of this reaction is not known; apparently it does not occur by substitution on the 3 position of the pyrrole ring but rather through substitution on the 2 position.[71] A similar type of reaction takes place upon the thermal decomposition of certain N-substituted pyrroles. N-benzylpyrrole gives 3-phenylpyridine, and ethyl N-pyrrylacetate

69 Aso, *J. Agr. Chem. Soc. Japan*, **15**, 629 (1939); **16**, 253, 249 (1940) [*C. A.*, **34**, 431 (1940)].

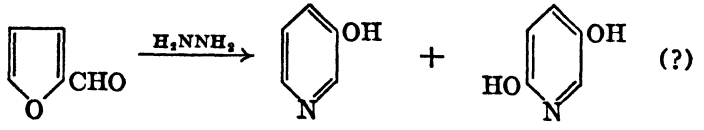
70 Clamician and Dennstedt, *Ber.*, **14**, 1154 (1881).

71 Oddo, *Gazz. chim. ital.*, **68**, 204 (1938); **69**, 10 (1939) [*C. A.*, **32**, 7450 (1938); **33**, 4239 (1939)].

(LXVIII) gives pyridine, carbon dioxide, ethylene, and hydrogen,[72] probably through the intermediates indicated below.



Furans (cf. p. 169). Furfural has been subjected to treatment with ammonia, ammonium salts, hydrazine, and hydroxylamine to obtain pyridine derivatives. Aso [74] reports the formation of 3-hydroxypyridine and 2,5-dihydroxypyridine on treatment of furfural with hydrazine sulfate under pressure at 152–153°. It seems probable that the prod-



uct described as 2,5-dihydroxypyridine is really the 2,3 isomer. 5-Methylfurfural gives 2-methyl-5-hydroxypyridine, but the conversions are poor.

Furfural with ammonia alone is not converted to pyridine, but under reducing conditions the formation of piperidine takes place.[75]

2,5-Dihydrofuran-2,5-dicarboxylic acid on treatment with concentrated ammonium hydroxide and ammonium bromide in a sealed tube at 160° for 12 hr. is reported to give a 40% yield of 6-hydroxypicolinic

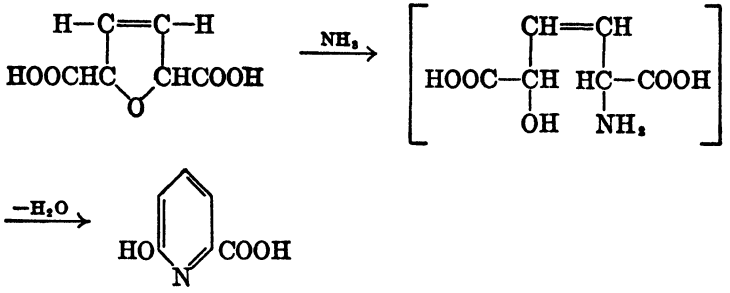
[72] Sohl and Shriner, *J. Am. Chem. Soc.*, **53**, 4168 (1931).

[73] For an example, see Granelli, *Farm. Ital.*, **5**, 708 (1937) [*C. A.*, **33**, 4245 (1939)].

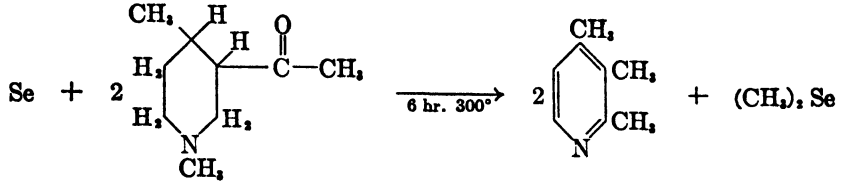
[74] Aso, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **18**, 177 (1939) [*C. A.*, **34**, 3273 (1940)].

[75] Schmidt, Blaser, and Manchen, Ger. pat. 695,472 (July 25, 1940) [*C. A.*, **35**, 5520 (1941)].

acid.[76] This apparently is the result of opening of the five-membered furan ring and closure through the carboxylic acid group to the six-membered pyridine ring.



Dehydrogenation of Piperidines. It is well known that piperidine can be dehydrogenated to pyridine,[77] but the method is of little practical value. The dehydrogenation of piperidine derivatives has led to some anomalous reactions as indicated below. Prelog et al.[78,79] have discussed the possible course of this reaction.



Oxidation of Benzopyridines. By the oxidation of many benzopyridines, the benzene nucleus is destroyed and a substituted pyridinecarboxylic acid remains (p. 422). Thus, quinoline gives quinolinic acid by permanganate oxidation in 70% yields. The oxidation of quinoline and isoquinoline is a reaction of preparative importance. In the several other instances, such as with the quinine alkaloids, it has served as an important degradative procedure for identifying the point of attachment of a ring to the pyridine nucleus.

Synthesis Starting with a Pyridine Ring Compound

The second large group of reactions which can be employed in the preparation of pyridine compounds is composed of those transforma-

76 Fischer, Hess, and Stahlschmidt, *Ber.*, **45**, 2456 (1912).

77 Taylor and Baker, *Sidgwick's Organic Chemistry of Nitrogen*, Oxford Press, London, 1937, p. 518.

78 Prelog, Moor, and Fuherer, *Helv. Chim. Acta*, **26**, 846 (1943).

79 Prelog, Komzak, and Moor, *Helv. Chim. Acta*, **25**, 1654 (1942).

tions which begin with the pyridine ring intact and further modify it by appropriate processes. In general, these reactions follow the broad principles for the analogous reactions in the benzene series, but of course they are conditioned by the special nature of the pyridine ring, especially its resistance to electrophilic attack and the unique nature of the reactions of the α- and γ-substituted derivatives. For synthesis of this type, all pyridine compounds produced by the coal-tar industry as well as all substituted pyridines which can be made by the many synthetic procedures outlined in the preceding section are available as starting materials. These reactions will not be considered as a group but will be taken up in connection with the discussion of specific pyridine compounds in the following sections.

PYRIDINE AND ITS HOMOLOGS

Pyridine Itself

Pyridine is a colorless liquid when pure, with a characteristic and disagreeable odor. It is hygroscopic, is miscible in all proportions with water, and forms an azeotrope corresponding approximately to $C_5H_5N \cdot 3H_2O$ which boils at 92–93°. Pyridine may be purified by drying over barium oxide at room temperature for several days followed by careful fractionation. Solid potassium hydroxide may serve as the drying agent, but it is not so efficient as barium oxide and a longer time is required. Pyridine turns yellow when it stands even in the dark but at a more rapid rate in sunlight. The colored impurity apparently is glutaconic dialdehyde or a derivative thereof, resulting from the cleavage of the pyridine ring.[1] The electron diffraction data for pyridine[2] furnishes a basis for calculating the carbon-nitrogen bond distance within the molecule, and the results indicate that the distance (1.37 ± 0.03 A) is almost the same as that for the carbon-carbon bond in benzene. The infrared spectrum of pyridine has been measured by Kline and Turkevich[3] and has served as the basis for calculating its heat of formation. The characteristic absorption spectrum of pyridine in the ultraviolet is quite similar to that of benzene, and the absorption line at 2550 A in sulfuric acid has been used for the determination of pyridine in vapors which may also contain ammonia or nicotine.[4]

1 Freytag, *Phot. Korr.*, **73**, 17, 37, 57 (1937) [*C. A.*, **32**, 2889 (1938)].
2 Schomaker and Pauling, *J. Am. Chem. Soc.*, **61**, 1769 (1939).
3 Kline and Turkevich, *J. Chem. Phys.*, **12**, 300 (1944).
4 Hofmann, *Arch. Hyg. Bakt.*, **128**, 169 (1942) [*C. A.*, **39**, 42 (1945)].

The only important source of pyridine at present is coal tar in which it is found to the extent of less than 0.1% but from which some 600,000 gal. are produced annually. It has many industrial applications, including those as a solvent, as an insecticide, as a starting material for the synthesis of various detergents, antiseptics, and other pharmaceuticals such as sulfapyridine, and for the manufacture of special dyestuffs. In the laboratory, it is valuable as a special solvent for many organic substances which are difficultly soluble in other media. In addition to dissolving a wide variety of organic compounds, anhydrous pyridine is a good solvent for several inorganic salts such as silver bromide, silver nitrate, cuprous and cupric chlorides, ferric chloride, mercuric chloride, lead nitrate, and lead acetate.[5] These solutions show conducting properties and are valuable for studies of the electrolytic properties of the salts not otherwise possible because of either their insolubility or hydrolysis in water.

Pyridine has a strong catalytic effect on certain reactions. The presence of pyridine speeds up the conversion of sucrose into sucrose octaacetate by acetic anhydride.[6] Similarly, pyridineacetate has been claimed as a catalyst in the Diels-Alder reaction.[7] It has been used in the preparation of mercaptans [8] and as a negative catalyst in esterifications with acetic acid.[9] The use of pyridine as an acid acceptor is discussed on p. 410.

The detection of pyridine in small amounts can be accomplished by several methods. A specific color reaction occurs between pyridine and ethylene oxide [10] by which either reactant may be detected. The color tests of widest applicability depend on the cleavage of the pyridine ring (p. 425) to glutaconic dialdehyde or its derivatives which, because of their conjugation, are highly colored. Thus, pyridine can be detected and determined quantitatively in the presence of its higher homologs by treating the unknown solution with cyanogen bromide followed by some aromatic amine such as β-naphthylamine [11] or benzidine.[12] By extracting the colored product from neutral solution with isoamyl alcohol, the pyridine can be determined colorimetrically

5 Nelson, *J. Am. Chem. Soc.*, **35**, 658 (1913).

6 Amagasa and Yanagita, *J. Soc. Chem. Ind., Japan*, **43**, Suppl. binding 444 (1940) [*C. A.*, **35**, 3841 (1941)].

7 Diels, *Ber.*, **75**, 1452 (1942).

8 Kharasch, U. S. pat. 2,365,561 (Dec. 19, 1944) [*C. A.*, **39**, 4618 (1945)].

9 Bailey, *Proc. Roy. Irish Acad.*, November 1944 [*C. A.*, **39**, 2448 (1945)].

10 Lehmann, *Z. angew. Chem.*, **52**, 407 (1939).

11 Borta and Marscheck, *Biochem. Zeit.*, **293**, 118 (1937).

12 Alekseev, *Zavodskaya Lab.*, **8**, 807 (1939) [*C. A.*, **34**, 56 (1940)].

in quantities of 0.37–0.05 mg. The color test based on the ultraviolet irradiation of pyridine followed by addition of the pyridine to an aromatic amine has the same chemical basis.[13]

Pyridine is decidedly toxic to human beings;[14] daily doses of 0.31–1.54 ml. are tolerated, but doses of 1.85–2.46 ml. per day are toxic, resulting in serious hepatic and renal damage, and may terminate in death. The many physiological tests of pyridine and pyridine derivatives have been reviewed by Van Oettingen.[15]

Many stable salts of pyridine and pyridine homologs have been described; they are useful for characterization, analysis, and purification. Most are made by combining the acid with pyridine in a dry organic solvent. Treatment of an ethereal solution of pyridine with dry hydrogen chloride deposits white crystals of the hydrochloride. With weaker acids, heat is sometimes necessary; e.g., boric acid and pyridine must be refluxed for 3–6 hr. in order to obtain the borate. Since the borate is a salt of a weak base and weak acid, boiling with water causes hydrolysis, and pyridine can be recovered from the borate by steam distillation. The aliphatic acids form compounds with pyridine and its homologs, and mention has been made of the pyridine-acetic acid azeotrope which boils at 139–140°; other aliphatic acids behave similarly.[16] With the exception of the chloroplatinate, chloroaurate, and mercurichloride, all the common pyridine salts are water soluble.

In addition to forming many salts with acids, pyridine forms a great variety of quaternary compounds with alkyl halides and sulfates. A vigorous exothermic reaction occurs when pyridine is mixed with methyl iodide.[17]

The lower alkylpyridinium halides are white crystalline hygroscopic solids which are very soluble in water. The higher alkyl derivatives differ only slightly in physical properties with the exception that the water solubility becomes less, that of the cetyl derivative being about 20%. The higher alkylpyridinium halides are valuable cationic germicides and have been thoroughly investigated because of this property. Reports on the bactericidal action of these compounds have

[13] Freytag and Neudert, *J. prakt. Chem.*, [2] **135**, 15 (1932).

[14] Pollock, Finkelman, and Arieff, *Arch. Internal Med.*, **71**, 95 (1943) [*C. A.*, **37**, 4468 (1943)].

[15] Van Oettingen, *Therapeutic Agents of the Pyrazol and Pyridine Series*, Edwards Brothers, Inc., Ann Arbor, Michigan, 1946.

[16] Gardner, *Ber.*, **23**, 1587 (1890).

[17] Hantzsch, *Ber.*, **42**, 80 (1909).

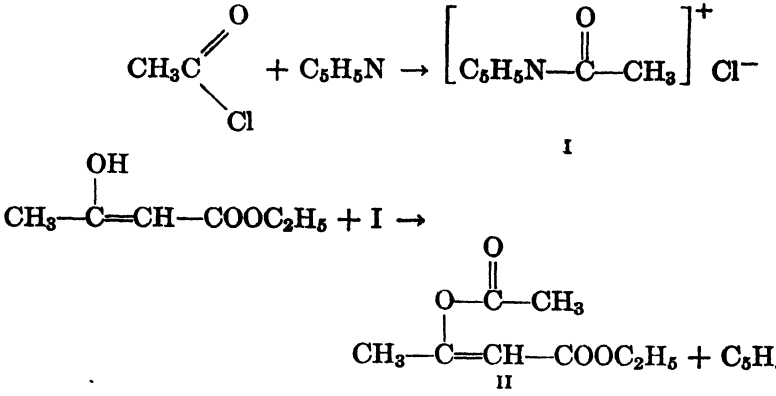
indicated[18-21] that this type of antiseptic is superior to many of the mercurials and phenols such as sodium ethyl mercurithiosalicylate and hexylresorcinol. One of the most promising of these, cetylpyridinium chloride, has been marketed under the trade name Ceepryn.

Other quaternary compounds have been of particular interest from the standpoint of their chemical value. Pyridine reacts vigorously with sulfur trioxide to give an addition compound $C_5H_5N \cdot SO_3$ (see p. 425). This, along with a similar compound from pyridine and chlorosulfonic acid ($C_5H_5\overset{+}{N}SO_3HCl^-$), is a valuable mild sulfating agent[22,23] for hydroxyl groups and has found application in studies on the sulfation of proteins, amines, ammonia, amides, polysaccharides,[24-28] and polyvinyl alcohol. It has been found, for instance, that a free phenolic hydroxyl group may be sulfated by this reagent without any nuclear sulfonation, as occurs with concentrated sulfuric acid.

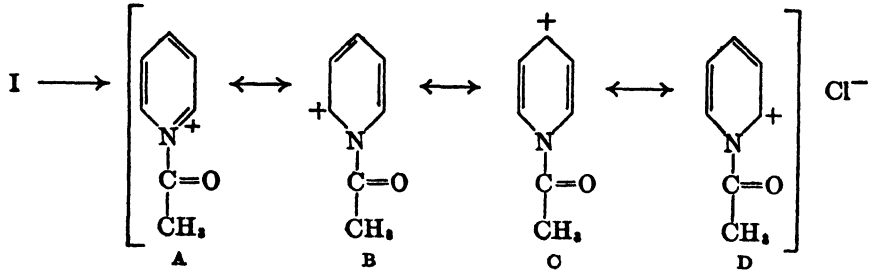
$$C_6H_5OH + C_5H_5\overset{+}{N}SO_3HCl^- \rightarrow C_6H_5{-}OSO_3H + C_5H_5N \cdot HCl$$

A spontaneous reaction occurs when acetyl chloride is added to pyridine; on distillation of the mixture, a stable addition compound is obtained,[29] along with some dehydracetic acid as a by-product. The chemical combination of the acetyl group in this compound is not so strong as that of an alkyl group in an alkylpyridinium halide. For instance, N-methylpyridinium chloride certainly cannot serve as a methylating agent, whereas N-acetylpyridinium chloride (I) has often been used for introducing the acetyl group, usually onto the oxygen of an enol.[30-32] A typical example is the formation of ethyl β-acetoxycrotonate (II) from ethyl acetoacetate. The structure of the N-ace-

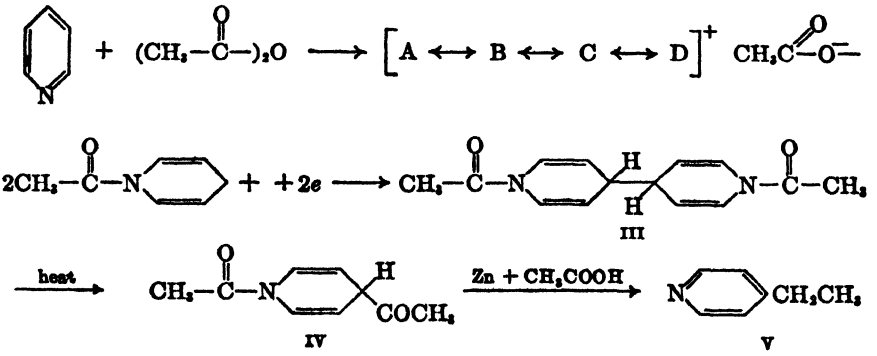
18 Green and Birkeland, *J. Infectious Diseases*, **74**, 32 (1944).
19 Shelton et al., *J. Am. Chem. Soc.*, **68**, 757 (1946).
20 Huyck, *J. Am. Pharm. Assoc.*, **34**, 5 (1945).
21 Kolloff et al., *J. Am. Pharm. Assoc.*, **31**, 51 (1942).
22 Reitz et al., *J. Am. Chem. Soc.*, **68**, 1031 (1946).
23 Baumgarten et al., *Z. physiol. Chem.*, **209**, 145 (1932).
24 Gebauer-Fülnegg, Stevens, and Dingler, *Ber.*, **61**, 2000 (1928).
25 Chargaff, Bancroft, and Stanley-Brown, *J. Biol. Chem.*, **115**, 155 (1936).
26 Karrer, Koenig, and Usteri, *Helv. Chim. Acta*, **26**, 1296 (1943).
27 Baumgarten, *Ber.*, **59**, 1976 (1926).
28 Baumgarten and Marggraff, *Ber.*, **64**, 301, 1582 (1931).
29 Dennstedt and Zimmermann, *Ber.*, **19**, 75 (1886).
30 Claisen, *Ann.*, **291**, 106, 110 (1896); **297**, 2 (1897).
31 Boveault and Borget, *Bull. soc. chim. France*, **27**, 1160 (1902).
32 Borsche, *Ber.*, **42**, 608 (1909).



tylpyridinium cation is undoubtedly that of A, with important contributions from the resonance states B, C, and D because of the electron attraction of the nitrogen atom. The existence of a resonance state



such as C accounts for several reactions of the N-acylpyridinium ion. Dimroth [33,34] isolated 1,1′-diacetyl-4,4′-tetrahydrodipyridyl (III) from the action of zinc dust on a pyridine-acetic anhydride reaction mixture. This can be represented as follows.

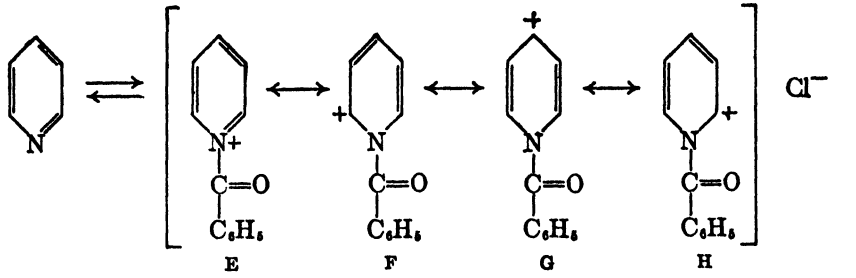


[33] Dimroth and Heene, *Ber.*, **54**, 2934 (1921).
[34] Dimroth and Frister, *Ber.*, **55**, 1223 (1922).

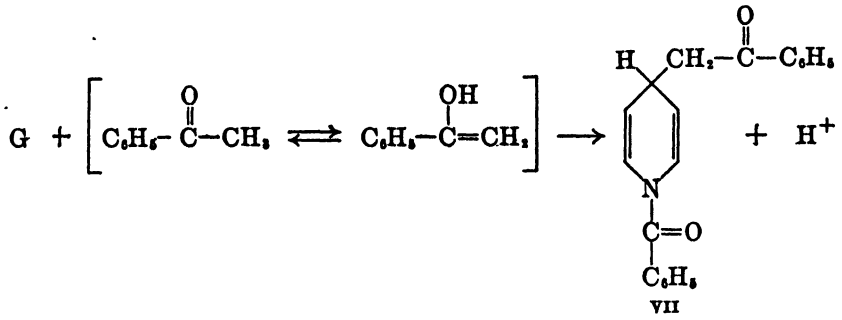
Wibaut and Arens[35] have investigated these reactions further and have shown the presence of both 1-acetyl-4-ethyldihydropyridine and 1,4-diacetyldihydropyridine (IV) in the reaction mixture. They have shown that III is an intermediate in the formation of these two, since, if it is isolated and treated with zinc dust and acetic acid, IV and V are formed. These steps have been combined in a suitable procedure for the synthesis of 4-ethylpyridine (35–38% yield).[35,36] The reaction is likewise applicable to the higher homologs of acetic anhydride[37] for the synthesis of other 4-alkylpyridines but not to the homologs of pyridine or pyridine derivatives such as 2-chloropyridine, 2-aminopyridine, 2-cyanopyridine, picolinic acid, or ethyl picolinate.[38] By substitution of ethylchloroformate for acetic anhydride in a similar series of reactions, Van Dorp and Arens[39] reported a 17% over-all yield of ethyl isonicotinate. One surprising fact is that none of the isomeric compounds with substituents in the 2 position, which should result from the reaction of forms such as B and D, has been observed.

McEwen[40] has made a study of the reactions of benzoylpyridinium chloride which, although it has not been isolated as such, must certainly exist in a mixture of pyridine and benzoyl chloride, as evidenced by the following reactions. In an attempt to obtain the enol benzoate of acetophenone, Claisen and Haase[41] treated acetophenone with a mixture of pyridine and benzoyl chloride. None of the desired benzoyl ester of the enol was obtained, but instead a yellow crystalline solid ($C_{20}H_{17}NO_2$) was formed. This was identified by McEwen as N-benzoyl-4-phenacyldihydropyridine (VII) and must have been formed according to the following equations by a reaction of the benzoylpyridinium ion (VI) in an activated state such as G. The proton is taken up by the excess pyridine and appears as pyridine hydrochloride in the final reaction mixture. This corresponds to the findings of McEwen that maximum yields were obtained when the molar ratio of pyridine, benzoyl chloride, and acetophenone was 2:1:1. The reactants were allowed to stand 4 months at room temperature, and the yield was 33%. The reaction was successfully extended to include propiophenone and cyclohexanone. The structures of the products

35 Wibaut and Arens, *Rec. trav. chim.*, **60**, 119 (1941).
36 Frank and Smith, *Org. Syntheses*, **27**, 38 (1947).
37 Arens and Wibaut, *Rec. trav. chim.*, **61**, 59 (1942).
38 Solomon, *J. Chem. Soc.*, 934 (1946).
39 Van Dorp and Arens, *Rec. trav. chim.*, **66**, 189 (1947).
40 W. E. McEwen, Ph.D. Thesis, Columbia University, 1947.
41 Claisen and Haase, *Ber.*, **33**, 1242 (1900).

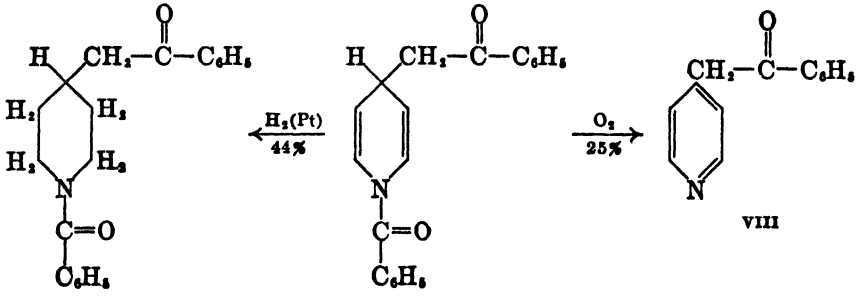


VI



VII

were proved by both oxidation and reduction, followed by comparison of the products with authentic samples made by independent methods.

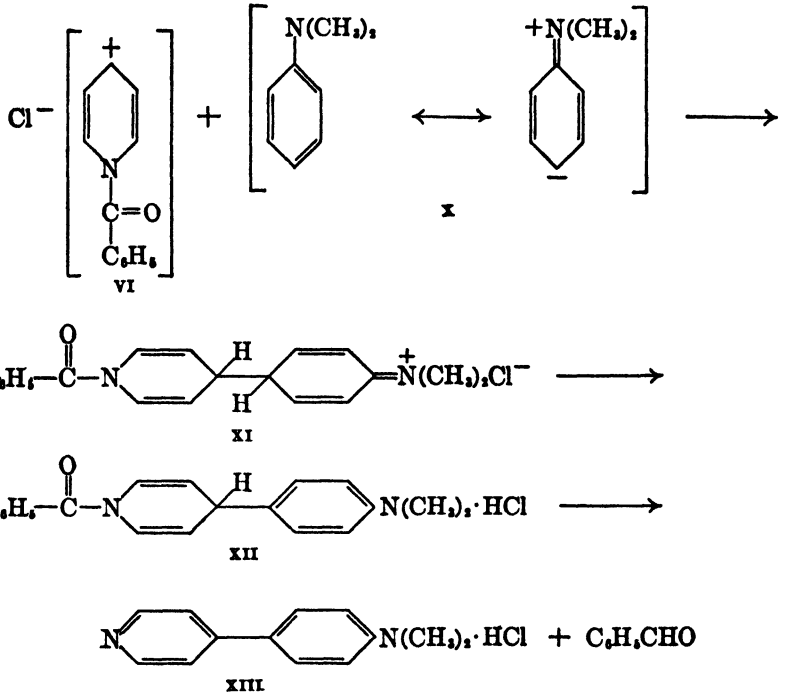


IX VII VIII

Only O benzoylation resulted when a β-keto ester or a β-diketone was substituted for acetophenone indicating that, whenever the rate of formation of the O-benzoyl derivative is appreciable, O benzoylation will take place in preference to the above nuclear substitution which is a very slow process.

A similar reaction of pyridine, benzoyl chloride, and dimethylaniline (X) [42] is explained by the following equations.

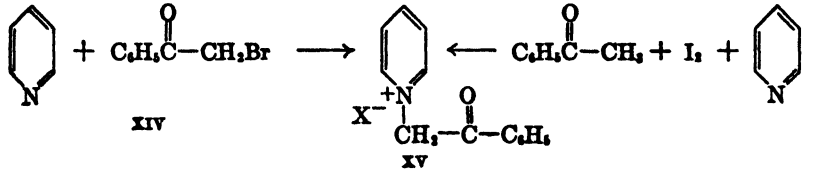
[42] Koenigs and Ruppelt, *Ann.*, **509**, 142 (1934).



The intermediate dihydropyridine (XII) was not isolated but apparently spontaneously lost benzaldehyde to give 4-(*p*-dimethylaminophenyl)pyridine (XIII).

Quinoline undergoes an interesting reaction with benzoyl chloride and potassium cyanide to form 2-cyano-1-benzoyl-1,2-dihydroquinoline, but attempts [43] to bring about an analogous reaction in the pyridine series have been unsuccessful.

When an α-bromo ketone such as ω-bromoacetophenone (XIV) is refluxed with pyridine in toluene, the quaternary phenacylpyridinium bromide (XV) is obtained in good yields.[44]

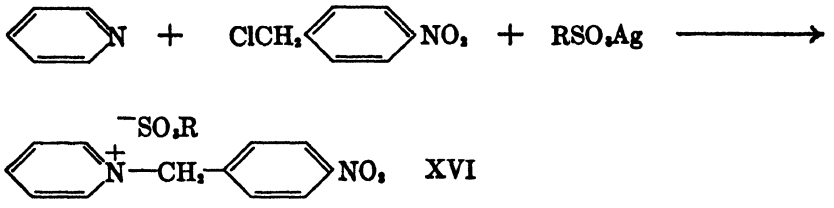


[43] Reissert, *Ber.*, **38**, 1603 (1905).
[44] Kröhnke, *Ber.*, **66**, 604, 1386 (1933).

It is extremely interesting that, when acetophenone is warmed with iodine in pyridine solution, phenacylpyridinium iodide is formed directly in excellent yields along with pyridine hydriodide.[45] The reaction is general and proceeds with various ketones such as 1-acetylnaphthalene, 1-acetylanthracene, and hydroxyacetophenone, as well as with some of the pyridine homologs such as the picolines.

Quaternary compounds of the type of XV show the unique property of undergoing hydrolysis to an acid which corresponds to the ketone from which they are formed but which has one less carbon atom. In this respect, the reaction accomplishes exactly the same conversion as does the haloform reaction. The fate of the pyridine portion of the molecule has not been determined. The phenacylpyridinium halides can also be reduced to the corresponding carbinols by catalytic hydrogenation, and the same carbinols can be obtained directly by the action of the bromohydrin on pyridine (57%).[46]

Huntress and Foote[47] have developed a reaction for the preparation of pyridinium sulfonic acid derivatives which are useful in the identification of sulfonic acids. Whereas carboxylic acids may be characterized by their *p*-nitrobenzyl esters, prepared from the salts of the acids and *p*-nitrobenzyl chloride, the analogous reaction with the salt of a sulfonic acid does not occur. In pyridine, however, the pyridinium derivative of the *p*-nitrobenzyl sulfonate (XVI) is readily formed.



XVI

The quaternary derivative, pyridine betaine hydrochloride (XVII), is formed from pyridine and chloroacetic acid when the two reactants are heated on the steam bath. The product is very soluble in water and decomposes at 202–205°, giving carbon dioxide, methyl chloride, and pyridine.[48]

[45] King et al., *J. Am. Chem. Soc.*, **66**, 894 (1944); **67**, 2089 (1945); **68**, 717 (1946).

[46] Riegel and Wittcoff, *J. Am. Chem. Soc.*, **68**, 1805 (1946).

[47] Huntress and Foote, *J. Am. Chem. Soc.*, **64**, 1017 (1942).

[48] Rezzi, *Atti. reale ist. Veneto sci.*, Pt. II, **94**, 167 (1935); *Chem. Zentr.*, **1937**, II, 3605.

$$C_5H_5N + ClCH_2COOH \xrightarrow{100^\circ} \underset{\text{XVII}}{C_5H_5\overset{+}{N}—CH_2COOH\ Cl^-} \begin{cases} \xrightarrow{205^\circ} C_5H_5N + CO_2 + CH_3Cl \\ \xrightarrow[Ag_2O]{} \underset{\text{XVIII}}{C_5H_5\overset{+}{N}—CH_2COO^-} \end{cases}$$

The properties of the product (XVIII) produced by treatment of XVII with silver oxide correspond to those expected of a typical betaine, i.e., high melting point, great water solubility, and insolubility in ether. Its structure has been discussed by Oster [49] from the aspect of its dipole moment, and its dipolar ion nature has been confirmed.

Of special interest is benzylpyridinium chloride, which is obtained by refluxing pyridine and benzyl chloride for 15 min. It is reduced either electrolytically or with sodium amalgam to give a product for which the properties of a free radical are claimed. Reduction of the benzoyl chloride-pyridine mixture and of N,N′-dibenzoyl-4,4′-bipyridinium dichloride is reported to give a similar product (see p. 623).

Pyridinium thiocyanate is formed when dry hydrogen cyanide gas is passed into a suspension of sulfur in pyridine.

The reaction of pyridine with such compounds as 2,4-dinitrochlorobenzene has been discussed in the section on ring cleavage. The substitution reactions of pyridine have been covered in a general manner previously and are discussed in detail under the respective products such as chloropyridine, nitropyridine, aminopyridine, etc.

Alkyl-, Alkylene-, and Aryl-pyridines

The alkylpyridines show the expected gradation in physical properties as the size and number of alkyl groups are increased; in general, they resemble pyridine closely. The α isomer has in every case the lowest boiling point, whereas the boiling points of the β and γ isomers are higher and very close together.

All the isomeric picolines (monomethylpyridines) and lutidines (dimethylpyridines) are known. Five of the six collidines (trimethylpyridines) and two of the three tetramethylpyridines are known.

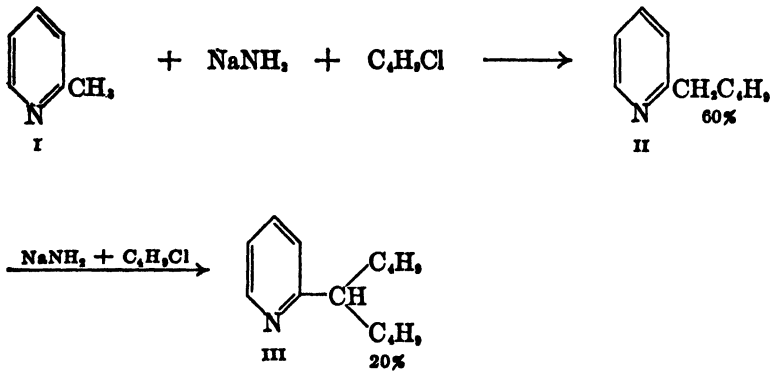
The picolines are somewhat stronger bases than pyridine, owing primarily to the inductive effect of the methyl group, which increases the availability of electrons at the nitrogen atom. As measured by the ability to donate an electron pair to a hydrogen ion, 3- and 4-picoline have approximately the same basic strength, but 2-picoline is

[49] Oster et al., *J. Am. Chem. Soc.*, **66**, 946 (1944).

decidedly stronger because of the shorter distance between the methyl group and ring nitrogen. Brown and Barbaras [50] have shown that, with the exception of 2-picoline, this same order of basic strengths holds when boron trifluoride is the reference acid. 2-Picoline is a decidedly weaker base when measured against boron trifluoride because of the steric factors involved.

The synthesis of alkylpyridines through the Friedel-Crafts reaction, which is of such importance in the benzene series, has never been achieved. This is undoubtedly one of the most important differences in the chemistry of pyridine and benzene from the standpoint of synthesis.

Not only are the three picolines available commercially from coal tar, but the commercial availability of several synthetic higher alkyl α- and γ-pyridines has been announced.[51] These can be made from α- and γ-picoline by condensation reactions which are characteristic of the active hydrogens on the α- and γ-methyl groups (p. 447). Thus, if α-picoline (I) is treated with sodium amide and an alkyl halide, such as butyl chloride, substitution takes place on the α-methyl group and the side chain is lengthened accordingly to give 2-*n*-amylpyridine (II).[52-54] Since active hydrogens still exist in the product (II), it is



I II III

possible in the presence of excess sodium amide for further reaction to occur to give 2-(5-nonyl)pyridine (III).

50 Brown and Barbaras, *J. Am. Chem. Soc.*, **69**, 1137 (1947).

51 *Reilly Coal Tar Chemicals*, Reilly Tar and Chemical Corp., Indianapolis, Indiana (1945).

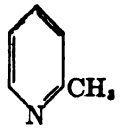
52 Chichibabin, Ger. pat. 676,114 (May 26, 1939) [*C. A.*, **33**, 6345 (1939)].

53 Chichibabin, *Bull. soc. chim. France*, [5] **3**, 1607 (1936); [5] **5**, 429, 436 (1938).

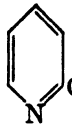
54 Knight and Shaw, *J. Chem. Soc.*, 682 (1938).

A large variety of alkylpyridines can be prepared by this reaction from 2- and 4-picolines, 2-methyl-5-ethylpyridine, 2,6- and 2,4-dimethylpyridines, and 4-methyl-3-ethylpyridine. It is necessary to increase the temperature of the reaction when a long-chain alkyl group is introduced. Thus, undecylenyl chloride gives 12-(2-pyridyl)-1-dodecene in 73% yield when heated with α-picoline at 100° for 36 hr.[55]

The method is not limited to simple alkyl halides, and some very interesting products with oxygen and nitrogen in the side chain have been synthesized by this same method,[53] e.g., I–IV and V–VI. In spite

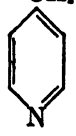


I + $NaNH_2$ + $ClCH_2CH_2N(C_2H_5)_2$ ⟶



IV + $CH_2CH_2CH_2N(C_2H_5)_2$ + NH_3 + NaCl

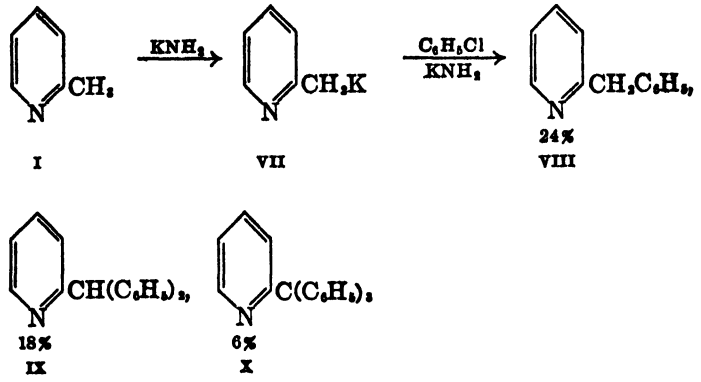
V + $NaNH_2$ + $ClCH_2CH_2OC_2H_5$ ⟶



VI + $CH_2CH_2CH_2OC_2H_5$ + NH_3 + NaCl

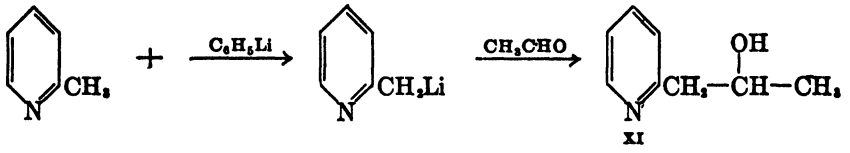
of the fact that one would expect the halogens on an aromatic ring, as in chlorobenzene, to be too inert to be of any practical value in this reaction, Dirstine and Bergstrom [56] found that 2-picoline, on treatment with an excess of potassium amide and chlorobenzene, gave a 48% yield of phenylated products (VII–X). Since the methyl group in

[55] Brody and Bogert, *J. Am. Chem. Soc.*, 65, 1077 (1943).
[56] Dirstine and Bergstrom, *J. Org. Chem.*, 11, 55 (1946).



3-picoline does not possess active hydrogens, this method is not applicable to the synthesis of β-substituted alkylpyridines.

The alkali metal salts of 2-picoline will also react with carbonyl compounds in a manner analogous to the reaction of the Grignard reagent.[57] When 2-picolyllithium is treated with acetaldehyde and the product is hydrolyzed, an over-all yield of 44–50% of 1-(α-pyridyl)-2-propanol (XI)[58] results. From ethylene oxide instead of acetalde-



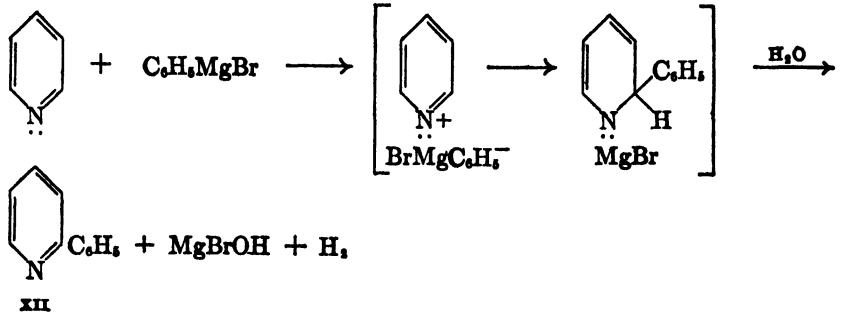
hyde, a 45–60% yield of 2-(γ-hydroxypropyl)pyridine can be obtained.[58] Although Bergstrom and McAllister[59a] have reported as high as 45% yields of 3-ethylpyridine by heating pyridine with an ethereal solution of ethylmagnesium bromide in an autoclave at 160°, the work has not been confirmed.[59b] However there seems to be no question concerning the introduction of the phenyl group by the action of phenylmagnesium bromide on pyridine under similar conditions to give 2-phenylpyridine (XII).[59b] In a very similar reaction, Ziegler and Zeiser[60] treated pyridine with butyllithium in benzene solution at 90–100° and, on decomposing the primary product with water, obtained 2-butylpyridine (XIII). The phenyl group may be introduced directly

[57] Bergstrom, *Chem. Revs.*, **35**, 117 (1944).

[58] Walter, *Org. Syntheses*, **23**, 83 (1943).

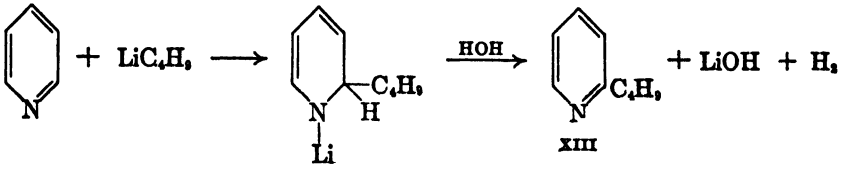
[59] (*a*) Bergstrom and McAllister, *J. Am. Chem. Soc.*, **52**, 2845 (1930); (*b*) Goetz-Luthy, *J. Am. Chem. Soc.*, **71**, 2254 (1949).

[60] Ziegler and Zeiser, *Ber.*, **63**, 1847 (1930).



XII

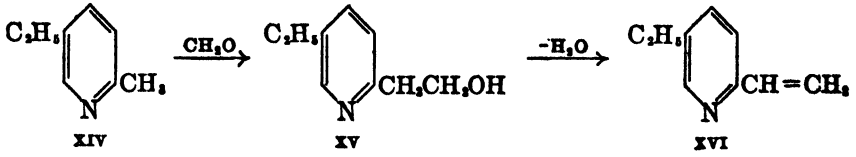
into the pyridine nucleus in the same manner in 40–50% yields by the action of phenyllithium.[61] Only the 2 derivative has been isolated from



XIII

this reaction, which apparently has not been extended to many pyridine homologs. Another method by which the phenyl group may be introduced into the pyridine ring but which gives a mixture of 2-, 3-, and 4-phenylpyridines, is the addition of phenyldiazonium chloride to pyridine (p. 404). It was also successful in giving a mixture of phthalimidopyridines, but apparently it has not been extended to any pyridine derivatives.

Other methods suitable for extending the chain in the 2 and 4 positions of the pyridine ring involve condensations with aldehydes and ketones, for example, the reaction of 5-ethyl-2-methylpyridine (XIV) with paraformaldehyde in ethanol at a temperature of 150–220° for 1 hr. The reaction is conducted in the presence of catalytic amounts of potassium persulfate ($K_2S_2O_8$) and a polymerization inhibitor, *t*-butylcatechol.[62] It gives a 21.5% yield of the ethanol derivative (XV) and a 10.3% yield of vinyl derivative (XVI); 42% of the start-



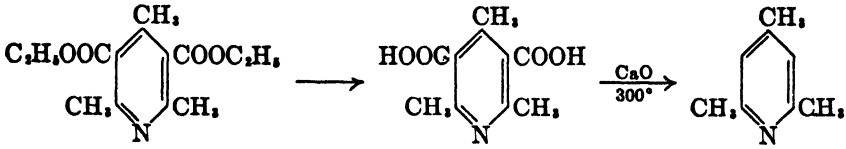
XIV XV XVI

61 Evans and Allen, *Org. Syntheses Coll. Vol.*, **2**, 517 (1943).
62 Frank et al., *J. Am. Chem. Soc.*, **68**, 1368 (1946).

ing material (XIV) is recovered. XV is readily dehydrated to XVI, which in turn may be reduced to 2,5-diethylpyridine. The similar condensation of formaldehyde with picoline to give 2-vinylpyridine has already been mentioned, and the various compounds that can be made from it are considered on p. 599.

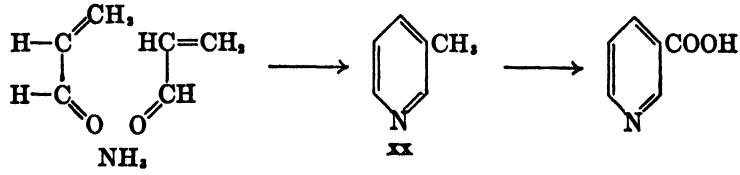
Not only will 2- and 4-methylpyridines condense with aldehydes as indicated above, but they will also condense with ketones. The required temperature for bringing about the reaction is usually higher, and a catalyst such as zinc chloride or acetic anhydride is necessary.

Many of the alkylpyridines are made either directly from aliphatic compounds, as in the case of the aldehyde ammonia synthesis of 2-methyl-5-ethylpyridine, or indirectly as in the Hantzsch synthesis, by a process of hydrolysis and decarboxylation [63] (cf. p. 462) (XVII–XIX).



XVII XVIII XIX

3-Methylpyridine, β-picoline, is valuable as a starting material for oxidation to nicotinic acid, but the amount available from coal tar is not sufficient to supply all the demand,[64] and various possible syntheses for the preparation of β-picoline (XX) have been studied. The



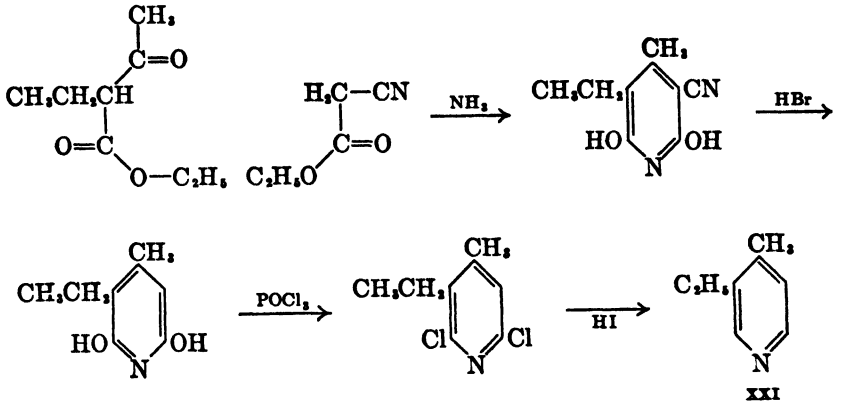
XX

most promising of these is the direct condensation of acrolein or an acrolein precursor with ammonia. The difficulty of obtaining acrolein formerly gave this synthesis only theoretical importance, but the appearance of acrolein as a commercial chemical derived from petroleum may make it possible for synthetic β-picoline to compete with the coal-tar product.

[63] Hantzsch, *Ann.*, **215**, 1 (1882).

[64] The production of β-picoline from coal tar in 1945 was approximately 500,000 lb.; the total production of nicotinic acid and amide in the same year amounted to approximately 1,000,000 lb.

Another method which is generally applicable for the synthesis of alkylpyridines is the reduction of 2- and 4-chloroalkylpyridine derivatives, either catalytically with palladium on barium sulfate or with phosphorus and hydriodic acid. The 2- and 4-chloropyridines are readily prepared from the 2- and 4-hydroxypyridines (pyridones), affording still another method for the preparation of alkylpyridines from synthetic pyridine derivatives. An example which illustrates an application of both decarboxylation and reductive dehalogenation is the synthesis of 4-methyl-3-ethylpyridine (XXI).[65]



XXI

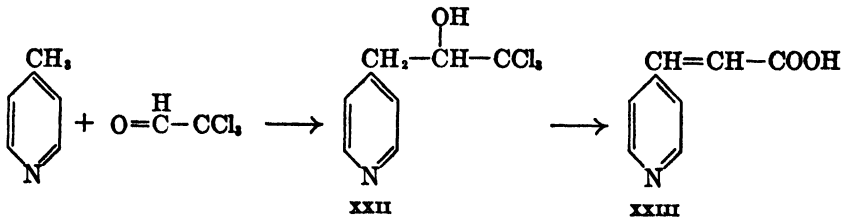
In contrast to their extensive applications in the pyrrole series, the Wolff-Kishner and Clemmensen reductions have not been investigated to any extent in the pyridine series. This is mainly a consequence of the scarcity of the pyridine ketones; however, some of the more difficultly available 3-alkyl- and 3,5-dialkylpyridines may perhaps be made by these methods, starting with corresponding ketones which are available through the Hantzsch-type synthesis.

The reactions of the alkylpyridines center around the activity of the hydrogens on the methyl or methylene groups in the 2 and 4 positions, as has already been indicated in the synthesis of some of the higher alkylpyridines.

The most characteristic reaction of an active methyl group is the condensation with aldehydes. Chloral reacts with 4-picoline to form trichloromethyl-4-picolylcarbinol.[66] This reaction is typical of the many aldol condensations in which 2- and 4-picolines take part, and other examples are given under the synthesis of the side-chain alcohols

[65] Ruzicka and Fournasir, *Helv. Chim. Acta*, **2**, 338 (1919).
[66] Kleiman and Weinhouse, *J. Org. Chem.*, **10**, 564 (1945).

(p. 582). This particular product (XXII) is valuable because it may be converted into β-(4-pyridyl)acrylic acid (XXIII) (74% crude



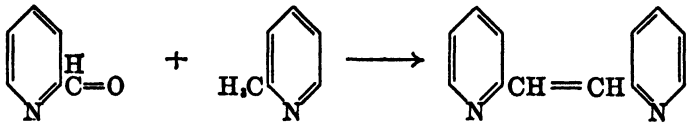
XXII XXIII

yield) by treatment with alcoholic potassium hydroxide. The product shows the expected reactivity of an unsaturated acid; it will add bromine and can be reduced or esterified to give several useful pyridine side-chain derivatives.

2-Stilbazole is formed in 80% yields by heating 2-picoline with benzaldehyde in the presence of zinc chloride at 200° for 24 hr. (p. 445). The product is an orange-red solid which shows the characteristic properties of an unsaturated compound. It adds bromine to give dibromo-2-stilbazole, or it may be reduced with HI to give dihydrostilbazole, the same product obtained by the action of benzyl chloride on 2-picoline in the presence of sodium amide. This reaction is quite general, and 4-methylpyridine reacts with only slightly less ease. If more than one active methyl group is present in the molecule, the condensation proceeds to condense first with one[67] and finally with the second methyl group. The introduction of the second benzylidene group is considerably more difficult than the first, and no report of the tribenzylidine derivative of symmetrical collidine appears.

Many substituted benzaldehydes such as *o*-hydroxybenzaldehyde, *o*-, *m*-, and *p*-nitrobenzaldehydes, methoxy-, ethoxy-, and dimethylamino-benzaldehydes have given good results. The aminostilbazoles are available by selective reduction of the nitrostilbazoles. Piperonal and salicylaldehyde,[68] furfural,[69] cinnamaldehyde, and anisaldehyde,[70] all condense in good yields. Of particular interest is the condensation of 2-picoline with pyridine-2-aldehyde,[71] which produces symmetrical 2,2-dipyridylethylene (XXIV). The use of these benzylidine compounds in the past has been limited almost entirely to identification

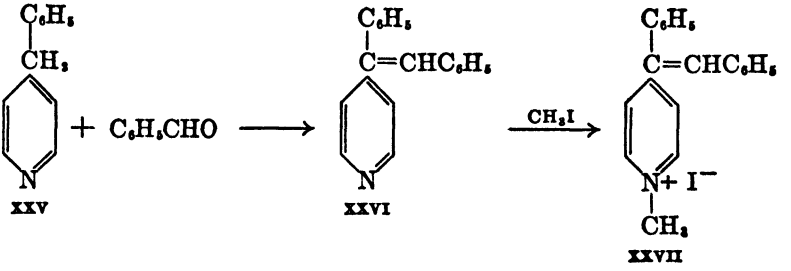
67 Schuster, *Ber.*, **25**, 2398 (1892).
68 Bramsch, *Ber.*, **42**, 1193 (1909).
69 Merck, *Ber.*, **21**, 2709 (1888).
70 Proske, *Ber.*, **42**, 1450 (1909).
71 Harries and Lénárt, *Ann.*, **410**, 95 (1915).



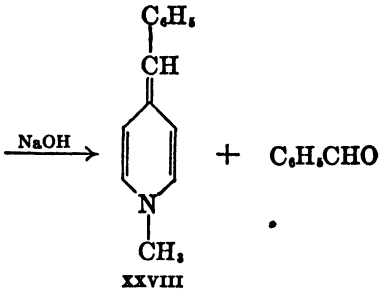
XXIV

and characterization purposes and occasionally as a means of separating an isomer containing a methyl group in the 2 or 4 position from one which has no such active methyl groups.

The condensation of higher 2- and 4-alkylpyridines with aldehydes will take place if there are two hydrogens on the carbon atom adjacent to the ring. Thus 4-benzylpyridine (XXV) readily condenses with benzaldehyde.[72] A condensation product such as XXVI or stilbazole itself forms the normal quaternary salt such as XXVII on treatment



XXV XXVI XXVII



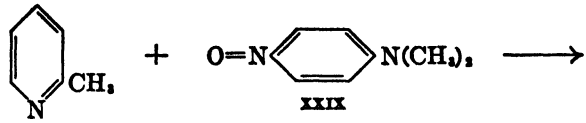
XXVIII

with an alkyl iodide. These quaternary salts are hydrolyzed at the double bond on treatment with sodium hydroxide with the formation of the methylene base (XXVIII). A similar condensation takes place between the 2- and 4- alkylpyridines and *p*-nitrosodimethylaniline (XXIX) to give an azomethine (XXX).[73] The condensation takes place with a basic catalyst such as piperidine at 100°, but with N-2-picolinium methiodide the condensation proceeds in the cold.[74] It is

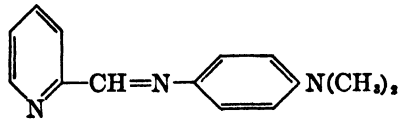
[72] Koenigs, Köhler, and Blindow, *Ber.*, **58**, 933 (1925).

[73] Kaufmann, Ger. pat. 243,078 (Jan. 4, 1911) [*C. A.*, **6**, 2291 (1912)].

[74] Vallette, *Ber.*, **45**, 1736 (1912); **46**, 49 (1913).

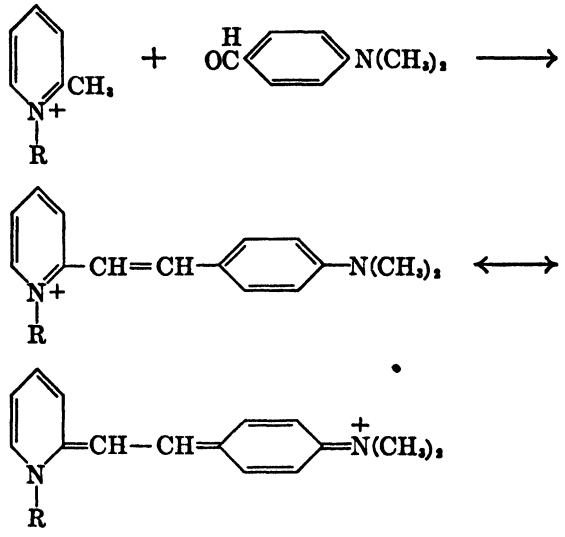


XXIX



XXX

characteristic of all such condensations in the pyridine series that the alkylpyridinium compounds condense much more readily than the tertiary bases. Whereas the condensation of an aldehyde such as *p*-dimethylaminobenzaldehyde with picoline occurs with some difficulty, usually requiring a temperature of 180° and a catalyst such as zinc chloride, the quaternary alkyl iodides of picoline readily condense with such aldehydes when refluxed in alcoholic solution in the presence of piperidine; yields of 75–85% are obtained.[75-77] The products

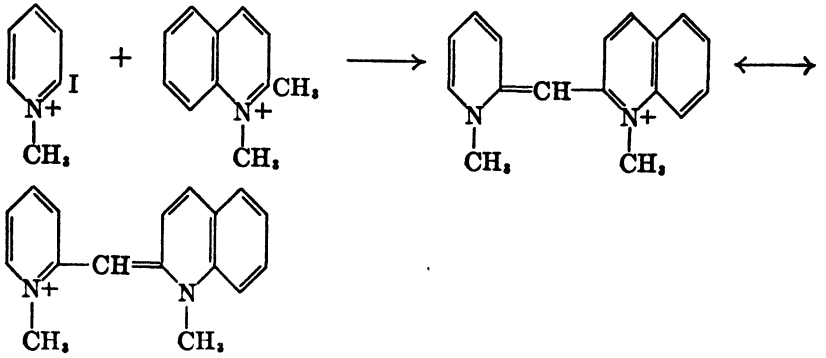


R = CH_3, C_2H_5, C_3H_7, C_4H_9

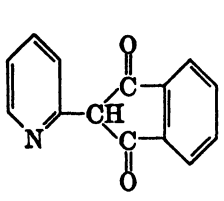
are cyanine dyes which are good sensitizers for photographic emulsions,[78] but none are fast to either sunlight or soap washing. The best-known cyanine dyes contain two quinoline nuclei. The pyridine ana-

[75] Doja, *J. Indian Chem. Soc.*, **17**, 347 (1940) [*C. A.*, **35**, 1232 (1941)].
[76] Doja and Prasad, *J. Indian Chem. Soc.*, **19**, 125 (1942) [*C. A.*, **36**, 6926 (1942)].
[77] Doja and Prasad, *J. Indian Chem. Soc.*, **19**, 377 (1942) [*C. A.*, **37**, 4248 (1943)].
[78] Doja, *Chem. Revs.*, **11**, 273 (1932).

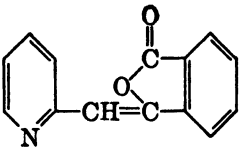
log of such dyes cannot be made by the reaction of 2-iodopyridine methiodide with 2-picoline in basic solution, which is the standard procedure with the corresponding quinoline compounds.[79] However, 2-iodopyridinemethiodide does react with quinaldine methiodide to give a 17% yield of the cyanine dye.



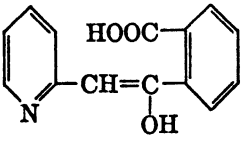
The condensation of 2-picoline with phthalic anhydride at 200° in the presence of zinc chloride or acetic anhydride[80,81] gives a golden yellow product called 2-pyrophthalone which has been used as a dye. 4-Picoline reacts similarly to give 4-pyrophthalone. The nature of these products has been discussed extensively and structures XXXI through XXXVI[82] have been variously assigned. The structural



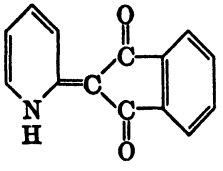
XXXI



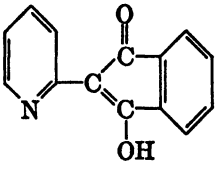
XXXII



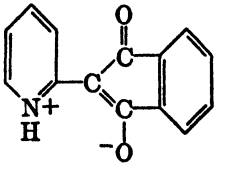
XXXIII



XXXIV



XXXV



XXXVI

79 Hamer and Kelly, *J. Chem. Soc.*, 777 (1931).

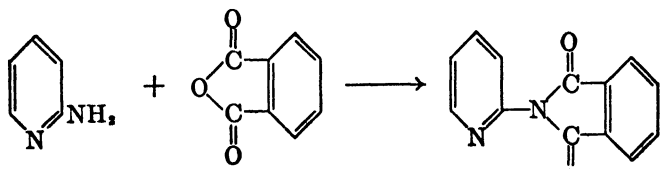
80 Jacobsen, Ger. pat. 23,188 (July 14, 1883); 25,144 (Apr. 12, 1883).

81 Jacobsen and Reimer, *Ber.*, 16, 2602 (1883).

82 Maier-Bode and Altpeter, *Das Pyridin und seine Derivate*, Wilhelm Knapp Halle, Saale, 1934, pp. 46–48. Photo-lithoprint reproduction by Edwards Brothers, Ann Arbor, Michigan.

problem is paralleled by that of quinoline yellow, the product obtained from 2-methylquinoline and phthalic anhydride.[83,84] Any structure postulated for pyrophthalone must account for the following facts. (1) Huber[85] has found that phthalic anhydride and 2-picoline, when heated for short lengths of time, form a substance called 2-isopyrophthalone, m.p. 126°, which is more soluble than pyrophthalone, forms a monoxime, a monophenylhydrazone, and an anil, and in general shows properties compatible with formula XXXII; (2) 2-isopyrophthalone, on being heated further with zinc chloride or acetic anhydride is converted to 2-pyrophthalone; (3) 2-pyrophthalone is very readily soluble in ammonium hydroxide, giving a more deeply colored solution; (4) it forms a monophenylhydrazone; (5) it has a golden yellow color; (6) it is easily oxidized by dilute nitric acid to phthalic acid and picolinic acid; (7) it can be readily methylated in basic solution; and, finally, (8) only a monopyrophthalone of 2,4-lutidine has been found.

Because of points 1 and 2 above, 2-pyrophthalone can hardly have structure XXXII. Since phthalic anhydride will condense with 2-aminopyridine to form the *colorless* N-2-pyridylphthalimide (XXXVII), it seems unlikely that the analogous symmetrical structure (XXXI) postulated for 2-pyrophthalone can be correct, in view

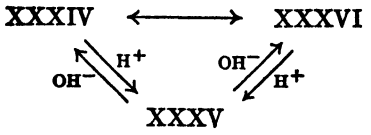


XXXVII

of point 5. The fact that only a monophenylhydrazone has been obtained is negative evidence against structure XXXI. 2-Pyrophthalone has never been converted to 2-isopyrophthalone, and this, coupled with analyses, eliminates structure XXXIII. Structures XXXIV, XXXV, and XXXVI should all be colored, and all could be strong enough acids to dissolve in ammonium hydroxide. Although XXXIV should form a dihydrazone, XXXV and XXXVI should form only a monohydrazone. On the other hand, XXXV and XXXVI should be very readily oxidized to phthalic acid and picolinic acid, whereas

[83] Bergstrom, *Chem. Revs.*, **35**, 183 (1944).
[84] Kuhn and Bär, *Ann.*, **516**, 155 (1935).
[85] Huber, *Ber.*, **36**, 1653 (1903).

XXXIV would presumably be oxidized to 2-pyridone. Actually, formulas XXXIV and XXXV are tautomeric, and formula XXXVI is the zwitterion form of XXXIV. Kuhn favors the interpretation that 2-pyrophthalone is tautomeric, involving all three of these structures. Two of these are resonance forms (XXXIV and XXXVI), and on this basis the structure can be written as follows.



The alkylpyridines show the characteristic reaction of oxidation to the parent pyridinecarboxylic acid, since the alkyl group is more susceptible to oxidation than is the pyridine ring. As may be predicted, the alkyl groups in the 2 and 4 positions are more readily oxidized than those in the 3 position. However, all three acids are readily available by permanganate oxidation of the corresponding picolines. Since the carboxyl group can be removed, this series of steps—oxidation and decarboxylation—offers a means of removing an undesired alkyl group. A further discussion of specific examples will be found under the pyridinecarboxylic acids. A phenyl group is not oxidized so readily as are alkyl groups, and the conversion of a phenylpyridine to a pyridinecarboxylic acid has been of value only in degradation studies for structural determinations.

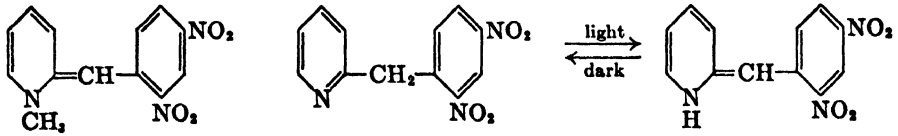
Various attempts have been made to achieve the direct oxidation of α- and γ-picolines to the aldehydes with selenium dioxide.[86-88] Although this reaction has been quite successful in the quinoline series,[89] the reports on the reaction in the pyridine series indicate that the primary product is the acid and only traces of the aldehyde are formed. It is possible that the poor yields described in the literature may be partially due to the age of the selenium dioxide employed and that with freshly prepared selenium dioxide the yields would be higher.

The characteristic action of the alkyl- and aryl-pyridines in such substitution reactions as halogenation, nitration, sulfonation, and amination will be considered under the respective halogen, nitro, sulfonic acid or amino pyridine derivatives.

86 Henze, *Ber.*, **67**, 750 (1934).
87 Henze and Henze, Ger. pat. 697,759 (Sept. 26, 1940) [*C. A.*, **35**, 6270 (1941)].
88 Borsche and Hartmann, *Ber.*, **73**, 839 (1940).
89 Kaplan, *J. Am. Chem. Soc.*, **63**, 2654 (1941).

No generalization can be made concerning the relative ease of ring openings in the various picolines as compared with pyridine, since practically no data are available. All alkylpyridines form normal quaternary salts with such reagents as methyl iodide and dimethyl sulfate, and the β-alkylpyridines form normal quaternary hydroxides, but treatment of the α- and γ-pyridinium salts with strong alkali results in the formation of methylene or anhydro bases (p. 417).

Although the methylene base from 2-methylpyridine cannot be isolated, conversion of the negatively substituted pyridine derivative, 2-(2,4-dinitrobenzyl)pyridine, to the methiodide and treatment with sodium hydroxide produces a stable dark-blue crystalline substance (m.p. 201°) which undoubtedly has the methylene-base structure XXXVIII.[72,90] The corresponding 2-(2,4-dinitrobenzyl)pyridine [86]



XXXVIII XXXIX XL
yellow blue

is reported to have the very interesting property of changing reversibly from yellow to blue, depending on whether it is exposed to light or is in the dark; the melting point of either the yellow or the blue form is 93°. Because of the similar blue color of the known methylene base, Chichibabin has formulated this phototropic change as indicated in XXXIX–XL. The blue form dissolves to give a colorless solution which turns yellow in the dark.

Bipyridyls

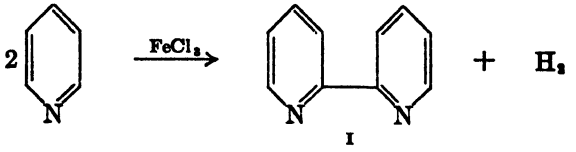
Whereas there is only one biphenyl, there are six possible bipyridyls, all of which are now known.[91] Just as with the alkylpyridines, the 2 derivatives have the lowest boiling point, whereas the 4 derivatives have the highest. Bipyridyls have been studied with respect to their insecticidal properties; although certain members such as 4,4′-bipyridyl have definite insecticidal value as contact and stomach poisons, it is not sufficient to be of practical use.[92]

90 Chichibabin, Kuindshi, and Benewalenskaja, *Ber.*, **58**, 1580 (1925).
91 Smith, *J. Am. Chem. Soc.*, **46**, 414 (1924).
92 Swingle, Gahan, and Mayer, *J. Econ. Entomology*, **37**, 70 (1944).

2,2′-Bipyridyl shows the property of forming colored complexes with various divalent metallic ions and has been suggested as an indicator for the colorimetric determination of ferrous iron.[93] Methyl groups in the 6,6′ positions of 2,2′-bipyridyl destroy this ability to form a colored complex with ferrous iron.[94]

Several reactions are available for the synthesis of bipyridyls and their derivatives. The Ullmann method is most often used when a specific bipyridyl is desired by a method which leaves little doubt as to its structure. The reaction is conducted in a manner analogous to that employed for the related benzene compounds.[95] The yields are usually poor. A more or less typical example is the treatment of 2-bromo-4-methylpyridine with copper powder to give a 33% yield of 4,4′-dimethyl-2,2′-bipyridyl.[96,97] In several experiments, Case found that the bromo compound was preferable to the iodo or chloro compound, in contrast to the findings in the benzene series. In addition, the presence of a *p*-nitro group did not seem to help as it does with the similar benzene compounds, since only a 2.2% yield of 5,5′-dinitro-2,2′-bipyridyl was obtained from 2-iodo-5-nitropyridine.

2,2′-Bipyridyl (I) is the predominant product resulting from the reaction of ferric chloride on pyridine at a temperature of 300–350° for 4–36 hr.[98,99] By-products in the reaction are 3,4′-, 2,3′-, 2,4′-



I

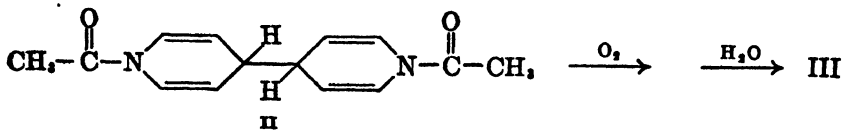
and traces of 3,3′-bipyridyl, along with some tripyridyls, resinous products, ammonia, nitrogen, and saturated and unsaturated hydrocarbons. The various isomers can be separated on the basis of relative solubilities With nickel catalyst at 325°, 2-methylpyridine is converted into 2,2′-bipyridyl in poor yield.[100]

As indicated in the discussion of the actions of alkali metals on pyridine bases (p. 407), a mixture of bipyridyls is formed when anhy-

93 Ignatieff, *J. Soc. Chem. Ind.*, **56**, 407 (1937).
94 Cagle and Smith, *J. Am. Chem. Soc.*, **69**, 1860 (1947).
95 Fanta, *Chem. Revs.*, **38**, 139 (1946).
96 Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).
97 Burstall, *J. Chem. Soc.*, 1662 (1938).
98 Hein and Schwedler, *Ber.*, **68**, 681 (1935).
99 Morgan and Burstall, *J. Chem. Soc.*, 20 (1932).
100 Willink and Wibaut, *Rec. trav. chim.*, **54**, 275 (1935).

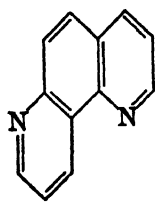
drous pyridine is warmed with sodium in the absence of a solvent.[101] 4,4′-Bipyridyl and 2,2′-bipyridyl are formed in the ratio of about 3:1 along with a small amount of the 3,4′ isomer.[102] The same results are obtained with alkali metal hydrides. 4,4′-Bipyridyl is also the major by-product in the amination of pyridine with sodium amide.[103]

The zinc dust and acetic anhydride reduction of pyridine which was first reported by Dimroth et al.[104–106] serves as still another method for preparing 4,4′-bipyridyl. When pyridine is refluxed in acetic anhydride and zinc dust is added, N,N′-diacetyltetrahydro-4,4′-bipyridyl (II) is formed (p. 407). This, on air oxidation and hydrolysis with base, gives 4,4′-bipyridyl (III).

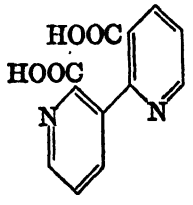


II

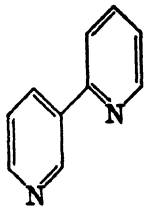
Oxidation of certain phenanthroline compounds has given bipyridyl derivatives[107–109] which have been employed to establish the nature of the phenanthroline, but the reactions are of no preparative value. For example, in the Skraup reaction on *m*-phenylenediamine, two possible modes of ring closure can occur. The isolation of 3,2′-bipyridyl (VI) from the oxidation and subsequent decarboxylation of the resultant phenanthroline leaves little doubt that its structure is IV.



IV



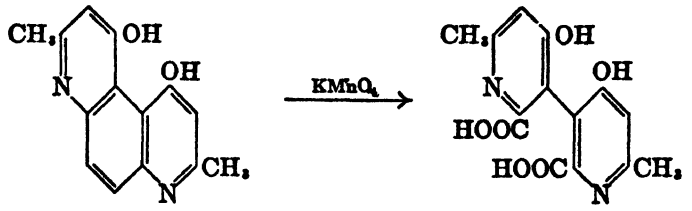
V



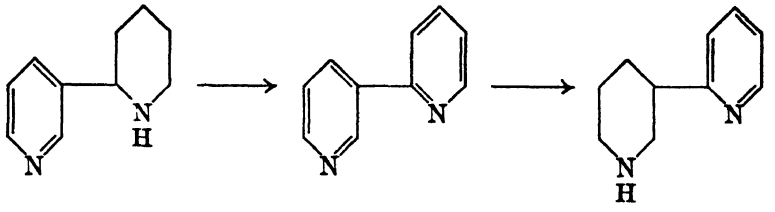
VI

From the work of Jacini and Salini,[107] it would appear that the fused benzene ring was oxidized even more readily than an α-methyl group.

101 Smith and Dosch, Brit. pat. 228,849 (Feb. 8, 1924) [*C. A.*, **19**, 2996 (1925)].
102 Schulenburg, Ger. pat. 588,041 (Nov. 13, 1933) [*C. A.*, **28**, 1486 (1934)].
103 Leffler, *Organic Reactions*, Vol. 1, John Wiley & Sons, New York, 1942, p. 95.
104 Dimroth and Heene, *Ber.*, **54**, 2934 (1921).
105 Dimroth and Frister, *Ber.*, **55**, 3693 (1922).
106 Arens and Wibaut, *Rec. trav. chim.*, **60**, 119 (1941); **61**, 452 (1942).
107 Jacini and Salini, *Gazz. chim. ital.*, **69**, 717 (1939) [*C. A.*, **34**, 4737 (1940)].
108 Smith, *J. Am. Chem. Soc.*, **52**, 397 (1930).
109 Skraup and Vortmann, *Monatsh.*, **3**, 570 (1882); **4**, 569 (1883).



The relative ease of reduction of the respective rings in the bipyridyls is of interest because of the possibility of synthesizing the alkaloid anabasine (α-piperidyl-β-pyridine) (VII) by direct reduction of 2,3′-bipyridyl (VI).[110,111] It is known that the reverse reaction, the



VII VI VIII

dehydrogenation of anabasine occurs on heating with silver acetate or zinc dust. In actual practice, Smith has found that, with tin and hydrochloric acid, the γ-substituted ring is most easily reduced, the β-substituted ring is next, and the α-substituted ring is most resistant to reduction, so that reduction of 2,3′-bipyridyl (VI) results in isoanabasine (VIII).

The few substituted bipyridyls which have been made show the normal reactions expected of pyridine compounds. Thus, bromination of 2,2′-bipyridyl at 500° gives substitution in the 6 and 6′ positions. The resulting bromine atoms in the 6 positions are active and undergo normal replacement with ammonia or cuprous cyanide. It is interesting that the bromo-substituted bipyridyls can be converted to the tetrapyridyls by the Ullmann reaction. By appropriate variations of this reaction and others which have been mentioned, Burstall has prepared many tri-, tetra-, and even penta-pyridyls.[97]

Bipyridylcarboxylic acids have also been prepared, and they are converted to the corresponding esters and amides. The latter participate in a normal Hofmann reaction to give bipyridylamines. The bipyridyls with carboxylic acid groups in the *o* positions show the same

110 Smith, *J. Am. Chem. Soc.*, **53**, 277 (1931); **54**, 397 (1932).
111 Menschikoff and Grigorovitch, *Ber.*, **69**, 496 (1936).

restricted rotation as the corresponding biphenyls, and the unsymmetrical compound V has been resolved.[112]

HALOGENATED PYRIDINES

A large number of the possible halogenated pyridines have been synthesized. With the exception of 3- and 4-iodopyridines, all the monohalogenated pyridines are liquids. In contrast to the picolines, the 2 isomer is the highest- instead of the lowest-boiling isomer. The 3 and 4 isomers, in common with the picolines, have very close boiling points. With the exception of the polyfluoropyridines which are as yet unknown, all the polyhalogenated derivatives are solids.

Of the nineteen possible chloropyridines, only the 2,4,5-trichloropyridine has not been reported in the literature.

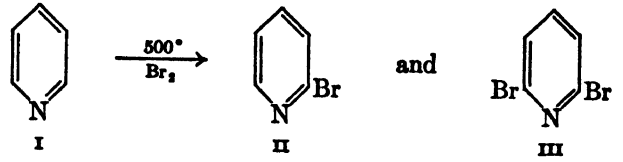
Preparation

Halogenation. 1. *Pyridine and Halopyridines.* Pyridine may be directly chlorinated, brominated, or iodinated, but, of these three processes, bromination has been subjected to the most extensive investigation. Wibaut [1-4] has studied the vapor-phase bromination of pyridine and has demonstrated that the nature of the products depends on the temperature of the reaction and on the catalyst employed. At approximately 300°, the major products are substituted in the 3 position, whereas, at approximately 500°, the orientation is predominantly to the 2 position. The shift in orientation from the β to the α position in going from 300 to 500° can sometimes be brought about without the increase in temperature by the presence of cuprous bromide catalyst. This has been explained on the assumption that the mechanism of bromination changes from an attack by positive bromine to one by free radicals (p. 404). McElvain [5] has further studied the vapor-phase halogenation method of Wibaut and Hertog and has described certain modifications which give slightly better yields.

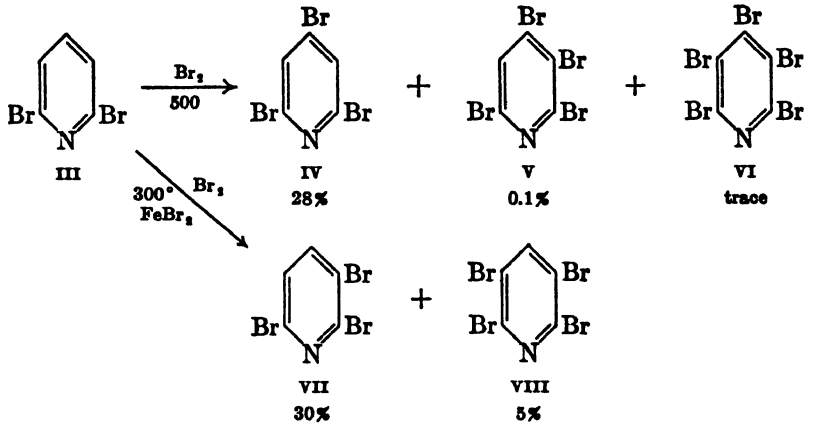
When bromine and pyridine vapors are passed through a tube packed with pumice or glass rings at approximately 500°, the pre-

112 Brydowna, *Rocsniki Chem.*, **14**, 804 (1934) [*C. A.*, **29**, 2535 (1935)].
1 Wibaut et al., *Rec. trav. chim.*, **64**, 55 (1945).
2 Hertog and Wibaut, *Rec. trav. chim.*, **51**, 940 (1932).
3 Wibaut and Bickel, *Rec. trav. chim.*, **58**, 994 (1939).
4 Wibaut and von Wagtendonk, *Rec. trav. chim.*, **60**, 22 (1941).
5 McElvain and Goese, *J. Am. Chem. Soc.*, **65**, 2227 (1943).

dominant products are 2-bromopyridine (II) (46% yield) and 2,6-dibromopyridine (III) (17% yield) which can be separated by taking

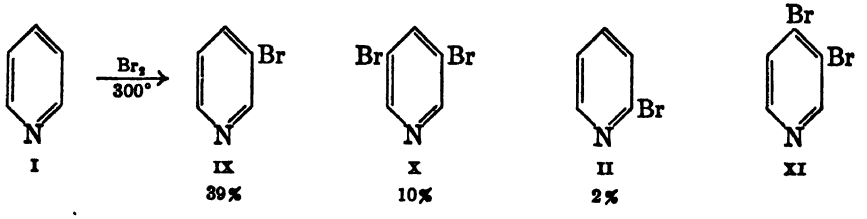


advantage of the volatility of II with steam. The higher-brominated products which are produced in progressively smaller amounts are 2,4,6-tribromopyridine (IV), 2,3,4,6-tetrabromopyridine (V), and, ultimately, the completely brominated product, 2,3,4,5,6-pentabromopyridine (VI). These last three compounds can be prepared directly by the bromination of 2,6-dibromopyridine (III). If substitution in the β position is desired, the 2,6-dibromopyridine can be further brominated at 300° in the presence of ferrous bromide to give 2,3,6-tribromopyridine (VII) in 30% yield and 2,3,5,6-tetrabromopyridine (VIII)

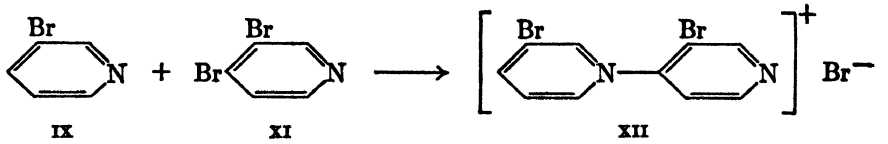


in 5% yield. The presence of cuprous bromide favors substitution in the α position, if it is free, even at the lower temperature. Thus, 2-bromopyridine, when brominated at 300° in the presence of cuprous bromide, gives a 66% yield of 2,6-dibromopyridine (III). Generally, some of the starting material is recovered so that the actual percentage yields are higher than the percentage conversions. It seems that the bromination at 500° attacks the α positions first, then the γ position, and finally a small amount of substituent can be forced into the β positions.

At approximately 300° in the absence of catalyst, the situation is quite different and substitution in the β positions is favored. When Wibaut passed pyridine and bromine vapors through a tube at 300°, the combined yield of 3-bromopyridine (IX) and 3,5-dibromopyridine (X) was 45–55%, with a 39% yield of the monobrominated product.

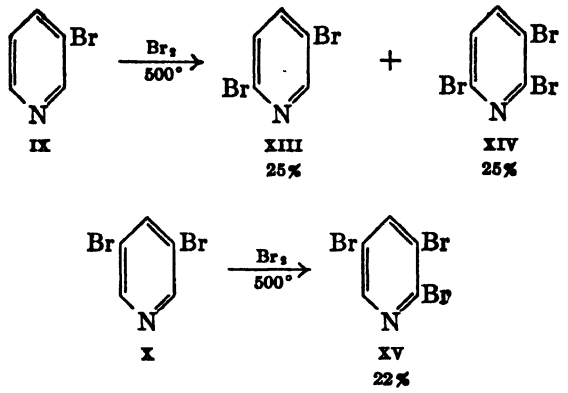


In the presence of cuprous bromide impregnated catalyst, the combined yield was 50–60%. Approximately 2% of 2-bromopyridine (II) was formed in this reaction along with some 3,4-dibromopyridine (XI). McElvain [5] was able to isolate a 27% yield of 3-bromopyridine under similar conditions and found the reaction slow and unsatisfactory. The primary reason for this is the continued formation of a black condensation by-product which clogs the reaction tube. In addition, the 3-bromopyridine that is obtained by fractionation is not pure, and a solid separates from it after a period of standing. This has been attributed to the presence of 3,4-dibromopyridine (XI) which reacts with 3-bromopyridine to give a pyridinium salt (XII).



heat → decomposition

The quaternary salt (XII) has been prepared from IX and XI and is known to decompose at approximately 70° to give a black material very similar to that which clogs the reaction tube. It is interesting to note that the products of the low-temperature bromination may be further brominated at the higher temperature in order to introduce bromine atoms into the α positions. In the reactions IX–XIV and X–XV, approximately the same yields of the products can be obtained at 300° if cuprous bromide catalyst is added.



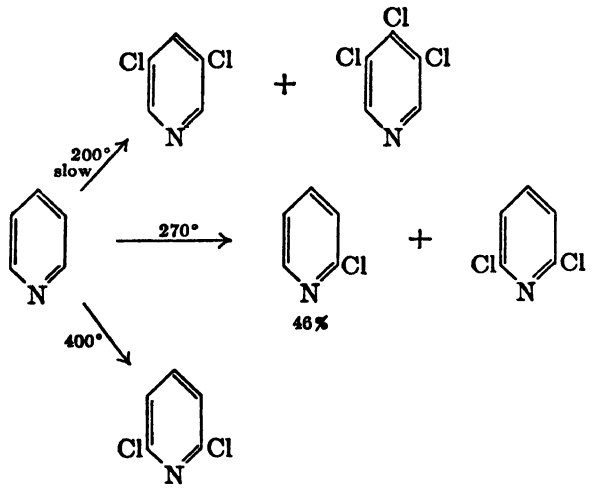
Bromination of pyridine salts is a more desirable synthetic method of obtaining 3-bromo- and 3,5-dibromo-pyridines. Maier-Bode [6] obtained a 35–40% yield of 3-bromopyridine and a 27% yield of 3,5-dibromopyridine by passing bromine through pyridine hydrochloride at 215° in the presence of mercuric chloride. Heating crystalline pyridine perbromide hydrobromide to 200° results in a similar yield.[7] If equivalent amounts of liquid bromine and solid pyridine hydrochloride are allowed to react at room temperature, heat is evolved and the perbromide is formed. This may be heated to 160° without loss of bromine, but, at this temperature and above, autobromination occurs, with the formation of a mixture of the hydrochlorides and hydrobromides of 3-bromo- and 3,5-dibromo-pyridines.[5] The products may be recovered by distillation of the reaction mixture under vacuum; the 3,5-dibromopyridine (35–40%) distils first as the free base, followed by the 3-bromopyridine hydrochloride (27%).

Application of this same method to chlorination is unsuccessful, and, when pyridine perchloride hydrochloride is heated, it loses chlorine before the temperature of chlorination is reached. If the heating is rapid, it is possible to bring about some chlorination, and 3-chloro- and 3,5-dichloro-pyridine are each formed in approximately 4% yield.

Pyridine, on vapor-phase chlorination even at 270°, gives 2-chloropyridine (46% yield) and some 2,6-dichloropyridine. This is in marked contrast to the bromination which at 300° gives perdominantly the 3-bromo and 3,5-dibromo products. If the temperature of chlorination is lowered to 200°, the rate of reaction is too slow to be practical, but the products are predominantly 3,5-dichloro- and 3,4,5-tri-

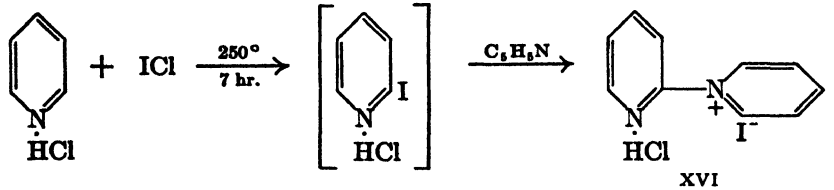
[6] Maier-Bode, *Ber.*, **69**, 1534 (1936).
[7] Englert and McElvain, *J. Am. Chem. Soc.*, **51**, 863 (1929).

chloro-pyridine.[8] On the other hand, at 400° the primary product is 2,6-dichloropyridine.



Treatment of pyridine with iodine in the vapor phase over pumice at 300° gives very small amounts of 3,5-diiodopyridine and pentaiodopyridine, whereas at 500° only the latter is formed. In either case, most of the pyridine is unchanged.[9] If, however, the vapor-phase iodination of pyridine at 300–320° is conducted in the presence of an oxidizing agent such as fuming sulfuric acid, an 18% yield of 3-iodopyridine results. If pyridine hydrochloride is treated with iodine and the resultant stable periodide is heated to 280–290°, a 37% yield (based on iodine) of pentaiodopyridine is obtained.

The action of iodine chloride in place of iodine in the reaction with pyridine at 250° gives predominantly 2-pyridylpyridinium iodide (XVI), indicating that 2-iodopyridine was formed initially, and underwent further reaction with pyridine to give the quaternary salt.



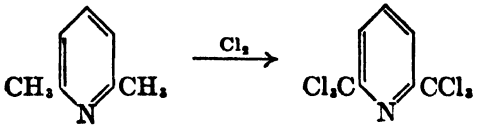
XVI

8 Wibaut and Nicolai, *Rec. trav. chim.*, **58**, 709 (1939).
9 Rodewald and Plazek, *Ber.*, **70**, 1159 (1937).

The structure of the product was shown by synthesis from pyridine hydrochloride and 2-iodopyridine.

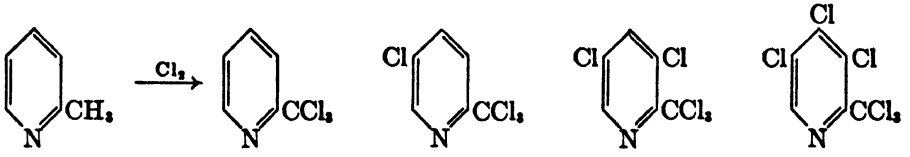
2. *Alkylpyridines.* Halogenation of various substituted pyridines takes place with greater or less ease, depending upon the substituent. Only pyridine derivatives with *o,p*-directing groups have been directly substituted by halogens. A pyridine derivative containing only *m*-directing groups cannot be halogenated;[10] if both *m*- and *o,p*-directing groups are present, substitution may or may not occur.

The picolines as a rule have not been successfully halogenated in the nucleus; 4-picoline gives solely black polymerization products containing only ionic halogen; 2-picoline behaves similarly but does give a 3% yield of 2-methyl-5-bromopyridine[5] on bromination; and 3-picoline, when brominated in concentrated hydrochloric acid solution at 150°, undergoes bromination of the methyl group.[11] McBee, Hass, and Hodnett[12] have studied the chlorination of 2-methylpyridine, 2,6- and 2,4-dimethylpyridine and 2,4,6-trimethylpyridine. Uniformly, the products in which all hydrogens on the methyl groups were substituted with chlorine, as well as some further chlorinated products, were found. For example, the chlorination of 2,6-dimethylpyridine, first at 50° for 3 hr., then at 150° for 2 hr., and finally at 180° for 6 hr. furnished a 37.8% yield of pure 2,6-di-(trichloromethyl)pyridine



XVII

(XVII); the 2,4-dimethyl isomer gave a 33% yield of 2,4-di-(trichloromethyl)pyridine; 2-picoline under similar conditions was reported to give the products indicated in the following equation, but no yields



10 An exception to this generalization is the anomalous nuclear chlorination of the pyridinecarboxylic acids with thionyl chloride (p. 572).

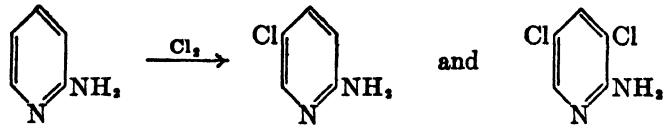
11 Kuhn and Richter, *J. Am. Chem. Soc.*, **57**, 1927 (1935).

12 McBee, Hass, and Hodnett, *Ind. Eng. Chem.*, **39**, 389 (1947).

were reported. Similar results were obtained by Sell.[13] When 2-methyl-5-ethylpyridine is treated with bromine in hydrochloric acid at 100°, 2-methyl-5-(α-bromoethyl)pyridine is formed.[14]

3. *Aminopyridines.* When the pyridine nucleus contains a strongly *o,p*-directing group such as amino, hydroxy, or alkoxy, halogenation proceeds with great ease in contrast to the difficulty of halogenation of pyridine itself. In the benzene series, the bromination of either phenol or aniline is so rapid that the product isolated is tribromophenol or tribromoaniline, even though a deficiency of bromine is employed. In order to control the bromination (or nitration) of aniline, it is customary to protect the amino group by acetylation. This is not necessary in the pyridine series, and 2-aminopyridine with an equivalent amount of bromine at 20° in ethanol gives a 46% yield of 2-amino-5-bromopyridine. As expected, the substitution is in the *p* position.[15] Some 2-amino-3,5-dibromopyridine is also isolated from the products of reaction of equivalent amounts of 2-aminopyridine and bromine in sulfuric acid; the dibrominated product may be obtained in 90% yield when two equivalents of bromine are employed.[16,17]

A certain small amount of 2-amino-3-bromopyridine would be expected, but it has not been reported (see the analogous situation in the nitration of 2-aminopyridine, p. 543). Treatment of 2-aminopyridine in aqueous solution with iodine results in 90–95% yields of 2-amino-5-iodopyridine.[18] In a like manner, chlorination of 2-aminopyridine (XVIII) in chloroform solution results in a mixture of 2-amino-5-chloro- (XIX) and 2-amino-3,5-dichloro-pyridine (XX). Chichibabin and Egorov [19] have reported a 68% yield of XIX and 12% yield of XX when the reaction is conducted in ethanol. 2,6-Diamino-



XVIII XIX XX

13 Sell, *J. Chem. Soc.*, **93**, 1993 (1908).

14 Graf, *J. prakt. Chem.*, [2] **133**, 19 (1932).

15 Case, *J. Am. Chem. Soc.*, **68**, 2576 (1946).

16 Chichibabin and Tyashelova, *J. Russ. Phys. Chem. Soc.*, **50**, 438 (1920) [*C. A.*, **18**, 1495 (1924)].

17 Chichibabin and Kirssanow, *Ber.*, **61**, 1236 (1928).

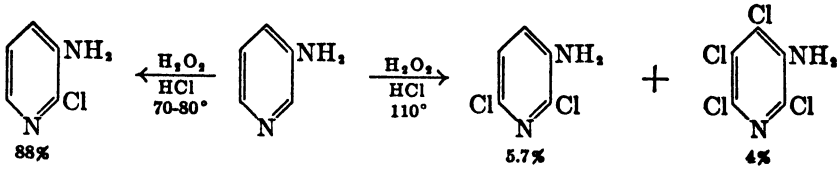
18 Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.*, **66**, 1481 (1944).

19 Chichibabin and Egorov, *J. Russ. Phys. Chem. Soc.*, **60**, 683 (1928) [*C. A.*, **23**, 2182 (1929)].

pyridine behaves similarly on chlorination, bromination, and iodination, giving 3-halo and 3,5-dihalo products.

Although the halogenation of 4-aminopyridine has not been studied to any extent, iodination is known to give 4-amino-3,5-diiodopyridine, and it is presumed that the reaction could be controlled in any halogenation to get either 4-amino-3-halo- or 4-amino-3,5-dihalo-pyridines.

The halogenation of 3-aminopyridine, however, is harder to control, and indefinite results were obtained by Schickh, Binz, and Schulz,[20] until chlorination was tried with hydrochloric acid and hydrogen peroxide at 70–80°. An 88% yield of 3-amino-2-chloropyridine was obtained in which the chlorine preferentially substituted in the α position. If the temperature was raised to 110°, a 5.7% yield of 3-amino-2,6-dichloropyridine and a 4% yield of 3-amino-2,4,5,6-tetrachloro-



pyridine were obtained. When this method was applied to the bromination of 3-aminopyridine, only the dibrominated product, 3-amino-2,6-dibromopyridine, could be isolated. Attempted iodination of 3-aminopyridine with iodine monochloride gives only an addition compound; treatment with hydriodic acid and hydrogen peroxide in a manner analogous to that which was successful for chlorination resulted in oxidation, and the only isolated product was the corresponding azo compound.

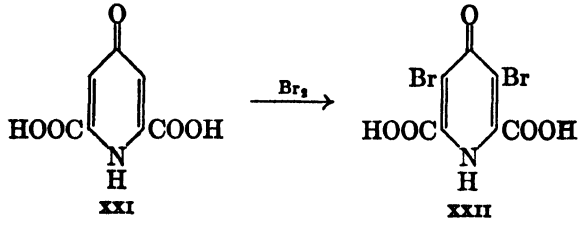
4. *Hydroxypyridines.* The halogenation of 2-hydroxy- and 4-hydroxy-pyridines (α- and γ-pyridones) follows the same general pattern as that for the corresponding aminopyridines and therefore will not be described in detail. 2-Hydroxy- and 4-hydroxy-pyridines both give a mixture of 3-bromo- and 3,5-dibromo-pyridines, simply on treatment in aqueous solution with bromine water.[21] The tendency is to form the dihalogenated product in which both 3 and 5 positions are substituted; if the monohalogen product is desired, precautions must be taken to ensure an excess of the hydroxypyridine derivative during the halogenation, and even then the formation of some of the 3,5-dihalo-

20 Schickh, Binz, and Schulz, *Ber.*, **69**, 2593 (1936).

21 Reitmann and Hecht, U. S. pat. 2,064,944 (Dec. 22, 1937) [*C. A.*, **31**, 817 (1937)].

gen product cannot be avoided. The halogenation of 3-hydroxypyridine has been studied by Binz [20,22] and appears to be analogous to the halogenation of 3-aminopyridine. Only a poor yield of 2-iodo-3-hydroxypyridine results from treatment of 3-hydroxypyridine with aqueous iodine solution.

5. *Pyridinecarboxylic Acids.* The pyridinecarboxylic acids have not been directly halogenated with the free halogens. This failure to halogenate also applies to other pyridine derivatives which possess *m*-directing groups such as nitro or sulfonic acid. However, chlorine has been directly introduced into the pyridinecarboxylic acids by extended treatment with thionyl chloride (p. 572). The deactivating effect of the carboxylic acid group toward substitution by electrophilic reagents is overcome in part by the introduction of a hydroxy or amino group. Thus, 6-hydroxynicotinic acid gives 2,5-diiodo-6-hydroxynicotinic acid by treatment with iodine and potassium iodide in hot ammonium hydroxide solution.[23] In a similar manner, chelidamic acid can be readily chlorinated,[24] brominated, or iodinated.[25] For example, an aqueous suspension of chelidamic acid (XXI) on treatment with bromine in the cold gives a good yield of 3,5-dibromochelidamic acid (XXII). Only when the halogen can enter the 3 or 5 position will the substitution take place with any facility.

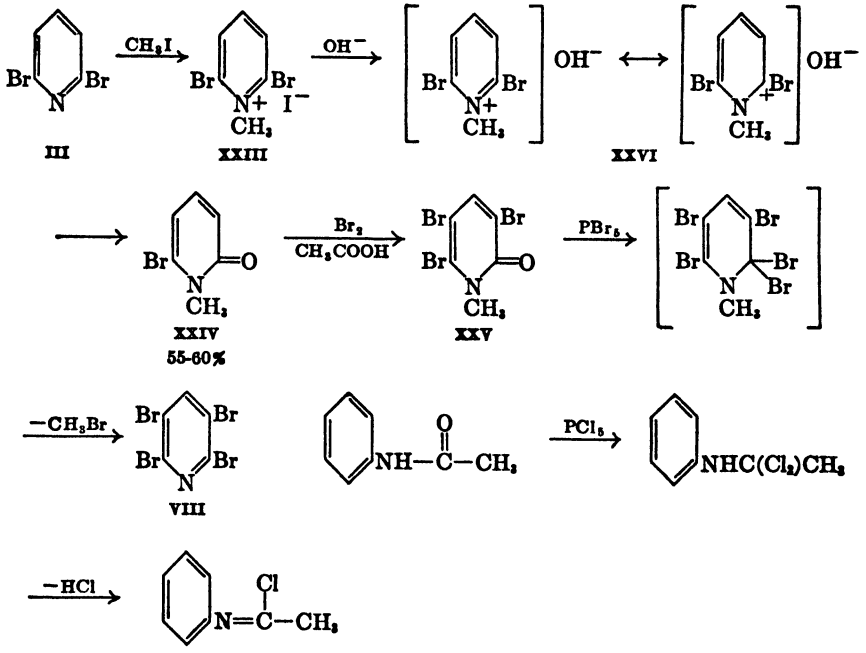


XXI XXII

6. *Pyridinium Compounds.* Bromination of the N-alkylpyridone derivatives takes place in a manner analogous to bromination of the hydroxypyridines. The sequence of reactions employed by Wibaut, Speekman, and von Wagtendonk [26] for the synthesis of 2,3,5,6-tetrabromopyridine (VIII) illustrates this point as well as some other interesting reactions. 2,6-Dibromopyridine (III) forms the quaternary salt (XXIII) in the usual manner. Whereas 2,6-dibromopyri-

22 Binz and Maier-Bode, *Z. angew. Chem.*, **49**, 486 (1936).
23 Burger and Bailey, *J. Am. Chem. Soc.*, **68**, 520 (1946).
24 Dohrn and Diedrich, *Ann.*, **494**, 284 (1932).
25 Lerch, *Monatsh.*, **5**, 867 (1884).
26 Wibaut, Speekman, and von Wagtendonk, *Rec. trav. chim.*, **58**, 1100 (1939).

dine is hydrolyzed to 2-bromo-6-hydroxypyridine when heated to 100° with 50–70% sulfuric acid,[27] the pyridinium compound (XXIII) suffers hydrolysis to N-methyl-2-bromo-6-pyridone (XXIV) with ease, merely by making its aqueous solution basic with sodium hydroxide.

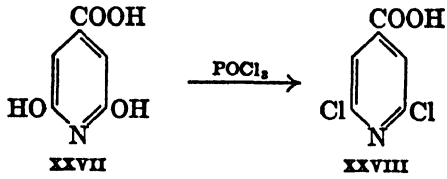


Presumably, the pyridinium hydroxide derivative (XXVI), which may be expected to be the product, spontaneously loses hydrogen bromide to give the pyridone. As indicated in the conversion of XXV into VIII, if an N-alkyl-2- or N-alkyl-4-pyridone is treated with a phosphorus pentahalide or a phosphorus oxyhalide, methyl halide is eliminated and the 2- or 4-halopyridine is formed. This is a general reaction and may proceed through a dibromodihydropyridine derivative which spontaneously loses methyl bromide to give the conjugated pyridine derivative and can be compared to the formation of an iminochloride in the aromatic series.

From Hydroxypyridines. Any 2- or 4-hydroxypyridine derivative will be converted to the corresponding bromo or chloro derivative on treatment with phosphorus pentabromide, phosphorus pentachloride, or the corresponding oxyhalide, but the reaction fails with the 3-hy-

27 Wibaut, Haayman, and Van Dijk, *Rec. trav. chim.*, **59**, 202 (1940).

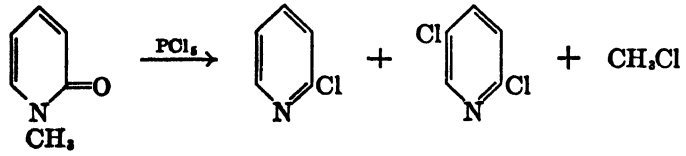
droxypyridine derivatives. The yields are generally good, and this constitutes a general method for preparing any 2- or 4-chloro- or bromopyridine for which a corresponding hydroxypyridine can be made. A more or less typical example is the conversion of citrazinic acid (XXVII) into 2,6-dichloroisonicotinic acid (XXVIII) in almost



XXVII XXVIII

quantitative yield by refluxing for 4 hr. with a threefold excess of phosphorus oxychloride.[28] Many more examples are known.[29] The accepted synthesis of 4-chloropyridine is from 4-hydroxypyridine.[30] The 2- and 4-chloropyridines can also be formed by the action of phosphorus oxychloride on pyridine N-oxide[31] (p. 413), but this method is of little preparative value. The reaction has not been studied with any of the substituted pyridines but does have considerable usefulness in the quinoline series.

It is interesting that in some cases substitution of chlorine on the pyridine ring is achieved by the treatment with phosphorus pentachloride.[32,33] Thus, N-methyl-2-pyridone gives not only 2-chloropyridine (80% yield) on treatment with this reagent but also 2,5-dichloropyridine.[34,35] Phosgene[36] and thionyl chloride[37] may also act



as chlorinating agents. Graf was able to obtain a 30–40% yield of 4-chloropicolinic acid chloride by heating picolinic acid with thionyl chloride at 100° for 20 hr.

28 Levelt and Wibaut, *Rec. trav. chim.*, **48**, 469 (1929).

29 See Maier-Bode and Altpeter, *Das Pyridin und seine Derivate*, Wilhelm Knappe Halle, Saale, 1934, pp. 76–87, 159–162, 258–263. Photo-lithoprint reproduction by Edwards Brothers, Ann Arbor, Michigan.

30 Wibaut and Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

31 Wibaut and Broekman, *Rec. trav. chim.*, **60**, 207 (1941).

32 Sell and Dootson, *J. Chem. Soc.*, **73**, 432, 442 (1898).

33 Seyfferth, *J. prakt. Chem.*, [2] **34**, 241 (1886).

34 Fischer, *Ber.*, **32**, 1297 (1899).

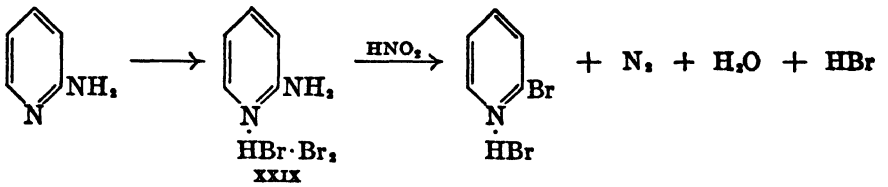
35 Steinhauser and Diepolder, *J. prakt. Chem.*, [2] **93**, 387 (1916).

36 Räth, *Ann.*, **486**, 71 (1931).

37 Graf et al., *Ber.*, **61**, 2202 (1928); **64**, 21 (1931); *J. prakt. Chem.*, [2] **133**, 86 (1932).

From Aminopyridines. The final method of synthesis of the halopyridines is from the corresponding amino compounds. With the 3-aminopyridines, this is a matter of the conventional Sandmeyer diazo reaction and follows the analogous reaction in the benzene series very closely. This is not so with the 2- and 4-aminopyridine derivatives which do not respond satisfactorily to the standard diazotization procedure. If, however, the method is modified as indicated by Craig,[38-40] good yields of many bromopyridines can be obtained.

The method consists of forming the perbromide hydrobromide of the pyridine derivative (XXIX) in constant boiling hydrobromic acid,



XXIX

followed by treatment with sodium nitrite at 5–10°. It gives yields of 46–92% and has worked successfully on 5-methyl-, 3-methyl-, 4-methyl-, 5-bromo-, and 5-chloro-2-aminopyridines.

The method has not been extended to the 4-aminopyridine derivatives but presumably should work with equal success. Neither does Craig's method appear to have been employed for the synthesis of chloro compounds. It has, moreover, not been successful for the preparation of 2-iodopyridine. The conversion of the 2- and 4-aminopyridines to the chloro compounds can be accomplished by treatment with sodium nitrite in concentrated or fuming hydrochloric acid.[41-44] The yields are generally less than 50%. An example is the 38% yield of 2-chloro-3-nitro-6-methylpyridine that Parker and Shive obtained by sealing a concentrated hydrochloric acid solution of 2-amino-3-nitro-6-methylpyridine in a tube with sodium nitrite in such a manner that the sodium nitrite did not mix with the acid solution until after the tube was sealed. The reactants were mixed at 0° and finally heated at 80° for 2 hr.

38 Craig, *J. Am. Chem. Soc.*, **56**, 232 (1934).

39 Case, *J. Am. Chem. Soc.*, **68**, 2574 (1946).

40 Allen and Thirtle, *Org. Syntheses*, **26**, 16 (1946).

41 Chichibabin et al., *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915) [*C. A.*, **10**, 2898 (1916)]; *ibid.*, **46**, 1236 (1914) [*C. A.*, **9**, 1902 (1915)].

42 Seide, *Ber.*, **57**, 791 (1924).

43 Graf, *J. prakt. Chem.*, [2] **133**, 36 (1932).

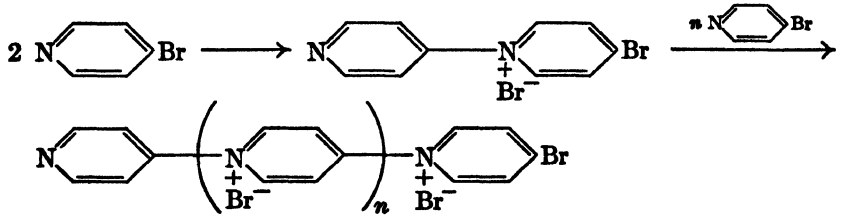
44 Parker and Shive, *J. Am. Chem. Soc.*, **69**, 63 (1947).

4-Chloropyridine has been made in 70% yield by treating 4-aminopyridine with sodium nitrite in concentrated hydrochloric acid and evaporating the solution to dryness.[45] 2-Fluoropyridine has been made by the action of amyl nitrite on 2-aminopyridine in hydrofluoric acid solution (30% yield).[46] Both 2- and 3-fluoropyridines (but not the 4 isomer) have been made from the corresponding amines by treatment with sodium nitrite in fluoroboric acid, according to the Scheimann reaction[47] (34% and 50% yields for the 2 and 3 isomer, respectively). Polyfluorinated pyridine derivatives have been prepared[12] by a replacement reaction with hydrogen fluoride on the polychloropyridines, but the fluorine atoms have been introduced exclusively on the methyl group and not on the ring.

It is interesting to note that 2-bromo-5-ethoxypyridine has been made by the treatment of 2-nitro-5-ethoxypyridine with hydrobromic acid (66% yield), and that this reaction takes precedence over cleavage of the ether to 2-nitro-5-hydroxypyridine.[48] This same replacement of a nitro group in the 2 position by a bromine atom has been observed in 2,6-dinitro-3,5-diethoxypyridine.

Reactions

Whereas 3-halopyridine derivatives in general are unreactive, just as are their nitrobenzene analogs, the 2- and 4-substituted halopyridine derivatives readily take part in replacement-type reactions. Both 2- and 3-halopyridines can be distilled without decomposition, but there is considerable loss upon the slow distillation of either 4-chloro- or 4-bromopyridine. 4-Bromopyridine in particular undergoes decomposition even when stored in the cold, with the formation of a solid material containing almost entirely ionic halogen. The polymerization apparently involves the formation of a pyridinium derivative, probably according to the following formulation.



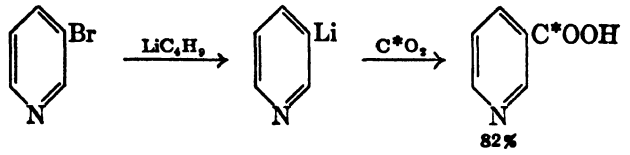
[45] Koenigs, Mields, and Gurlt, *Ber.*, **57**, 1179 (1924).
[46] Chichibabin and Rjazancev, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915).
[47] Roe and Hawkins, *J. Am. Chem. Soc.*, **69**, 2443 (1947).
[48] Koenigs, Gerdes, and Sirot, *Ber.*, **61**, 1022 (1928).

It is not clear why 4-bromopyridine should polymerize so readily, whereas the 2 isomer can be stored almost indefinitely, although Bergstrom has attributed it to a steric effect.

3-Halopyridines. *Replacement Reactions.* In spite of the general inert character of the 3-halopyridines, they do undergo some reactions under more strenuous conditions. By application of the Rosenmund-v. Braun nitrile synthesis,[49] 3-cyanopyridine can be prepared from either 3-bromo- or 3-iodo-pyridine and cuprous cyanide at 165–170° in yields of 50–60% and 80–90%, respectively.[18,50] 3-Methoxypyridine can be prepared by heating 3-bromopyridine with sodium methoxide in methyl alcohol at 150° for 48 hr. (87% yield).[48] Under comparable conditions, ammonium hydroxide in the presence of copper sulfate gives 3-aminopyridine (60–70% yields, p. 549).

It is not surprising that 3-bromopyridine is converted into 3-cyanopyridine by cuprous cyanide since bromobenzene is converted to benzonitrile under similar conditions, but the good yields of 3-methoxypyridine and 3-aminopyridine are quite surprising in view of the fact that the corresponding conversions of bromobenzene to anisole or aniline do not take place under these conditions.

3-Bromopyridine is converted into 3-pyridyllithium by treatment with butyllithium.[51] The C^{13} and C^{14} isotopically labeled nicotinic acids have been made by direct carbonation of the lithium compounds. C^*O_2 is either $C^{13}O_2$ or $C^{14}O_2$.[52]

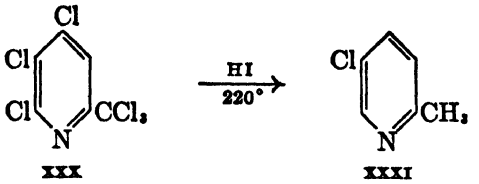


A halogen in the 3 position is not usually replaced by hydrogen on catalytic reduction with palladium on barium carbonate or platinum in basic solution, but 2- and 4-halopyridines are readily converted to the parent pyridine compounds by this method.

If the halogen in the 3 position is activated by a *m*-directing group in the *o* or *p* positions, it can be replaced by an hydroxy group as indicated by the hydrolysis of 3-chloroisonicotinic acid to 3-hydroxyisonicotinic acid after a period of refluxing with 50% potassium hydroxide.

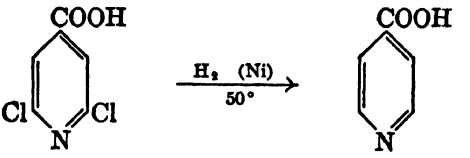
49 Koelsch and Whitney, *J. Org. Chem.*, **6**, 795 (1941).
50 McElvain and Goese, *J. Am. Chem. Soc.*, **63**, 2283 (1941).
51 Gilman and Spatz, *J. Am. Chem. Soc.*, **62**, 446 (1940).
52 Murray, Foreman, and Langham, *Science*, **106**, 277 (1947).

2-, 4-, and 6-Halopyridines. 1. *Replacement by Hydrogen.* The simplest replacement reaction of the pyridine derivatives which are substituted in the 2, 4, or 6 positions with halogen is reduction. This can be accomplished either with chemical reducing agents such as tin and hydrochloric acid, zinc and sulfuric acid,[53] or hydriodic acid,[54] or more conveniently by catalytic reduction with Raney nickel in basic solution or with palladium on barium sulfate or barium carbonate.[55] An illustration of the relative ease of replacement of halogens by hydrogen is the reduction of the hexachloropicoline (XXX) by hydriodic acid [54] to give 5-chloro-2-picoline (XXXI). It is ap-



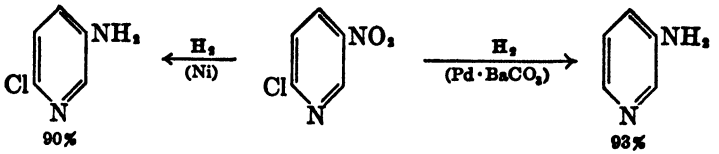
XXX XXXI

parent that only the β-chlorine is stable to reductive cleavage. By catalytic reduction with nickel catalyst in sodium hydroxide solution, 2,6-dichloropyridine-4-carboxylic acid has been reduced to isonicotinic acid.[56] Reductive elimination of a halogen furnishes a convenient

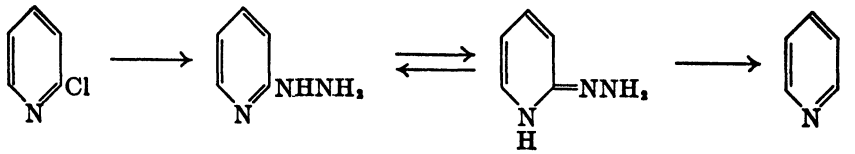


means for removing a hydroxyl group (or the oxygen of an N-alkylpyridone) by conversion to the corresponding chloro compound and subsequent reduction. In many of the variations in the syntheses of the vitamin, pyridoxine (p. 602), and the alkaloid, ricinine (p. 561), this device has served for removal of an unwanted hydroxyl group. By the proper choice of conditions and catalyst, the readily available 2-chloro-5-nitropyridine can be reduced either to 5-amino-2-chloropyridine, in which only the nitro group is reduced, or to 3-aminopyridine, in which the halogen has also been removed by reductive cleavage.[57] This method compares very favorably with the other methods of synthesis of 3-aminopyridine.

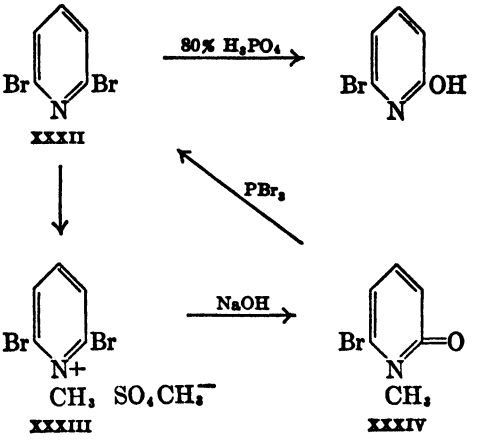
53 Schroeter et al., *Ber.*, **65**, 432 (1932).
54 Ost, *J. prakt. Chem.*, [2] **27**, 257 (1883).
55 Bruce et al., *J. Am. Chem. Soc.*, **67**, 157 (1945); **66**, 2092 (1944).
56 Wibaut, *Rec. trav. chim.*, **63**, 141 (1944).
57 Binz and Schickh, *Ber.*, **68**, 320 (1935).



Still another scheme for the removal of a halogen in the 2 position involves conversion to the hydrazine derivative and hydrolysis, with a boiling 10% copper sulfate solution.[58,59] This can be considered as a modified Wolff-Kishner reduction of a hydrazone. The hydrazone cannot, of course, be made from 2-hydroxypyridine directly.



2. *Replacement by Hydroxyl and Mercapto Groups.* The 2- and 4-halogens can also be readily hydrolyzed. The ease of hydrolysis is greatly dependent on the other substituents in the molecule. 2-Chloropyridine gives an almost quantitative yield of 2-hydroxypyridine when heated to 175° with potassium hydroxide.[60] On the other hand, 2-chloro-5-nitropyridine is rapidly hydrolyzed at 100° under similar conditions, whereas 2-bromo-6-hydroxypyridine is very resistant to hydrolysis. Wibaut [27] studied the hydrolysis of 2,6-dibromopyridine (XXXII) and found that heating it at 160° with 60% sulfuric acid

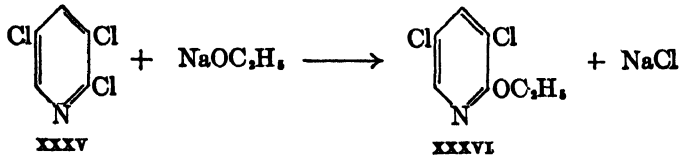


58 Thielepape and Sprechelsen, *Ber.*, **55**, 2929 (1922).
59 Buchi, Labhart, and Ragaz, *Helv. Chim. Acta*, **30**, 513 (1947).
60 Räth, Brit. pat. 288,628 (Apr. 14, 1927) [*C. A.*, **23**, 607 (1929)].

for 4 hr. results in a 53% yield of 2-bromo-6-hydroxypyridine. The best yield (82%) was obtained by heating (XXXII) at 160° with 80% phosphoric acid for 3 hr. In marked contrast, the quaternary salt (XXXIII) is converted into the pyridone derivative (XXXIV) in sodium hydroxide solution at room temperature.

2-Bromopyridine reacts with potassium hydrogen sulfide in refluxing propanol to give 2-mercaptopyridine (83–87% yield after 20 hr.).[61]

3. *Replacement with Alkoxy.* 4-Chlorolutidine reacts with sodium methoxide[62] at 150° to give 4-methoxylutidine. A further example illustrating the greater reactivity of the 2-halogen atom is the reaction of 2,3,5-trichloropyridine (XXXV) with sodium ethoxide in boiling ethanol to give 2-ethoxy-3,5-dichloropyridine (XXXVI).[63]

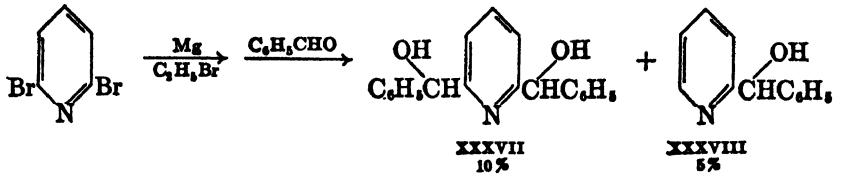


XXXV XXXVI

2-Chloro-5-nitropyridine readily reacts with sodium alkoxides at 80–90° to give up to 90% yields of 2-alkoxy-5-nitropyridines. This reaction has been thoroughly studied by Friedman et al., and a large number of such ethers have been made for study as tuberculostatic drugs.[64]

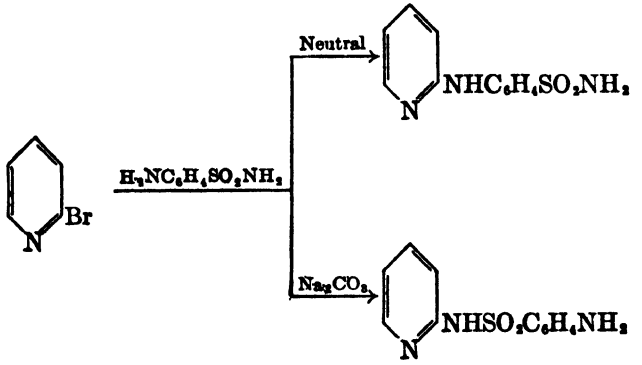
4. *Replacement by Active Metals.* Proost and Wibaut[65] have been able to force a Grignard reaction with 2-bromopyridine by carrying out a concurrent reaction between ethyl bromide and magnesium. The resulting 2-pyridylmagnesium bromide successfully reacts with acetophenone, benzophenone, and ethyl benzoate to give methylphenyl-2-pyridylcarbinol (12%), diphenyl-2-pyridylcarbinol (15%), and phenyl-di(2-pyridyl)carbinol (32%) respectively. 2,6-Dibromopyridine reacts with magnesium under the same conditions and, when coupled with benzaldehyde, gives the expected product, 2,6-di(phenylmethylol)pyridine (XXXVII) as well as some of the reduction product, phenyl-2-pyridylcarbinol (XXXVIII).

61 Thirtle, *J. Am. Chem. Soc.*, **68**, 242 (1946).
62 Conrad and Eckhardt, *Ber.*, **22**, 73 (1889).
63 Koenigs and Geigy, *Ber.*, **17**, 1832 (1884).
64 Friedman et al., *J. Am. Chem. Soc.*, **69**, 1204 (1947).
65 Proost and Wibaut, *Rec. trav. chim.*, **59**, 971 (1940).



5. *Replacement with Ammonia and Amines.* The reaction of 2- and 4-halopyridines with ammonia and substituted amines takes place with greater or less ease, depending on the basicity of the amines and the steric factors involved. Thus, the strongly basic hydrazine reacts with 2-chloropyridine at 100° to give a 64% yield (quantitative conversion based on 2-chloropyridine consumed) of 2-hydrazinopyridine in 4 hr.,[66] but the weaker base, ammonia, must be heated with 2-bromopyridine in a sealed tube at 200° for 10 hr. in order to obtain a 60–70% yield of 2-aminopyridine.[67]

In studies on the reactions of basically substituted amines with 2-bromopyridine [68] and 4-chloropyridine,[69] it was found that pyridine was the best solvent for the reaction, and yields of better than 80% were obtained when an excess of the amine was present. 2-Halopyridines condense with sulfanilamide, giving substitution on either the amino nitrogen or the amido nitrogen, depending on whether or not a basic catalyst is present.[70]

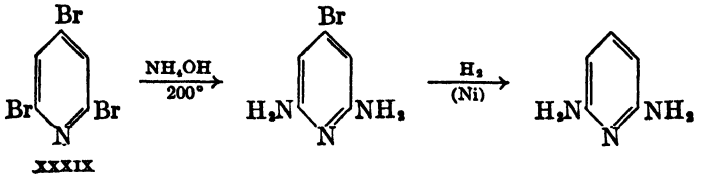


Banks [71] has found that α-halo heterocyclic compounds will condense with aromatic amines in aqueous acid solution in good yields and,

66 Fargher and Furness, *J. Chem. Soc.*, **107**, 688 (1915).
67 Hertog and Wibaut, *Rec. trav. chim.*, **55**, 122 (1936).
68 Whitmore et al., *J. Am. Chem. Soc.*, **67**, 393 (1945).
69 Henry Norris, M.S. Thesis, The Pennsylvania State College, 1943.
70 Phillips, *J. Chem. Soc.*, 9 (1941).
71 Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

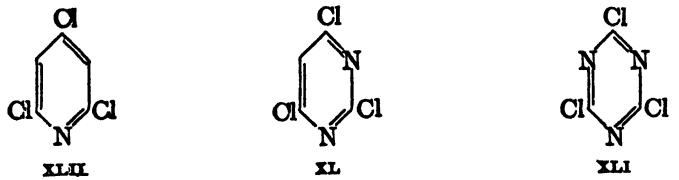
in fact, that small amounts of base even inhibit the replacement. This is the reverse of the usual procedure in which a base such as potassium carbonate neutralizes halohydrogen acid liberated in the reaction. Although this procedure has not as yet been utilized in the pyridine series to any extent, Cragoe and Hamilton [72] have extended the method to the reaction of 2-chloro- and 2-chloro-5-nitropyridine with *o*-, *m*-, and *p*-arsenilic acids in yields of 52–73%.

It is very interesting that 2,4,6-tribromopyridine (XXXIX) will not give 2,4,6-triaminopyridine directly on treatment with ammonia. After 11 hr. at 200° with concentrated ammonium hydroxide, only two halogens are replaced with the formation of 2,6-diamino-4-bromopyridine. The structure of the product has been proved by reduction to 2,6-diaminopyridine.[73] This observation has been confirmed in the



XXXIX

comparable treatment of 2,4-dichloro-6-aminopyridine with ammonia; only 2,6-diamino-4-chloropyridine is obtained. Such behavior parallels that observed in the pyrimidine and triazine series, namely, that, as each chlorine atom reacts, the replacement of the next becomes increasingly more difficult. The conditions employed with 2,4,6-tribromopyridine (XXXIX), however, are more than sufficient to replace completely all of the halogens in either 2,4,6-trichloropyrimidine (XL) or 2,4,6-trichloro-*sym*-triazine (XLI). The above facts confirm the general observation that the 2, 4, and 6 halogens in a pyridine compound (e.g., XLII) are considerably less active than the corre-



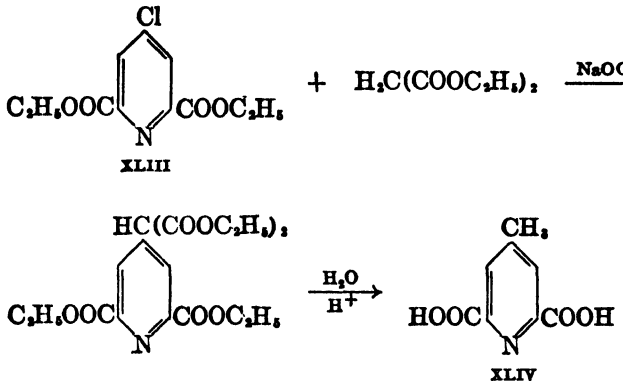
XLII XL XLI

sponding halogens in either pyrimidine or *sym*-triazine compounds. Substituted pyridine derivatives such as 2-chloro-3-aminopyridine

[72] Cragoe and Hamilton, *J. Am. Chem. Soc.*, **67**, 536 (1945).
[73] Wibaut, Rickel, and Brandon, *Rec. trav. chim.*, **58**, 1124 (1939).

have also proved valuable as intermediates in replacement reactions with ammonia, amines, and sodium alkoxides.[20] An interesting series of *o*-diamines have been made in this way.[74]

6. *Malonic Ester Condensation.* 4-Chloro-2,6-dicarbethoxypyridine (XLIII) has been condensed with sodiomalonic ester, and the product on subsequent hydrolysis and decarboxylation gives 4-methylpyridine-2,6-dicarboxylic acid (XLIV) in an over-all yield of 35%.[75] With

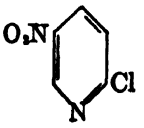
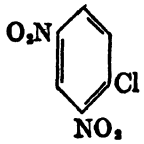


XLIII XLIV

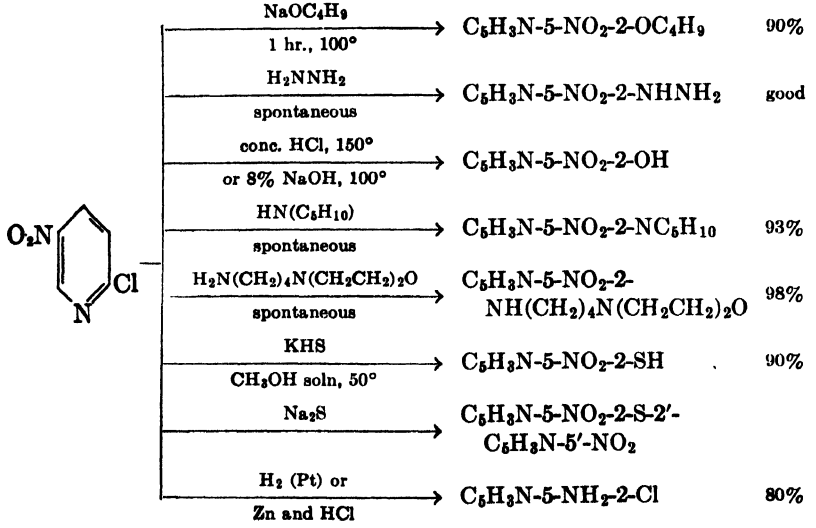
diethyl ethylmalonate, 4-propylpyridine-2,6-dicarboxylic acid was prepared in the same way. A similar reaction with 3-nitro-4-methoxypyridine gave ethyl 4-(3-nitropyridyl)malonate which on hydrolysis and decarboxylation was converted into 3-nitro-4-methylpyridine.[76] The intermediate 4-pyridylacetic acid derivative is not isolated in any of these reactions because of its easy decarboxylation (p. 595). 3-Bromomethylpyridine reacted in the expected manner with ethyl sodiomalonate, but the reaction failed with 2-bromopyridine.[77]

Activating Effects. The presence of a *m*-directing group *ortho* or *para* to the 2- or 4-halogen atom also enhances its reactivity. It is for this reason that 2-chloro-5-nitropyridine (p. 545) is such a valuable intermediate for the synthesis of many compounds. Mangini [78] has compared the reactivity of the chlorine in 2-chloro-5-nitropyridine to that in 2,4-dinitrochlorobenzene in some competitive reactions and has concluded that the halogen in the dinitrobenzene derivative is more active than that in the nitropyridine. The activating influence of

74 Schickh, Ger. pat. 667,219 (Nov. 7, 1938) [*C. A.*, **33**, 2150 (1939)].
75 Koenigs and Jaeschke, *Ber.*, **54**, 1351 (1921).
76 Bremer, *Ann.*, **529**, 290 (1937).
77 Kuhn and Richter, *J. Am. Chem. Soc.*, **57**, 1927 (1935).
78 Mangini and Frenguelli, *Gazz. chim. ital.*, **69**, 86 (1939) [*C. A.*, **33**, 5398 (1939)].

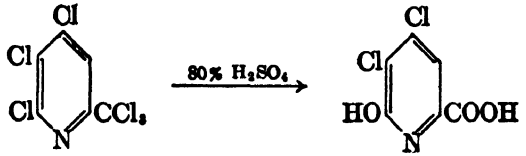
the *p*-nitro group is strikingly illustrated by the comparative reactivities of 2-chloro-5-nitropyridine and 2-chloro-5-aminopyridine. When the former is mixed with morpholine at room temperature, a spontaneous reaction ensues, and after 15–20 min. a good yield of 2-morpholino-5-nitropyridine is obtained.[72,79] On the other hand, when 2-chloro-5-aminopyridine is heated in a sealed tube with an excess of morpholine and copper bronze catalyst for 8 hr. at 208°, over 80% of the 2-chloro-5-aminopyridine is recovered unchanged.[79] The chlorine atom in 2-chloro-5-nitropyridine is readily replaced by the hydrazino group,[80] dialkylamino or basically substituted amino radicals,[72,79] alkoxy groups,[64,81] the mercapto group,[82] or the hydroxyl group.[60] It also reacts readily with sodium sulfide to give a substituted dipyridyl thio ether.[83]



79 Earl Chapin, Ph.D. Thesis, The Pennsylvania State College, 1945, pp. 76–83.
80 Brit. pat. 255,811 (July 22, 1925) [*C. A.*, **21**, 2906 (1927)].
81 Caldwell and Kornfeld, *J. Am. Chem. Soc.*, **64**, 1696 (1942).
82 Kochendoerfer, U. S. pat. 1,753,658 (Apr. 8, 1930) [*C. A.*, **24**, 2471 (1930)].
83 Surrey and Lindwall, *J. Am. Chem. Soc.*, **62**, 173 (1940).

The chlorine atom in 4-chloro-3-nitropyridine is activated in a similar manner [76,84-86] and, as far as the reactions have been studied, behaves in a completely analogous fashion. The halogen in 3-chloropyridine-4-carboxylic acid is activated to a certain extent, as illustrated by its relative ease of hydrolysis to 3-hydroxypyridine-4-carboxylic acid.[87] In contrast to these results, it has been reported [88] that 2-nitro-5-chloropyridine reacts with sodium ethoxide or sodium cyanide to give only decomposition products.

The relative reactivities of the chlorine atoms in various positions on the pyridine nucleus are well illustrated by the hydrolysis of hexa-



XXX

chloro-2-picoline (XXX). This reaction should be compared with the reduction of hexachloro-2-picoline on p. 518.

The reactions of the halopyridines in the Ullmann synthesis of the bipyridyls have already been considered.

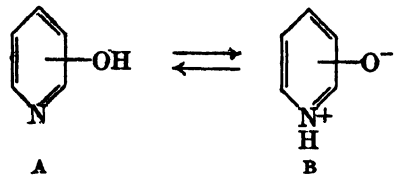
HYDROXYPYRIDINES OR PYRIDONES

The unique tautomerism of the hydroxypyridines makes this group of compounds one of the most interesting and versatile, from the standpoint of both reactions and methods of synthesis. Besides the unsubstituted hydroxypyridines, a large number of amino-, nitro-, halo-, alkyl-, cyano-, carboxylic acid and sulfonic acid derivatives of the hydroxypyridines have been studied. These pyridine derivatives are uniformly higher-melting and higher-boiling compounds than the analogous benzene derivatives.

The N-methylpyridones also show the high boiling and melting points characteristic of the hydroxypyridines, but, in contrast to both of these, the methoxypyridines do not differ substantially from the benzene analogs.

84 *Medicine in Its Chemical Aspects*, Vol. II, I.G. Farbenindustrie, A.G., 1934, p. 367.
85 Koenigs and Freter, *Ber.*, **57**, 1187 (1924).
86 Koenigs and Felde, *Ber.*, **60**, 2106 (1927).
87 Meyer and Graf, *Ber.*, **61**, 2202 (1928).
88 Bystritskaya and Kirsonov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1101 (1940) [*C. A.*, **35**, 4023 (1941)].

The fact that 3-hydroxypyridine, which cannot exist in a pyridone form, has a higher melting point than 2-hydroxypyridine indicates that the property of a high melting point is not due solely to pyridone formation but is attributable to the inherent amphoteric nature common to all hydroxypyridines. This is represented by the zwitterion structure B. The structures of the hydroxypyridines as based on spectroscopic evidence have been discussed (p. 437).



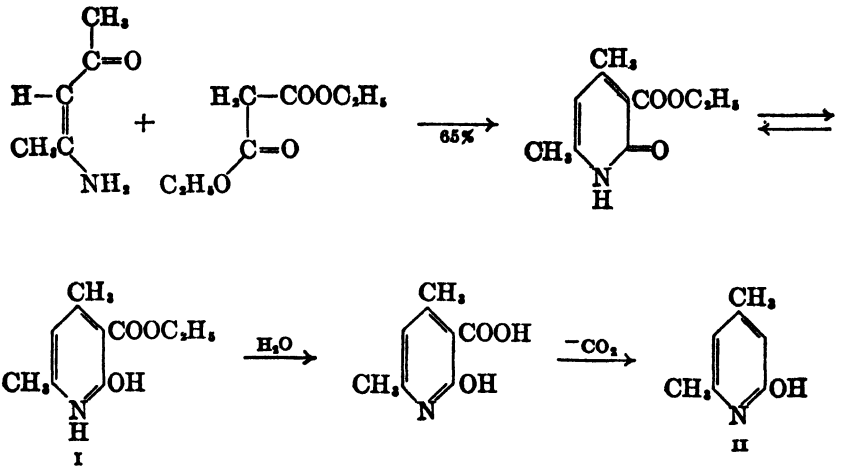
A B

All hydroxypyridines show the reactions of a phenol with respect to the ferric chloride color test (although the color is lighter and weaker with the 2- and 4-hydroxypyridines), and all show the typical coupling reaction with diazonium salts.[1,2] In addition, all hydroxypyridines show a marked increase in the ease of substitution with electrophilic reagents when compared to pyridine itself. There are, however, many reactions and properties in which the hydroxypyridines show marked differences. These reactions, along with the methods of preparation, will be emphasized in the following section.

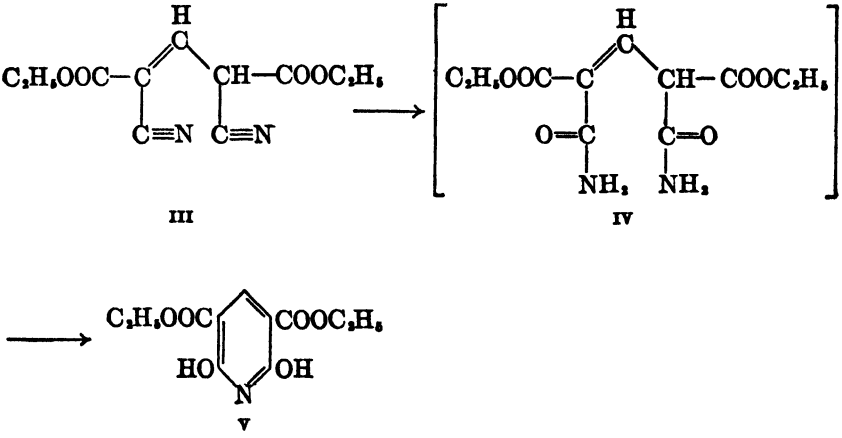
Preparation

Synthesis from Non-Pyridine Compounds. The largest number of the hydroxypyridines is synthesized from aliphatic compounds by methods already indicated (pp. 452 ff.). The condensation of malonic ester and acetylacetonimine with sodium to give 4,6-dimethyl-2-hydroxy-3-carbethoxypyridine (I) serves as a representative example.[3] Many 1,3-diketones and ammonia or β-keto esters and ammonia may be substituted for the acetylacetonimine, and β-aminocrotonic ester or acetoacetamide may be substituted for the malonic ester in order to obtain a large group of different hydroxypyridine derivatives. Because of the possibility of removing the carbethoxy group by hydrolysis and decarboxylation (I–II), the usefulness of these compounds as intermediates is greatly increased.

1 Mills and Widdows, *J. Chem. Soc.*, **93**, 1372 (1908).
2 Gattermann and Skita, *Ber.*, **49**, 494 (1916).
3 Knoevenagel and Cremer, *Ber.*, **35**, 2390 (1902).



All ring closures involving substituted glutaconic acid derivatives give 2,6-dihydroxypyridines directly. In the synthesis due to Ruhemann and Browning [4] and employed extensively by Thorpe,[5] an α,γ-dicyanoglutaconate (III) was treated with dilute hydrochloric acid and hydrolyzed to the amide (IV) which underwent ring closure to a



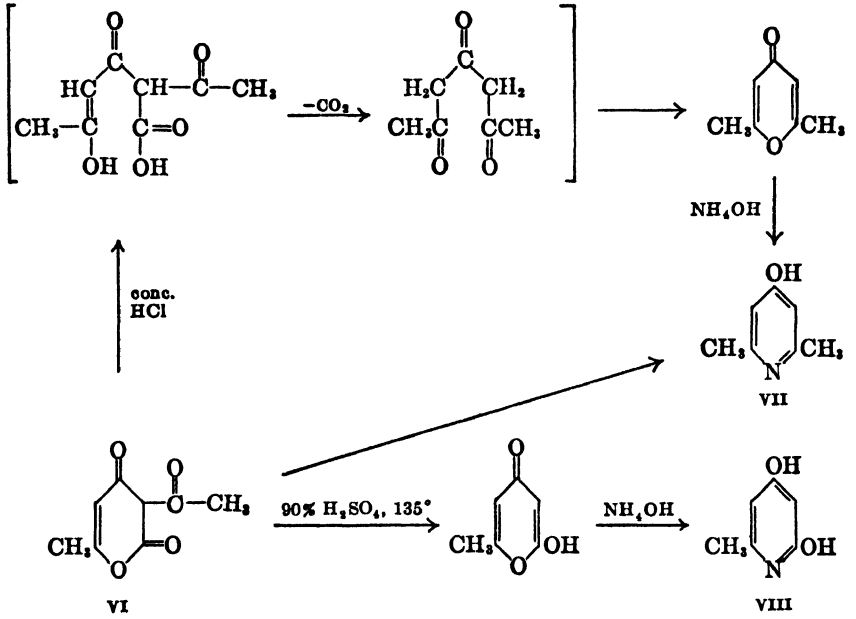
2,6-dihydroxypyridine derivative (V). This product has been hydrolyzed and decarboxylated in steps to give, first, 2,6-dihydroxy-3-carbethoxypyridine and, finally, 2,6-dihydroxypyridine. Difficulties were encountered in trying to make the latter compound from glutaconic

[4] Ruhemann and Browning, *J. Chem. Soc.*, **73**, 284 (1898).
[5] Thorpe, *J. Chem. Soc.*, **87**, 1669 (1905).

acid and ammonia directly because of the rapidity with which it is oxidized by air.[5]

The conversion of the various available pyrones into pyridones constitutes a second general and valuable method for the synthesis of hydroxypyridines (p. 472). This method is limited only by the availability of the corresponding pyrones (see Chapter 7).

Dehydracetic acid (VI) (p. 376) which is readily available from acetoacetic ester [6] serves as a convenient source for two hydroxypyridines. If VI is refluxed with concentrated hydrochloric acid, ring opening and decarboxylation occur to give a 1,5-diketone which is not isolated but loses water to give 2,6-dimethyl-γ-pyrone. This, on treatment with ammonia, is converted into 2,6-dimethyl-4-hydroxypyridine (4-lutidone) (VII). The reaction may be accomplished in one step (75% yield) by heating VI with concentrated ammonium hydroxide



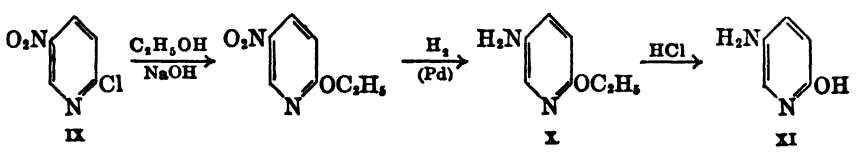
at 120° in a sealed container for 6–8 hr. If dehydracetic acid is heated at 135° with 90% sulfuric acid, 6-methyl-2-hydroxy-γ-pyrone is formed which reacts with ammonia to form 2,4-dihydroxy-6-methylpyridine (VIII). The number of hydroxypyridines which have been made by these and related methods is toc numerous to consider in

[6] Arndt, *Org. Syntheses*, **20**, 26 (1940).

detail here, and the reader is referred to the reviews presented in the books by Hollins, and Maier-Bode and Altpeter.

Synthesis from Other Pyridine Compounds. 1. *By Hydrolysis.* Hydroxypyridines are readily prepared by the hydrolysis of various pyridine compounds such as the 2- and 4-halopyridines, the alkoxypyridines, the pyridinesulfonic acids, and special pyridine derivatives such as 4-pyridylpyridinium chloride. Since many of the 2- and 4-halopyridines and 2- and 4-alkoxypyridines are obtained from the hydroxypyridines, the hydrolysis of these compounds is of limited importance from the standpoint of synthesis. When the halopyridines are obtained directly the method becomes of practical value. Such an example is the synthesis of 2-hydroxy-6-bromopyridine by the partial hydrolysis of 2,6-dibromopyridine (p. 519) or the hydrolysis of hexachloropicoline to 4,5-dichloro-6-hydroxypyridine-2-carboxylic acid.

The reduction of 2-chloro-5-nitropyridine (IX) in alcoholic sodium hydroxide produces 2-ethoxy-5-aminopyridine (X) in good yield. This can be readily hydrolyzed to 2-hydroxy-5-aminopyridine (XI) if it is refluxed for a short time with 6 *N* hydrochloric acid.[7,8]

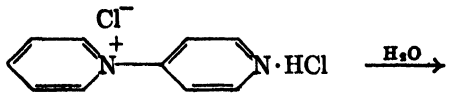


IX X XI

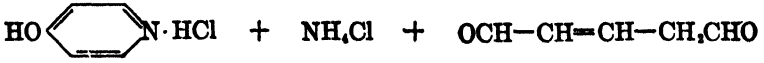
An amino group in the pyridine ring is not ordinarily hydrolyzed with any great ease. If it is situated in the 2 or 4 position and is activated by the presence of a *m*-directing group such as nitro in the *o* or *p* positions, hydrolysis will take place with comparative ease in either acid or basic solution, e.g., the hydrolysis of 3-nitro-4-aminopyridine to 3-nitro-4-hydroxypyridine.[9]

A method of special importance in the preparation of 4-hydroxypyridine is the hydrolysis of 4-pyridylpyridinium chloride. Koenigs and Greiner [10] report an 84% yield of 4-pyridone (XIII) by hydrolysis of 4-pyridylpyridinium chloride hydrochloride (XII) in water at 150° for 8 hr. The other half of the molecule is converted into glutaconic dialdehyde (XIV) or some derivative thereof. By modification of this

7 Haack, Ger. pat. 596,728 (May 9, 1934).
8 Binz and Räth, *Ann.*, **486**, 99 (1931).
9 Koenigs and Freter, *Ber.*, **57**, 1187 (1924).
10 Koenigs and Greiner, *Ber.*, **64**, 1049 (1931).



XII



XIII XIV

method, Leis and Curran [11] obtained a 60% crude yield of 4-hydroxypyridine by refluxing an aqueous solution of XII for 60 hr. Since the starting 4-pyridylpyridinium chloride hydrochloride is obtained in approximately 65% yield, this represents an over-all yield of 35–40% in the two steps from pyridine.

2. *From Sulfonic Acids.* Of the methods of synthesis for the hydroxypyridine derivatives mentioned so far, only that involving the ammonolysis of a 3-hydroxypyrone such as kojic or comenic acid has been generally applicable for the preparation of 3-hydroxypyridine derivatives. Another valuable method for the synthesis of these 3-hydroxypyridines is the fusion of pyridine sulfonic acids with potassium hydroxide. Weidel and Murmann [12] have claimed a quantitative yield of 3-hydroxypyridine by heating pyridine-3-sulfonic acid with a fourfold excess of potassium hydroxide at 170° for 1–2 hr. A 60–70% yield has been claimed for the 4-methyl homolog,[13] and the syntheses of 2-methyl-5-hydroxypyridine [14,15] and 2-methyl-5-ethyl-3-hydroxypyridine [16] by this method have also been reported.

3. *From Aminopyridines.* All aminopyridines can be converted into the corresponding hydroxypyridines by treatment with nitrous acid. The readily available 2-aminopyridine reacts with nitrous acid in dilute sulfuric acid solution in the cold, and, when the resulting solution is treated with 25% sodium hydroxide, the sodium salt of 2-hydroxypyridine separates in white leaflets.[16] In the preparation of 2-halopyridines by treatment with nitrous acid in concentrated hydrochloric or hydrobromic acid, a certain amount of the 2-hydroxypyridine is always formed as a by-product. This may even be the major product in some cases.[15]

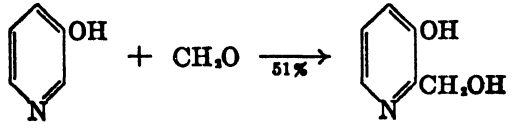
11 Leis and Curran, *J. Am. Chem. Soc.*, **67**, 79 (1945).
12 Weidel and Murmann, *Monatsh.*, **16**, 749 (1895).
13 Wulff, Ger. pat. 563,873 (Oct. 22, 1929) [*C. A.*, **27**, 1002 (1933)].
14 Wulff, U. S. pat. 1,880,645 (Oct. 4, 1933) [*C. A.*, **27**, 513 (1933)].
15 Parker and Shive, *J. Am. Chem. Soc.*, **69**, 63 (1947).
16 Chichibabin and Rjazancev, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915) [*C. A.*, **10**, 2898 (1916)].

The diazotization of 3-aminopyridine in sulfuric acid procceds as would be expected from analogy with aniline, and the resulting diazonium salt reacts when warmed with water to give 3-hydroxypyridine in good yields. Since the starting 3-aminopyridine is not so available as the corresponding pyridinesulfonic acid, potassium hydroxide fusion of the sulfonic acid is the preferred synthetic method. In general, the reaction with nitrous acid is useful for preparation of those hydroxypyridines for which the corresponding amine is readily available, either through the direct amination reaction or by nitration of some suitably substituted pyridine derivative followed by reduction. The former approach leads exclusively to 2- or 4-hydroxypyridine derivatives, whereas the latter method gives 3-hydroxypyridine derivatives in almost every case.

4. *Direct Introduction of an Hydroxyl Group.* Finally, a few hydroxypyridines have been prepared by direct replacement of nuclear hydrogen by the hydroxyl radical. The action of molten potassium hydroxide (300–320°) on pyridine vapor to give 2-hydroxypyridine was reported by Chichibabin.[17] Kudernatsch [18] had discovered earlier that a second hydroxyl group was introduced into 3-hydroxypyridine (but not into 2-hydroxypyridine) by fusion of 3-hydroxypyridine with sodium hydroxide at 290–310°. The product, formed in 40–50% yield, was believed by Kudernatsch to be 2,5-dihydroxypyridine, but it has since been proved to be the 2,3 isomer.[19] In a similar manner, quinolinic acid is reported to give 6-hydroxyquinolinic acid in about 50% yield.[20]

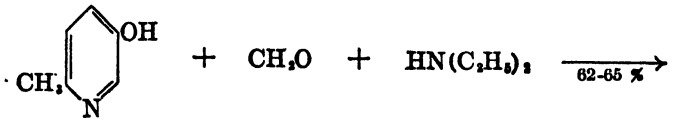
Reactions

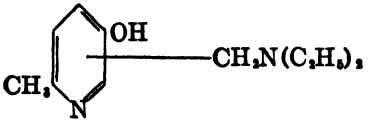
3-Hydroxypyridines. As indicated in the discussion of the structure of the hydroxypyridines (p. 442), 3-hydroxypyridine shows the more or less normal reactions of a phenol, giving a positive ferric chloride test, methylating to 3-methoxypyridine, acetylating to 3-acetoxypyridine, and undergoing such reactions as condensation with formaldehyde to give 2-methylol-3-hydroxypyridine.[21] The structure of the



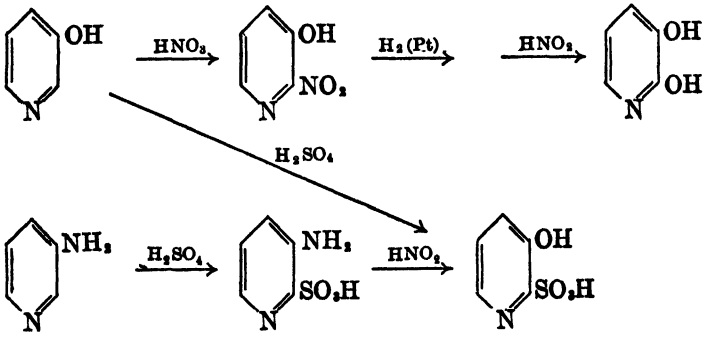
17 Chichibabin, *Ber.*, **56**, 1879 (1932).
18 Kudernatsch, *Monatsh.*, **18**, 613 (1897).
19 Schickh, Binz, and Schulz, *Ber.*, **69**, 2593 (1936).
20 Koenigs and Koerner, *Ber.*, **16**, 2152 (1883).
21 Urbanski, *J. Chem. Soc.*, 1104 (1946).

product was proved by oxidation to 3-hydroxypicolinic acid. The decreased reactivity of the pyridine ring in 3-hydroxypyridine compared to the benzene ring in phenol is demonstrated in this reaction, for, although it is extremely difficult to control the reaction of phenol and formaldehyde in order to prevent polymer formation, the above reaction with 3-hydroxypyridine is readily controllable. 2-Methyl-5-hydroxypyridine shows the characteristic reactions of a phenol in the Mannich condensation with formaldehyde and diethylamine,[22] giving a 4- (or 6-) diethylaminomethyl derivative of 2-methyl-5-hydroxypyridine.[23]





3-Hydroxypyridine reacts with mixed nitric and sulfuric acids vigorously, and, unless the reaction is carefully controlled, destruction of the pyridine ring results.[12] If the conditions are carefully controlled, two mononitro-3-hydroxypyridines and one dinitro-3-hydroxypyridine can be isolated from the reaction mixture.[24] Plazek [25-27] has investi-



22 Brown and Miller, *J. Org. Chem.*, **11**, 388 (1946). In this reference, the authors represent the reaction as taking place between 2-methyl-3-hydroxypyridine, but it has since been shown [15] that their starting material was 2-methyl-5-hydroxypyridine.

23 Perez-Medina, Mariella, and McElvain, *J. Am. Chem. Soc.*, **69**, 2575 (1947).

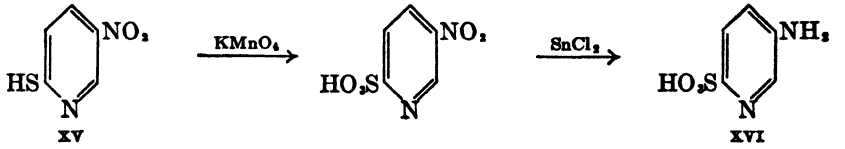
24 I.G. Farbenindustrie, Brit. pat. 369,850 (Mar. 31, 1932) [*C. A.*, **27**, 2161 (1939)].

25 Rodewald and Plazek, *Roczniki Chem.*, **16**, 444 (1936) [*C. A.*, **31**, 1808 (1937)].

26 Plazek and Rodewald, *Roczniki Chem.*, **16**, 502 (1936) [*C. A.*, **31**, 3018 (1937)].

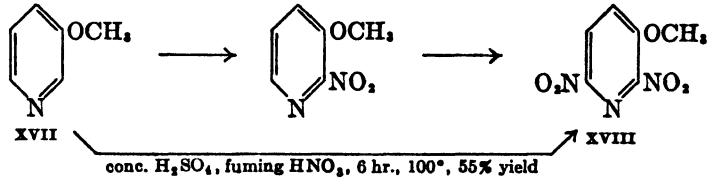
27 Plazek, *Roczniki Chem.*, **17**, 97 (1937) [*C. A.*, **31**, 4669 (1937)].

gated the nitration, sulfonation, and iodination of 3-hydroxypyridine and has shown that *o* substitution predominates in each of the reactions. Sulfonation of 3-aminopyridine gave a product which was converted by nitrous acid into a hydroxypyridinesulfonic acid identical to that obtained by the sulfonation of 3-hydroxypyridine. The main evidence for the structure of this sulfonation product was the nonidentity of the 3-aminopyridinesulfonic acid obtained in this manner and that obtained by the following established reactions (XV–XVI).



XV XVI

The nitration of a 3-alkoxypyridine is much more easily controlled. Although nitration of 3-ethoxypyridine was first reported as giving 5-ethoxy-2-nitropyridine in which the nitro group entered the *p* position,[28] it has subsequently been shown that the predominant product is 3-ethoxy-2-nitropyridine in which the nitro group enters the *o* position.[19,29] The nitration of 3-methoxypyridine has been carefully studied,[18] and it has been demonstrated that the action of fuming nitric acid and concentrated sulfuric acid gives 3-methoxy-2-nitropyridine (approximately 55% yield) which can be readily converted by more fuming acid into 2,6-dinitro-3-methoxypyridine. The conversion to the dinitro compound can be carried out more conveniently in one step (XVII–XVIII).



XVII XVIII

Thus, the nitration of 3-hydroxypyridine, as well as sulfonation and iodination, favors *o* substitution and is in general agreement with the fact that phenol, on nitration, gives approximately 30–40% of the *o*-nitrophenol and only 14% of the *p* isomer.

Sulfonation of 3-hydroxypyridine with 100% sulfuric acid in the presence of vanadium sulfate catalyst gives 3-hydroxypyridine-2-sulfonic acid.[24] Although the chlorination and bromination of 3-hydroxy-

28 Koenigs, Gerdes, and Sirot, *Ber.*, **61**, 1022 (1928).
29 Bernstein et al., *J. Am. Chem. Soc.*, **69**, 1147 (1947).

pyridine have not been reported, iodination with iodine in potassium iodide solution [19,25] in the cold results in the formation of 3-hydroxy-2-iodopyridine along with unidentified di- and tri-iodo compounds and accordingly appears to follow the same general pattern as nitration of 3-methoxypyridine.

2- and 4-Hydroxypyridines. Although 2-hydroxypyridine shows some of the properties of a phenol, the extent of these properties is considerably altered and the intensity of many of the reactions is significantly diminished. Thus, with 2-hydroxypyridine, the characteristic phenol ferric chloride test shows only a slight red instead of an intense violet. On the other hand, 2-hydroxypyridine is very readily halogenated and nitrated (sulfonation seems not to have been studied), and the orientation, as expected, is to the 3 and 5 positions. Halogenation with chlorine in carbon tetrachloride,[30] with bromine water,[31] or with iodine or iodine monochloride [30,32,33] gives first the 2-hydroxy-5-halopyridine compound and next the 2-hydroxy-3,5-dihalopyridine. Iodine is the most reactive and chlorine the least. It is quite easy to proceed to the dihalogenated derivative but very difficult to go beyond this stage.

When 2-hydroxypyridine is nitrated in sulfuric acid below 40°, the major product according to Chichibabin [34] is 2-hydroxy-3-nitropyridine, 2-hydroxy-5-nitropyridine being formed in smaller amounts. The preferential formation of the 2,3 isomer is in accord with the results on the analogous nitration of phenol but is the reverse of the situation found on nitration of 2-aminopyridine. 4-Hydroxypyridine nitrates on treatment with a mixture of fuming nitric and sulfuric acids at 100° to give a 70% yield of 3-nitro-4-hydroxypyridine.[9,35,36]

It is in its reactions with alkylating agents that 2-hydroxypyridine shows its greatest deviation from the reactions of a phenol. Although methylation of phenol with methyl iodide or dimethyl sulfate in basic solution forms anisole in excellent yields, similar treatment of 2-hydroxypyridine gives primarily N-methyl-2-pyridone.[37] If, however, 2-hydroxypyridine is treated with diazomethane in neutral solution,

30 Dohrn and Dirksen, Ger. pat. 490,416 (Apr. 1, 1927) [*C. A.*, **24**, 2148 (1930)].

31 Koenigs and Geigy, *Ber.*, **17**, 589 (1884).

32 Binz and Maier-Bode, *Biochem. Z.*, **257**, 351 (1933).

33 Kochendoerfer, U. S. pat. 1,753,170 (Apr. 1, 1930) [*C. A.*, **24**, 2472 (1930)].

34 Chichibabin and Schapiro, *J. Russ. Phys. Chem. Soc.*, **53**, 233 (1921) [*C. A.*, **18**, 2342 (1924)].

35 Koenigs and Freter, *Ber.*, **57**, 1187 (1924).

36 Bremer, *Ann.*, **529**, 290 (1937).

37 Räth, *Ann.*, **489**, 108 (1931).

the only product isolated is 2-methoxypyridine.[38] There is no doubt as to the structure of these two methylated products, since treatment of 2-hydroxypyridine with phosphorus oxychloride produces 2-chloropyridine which reacts with sodium methoxide to give 2-methoxypyridine. It appears from this that neutral or acid solution favors reaction in the 2-hydroxypyridine form, whereas basic solution favors reaction in the 2-pyridone structure. The fact that the silver salt of 2-hydroxypyridine on treatment with methyl iodide forms a mixture of approximately equal amounts of N-methyl-2-pyridone and 2-methoxypyridine can be reconciled with the weakly basic nature of silver oxide. The fact that diazomethane reacts with 4-hydroxypyridine to give a mixture of the 4-methoxypyridine and N-methyl-4-pyridone indicates that the pyridone structure is much more important in the 4 isomers than in the 2 isomers. Direct methylation with diazomethane or the action of methyl iodide on the silver salt of 2- or 4-hydroxypyridines cannot be relied on to give the methoxy derivative. When the pure alkoxypyridine derivative is desired, it is preferable to convert the hydroxypyridine to the chloro compound which is then treated with the desired sodium alkoxide.

In contrast to these methylations which usually give mixtures, the alkylation of the sodium salt of any 2- or 4-hydroxypyridine (or alkylation in strong sodium hydroxide solution) results in the almost exclusive formation of the N-alkylpyridone. This applies to such diverse hydroxypyridines as 2-hydroxypyridine-5-arsonic acid,[39] 2-hydroxy-5-iodopyridine, 2-hydroxy-5-nitropyridine,[40] 2,4-dihydroxy-3-cyano-6 chloropyridine,[41] and 2-hydroxy-3-nitro-5-iodopyridine,[41] but the same reaction does not apply to methylation of 2-mercaptopyridine, which gives exclusively 2-methylmercaptopyridine on treatment with methyl iodide in basic solution.[42] This reaction also does not apply to acylations or aroylations, since Chichibabin and Oparina [43] have found that treatment of 2-hydroxypyridine in concentrated sodium hydroxide with benzoyl chloride gives 2-pyridyl benzoate, and treatment of the dry sodium salt of 2-hydroxypyridine with acetyl chloride gives 2-pyridyl acetate.[44] The latter compound hydrolyzes with ex-

38 Meyer, *Monatsh.*, **26**, 1311 (1905).

39 Maier-Bode, *Z. angew. Chem.*, **44**, 835 (1931).

40 Räth, *Ann.*, **484**, 52 (1930).

41 Schroeter et al., *Ber.*, **65**, 442 (1932).

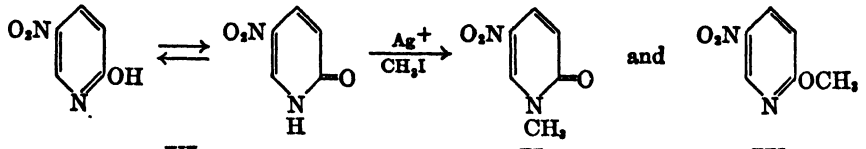
42 Marckwald, Klemm, and Trabert, *Ber.*, **33**, 1556 (1900).

43 Chichibabin and Oparina, *J. Russ. Phys. Chem. Soc.*, **56**, 153 (1925) [*C. A.*, **19**, 3489 (1925)].

44 Chichibabin and Szakow, *Ber.*, **58**, 2650 (1925).

treme ease and in this respect does not resemble a normal acetylated phenol.

The presence of a *m*-directing group in the 3 or 5 position of a 2-hydroxypyridine compound apparently favors the pyridone structure of the molecule, for, although the silver salt of 2-hydroxypyridine gives almost entirely 2-methoxypyridine when treated with methyl iodide, the silver salt of 2-hydroxy-5-nitropyridine (XIX) gives only 15% of the 2-methoxy-5-nitropyridine (XX) and 60% is converted



XIX XX 60% XXI 15%

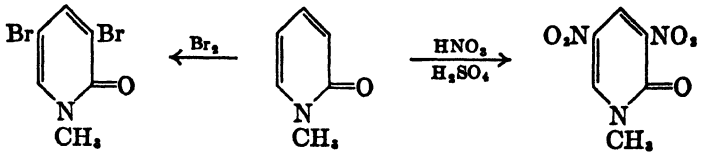
to the N-methyl-5-nitro-2-pyridone (XXI).[39] Methyl iodide in strongly basic solution gives predominantly the pyridone (XX) (83%) with only traces of the methoxypyridine (XXI) (0.8%).

The isomeric methoxypyridines and N-alkylpyridones differ greatly in properties. They can generally be separated with ease merely by steam distillation, the methoxy derivative being volatile and the pyridone remaining behind. As may be expected from this behavior, the methoxypyridines are the isomers with the lower melting and lower boiling points. In addition to alkylation of 2- and 4-hydroxypyridine derivatives in strongly basic solution, the N-alkylpyridones can be made by the oxidation of the quaternary alkyl halide in basic solution with potassium ferricyanide [45,46] (p. 416). It has also been observed that the 2- and 4-alkoxypyridines rearrange into the N-alkylpyridones when heated to 290° or above.[47] The N-alkyl- and N-aryl-pyridones are often made with greater ease from the corresponding pyrone by treatment with a primary amine instead of with ammonia (p. 473). In this way, chelidonic acid reacts with aniline to give N-phenylchelidamic acid which can be decarboxylated to N-phenyl-4-pyridone.[48]

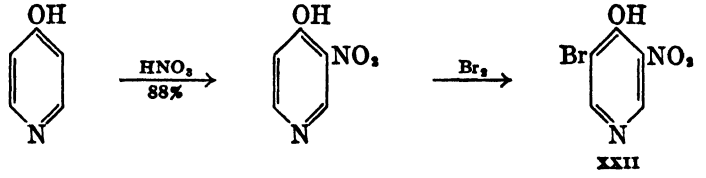
That the N-alkylpyridones still retain their essential aromatic character is indicated not only by the absorption spectra (p. 436) but also by the ease of bromination [45] and nitration [49] of N-methylpyridone.

[45] Decker et al., *J. prakt. Chem.*, [2] **84**, 432 (1911).
[46] Fargher and Furness, *J. Chem. Soc.*, **107**, 690 (1915).
[47] Meyer, *Monatsh.*, **28**, 47 (1907).
[48] Smirnoff, *Helv. Chim. Acta*, **4**, 599 (1921); *Ber.*, **55**, 612 (1922).
[49] Fischer and Chur, *J. prakt. Chem.*, [2] **93**, 363 (1916).

These substitution reactions proceed in a manner little different from the corresponding reaction with 2-hydroxypyridine.



It has already been mentioned that 4-hydroxypyridine undergoes nitration and bromination with substitution in the 3 and 5 positions. An interesting further example is the successive nitration and bromination of 4-hydroxypyridine [9] to give 3-nitro-5-bromo-4-hydroxypyridine (XXII).



XXII

Dihydroxypyridines

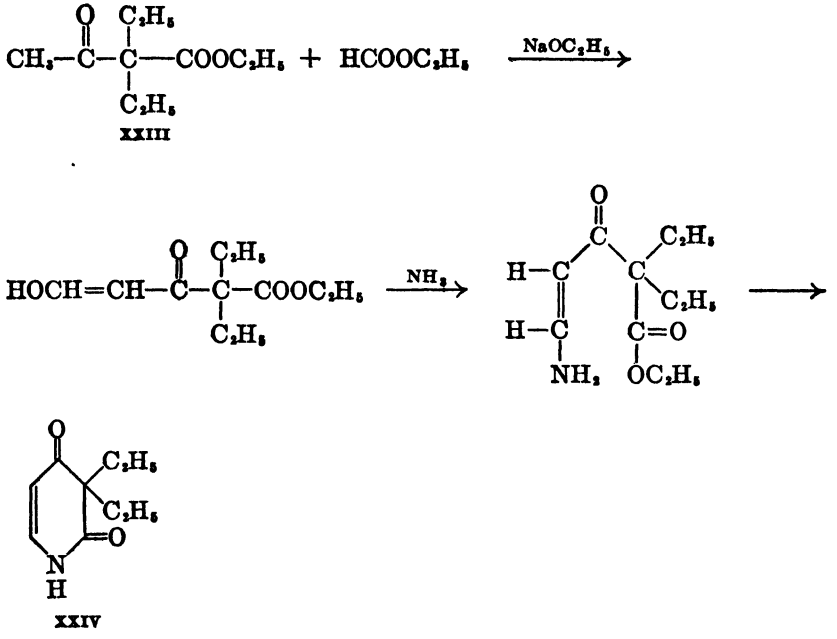
The dihydroxypyridines have been made by variations of the general syntheses already cited and for the most part show the expected reactions. They are all neutral or acidic, white, high-melting solids which give a positive ferric chloride test. The intensity of the color developed with ferric chloride depends on whether or not a 3-hydroxyl group is present. If so, the color is a deep blue or violet, but if the hydroxyl groups are 2,4 or 2,6 the color is red to red-brown or green. Very few exceptions have been found to the generalization that any 2- or 4-hydroxyl group can be replaced with chlorine by treatment with phosphorus pentachloride or phosphorus oxychloride. 2,3-Dihydroxypyridine is reported to be such an exception, however. In addition, it gives only a monoacetyl derivative after being refluxed for 6 hr. with acetic anhydride and sodium acetate.[18,19]

Bromination and nitration of the dihydroxypyridines take place very easily, with the entering group filling either one or both of the 3 and 5 positions available. 2,6-Dihydroxypyridine reacts with phthalic anhydride in a manner analogous to the reaction of resorcinol to give a phthalein dye [50] which is red in alkaline solution and shows

[50] Ruhemann, *Ber.*, **26**, 1559 (1893).

a blue-green fluorescence. This resemblance to resorcinol is extended to its reducing action on ammoniacal silver nitrate solution.

Pyridine compounds which possess the characteristic structural features of barbiturates and also show a similar soporific action have been described.[51,52] These compounds are made by the very interesting reactions outlined in XXIII–XXIV.



XXIII

XXIV

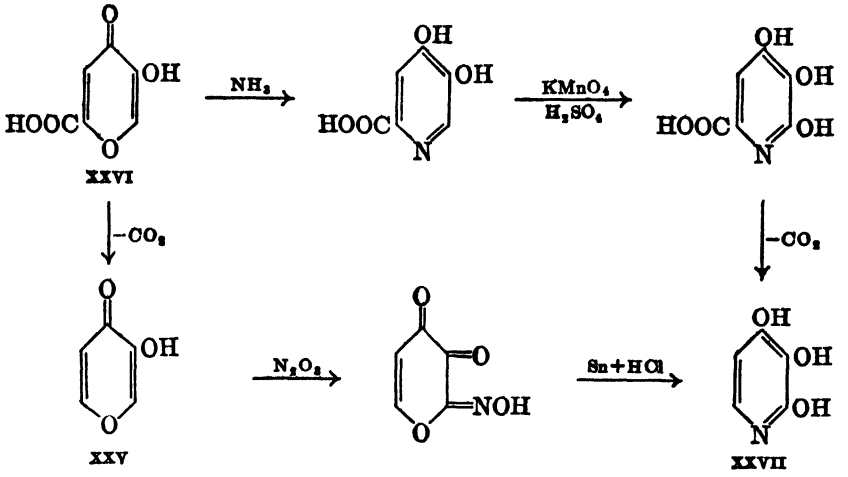
Trihydroxypyridines

Only two of the four possible trihydroxypyridines are known with certainty. The first, 2,3,4-trihydroxypyridine (XXVII),[53] has been made from the pyrones, pyromeconic acid (XXV) or comenic acid (XXVI), by the series of steps outlined below. This *vic*-trihydroxypyridine (XXVII) can be compared with the benzene analog, pyrogallol. Like pyrogallol, it is relatively stable in acid solution but is a powerful reducing agent in basic solution, rapidly absorbing oxygen from the air.

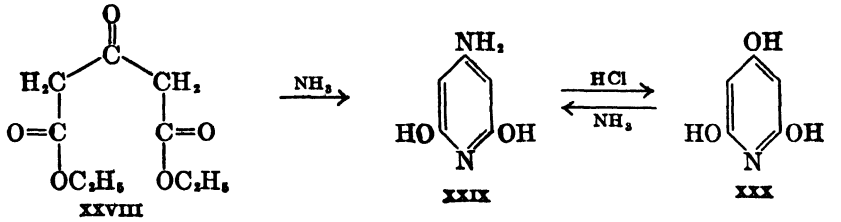
51 Hoffmann-La Roche and Co., Ger. pat. 634,284 (Aug. 25, 1936) [*C. A.*, **31**, 219 (1937)]; Brit. pat. 471,237 (Aug. 31, 1937) [*C. A.*, **32**, 1280 (1938)].

52 Freed, *J. Lab. Clin. Med.*, **32**, 895 (1947).

53 Ost, *J. prakt. Chem.*, [2] **19**, 203 (1879); **23**, 441 (1881); **27**, 257 (1883).



The symmetrical trihydroxypyridine (XXX) has been made from acetonedicarboxylic ester (XXVIII) via glutazine (XXIX).[54,55] It



resembles phloroglucinol, its benzene analog, in its properties and reactions as far as they have been studied. It shows an acid reaction in solution and gives an intense red-violet color with ferric chloride. When XXX is heated with ammonium hydroxide for only a few minutes, glutazine (XXIX) is formed. Although it is only slightly soluble in cold water, 2,4,6-trihydroxypyridine forms a very water-soluble potassium or sodium salt. The reaction with phosphorus oxychloride or phosphorus pentachloride apparently has not been studied.

NITROPYRIDINES

Nitration of Pyridines

Pyridine is directly nitrated under extreme conditions to give poor yields of 3-nitropyridine. Friedl,[1] who was the first to accomplish this

54 Niementowski and Sucharda, *J. prakt. Chem.*, [2] **94**, 208 (1916).
55 Stokes and Pechmann, *Ber.*, **19**, 2694 (1886).
1 Friedl, *Ber.*, **45**, 428 (1912).

nitration successfully, reported obtaining a 15% yield by adding potassium nitrate to a solution of pyridine in sulfuric acid at 300°. By slight modifications and with iron as a catalyst, Kirpal and Reiter [2] obtained a 22% yield, and it has been shown that vapor phase nitration takes place at 115–120°,[3] but the yield is still low (10%). Pyridine has not been dinitrated, and no otherwise unsubstituted di- or polynitropyridines have been reported.

Although the nitration of pyridine itself is quite difficult, the substitution of a nitro group into any pyridine molecule which contains the strongly *o,p*-directing amino, hydroxyl, or alkoxyl group is usually quite satisfactory. When the *o,p*-directing substituent is in the 2, 4, or 6 position, substitution invariably takes place in the 3 or 5 position. If the substituent is in the 3 or 5 position, nitration will take place in the 2 or 6 position. When the activating group is hydroxyl or methoxyl, *o* substitution predominates. The activating effect of one methyl group is not sufficient to render nitration of the picolines a satisfactory reaction,[4] but Plazek was able to obtain excellent yields of 3-nitro-2,4,6-trimethylpyridine by the action of fuming nitric and fuming sulfuric acids at 100° on *sym*-collidine. 2,6-Lutidine under similar conditions gave good yields of 3-nitro-2,6-dimethylpyridine. Direct nitration of 3-chloropyridine is reported to give some 3-chloro-5-nitropyridine, but the reaction fails with 2- and 4-chloropyridines.[5]

The 2- and 4-nitropyridines are available by oxidation of the corresponding aminopyridines with such oxidizing agents as Caro's acid (H_2SO_5). The direct oxidation of an aromatic amine to a nitro compound is not usually practical in the benzene series, but with the 2- and 4-amino derivatives of the pyridine series it is a very excellent and useful reaction, giving yields of 75–80%,[6] and it has also been employed successfully with 3-aminopyridine.[7]

In general, the nitropyridines are of value only as intermediates in the synthesis of the aminopyridines. This reverse conversion is therefore useful only when it is desirable to introduce a nitro group in the 2 or 4 positions for some purpose such as activating a halogen (or some other group) in the 3 or 5 position. Occasionally it is desirable to convert a nitro group to an amino group as the last step of a series

2 Kirpal and Reiter, *Ber.*, **58**, 699 (1925).

3 Schorigin and Toptschiew, *Ber.*, **69**, 1874 (1936).

4 Plazek, *Ber.*, **72**, 577 (1939).

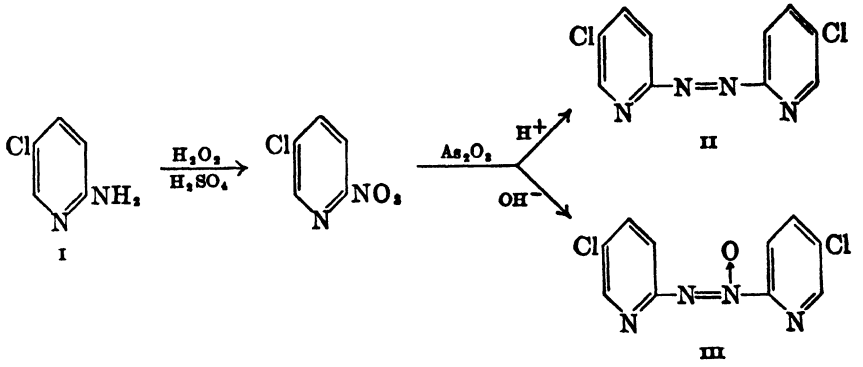
5 Plazek, Sorokowska, and Tolopka, *Roczniki Chem.*, **18**, 210 (1938) [*C. A.*, **33**, 3879 (1939)].

6 Kirpal and Böhm, *Ber.*, **64**, 767 (1931); **65**, 680 (1932).

7 Schickh, Binz, and Schulz, *Ber.*, **69**, 2593 (1936).

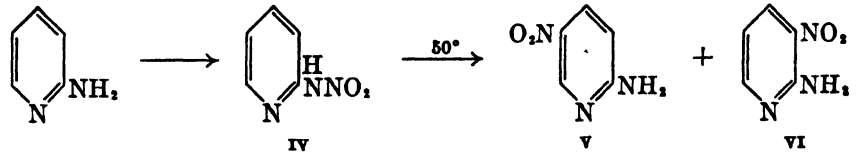
of reactions, and, in such instances, it may be necessary to employ the 2- or 4-nitropyridine as starting material.

Reduction products other than the amine can be obtained from the nitro compound. This is the other reason for the synthesis of 2-nitropyridines from 2-aminopyridines. 2-Amino-5-chloropyridine (I) has been converted into 2-nitro-5-chloropyridine which on reduction with arsenious oxide in acid solution gives 5,5′-dichloro-2,2′-azopyridine (II) and in basic solution gives the corresponding azoxy compound (III).[8] These substances are not readily obtainable by any other method.



Nitroaminopyridines

The best-known and most utilized nitropyridine is 2-amino-5-nitropyridine (V). A discussion of its synthesis and properties will illustrate the possible uses of the nitropyridines. 5-Nitro-2-aminopyridine is obtained from 2-aminopyridine, either directly by nitration in sulfuric

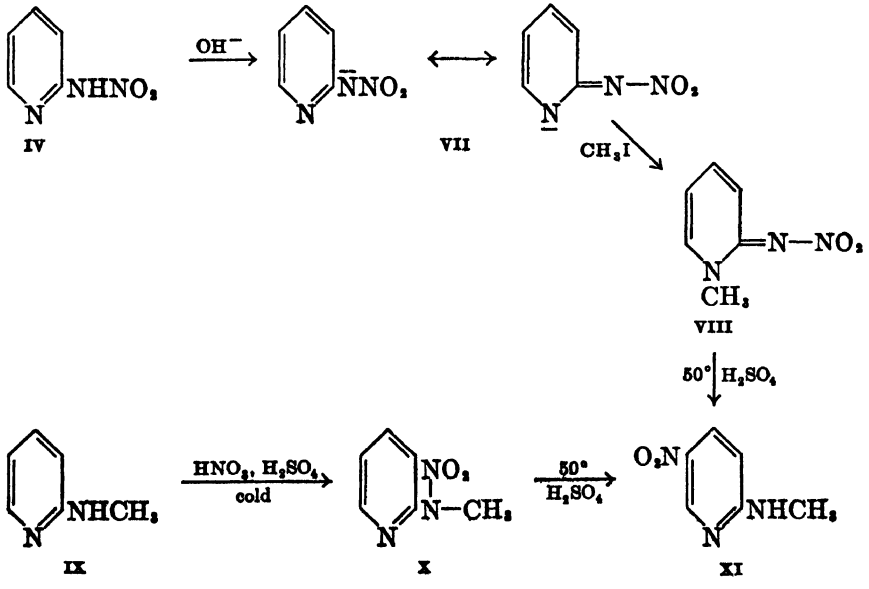


acid or stepwise from the intermediate 2-nitraminopyridine (IV). The ratio in which the two isomers (V and VI) are formed appears to depend on the temperature at which the conversion is done. When the nitraminopyridine is heated with concentrated sulfuric acid at 50°,

[8] Bystritskaya and Kirsanov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1101 (1940) [*C. A.*, **35**, 4023 (1941)].

an 80% yield of 5-nitro-2-aminopyridine is formed along with 10% of the 2-amino-3-nitro isomer (VI); however, at 100°, 75% of the 5-nitro isomer and 24% of the 3-nitro isomer are formed, respectively. The separation of these two isomers is readily accomplished by steam distillation of the more volatile 2-amino-3-nitropyridine. In this isomer the nitro and amino groups are adjacent to each other and hydrogen bonding can take place within the molecule to form a chelate ring, whereas in the 2-amino-5-nitropyridine any hydrogen bonding will be between molecules and will therefore result in association and lowered volatility. Depending on the conditions of the nitration of 2-aminopyridine, small amounts of 2-hydroxypyridine are also produced.[9] The formation of 2-hydroxypyridine from 2-nitraminopyridine can be accomplished in 60% yield if the latter is refluxed in acetic acid-acetic anhydride mixture.

2-Nitraminopyridine (IV) is formed in good yield by the action of a mixture of concentrated sulfuric acid and nitric acid on 2-aminopyridine in the cold. Its structure is shown by reduction with zinc dust and sodium hydroxide to 2-hydrazinopyridine [10] which is identical with the product obtained from 2-chloropyridine and hydrazine. 2-Nitraminopyridine is stable in basic solution, and a crystalline sodium

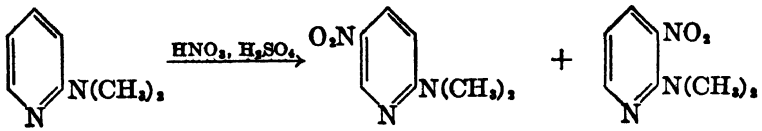


9 Chichibabin and Kirssanow, *Ber.*, **60**, 2433 (1927).

10 Chichibabin and Razorenov, *J. Russ. Phys. Chem. Soc.*, **47**, 1286 (1915) [*C. A.*, **9**, 3057 (1915)].

salt precipitates from concentrated sodium hydroxide solution. It is interesting to note that, on methylation, this sodium salt gives a compound (VIII), the structure of which is related to N-methyl-2-pyridone and differs from the nitramino compound (X) obtained from 2-methylaminopyridine (IX) and mixed sulfuric and nitric acids. Both VIII and X, however, give the same 5-nitro-2-methylaminopyridine (XI) and a small amount of the 2-methylamino-3-nitro isomer when warmed in sulfuric acid.[11,12]

The direct nitration of 2-aminopyridine[13] has been achieved by careful control of the temperature during addition of concentrated nitric acid to a sulfuric acid solution of the aminopyridine. The product (ca. 80–85% yield) consists of 2-amino-3-nitropyridine and 2-amino-5-nitropyridine in the ratio of about 1:12. Whether or not this reaction is a true intermolecular reaction between two different molecules of IV, a direct nitration of 2-aminopyridine, or a competitive reaction involving more than one of these reactions is not known. The fact that 2-nitraminopyridine, when warmed in sulfuric acid, is converted into 2-amino-5-nitro- and 2-amino-3-nitro-pyridine would favor a rearrangement theory. However, in a true rearrangement one would expect that the 2-amino-3-nitropyridine would be the major product in direct contrast to the ratio of isomers which is actually produced. It is certainly not necessary for the nitration to proceed via the nitramino intermediate, as indicated by the behavior of 2-dimethylaminopyridine,[14] the nitramino derivative of which cannot exist and which gives 2-dimethylamino-5-nitropyridine (XII) (90% yield) and 2-dimethylamino-3-nitropyridine (XIII) (10% yield) on nitration.



XII XIII

2-Amino-6-methylpyridine, which is readily available by the amination of 2-picoline, is nitrated in the normal manner to give a 58% yield of 2-amino-5-nitro-6-methylpyridine in which the nitro group

11 Chichibabin and Knowalowa, *Ber.*, **58**, 1712 (1925).
12 Chichibabin and Kirssanow, *Ber.*, **61**, 1223 (1928).
13 Caldwell and Kornfeld, *J. Am. Chem. Soc.*, **64**, 1696 (1942).
14 Chichibabin and Knunyantz, *Ber.*, **62**, 3053 (1929).

enters *para* to the amino group and a 25% yield of 2-amino-3-nitro-6-methylpyridine in which the nitro group substitutes *ortho*.[15]

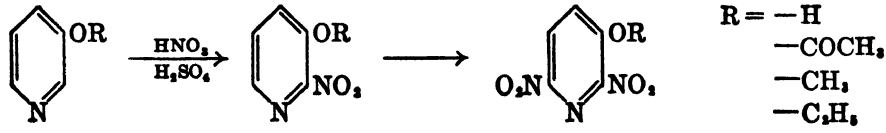
In complete contrast to the situation which exists in the benzene series, 2-acetylaminopyridine is resistant to nitration.[16] 2-Amino-5-nitropyridine can be obtained by other methods from 2-hydroxy-5-nitropyridine and N-methyl-5-nitro-2-pyridone, but these methods are not of preparative value.

Since 2-aminopyridine is commercially available, its nitration product, 2-amino-5-nitropyridine, serves as a starting material for many other typical reactions; it can be further nitrated to 2-amino-3,5-dinitropyridine[10] or brominated to 2-amino-3-bromo-5-nitropyridine.[17]

The effect of the nitro group in 2-amino-3-nitro- and 2-amino-5-nitro-pyridine (and also presumably in 4-amino-3-nitropyridine) is manifest in the product resulting from methylation. Although treatment of 2-aminopyridine with methyl iodide gives only N-methyl-2-iminopyridine, methylation of either 2-amino-5-nitropyridine or the 2-amino-3-nitro isomer results in methylation exclusively on the amino nitrogen to give 2-methylamino-5-nitropyridine or 2-methylamino-3-nitropyridine.

Nitrohydroxypyridines

Nitration of 3-hydroxypyridine is accompanied by oxidative cleavage of the ring, except under mild conditions[18] (cf. pp. 534 ff.), when mono- and di-nitropyridine compounds are the main products. Plazek[19] has shown that the mononitropyridine formed is 2-nitro-3-hydroxypyridine and that presumably the dinitropyridine is the 2,6 derivative. There is a discrepancy, however, between the melting points of these products and the melting points of those obtained by Weidel and Murmann[20] by the nitration of 3-acetoxypyridine and subsequent hydrolysis. The nitration of 3-alkoxypyridines clearly gives the 2-nitro-3-alkoxypyridine first, and this is further nitrated to 2,6-dinitro-3-alkoxypyridine.

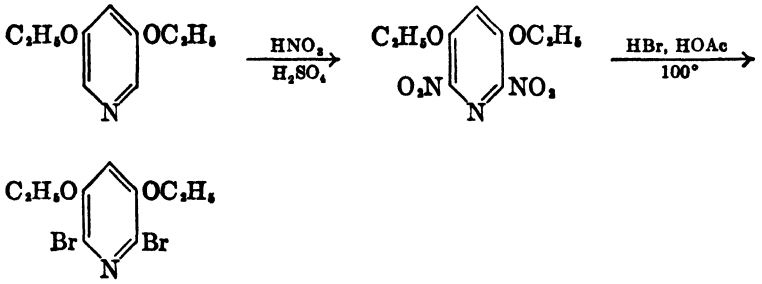


15 Parker and Shive, *J. Am. Chem. Soc.*, **69**, 63 (1947).
16 Plazek and Sucharda, *Ber.*, **61**, 1813 (1928).
17 Chichibabin, *J. Russ. Phys. Chem. Soc.*, **50**, 492 (1920) [*C. A.*, **18**, 1495 (1924)].
18 Wulff, U. S. pat. 1,889,303 (Nov. 29, 1933) [*C. A.*, **27**, 1366 (1933)].
19 Plazek, *Roczniki Chem.*, **16**, 403 (1936) [*C. A.*, **31**, 1808 (1937)].
20 Weidel and Murmann, *Monatsh.*, **16**, 749 (1895).

In an analogous manner, 2-hydroxypyridine first gives the *o*-substituted product, 2-hydroxy-3-nitropyridine, and then the dinitro product, 3,5-dinitro-2-hydroxypyridine.

4-Hydroxypyridine on treatment with 100% sulfuric acid and fuming nitric acid first gives 3-nitro-4-hydroxypyridine and then 3,5-dinitro-4-hydroxypyridine.

A very interesting reaction in which a nitro group is replaced by halogen in good yield has been described by Koenigs, Gerdes, and Sirot [21] and is illustrated by the following series of equations.



It is strange that the ethoxyl groups were not cleaved by this treatment. Warming the product with sodium hydroxide gave a substance which was not positively identified but may possibly be 2,3,5,6-tetrahydroxypyridine. 2-Nitro-3-ethoxypyridine, mistakenly described as 6-nitro-3-ethoxypyridine,[21] likewise was converted either to 2-bromo-3-ethoxypyridine (66%) or to 2-chloro-3-ethoxypyridine when boiled with a solution of the halogen acid in glacial acetic acid.

Of the nitrohydroxypyridines, 2-hydroxy-5-nitropyridine is undoubtedly the best known and most thoroughly studied. It is made by the action of nitrous acid on crude 2-amino-5-nitropyridine in good yield. This product serves as a useful intermediate in the synthesis of a variety of substituted pyridines and can be directly converted to the even more useful 2-chloro-5-nitropyridine by the action of phosphorus oxychloride or a mixture of phosphorus oxychloride and phosphorus pentachloride.[13,22]

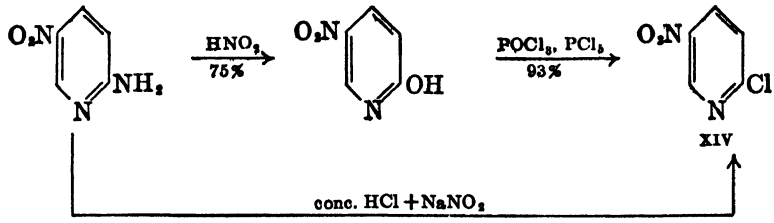
2-Chloro-5-nitropyridine can also be obtained by treating 2-amino-5-nitropyridine with sodium nitrite in concentrated hydrochloric acid; [23] 2-hydroxy-5-nitropyridine is formed as a by-product. Although this is the more direct route, the stepwise method is preferable.[13]

21 Koenigs, Gerdes, and Sirot, *Ber.*, **61**, 1022 (1928).

22 Philips, *J. Chem. Soc.*, 9 (1941).

23 Chichibabin, *J. Russ. Phys. Chem. Soc.*, **46**, 1236 (1914) [*C. A.*, **9**, 1902 (1915)].

The many reactions which are possible with XIV have been discussed under the reactions of the halopyridines. A completely com-



parable series of reactions is possible, starting with 4-aminopyridine. The chlorine atom in 4-chloro-3-nitropyridine is, in fact, even more active than that in the isomeric 2-chloro-5-nitropyridine. The usefulness of this series of reagents is greatly reduced by the greater difficulty connected with obtaining the starting material, 4-aminopyridine.

AMINOPYRIDINES

Synthesis

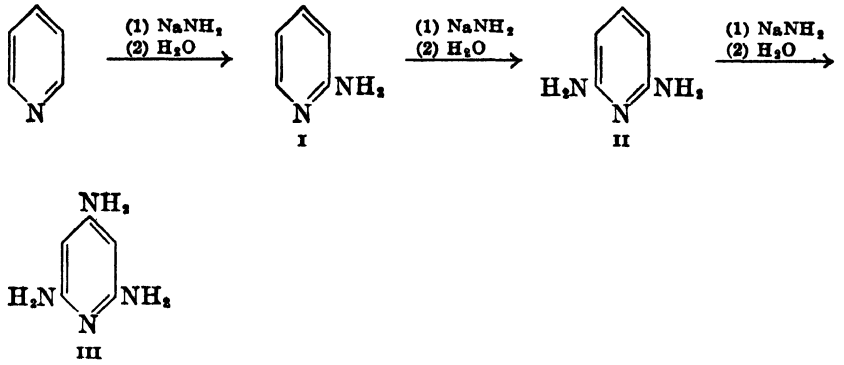
No one method for the synthesis of aminopyridines holds the dominant position of importance that is occupied by the method of nitration and reduction in the benzene series. Amination, nitration and reduction, and ammonolysis of a halopyridine play important roles in the synthesis of the aminopyridines. In addition, the Hofmann rearrangement of an acid amide, the Curtius rearrangement of an acid azide, reduction of azo compounds and ammonolysis of a substance such as 4-pyridylpyridinium chloride hydrochloride are of value in specific cases.

Amination. The most direct synthesis is the amination reaction with sodium amide (cf. p. 405 for the mechanism of the reaction), a reaction which was discovered in 1914 by Chichibabin and Seide [1] and which has since developed into one of the most important reactions of the pyridine series. Because of its value in the synthesis of 2-aminopyridine as an intermediate for sulfapyridine, the reaction with pyridine itself has been studied the most thoroughly.[2]

1 Chichibabin and Seide, *J. Russ. Phys. Chem. Soc.*, **46**, 1216 (1914) [*C. A.*, **9**, 1901 (1915)].

2 The scope and limitations of the reaction have been subjected to an excellent review by Leffler in "The Amination of Heterocyclic Bases by Alkali Amides," Chapter 4 in *Organic Reactions*, Vol. I, John Wiley & Sons, New York, 1942.

In Chichibabin's original procedure, pyridine was refluxed in an inert solvent such as xylene with sodium amide until no more hydrogen was evolved. On hydrolysis, a 43–51% yield of 2-aminopyridine was obtained. By slight modifications, most important of which is the substitution of dimethylaniline as solvent, the yields have been raised to 66–85%. 2-Aminopyridine (I) is not the sole product of the reaction. Depending primarily on the temperature of the reaction and on the excess of sodium amide, 2,6-diaminopyridine (II) and 2,4,6-tri-

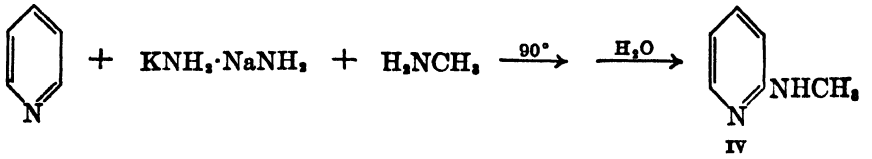


aminopyridine (III) are successively formed. A temperature of approximately 110° is best for the introduction of one amino group; at 170°, in boiling dimethylaniline or without solvent, two amino groups are introduced in the 2,6-positions (80–90% yield); and the third amino group is forced into the 4 position only in the presence of a large excess of sodium amide and then with difficulty and in very poor yield.

In addition to the amination products, various bipyridyls (primarily 4,4′-bipyridyl and 2,2′-bipyridyl) as well as 2,2′-dipyridylamine are formed. The reaction has been successfully applied to α-, β-,[3] and γ-picolines, several other alkyl and dialkyl pyridines, 2,2′- and 4,4′-bipyridyl, and some of the pyridine alkaloids. Attempted amination of 3-hydroxypyridine resulted in reduction, and 2,6-diaminopyridine was the only product isolated.[4] In contrast to this, a patent[5] claims that 2-hydroxypyridine reacts with sodium amide to give 2-hydroxy-6-aminopyridine. Bergstrom[6] found that fairly good yields of 2-alkylaminopyridines could be obtained by heating a solution of pyridine in

3 Bernstein et al., *J. Am. Chem. Soc.*, **69**, 1156 (1947).
4 Plazek, *Roczniki Chem.*, **16**, 403 (1936) [*C. A.*, **31**, 1808 (1937)].
5 Chichibabin, Ger. pat. 374,291 [*C. A.*, **18**, 2176 (1924)].
6 Bergstrom, Sturz, and Tracy, *J. Org. Chem.*, **11**, 239 (1946).

a primary amine as solvent with the amide from the sodium-potassium eutectic. An example is the 73% yield of 2-methylaminopyridine (IV) obtained by heating the reactants in a sealed tube in methylamine at 90° for 1½ hr.



IV

Curtius and Hofmann Reactions. The direct amination method is not satisfactory for the preparation of many specific aminopyridine compounds; 3-aminopyridine and 4-aminopyridine are such examples, and other synthetic methods must be resorted to for them. Although pyridine nitrates to give a small yield of 3-nitropyridine (10–20%) which can be reduced to 3-aminopyridine, this method is not satisfactory, and 3-aminopyridine is usually made by some other method such as the pressure reaction of ammonia on 3-bromopyridine or the Hofmann or Curtius reaction. The latter two reactions are general and have been successfully applied to the preparation of the three isomeric aminopyridines as well as to several aminopicolines and aminopyridinecarboxylic acids.[7]

The Curtius rearrangement of the acid azide to the isocyanate (or urethane) and eventual hydrolysis to the amine is the preferred method in making small amounts of both 3-aminopyridine [8] and 4-aminopyridine.[9] The Curtius reaction has been applied to a larger number of pyridine derivatives than the Hofmann reaction and in general seems to be capable of higher yields. It has been successful in the synthesis of the isomeric aminopyridines, several aminopicolines, aminochloropyridines, aminodichloropyridines, diaminopyridines, and phenylazopyridines. Since there is an excellent review of the Curtius reaction, including the applications in the pyridine series,[7] it will suffice to describe a single, more-or-less typical example.[10] Graf found that the ester of 2-methylpyridine-5-carboxylic acid deposited

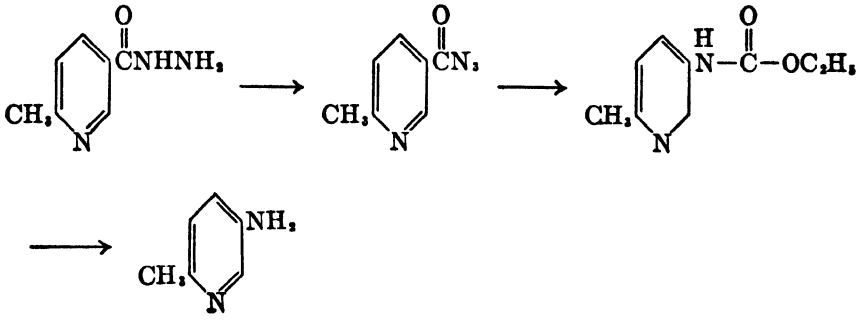
7 For a complete discussion of the Hofmann and Curtius reactions and the examples in the pyridine series, the reader is referred to Wallis and Lane, "The Hofmann Reaction," Chapter 7 in *Organic Reactions*, Vol. III, John Wiley & Sons, New York, 1946, and Smith, "The Curtius Reaction," *ibid.*, Chapter 9.

8 Cavallito and Haskell, *J. Am. Chem. Soc.*, **66**, 1169 (1944).

9 Leis and Curran, *J. Am. Chem. Soc.*, **67**, 79 (1945).

10 Graf, *J. prakt. Chem.*, [2] **133**, 19 (1932).

crystals of the hydrazide (86% yield) merely on being mixed with hydrazine at room temperature and that the hydrazide was converted to the azide (75% yield) by treatment with sodium nitrite in hydrochloric acid solution. If the azide was boiled with dilute acetic acid, only a small yield of 2-methyl-5-aminopyridine resulted, but if it was converted to the urethane by being refluxed with absolute ethanol until all the nitrogen was evolved, and the urethane hydrolyzed with 40% sodium hydroxide, a 95% yield of 5-amino-2-methylpyridine resulted. The several steps can be conducted without purification of the intermediates, and the over-all yield (61%) is quite acceptable.



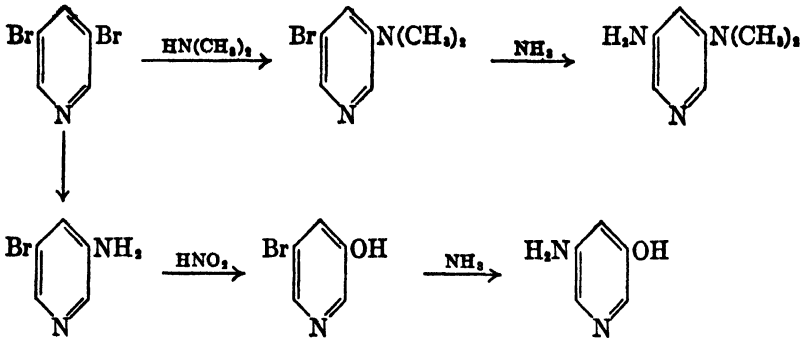
Replacement of Halogens. The replacement of a halogen by an amino group in the benzene series is practical only with substances such as *p*-chloronitrobenzene and is therefore of very limited application in the chemistry of the benzenoid compounds. In contrast to this, the replacement of a halogen by an amino group is of wide applicability in the pyridine series. The reaction takes place primarily with the more reactive 2- and 4-chloropyridines, but it is not limited to them. Thus, if 3-bromopyridine is heated with concentrated ammonium hydroxide in the presence of copper sulfate catalyst in a sealed reactor for 20 hr. at 140°, a 62% yield (73% conversion when the recovered starting material is considered) of 3-aminopyridine can be obtained.[11] Hertog and Wibaut [12] reported a 75–80% yield after heating 3-bromopyridine with concentrated ammonium hydroxide at 200° for 30 hr.

3,5-Dibromopyridine will also react with ammonia and amines. Marcinkow and Plazek [13] have reported the following successful reactions.

11 Dr. C. R. Hauser, private communication.

12 Hertog and Wibaut, *Rec. trav. chim.*, **55**, 122 (1936).

13 Marcinkow and Plazek, *Roczniki Chem.*, **16**, 136 (1936) [*C. A.*, **31**, 2216 (1937)].



A halogen occupying the 2 or 4 position of the pyridine ring is usually considered much more reactive than a halogen in the 3 position. Strangely enough, it appears that the conversion of 2-bromopyridine into 2-aminopyridine is, if anything, more difficult than the corresponding reaction for 3-bromopyridine. Hertog and Wibaut [14] found that it was necessary to heat 2-bromopyridine with concentrated ammonium hydroxide at 200° to effect satisfactory reaction; 2-chloropyridine and concentrated ammonium hydroxide react at 250° in the presence of copper sulfate to give a 50% yield of 2-aminopyridine.[15] At these temperatures, the pressure of the ammonium hydroxide solutions is considerable, and this fact limits the usefulness of the reaction. Use of ammonia in the form of the solid zinc chloride ammonia complex allows the reaction to proceed at the higher temperature without excessive pressures. With this reagent at 200°, Fischer [16] reported a quantitative yield of 2-aminopyridine from 2-chloropyridine.

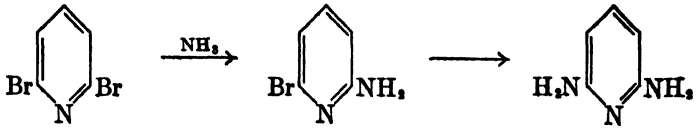
The relative reactivities of 2-bromo- and 3-bromo-pyridines with ammonia appear to be unique, since in similar reactions with alkyl and dialkyl amines the 2-bromopyridine is the more reactive. Thus, 2-bromopyridine will react with a basically substituted amine such as γ-morpholinopropylamine at 120–155° in 6 hr. to give a 75% yield of the metathetical reaction product,[17] whereas 3-bromopyridine must be heated to 200° with β-diethylaminoethylamine for 24 hr. to give even a 15% yield of the corresponding replacement product.[18]

Convincing evidence that the halogen in the 2 position is more reactive is offered by the reaction of 2-chloro-5-iodopyridine with di-

14 Hertog and Wibaut, *Rec. trav. chim.*, **51**, 381 (1932).
15 Räth, Ger. pat. 510,432 (Oct. 18, 1930) [*C. A.*, **25**, 974 (1931)].
16 Fischer, *Ber.*, **32**, 1297 (1899).
17 Whitmore et al., *J. Am. Chem. Soc.*, **67**, 393 (1945).
18 R. R. Adams, Ph.D. Thesis, The Pennsylvania State College, 1944.

ethylamine.[19] A 50% yield of 2-diethylamino-5-iodopyridine is obtained when the two reactants are heated at 160° for 36 hr., and the reaction solution gives a negative test for iodide ion.

Similar replacement reactions have been carried out satisfactorily for 4-chloropyridine [20] and for 2,6-dimethyl-4-chloropyridine.[21] When 2,6-dibromopyridine is treated with ammonia, the first bromine is replaced (200°, 8 hr.) to give 2-amino-6-bromopyridine,[12] but the second amine group cannot ordinarily be introduced except in very poor yield.



That the replacement of halogen in the 2 position is catalyzed by the presence of copper sulfate is shown by the experiments of Bernstein et al.[3] 2-Diethylamino-6-bromopyridine was heated at 190° with both aqueous and alcoholic ammonia, but essentially no reaction occurred; the same reaction with aqueous ammonium hydroxide at 145° in the presence of copper sulfate gave a 44% yield of 2-amino-6-diethylaminopyridine. A large number of 2,6-diaminopyridine derivatives have been synthesized from 2,6-dibromopyridine according to these methods.[3]

The replacement reaction of the more reactive 2-chloro-5-nitropyridine (p. 523) leads to a variety of 2-amino-5-nitropyridine compounds.[22]

Nitration and Reduction. Nitration and reduction of pyridine derivatives which already have an amino or hydroxy group within the molecule is a very satisfactory method for the synthesis of 3-amino- and 3,5-diamino-pyridines. Since the 2-amino- and 2,6-diaminopyridines can be made by the direct amination reaction, these two methods are complementary. The nitropyridines can be reduced by any of the methods employed for similar reductions in the benzene series such as catalytic reduction and reduction with iron and acetic acid. Raney nickel, platinum, or palladium catalysts are all useful. The only consideration in catalytic reduction is to make sure that the conditions are such that nuclear reduction to a piperidine

19 Bernstein et al., *J. Am. Chem. Soc.*, 69, 1147 (1947).
20 Henry Norris, M.S. Thesis, The Pennsylvania State College, 1942.
21 R. R. Adams, unpublished work, The Pennsylvania State College. 1944.
22 Earl Chapin, Ph.D. Thesis, The Pennsylvania State College, 1944.

compound does not occur. Since the ease of reduction of a nitro group and the pyridine ring differ markedly, there is very little difficulty from this source. For example, Raney nickel reduces the nitro group of 3-nitropyridine to the amino group at room temperature, whereas Adams catalyst catalyzes the reduction of the 3-aminopyridine dihydrochloride to the 3-aminopiperidine in 85–90% yields.[23] An example of a typical iron and acetic acid reduction is the formation of 2-butoxy-5-aminopyridine from the corresponding nitro compound.[24]

Miscellaneous Methods. Many of the pyridine derivatives couple with diazotized aromatic amines to give azo dyes (p. 556). These azo compounds should be reducible with sodium hydrosulfite to amines, but this method does not seem to have been explored to any extent. With Pyridium, the results are not too successful.[25]

4-Aminopyridine may be prepared according to the method of Koenigs and Greiner by the ammonolysis of 4-pyridylpyridinium chloride hydrochloride at 150°. Others have not been able to duplicate these yields, and until some refinement is developed which will render this method more reliable, the method involving the Hofmann or Curtius rearrangement of the isonicotinic acid is to be preferred.[9]

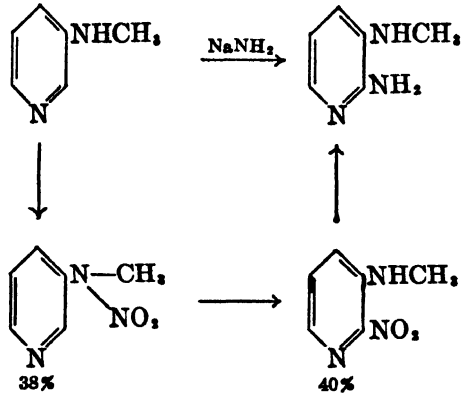
Reactions

The conversion of the aminopyridines into hydroxy, halo, and nitro compounds has already been discussed under the synthesis of these three types. In addition, the nitration and halogenation of amino compounds have been considered in a general manner in connection with the nitro and halo pyridines. It will, therefore, not be necessary to go into detail concerning these reactions, but certain generalizations will be made and some additional examples will be given to illustrate specific reactions.

Nitration. Any 2- or 6-aminopyridine can be readily nitrated if the 3 or 5 position is free. If both 3 and 5 positions are available, a mixture of the two possible isomers results with the *p* compound predominating. Under more vigorous conditions, two nitro groups will usually be introduced to give a 3,5-dinitropyridine derivative. With 4-aminopyridine, nitration occurs stepwise, the nitro groups entering successively the 3 and 5 positions, but, since 4-aminopyridine has

[23] Jenkins and Taylor, *J. Chem. Soc.*, 495 (1937).
[24] Friedman et al., *J. Am. Chem. Soc.*, 69, 1206 (1947).
[25] Edward Conroy, Ph.D. Thesis, The Pennsylvania State College, 1946.

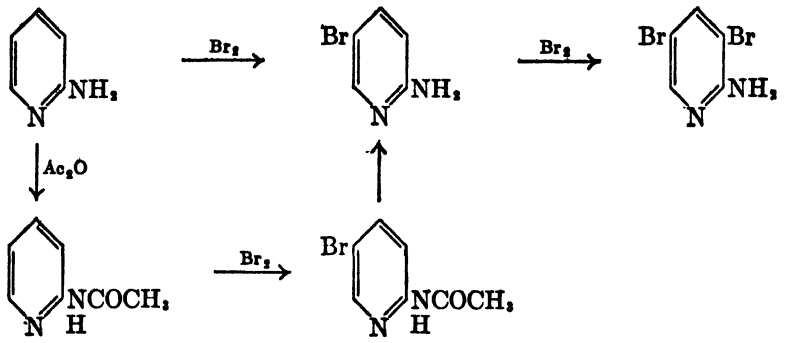
never been readily available in large amounts, these products have not received the same attention as the isomeric products obtained from 2-aminopyridine. The nitration of 3-aminopyridine and its derivatives has been studied even less, both because of the difficulty of obtaining the starting material in sufficient amounts, and because of the greater instability of the 3-aminopyridine towards oxidizing substances. 3-Methylaminopyridine [26] reacts with nitric acid to give 3-nitromethylaminopyridine, which is converted into 2-nitro-3-methylaminopyridine when heated in a yield of about 15%. The orientation is indicated by its reduction to an amino-3-methylaminopyridine (m.p. 124°), which is different from the previously known 2-amino-5-methylaminopyridine (m.p. 70°) and identical with the product obtained by the direct action of sodium amide on 3-methylaminopyridine.



Halogenation. Halogenation of the 2-, 4-, and 6-aminopyridines follows the same general rules of orientation observed in the nitration of these compounds. However, it is sometimes difficult to stop the halogenation so that the monohalogen compound is obtained, and often only the 3,5-dihalopyridine can be isolated in satisfactory yield. When, however, the monohalo compound is formed, all published work indicates that, if the *p* position is free, the *p* substitution product is the only one isolated and the *o* compound is present in insignificant amounts. Accordingly, bromination of 2-aminopyridine gives either 2-amino-3,5-dibromopyridine or recovered starting material. Only small amounts of 2-amino-5-bromopyridine can be obtained. 2-Amino-5-bromopyridine can be prepared in an over-all yield of 50–

[26] Plazek, Marunikow, and Stammer, *Roczniki Chem.*, 15, 365 (1935) [*C. A.*, 30, 1377 (1936)].

60% if preliminary acetylation of the amino group is done.[27] Iodinations, however, can be stopped at the monoiodo compound stage (80–

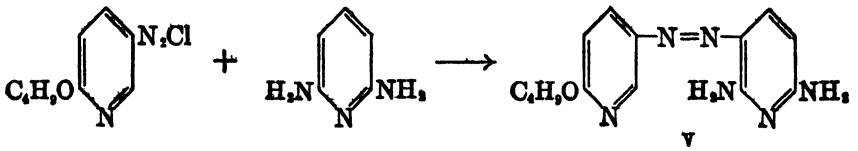


90% yield).[27] These generalizations, as far as they have been tested, hold not only for simple 2-, 4-, and 6-aminopyridines, but also for their nuclear substituted derivatives. Bromination of 3-methylaminopyridine [26] gives the 2,6-dibromo-3-methylaminopyridine.

Substitution in 3-aminopyridine derivatives has not been studied sufficiently to permit generalizations. The one successful reaction is chlorination with a mixture of hydrochloric acid and hydrogen peroxide as a chlorinating agent, which gives a good yield of 3-amino-2-chloropyridine (p. 511).

Sulfonation. The results on the sulfonation of 2-aminopyridine and 4-aminopyridine [28] indicate that approximately the same conditions and orientations are found as in nitration; there is very little substantiating evidence available from experiment on other aminopyridines.

Diazo Reaction. 3-Aminopyridine shows the normal reactions of an aromatic amine in the diazo reaction. Its diazonium solution will couple normally with phenols and aromatic amines to give typical azo dyes. An example involving two pyridine molecules is the coupling of diazotized 2-butoxy-5-aminopyridine with 2,6-diaminopyridine to give V. V is called Neotropin, and it has been studied along with



V

[27] Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).
[28] Koenigs and Jungfer, *Ber.*, **57**, 2080 (1924).

many analogous substances as a bactericide.[29] 3-Aminopyridine participates in the normal Sandmeyer reaction to yield the chloro-, bromo-, iodo-, or cyano-pyridine in a manner completely analogous to that of aniline.

2-Aminopyridine will likewise undergo most of these same conversions, and yet it cannot be considered a typical aromatic amine because of the special conditions necessary to bring about these reactions. Thus, the sodium salt of 2-diazopyridine is obtained only if an alcoholic or ethereal solution of the sodium salt of 2-aminopyridine is refluxed with amyl nitrite for many hours. In aqueous solution, this diazo salt couples with a compound such as β-naphthol, giving a characteristic azo dye.[30] From this it seems that the diazo compound from 2-aminopyridine shows normal reactions once it is formed, but attempts to make the diazonium salt with nitrous acid under ordinary conditions have been unsuccessful. Thus, attempted diazotization of 2-aminopyridine with nitrous acid in aqueous solution followed by treatment with phenol gives no azo dye.

The procedure for converting 2-aminopyridine into 2-bromopyridine by the method of Craig (p. 515) deviates radically from the accepted Sandmeyer procedure for aromatic amines. If the normal Sandmeyer procedure is employed with 2-aminopyridine, only a small yield of the product (but a large amount of 2-hydroxypyridine) is formed. Formation of the hydroxy compound is by no means unique to an aromatic amine since the same conversion is represented by the action of nitrous acid on an aliphatic primary amine to give the alcohol or on an amide to give the acid. Although 3-aminopyridine gives 3-cyanopyridine by the Sandmeyer procedure, there is no report of the successful conversion of a 2- or 4-aminopyridine into a 2- or 4-cyanopyridine by any modification of the diazo procedure. With 2,6-diaminopyridine, the substitution reaction with nitrous acid takes place in preference to the formation of a diazo compound, with the result that 2,6-diamino-3-nitrosopyridine is formed in good yield.

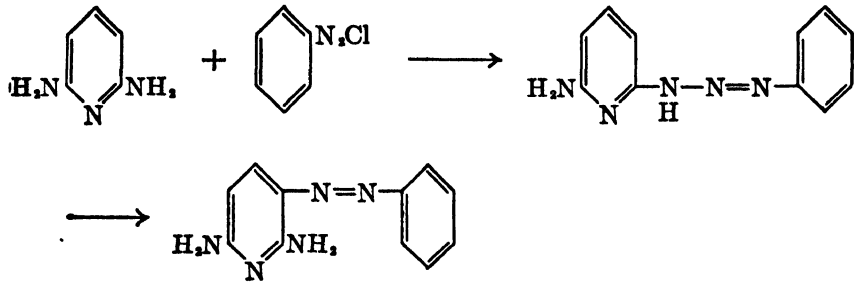
The many possible reactions of almost any 3-aminopyridine compound which involve only the amino group and are characteristic of an aromatic amine are illustrated by the large number of derivatives of 5-amino-2-butoxypyridine prepared by Friedman et al.[31]

29 Ger. pat. 617,187 (Aug. 14, 1935) [*C. A.*, **29**, 8242 (1935)].

30 Chichibabin and Rjazancev, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915) [*C. A.*, **10**, 2898 (1916)]; *ibid.*, **50**, 512 (1920) [*C. A.*, **18**, 1496 (1924)].

31 Friedman et al., *J. Am. Chem. Soc.*, **69**, 1795 (1947).

Coupling. Many 2-aminopyridine derivatives themselves couple with diazotized aromatic amines. The most widely known of these is 2,6-diamino-3-phenylazopyridine, marketed commercially in the United States as Pyridium (VI) as an urinary antiseptic. It is prepared by coupling 2,6-diaminopyridine with diazotized aniline.[32] The



VI

reaction is a typical coupling reaction open to wide applications. When the coupling is carried out in strong acid, the azo compound is formed directly. In acetic acid solution, the diazoamino compound is formed which can be rearranged to the aminoazo compound if it is heated in hydrochloric acid solution.

Not only will the amino- and hydroxy-pyridines that have an unoccupied 3 or 5 position couple with diazonium chlorides, but 3- and 5-aminopyridine derivatives such as 2-chloro-5-aminopyridine, 2-alkoxy-5-aminopyridine, 2-alkoxy-3-aminopyridine, and 2-acetylamino-5-aminopyridine, which contain an aromatic amino group, can themselves be converted to diazo salts and thus couple.

Diaminopyridines

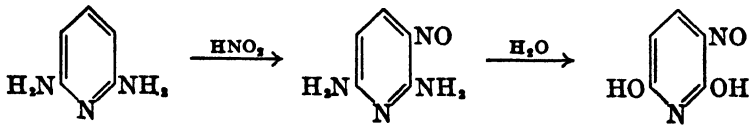
All six possible diaminopyridines are known. They have been made by standard methods such as amination of pyridine or a monoaminopyridine (2,3 and 2,6), Curtius or Hofmann degradation of a dicarboxylic acid derivative (2,4 and 3,5), and reduction of a nitroaminopyridine (2,5 and 3,4). 2,6-Diaminopyridine serves as a versatile starting material for many syntheses. Its coupling with diazotized amines to give azo dyes has already been mentioned. In addition, it is readily nitrated to 2,6-diamino-3-nitropyridine or nitrosated to 2,6-diamino-3-nitrosopyridine.[33]

Although 2-aminopyridine itself is not ordinarily hydrolyzed to 2-hydroxypyridine, 2,6-diamino-3-nitrosopyridine is readily hydrolyzed

[32] Shreve, Swaney, and Riechers, *J. Am. Chem. Soc.*, **65**, 2241 (1943).

[33] Titov, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 1483 (1938) [*C. A.*, **33**, 4248 (1939)].

by concentrated hydrochloric acid at 15°. After 12 days, a 90% yield of 2,6-dihydroxy-3-nitrosopyridine is obtained. The presence of a



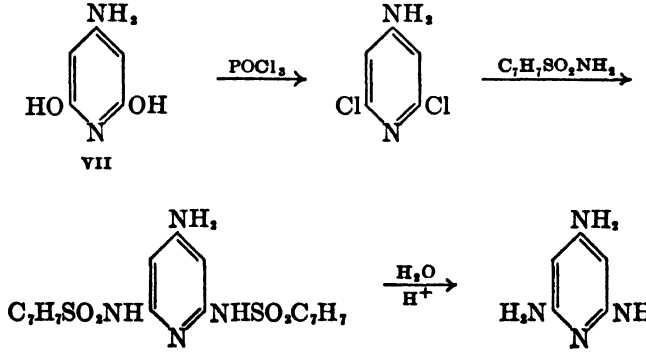
nitro or nitroso group in the *o* or *p* position to an amino group greatly facilitates the hydrolysis just as it does in the benzene series. 2,6-Diaminopyridine can itself be hydrolyzed to 2-amino-6-hydroxypyridine in good yield by being heated at 100° for approximately 2 hr. with 70% sulfuric acid.[34]

The two *o*-diaminopyridines serve as starting materials for a series of fused pyridine compounds analogous to benzimidazole, benzotriazole, and quinoxaline obtained from *o*-phenylenediamine in the benzene series.

Triaminopyridines

Three of the five triaminopyridines are known: 2,4,6-triaminopyridine, 3,4,5-triaminopyridine,[35] and 2,3,6-triaminopyridine.[36] These three compounds show greatly differing properties. The symmetrical compound is reported to be a completely stable white powder with a melting point of 185°,[37] whereas the 2,3,6-triamino compound is extremely unstable in air and can only be kept in acid solution or in the form of its acid salts.

The symmetrical triaminopyridine is made from glutazine (VII) (p. 454) by successive treatment with phosphorus oxychloride, *p*-



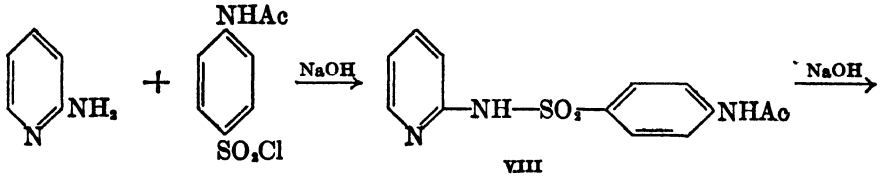
34 Selde and Titov, *Ber.*, **69**, 1884 (1936).
35 Hatzig, Ger. pat. 670,920 (Jan. 27, 1939) [*C. A.*, **33**, 6351 (1939)].
36 Engelman, U. S. pat. 2,136,044 (Nov. 8, 1939) [*C. A.*, **33**, 1348 (1939)].
37 Meyer and von Beck, *Monatsh.*, **36**, 731 (1915).

toluenesulfonamide, and dilute sulfuric acid. Reaction of 2,6-dichloro-4-aminopyridine with ammonia directly gives only 2,4-diamino-6-chloropyridine (p. 522).

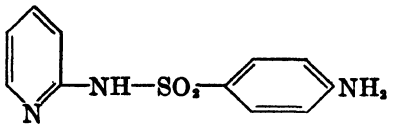
Sulfapyridine

The discovery of the bacteriostatic activity of sulfapyridine (IX) did much to further our knowledge of the chemistry of the aminopyridines, since its production demanded the availability of the intermediate 2-aminopyridine in quantity. The importance of this is better understood when we realize that up to this time the only commercially available pyridine derivatives, other than the pyridine bases from bone and coal, were nicotine and nicotinic acid. In addition to providing a valuable intermediate for further synthesis, this discovery stimulated much further research into other aminopyridines and substituted aminopyridines which might be converted into valuable sulfa drugs. Of all the sulfa drugs of the pyridine series which have been prepared, there has been no report of any which is superior to sulfapyridine.

Sulfapyridine (IX) is prepared in 60–70% yields according to the following equations [38] by a modified Schotten-Baumann reaction via the intermediate VIII.



VIII



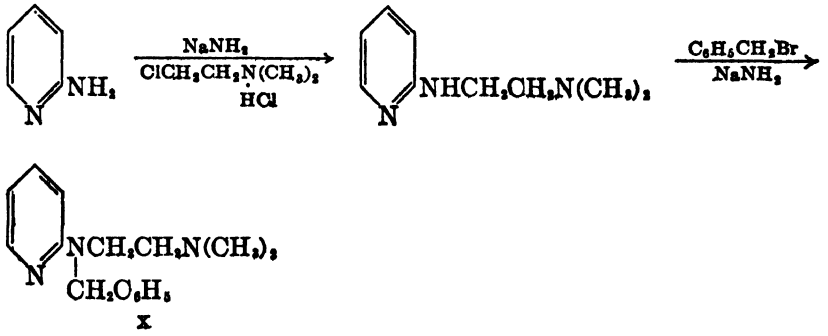
IX

Pyribenzamine

A substituted aminopyridine of special importance is the antihistamine drug, Pyribenzamine, (X) [39] which, along with Benadryl, has been quite successful in alleviating the symptoms of many allergic

[38] *U. S. Dept. Commerce, Publication Board Report* 237, pp. 18–20.
[39] Huttrer et al., *J. Am. Chem. Soc.*, 68, 1999 (1946).

conditions such as hay fever, allergic eczema, ivy poisoning, and, to a lesser extent, bronchial asthma. Pyribenzamine can be made by several methods, all starting with 2-aminopyridine. The method illustrated is the most satisfactory and the one adopted commercially.



x

The pyridine compound is first refluxed with sodium amide in an inert solvent such as toluene until no more ammonia is evolved, indicating that the formation of the sodium salt of the aminopyridine is complete. The sodium salt is then refluxed with the halogen compound to effect replacement. Sodium amide (or lithium amide) is necessary in order to ensure alkylation on the amino group instead of on the ring nitrogen atom of the tautomeric imino form.

CYANOPYRIDINES

Preparation

The cyanopyridines are prepared both from alipathic compounds and from substituted pyridines. The general methods outlined on pp. 469 ff. from such compounds as cyanoacetamide, cyanoacetic ester, or "dinitriles" result in the direct formation of cyanopyridines, or the compounds may be synthesized from pyridine derivatives such as the bromopyridines, 3-aminopyridines, or pyridine acid amides.

From Aliphatic Compounds. The synthesis of the cyanopyridines has been studied thoroughly because of their value as intermediates in the preparation of pyridoxine and because of the interest in the alkaloid ricinine. 3-Cyanopyridines are usually obtained by condensation of 1,3-dicarbonyl compounds with cyanoacetamide (p. 469) or by some variation of this general reaction, whereas the 2- and 4-cyanopyridines in general are prepared directly from appropriate pyridine derivatives.

From Pyridine Compounds. The synthesis of 3-cyanopyridine from 3-bromopyridine is more or less typical of the replacement of a bromo group by a nitrile according to the Rosenmund-v. Braun synthesis. By heating a mixture of 3-bromopyridine with cuprous cyanide at 165–170° for 1 hr. and vacuum-distilling the crude product, McElvain and Goese [1] obtained a 50% yield of 3-cyanopyridine. Craig [2] found that 2-cyanopyridine was formed in 74% yield by essentially the same method, but a shorter heating time was required and it was necessary to work up the reaction mixture immediately to prevent loss of product as a result of polymer formation. Sodium cyanide cannot be substituted for cuprous cyanide in this reaction.[3] Since 2-bromopyridine is most conveniently prepared from 2-aminopyridine, this method is equivalent to the replacement of an amino group by a cyano group but by an indirect route. This is in contrast to the direct conversion of an amino group to a cyano group by the Sandmeyer method which is of universal applicability in the benzene series. In the pyridine series, the Sandmeyer procedure has been successfully applied only to 3-aminopyridine and its derivatives, and the reaction shows no significant deviation from the method in the benzene series.

The pyridinesulfonic acids are converted into the nitriles by fusion with potassium cyanide,[4,5] which presents still another method for the synthesis of pyridine nitriles. With very minor exceptions, the available pyridinesulfonic acids are the 3 or 5 compounds; this method is therefore practical only for introducing a cyano group into the β position of the ring. The yields are generally poor in the over-all preparation of cyanopyridines by this method.

Finally, the cyanopyridines can be prepared by the dehydration of the corresponding amides, usually with phosphorus pentoxide or thionyl chloride.[6,7] Since a large number of pyridine acids are available, this method renders potentially available an equally large number of nitriles. Adkins [8] found that a 40–45% yield of 3-cyanopyridine could be obtained directly from nicotinic acid by refluxing the acid in a solution of ammonium acetate in acetic acid and removing the water as formed.

1 McElvain and Goese, *J. Am. Chem. Soc.*, **63**, 2283 (1941).

2 Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).

3 Bystritskaya and Kirsanov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1101 (1940) [*C. A.*, **35**, 4023 (1941)].

4 McElvain and Goese, *J. Am. Chem. Soc.*, **65**, 2233 (1943).

5 Webb and Corwin, *J. Am. Chem. Soc.*, **66**, 1456 (1944).

6 Kuhn and Westphal, Ger. pat. 701,955 (Jan. 2, 1941) [*C. A.*, **35**, 7978 (1941)].

7 LaForge, *J. Am. Chem. Soc.*, **50**, 2477 (1928).

8 Adkins et al., *J. Am. Chem. Soc.*, **66**, 1293 (1944).

Reactions

The pyridine nitriles undergo the usual reactions of hydrolysis, alcoholysis, ammonolysis, and reduction, to give the respective amides and esters, imino ethers and esters, amidines,[9,10] and amines.[11] Special comment on most of these reactions in the pyridine series is unnecessary.

Some of the nitriles in the pyridine series are very resistant to hydrolysis.[12] This inert character can usually be attributed to a steric effect and is therefore comparable to that observed in benzene derivatives such as 2,6-dimethylbenzonitrile,[13,14] which is not appreciably hydrolyzed by boiling with potassium hydroxide even in amyl alcohol and is only partially converted into the amide with sulfuric acid.

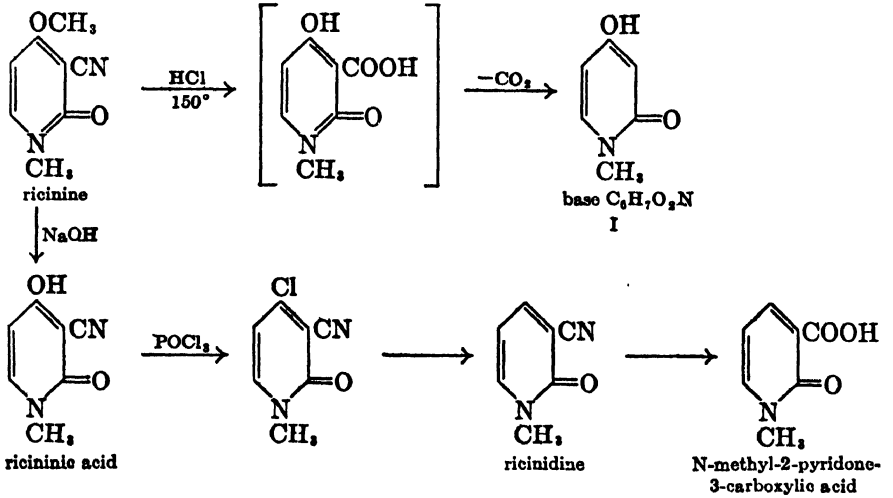
Ricinine

In 1864, Tyson isolated ricinine ($C_8H_8O_2N_2$) [15] as a neutral, optically inactive, white crystalline solid, m.p. 201.5°, from the oil of the castor bean. Its structure was deduced by subsequent workers and was finally proved in 1923 by the total synthesis of Späth and Koller which was based on the following observations.

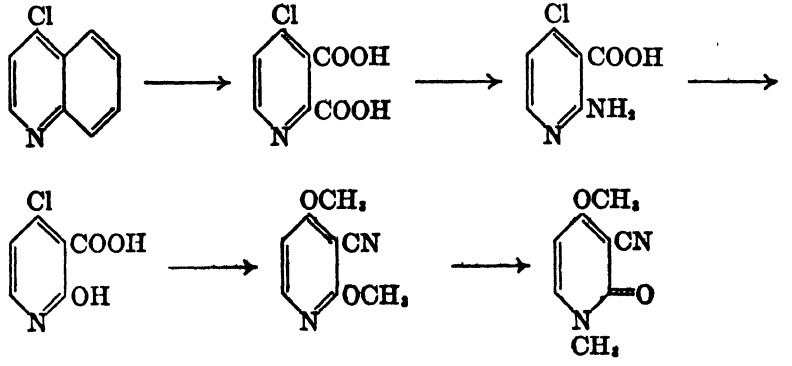
Distillation of ricinine with zinc dust gave pyridine. Hydrolysis with sodium hydroxide gave methyl alcohol and a compound which was named ricininic acid ($C_7H_6O_2N_2$); ricinine was decomposed by the action of hydrochloric acid at 150° into ammonium chloride, carbon dioxide, and a basic substance, $C_6H_7O_2N$. One of the carbon atoms in this base was found to be present as an N-methyl group, and the base was therefore postulated to be a hydroxy-N-methylpyridone. Synthesis established the structure of this substance as the N-methyl derivative of 2,4-dihydroxypyridine (I). The conversion of ricininic acid ($C_7H_6O_2N_2$) to ricinidine ($C_7H_6ON_2$) by treatment with phosphorus oxychloride and reductive cleavage of the halogen can be explained best by assuming that ricinine is a methyl ether and not a methyl ester, as at first supposed, and that the acid properties of rici-

9 Gregory, Holt, and Slack, *J. Chem. Soc.*, 87 (1944).
10 Barber and Slack, *J. Am. Chem. Soc.*, **66**, 1607 (1944).
11 Koltoff and Huntress, *J. Am. Chem. Soc.*, **63**, 490 (1941).
12 Reider and Elderfield, *J. Org. Chem.*, **7**, 286 (1942).
13 Berger and Olivier, *Rec. trav. chem.*, **46**, 600 (1927).
14 Olivier, *Rec. trav. chem.*, **48**, 568 (1929).
15 This and other pyridine alkaloids are discussed in detail in Henry, *The Plant Alkaloids*, 4th ed., Blakiston, Philadelphia, 1949.

ninic acid are due to a phenolic hydroxyl group instead of to a carboxylic acid. Ricinidine can be hydrolyzed to give first an amide and then an acid. This characteristic obviously indicates a nitrile group and was quite unexpected, since the occurrence of a free nitrile group in a naturally occurring compound is quite rare, amygdalin, the glucoside of benzaldehyde cyanohydrin, being the other well-known example. The position of the nitrile group was proved by synthesis of the possible hydrolysis products and demonstration that N-methyl-2-pyridone-3-carboxylic acid was identical to the acid obtained from ricinidine.

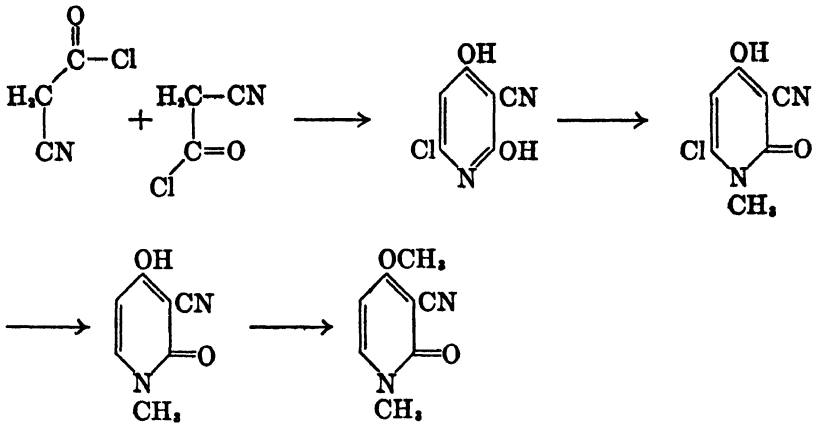


The structure of ricinine itself was confirmed by its total synthesis from 4-chloroquinoline by the series of steps briefly outlined below.[16]



16 Späth and Koller, *Ber.*, **56**, 880, 2454 (1923).

A much simpler synthesis has been devised by Schroeter [17] and is based on 6-chloro-2,4-dihydroxy-3-cyanopyridine (chloronorricinine) obtained from the spontaneous polymerization of cyanoacetyl chloride.



PYRIDINECARBOXYLIC ACIDS

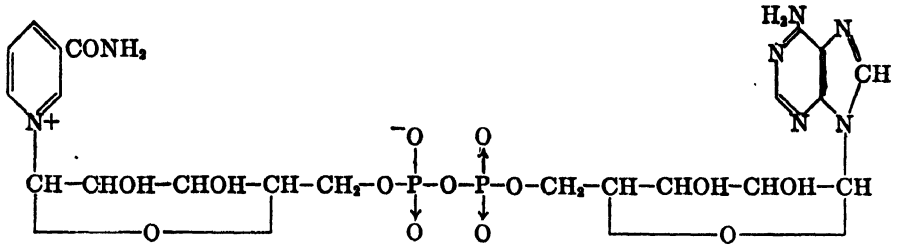
Introduction

All nineteen possible unsubstituted pyridinecarboxylic acids are known. They have been synthesized (1) by the general methods for the preparation of pyridine compounds from aliphatic substances, (2) by oxidation of various substituted pyridines, (3) by decarboxylation of pyridinepolycarboxylic acids, (4) by hydrolysis of cyanopyridines, and (5) by special isolated methods such as carbonation of a metallopyridine compound, Kolbe-type synthesis, and the Wibaut-Arens method.

Nicotinic acid has been the most widely studied of the pyridine acids because of its function as a vitamin in human metabolism. Funk [1] and Suzuki [2] independently isolated nicotinic acid from rice bran and yeast in their search for the substance, a deficiency of which was responsible for the disease, beriberi. Nicotinic acid did not, however, prove to be the active factor, and the significance of this discovery was not completely realized until 1937 when Elvehjem and co-workers [3] conclusively proved that nicotinic acid would prevent

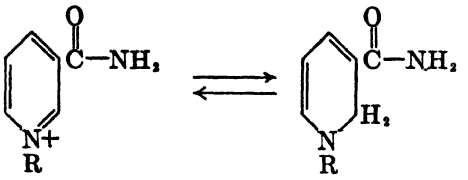
17 Schroeter et al., *Ber.*, **65**, 432 (1932); **71**, 671 (1938).
1 Funk, *J. Physiol.*, **46**, 173 (1913).
2 Suzuki et al., *Biochem. Z.*, **43**, 89, 99 (1912).
3 Elvehjem et al., *J. Am. Chem. Soc.*, **59**, 1767 (1937).

black tongue, which is the disease of dogs comparable to human pellagra. It was soon shown that nicotinic acid or its amide was a true vitamin and would cure human pellagra. It has since been determined that the nicotinic acid functions in the body as a portion of coenzymes I and II (diphosphopyridinenucleotide and triphosphopyridinenucleotide) which serve the physiological function of promoting cellular oxidation.[4] Coenzyme I serves as a reversible reduction-oxidation sys-



Coenzyme I

tem, presumably by conversion to a dihydropyridine derivative as indicated by the following equations, where R is the phosphonucleotide moiety. Karrer and Blumer[5] have accomplished the synthesis of the



parent N-methyldihydronicotinic amide where R = CH_3 by treating the methiodide of nicotinamide with sodium carbonate solution in the cold, followed by reduction with sodium hydrosulfite.

The isomeric picolinic and isonicotinic acids and their derivatives have been studied by Elvehjem[6] for their antipellagra activity, and it was found that activity was limited to the derivatives of nicotinic acid.

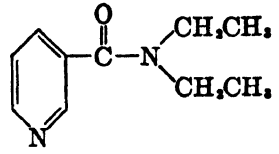
Since that time, the production of nicotinic acid has changed from that of a rare organic compound to an important item of the chemical industry. The production of nicotinic acid as such or in the form of its amide approximated one million pounds in 1945, and the price had fallen to approximately two dollars per pound in that year.

[4] For a review of the literature on coenzymes I and II and the evidence for the structures which are given below, see Rosenberg, *Chemistry and Physiology of the Vitamins*, Interscience Publishers, New York, 1945.

[5] Karrer and Blumer, *Helv. Chim. Acta*, **30**, 1157 (1947).

[6] Elvehjem, *Physiol. Rev.*, **20**, 249 (1940).

An important derivative of nicotinic acid is the N,N-diethylamide, Coramine (I), which possesses a powerful stimulant action on the cen-



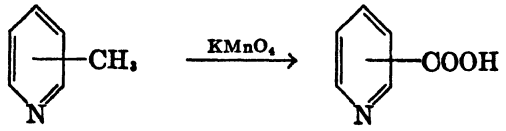
I

tral nervous system and has therefore found use in medicine as a respiratory stimulant. It is especially valuable for the treatment of an overdose of a central nervous system depressant such as the barbiturates and morphine and in the "shock therapy" of schizophrenia. Twenty-two thousand pounds of N,N'-diethylnicotinamide were produced in 1945.

Preparation

The general methods of synthesis of the pyridinecarboxylic acids from aliphatic substances have already been outlined (pp. 462–470). A large number of these methods, such as the Hantzsch synthesis, lead to pyridinecarboxylic esters, and therefore many substituted alkyl, aryl, hydroxy, and cyano carboxylic acids are available by such methods.

Oxidative Methods. The simple pyridinemonocarboxylic acids cannot, however, be made directly by such ring closures. However, they are readily obtained by oxidative methods such as, for instance, the oxidation of the picolines.[7] Alkaline permanganate oxidation of α-



picoline gives picolinic acid (50% yield), of β-picoline gives nicotinic acid (60% yield),[8–10] and of γ-picoline gives isonicotinic acid (65% yield).[11–13] Since the picolines are commercially available from coal tar, this is an excellent method for the synthesis of picolinic, nicotinic,

7 Singer and McElvain, *Org. Syntheses*, **20**, 79 (1940).
8 Woodward, Badgett, and Willaman, *Ind. Eng. Chem.*, **36**, 540 (1944).
9 Kaufman, *J. Am. Chem. Soc.*, **67**, 497 (1945).
10 Kulka, *J. Am. Chem. Soc.*, **68**, 2472 (1946).
11 Koelsch, *J. Am. Chem. Soc.*, **65**, 2464 (1943).
12 Burrus and Powell, *J. Am. Chem. Soc.*, **67**, 1468 (1945).
13 Leis and Curran, *J. Am.. Chem. Soc.*, **67**, 79 (1945).

and isonicotinic acids, and the three pyridinemonocarboxylic acids are readily available starting materials for further syntheses. Nicotinic acid, however, can be obtained in equally good yields and as cheaply by the oxidation of by-product nicotine from the tobacco industry.[14,15] Commercially it is obtained by the oxidation of quinoline and decarboxylation of the resulting quinolinic acid.[10,15,16] The method employing the oxidation of the picolines to the corresponding pyridinemonocarboxylic acids is completely general and quite comparable to the corresponding oxidation of such a compound as toluene to benzoic acid in the benzene series. Because of the water solubility of picolines, the oxidation reaction is homogeneous in contrast to the oxidation of toluene. In addition, the methods of isolating the respective oxidation products differ considerably, since the pyridinecarboxylic acids are essentially amphoteric and dissolve in acidic as well as in basic solution.

Picolinic acid is the most soluble of the three pyridinemonocarboxylic acids, being approximately one hundred times more soluble than isonicotinic acid. It is extremely soluble in either acid or in basic solution, and it is therefore difficult to separate from contaminating salts. In the presence of inorganic impurities, its isolation is best accomplished as the copper salt, followed by liberation with hydrogen sulfide, a typical method employed in the study of amino acids. However, isonicotinic acid is only very slightly soluble in cold water, and, if the *p*H of the solution is adjusted properly, the acid can be precipitated from solution without appreciable loss. Nicotinic acid is intermediate in its solubility and has been isolated either as its insoluble copper salt, the free base, or its hydrochloride. Often it is the ester which is desired, and then it is usually more convenient to convert the crude acid to the ester and purify by distillation.

Not only are alkylpyridines, but also arylpyridines and benzopyridines, oxidized to pyridinecarboxylic acids in good yields. The oxidation of phenylpyridines, quinoline, and isoquinoline has been mentioned in connection with the comparative stabilities of the pyridine and benzene rings to oxidation (pp. 422–423). In spite of the findings of Chichibabin that the pyridine ring in 2-phenylpyridine is more susceptible to oxidation by permanganate in basic solution than in acid,

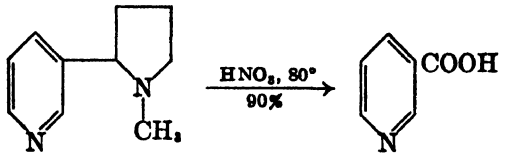
14 McElvain, *Org. Syntheses, Coll. Vol.* **1**, 385 (1941).

15 Stix and Bulgatsch, *Ber.*, **65**, 11 (1932).

16 Van de Kamp and Sletzinger, U. S. pat. 2,392,437 (Jan. 8, 1946) [*C. A.*, **40**, 2473 (1946)].

most oxidations of the pyridine homologs to the pyridinecarboxylic acids are conducted in basic solution.

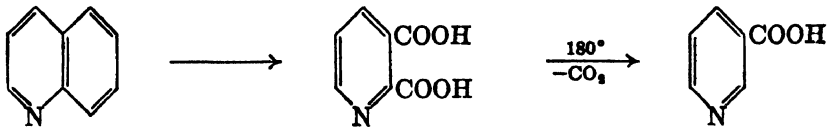
As illustrated by the oxidation of nicotine (II) to nicotinic acid (III), many alkaloids of the pyridine series are oxidized to pyridine-



II III

carboxylic acids. In the oxidation of the alkaloids, nitric acid is often the oxidizing agent, particularly when the substituent on the pyridine ring contains a nitrogen atom, is oxygenated, or is unsaturated. Only for the synthesis of nicotinic acid by the oxidation of nicotine is the method of preparative importance. Such oxidations, however, have been of great value in structural studies, especially in the alkaloid field.

Decarboxylation. One very useful synthesis of pyridine acids (and pyridine compounds in general) involves the decarboxylation of pyridinepolycarboxylic acids. Since the 2- and 4-carboxylic acid groups are most easily lost, this process ultimately produces only nicotinic acid derivatives. This is illustrated by the oxidation of quinoline (IV) to quinolinic acid (V), followed by its facile decarboxylation



IV V VI

to nicotinic acid (VI). The ease with which quinolinic acid loses carbon dioxide should be contrasted to the stability of phthalic acid which, if heated above the melting point (184°), loses water to give the anhydride instead of decarboxylating.

Because of its ready availability by the oxidation of coal-tar quinoline, quinolinic acid is the best known of the pyridinedicarboxylic acids. When commercial quinoline is oxidized with alkaline permanganate, a 60–70% yield of quinolinic acid results. If calcium hydroxide is the base, the oxalic acid produced from the oxidation of the remainder of the benzene ring is precipitated as calcium oxalate. The oxidation has likewise been conducted in concentrated sulfuric acid at

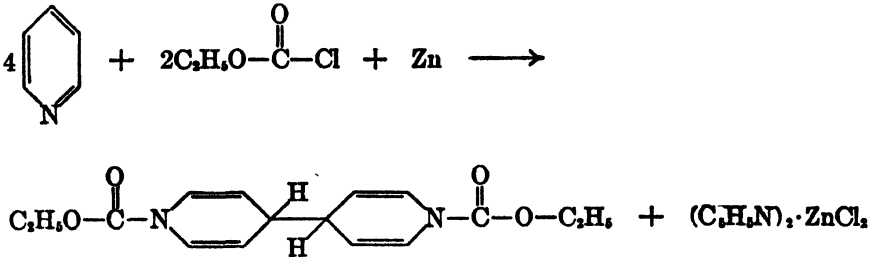
temperatures of 165–175° with manganese dioxide.[16] The presence of an easily oxidized group in the benzene portion of the quinoline ring greatly facilitates the oxidation, and 8-hydroxyquinoline can thus be oxidized with concentrated nitric acid to give quinolinic acid in 77–85% yield.[17]

If an ester of nicotinic acid is desired, the very convenient preparation, worked out by Kaufman,[9] in which quinoline is simultaneously oxidized and decarboxylated in an excess of sulfuric acid with selenium metal when heated to a maximum of 300°, is useful. Under these conditions, water and carbon dioxide are rapidly evolved, and the cooled sulfuric acid solution of nicotinic acid is esterified directly by being refluxed with an alcohol such as methanol for 6 hr. The reaction mixture is poured into ice and made basic with ammonium hydroxide, and the ester is ether-extracted and vacuum-distilled. In this way, the methyl, ethyl, and propyl esters of nicotinic acid were obtained from quinoline in 60%, 55%, and 57% yields, respectively.

Hydrolysis of Cyanopyridines. The cyanopyridines are still another potential source of pyridinecarboxylic acids, since all but a very few resistant ones [18] can be readily hydrolyzed to the corresponding acids.

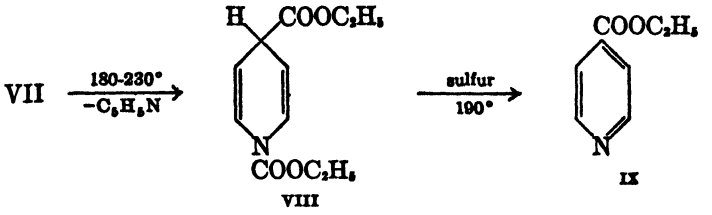
The Kolbe Synthesis. The Kolbe salicylic acid synthesis has been applied successfully to the pyridine series, as shown by the conversion of 2-hydroxypyridine to 2-hydroxypyridine-5-carboxylic acid when the compound is heated with potassium hydroxide under 20 atm. pressure of carbon dioxide at 180–200°.[19]

Method of Arens and Wibaut. Finally, Arens and Wibaut have discovered a unique method for obtaining ethyl isonicotinate.[20] Pyridine when heated with zinc dust and ethyl chloroformate, gave a 4,4′-tetrahydrodipyridyl derivative (VII) which, when heated further



VII

17 Sucharda, *Ber.*, **58**, 1728 (1925).
18 Reider and Elderfield, *J. Org. Chem.*, **7**, 286 (1942).
19 Chichibabin and Kirssanow, *Ber.*, **57**, 1161 (1924).
20 Van Dorp and Arens, *Rec. trav. chim.*, **66**, 189 (1947).

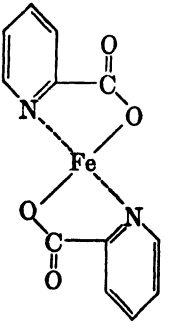


was converted to the ethyl ester of 1,4-dihydro-N-carbethoxyisonicotinic acid (VIII). Dehydrogenation with sulfur gave the true pyridine derivative (IX) in 17% yield based on pyridine.

Reactions

The pyridinecarboxylic acids behave as typical aromatic acids. The greatest deviation from true aromatic character is in the ease of decarboxylation. The acids form esters, anhydrides, acid chlorides, and amides in the expected fashion, and the acid derivatives undergo the typical reactions as illustrated by the Hofmann rearrangement of the amide to the amine or dehydration to the nitrile. In a few special instances, owing to some abnormal factor such as steric influence, the expected reaction does not take place.

Complex Formation. Because of their ability to form colored complexes with ferrous and cupric ions, the α-pyridinecarboxylic acids can be readily distinguished from either β or γ derivatives. The nature of the colored complex is probably as indicated in X. Only in the α



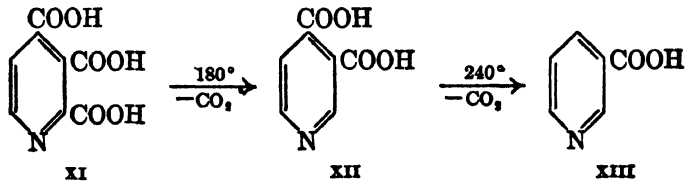
X

acid does the spatial arrangement allow both a primary bond to the carboxylic acid group and a coordinate link to the ring nitrogen.[21]

21 Ley, Schwarte, and Münnich, *Ber.*, **57**, 349 (1924).

This qualitative test is therefore a valuable tool, not only in the pyridine series but in the quinoline series as well.

Decarboxylation. In general, decarboxylation in the pyridine series proceeds with much greater facility than in the benzene series. The ease of decarboxylation of the pyridine acids follows the same order as the dissociation constants, decreasing in the order: picolinic, isonicotinic, and nicotinic. This is the order of increasing dissociation constants for these acids and is a direct result of the decreased electron densities at the 2 and 4 positions in the ring. The relative ease of decarboxylation is illustrated by the products obtained when quinolinic acid and cinchomeronic acid are heated. From both acids, nicotinic acid is the major product. In the case of pyridine-2,3,4-tricarboxylic acid (XI), the stepwise loss of carbon dioxide can be accomplished to give first cinchomeronic acid (XII) and finally



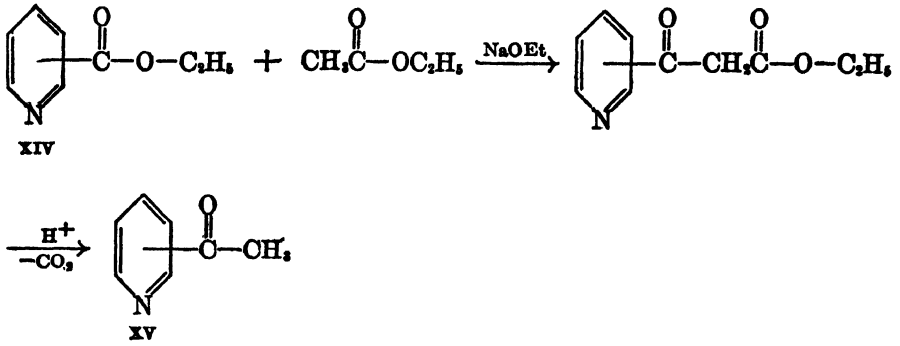
XI XII XIII

nicotinic acid (XIII) mixed with small amounts of isonicotinic acid. It is thus apparent that the α-carboxylic acid group is lost with much greater ease than either the β or γ group, since there is no indication that a mixture is formed in the first reaction. These observations concerning the relative ease of decarboxylation are confirmed in similar reactions with pyridine-2,3,5,6-tetracarboxylic acid and pyridine-2,4-dicarboxylic acid. This point is discussed in greater detail in Vol. 3 of this series in connection with the quinoline acids.

Esterification. Acid-catalyzed esterification of the three pyridinemonocarboxylic acids is more difficult than expected from the analogous reaction with benzoic acid. Of the three acids, picolinic acid is the most resistant, but all can be esterified in good yields with concentrated sulfuric acid and in excellent yields via the acid chlorides. The acid chlorides should be used in the form of their hydrochlorides, however, and must not be stored for any length of time since they hydrolyze readily and the yields suffer accordingly.

Ester Condensation. One of the more important chemical reactions of the esters of the pyridinecarboxylic acids is the ester condensation in the presence of sodium ethoxide, hydride, or amide to give a β-

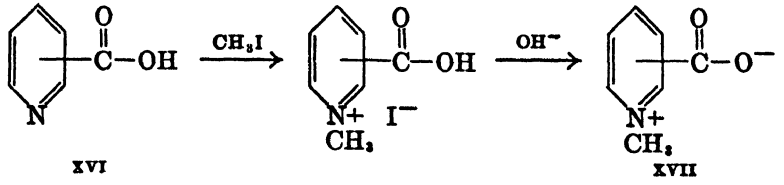
keto ester which can be hydrolyzed and decarboxylated to the pyridyl methyl ketone [22] (XIV–XV). The synthesis gives better yields than



XIV XV

the corresponding reaction in the benzene series and is of broad applicability. Since the introduction of an acetyl group by way of the Friedel-Crafts reaction has not been accomplished in the pyridine series, such condensations are the most important method for the synthesis of these compounds and are discussed further on p. 590.

Betaine Formation. A characteristic property of the pyridinecarboxylic acids which is connected with their fundamental amino acid nature is the formation of betaines when the acids are treated with alkyl halides in basic solution (XVI–XVII). The best known of such



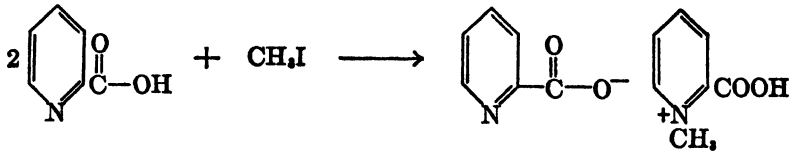
XVI XVII

betaines is trigonelline which can be synthesized from nicotinic acid by the action of methyl iodide and a base. Trigonelline also occurs widely in nature in such plants as wheat, oats, hemp, and the coffee bean and is known to be one of the forms in which nicotinic acid is excreted by dogs.[23] The betaines are characteristically neutral, high-melting solids which are very water soluble but only slightly soluble in organic solvents.

An abnormal reaction is sometimes obtained on methylation of a pyridinecarboxylic acid. When picolinic acid is heated with an excess

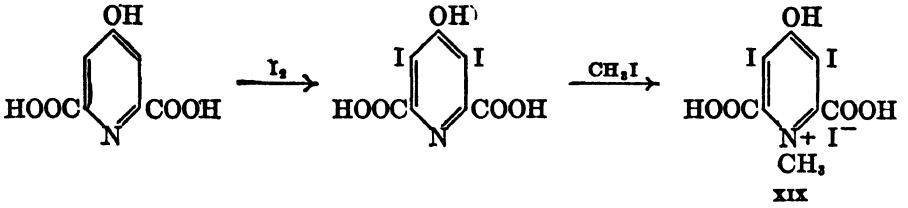
22 Koelsch, *J. Org. Chem.*, **10**, 34 (1945).
23 Sendju, *J. Biochem. (Japan)*, **6**, 161 (1926).

of methyl iodide at 100° in a sealed tube, an "intermolecular betaine" (XVIII) is formed,[24] as indicated. A similar material is obtained as a by-product in the methylation of isonicotinic acid.[24]



XVIII

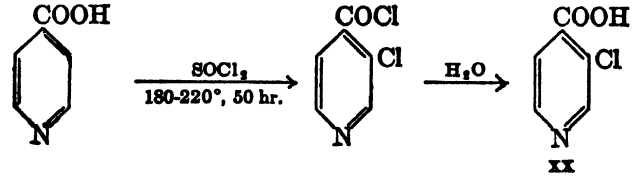
Pyridine-2,6-dicarboxylic acid apparently fails to form a betaine, since treatment with methyl iodide in methanol solution simply gives the dimethyl ester. The action of methyl iodide on the sodium or silver salts of pyridine-2,6-dicarboxylic acid gives the same result. This is not general, however, since N methylation of a substituted pyridine-2,6-dicarboxylic acid is possible, as illustrated by the synthesis of N-methyl-3,5-diiodochelidamic acid (XIX).[25] The product,



XIX

which has been known as Uroselectan B, is rapidly excreted in the urine and has been used as an opaque material for urological x-ray studies.

Reactions with Thionyl Chloride. One of the very unexpected and apparently quite general reactions of the pyridinecarboxylic acids occurs with thionyl chloride at high temperature, and goes beyond the formation of the acid chloride, to give substitution by chlorine. A typical example is the formation of 3-chloropyridine-4-carboxylic acid (XX).[26] In spite of the fact that the yields are generally poor, it is



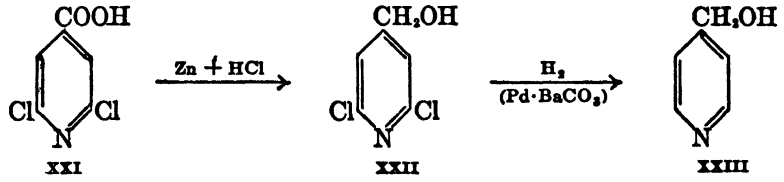
XX

[24] Turnau, *Monatsh.*, **26**, 537 (1905).
[25] Dohrn and Diedrich, *Ann.*, **494**, 284 (1932).
[26] Meyer and Graf, *Ber.*, **61**, 2202 (1928).

nevertheless surprising that any substitution occurs, for the pyridine nucleus is relatively inert to electrophilic attack, and the *m*-directing carboxylic acid would deactivate the ring even further for such substitution. When the hydrochloride of picolinic acid was refluxed with thionyl chloride for 10 days, Graf [27] obtained the following substances upon hydrolysis: 4-chloropicolinic acid (15%), 4,6-dichloropicolinic acid (41.5%), and 4,5,6-trichloropicolinic acid (10%).

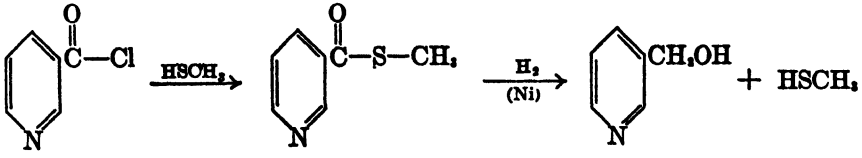
When heated with thionyl chloride for 50 hr. at 130°, nicotinic acid hydrochloride is reported to give 3-chloropyridine-5-carboxylic acid,[27] and, at 150°, 2,3-dichloropyridine-5-carboxylic acid. The compounds have well-established structures and have been synthesized by other methods.

Reduction. Although pyridine acids do not ordinarily undergo reduction, Rabe [28] has reported several cases in which an acid has been converted into an alcohol, although in poor yield. Treatment of 2,6-dichloroisonicotinic acid (XXI) with zinc and 30% hydrochloric acid gave a 36% yield of 2,6-dichloro-4-methylolpyridine (XXII). (XXII) was further reduced to 4-methylolpyridine (XXIII) in 71% yield to confirm its structure.



XXI XXII XXIII

A method [29] for the reduction of acids to alcohols under mild conditions, by conversion to the ester of the thiolic acid followed by desulfurization with Raney nickel catalyst charged with hydrogen, has been applied to nicotinic acid successfully. The Bouveault-Blanc reduc-



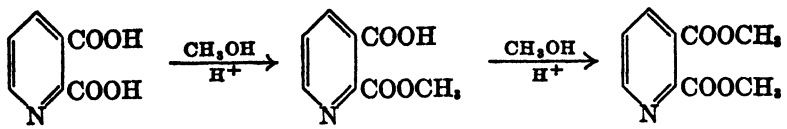
tion of the pyridine esters cannot be employed since the ring is also reduced.

27 Graf, *J. prakt. Chem.*, [2] **133**, 36 (1932); *Ber.*, **64**, 21 (1931).
28 Rabe et al., *J. prakt. Chem.* [2] **151**, 65 (1938).
29 Jeger et al., *Helv. Chim. Acta*, **29**, 684 (1946).

Substituted Pyridinecarboxylic Acids

It is beyond the purpose of this treatment to consider the syntheses and properties of the numerous individual alkyl-, aryl-, chloro-, hydroxy-, and amino-carboxylic and dicarboxylic acids which have been made and studied, except where the over-all reactions of the molecule are not those that would be predicted by the summation of the individual reactions of the groups. In general, the reactions which may be considered as abnormal involve either *o*-substituted groups (which give unique reactions because of chelation, true ring formation, or steric hindrance) or the interaction of groups (which may result in enhanced activity of certain groups within the molecule). The compounds in the pyridine series show characteristics demonstrated by the analogous compounds of benzene, and it is therefore found that anthranilic acid, salicylic acid, phthalic acid, *o*-chlorobenzoic acid, *o*-aminophenol, and such compounds as 2,4-dinitrochlorobenzene all have their counterparts in the pyridine series. Because of the nitrogen atom in the heterocyclic nucleus, there is always more than one such analog possible.

Dicarboxylic Acids. The methods of synthesis and the reactions of the 2,4-, 2,5-, 2,6-, and 3,5-dicarboxylic acids in which the carboxylic acid groups are not on adjacent carbon atoms are readily predictable on the basis of the conventional reactions in the benzene series and on the basis of the decarboxylation, etc., of pyridinecarboxylic acids. The properties and reactions of pyridine-2,3-dicarboxylic acid (quinolinic) and pyridine-3,4-dicarboxylic acid (cinchomeronic) in which the acid groups are *ortho* to each other are not so readily predicted. This is well illustrated by the esterification experiments with the respective acids. Esterification of quinolinic acid (XXIV) with methanol and sulfuric acid catalyst is reported to give[30] quinolinic acid-2-methyl

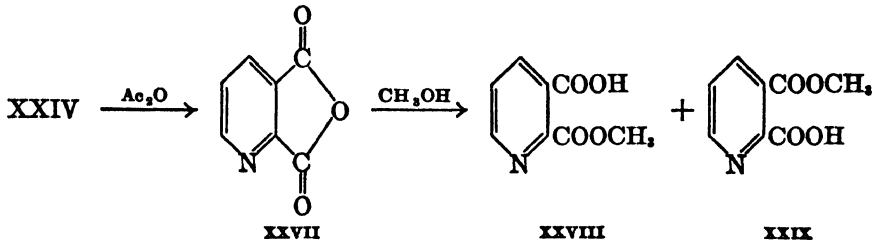


XXIV XXV XXVI

ester (XXV). None of the isomeric quinolinic acid-3-methyl ester has been reported from this reaction. Since the properties of these compounds differ considerably, any significant amount of the 3 ester

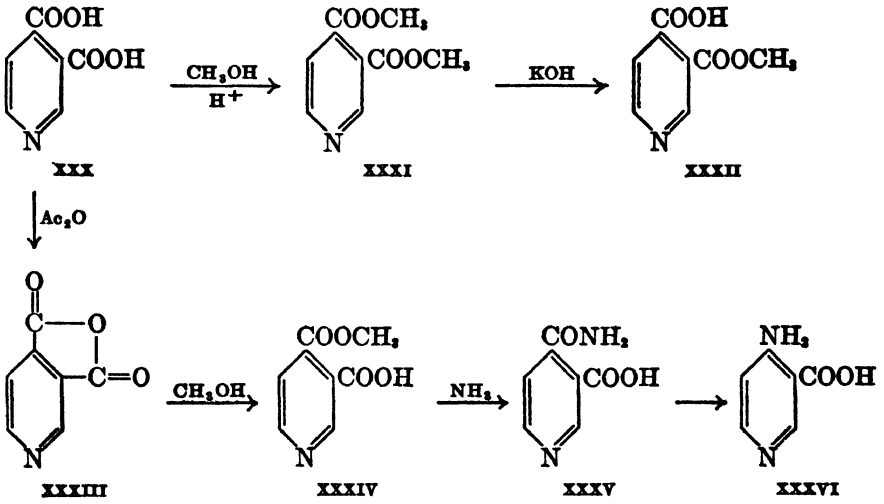
[30] Kirpal, *Monatsh.*, **20**, 766 (1899).

should be readily detected. Under more strenuous conditions, e.g., a large excess of the alcohol and continuous passage of dry hydrogen chloride, the dimethyl (XXVI), diethyl, and dipropyl esters have been prepared.[31] It is interesting that treatment of the anhydride of quinolinic acid (XXVII) (prepared by refluxing quinolinic acid with acetic anhydride or thionyl chloride) with methanol, but not with sodium methoxide, gives a mixture of quinolinic acid-3-methyl ester (XXIX) and quinolinic acid-2-methyl ester (XXVIII), in which the latter is reported to predominate.



XXVII XXVIII XXIX

Similar reactions are observed with cinchomeronic acid (XXX) obtained from the oxidation of isoquinoline. Acid-catalyzed esterification with an excess of methanol gives the pyridine-3,4-dimethyl ester (XXXI) which can be half-hydrolyzed to give the half ester (XXXII).



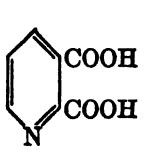
XXX XXXI XXXII XXXIII XXXIV XXXV XXXVI

If cinchomeronic acid anhydride (XXXIII) is treated with methanol, the half ester (XXXIV) is obtained. The structures of both these

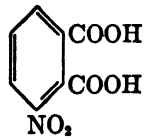
[31] Engler, *Ber.*, **27**, 1784 (1894).

esters are established in part by their conversion with ammonia to the corresponding amide (XXXV), followed by Hofmann degradation to the amine (XXXVI), as indicated with the 4 ester.[32]

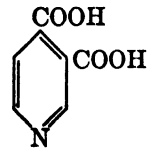
It is interesting to compare the reactions of quinolinic (XXIV) and cinchomeronic (XXX) acids and anhydrides with the analogous nitrophthalic acids and anhydrides. From the standpoint of the charge distribution on the rings, 3-nitrophthalic (XXXVII) is analogous to



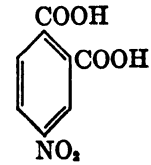
XXIV



XXXVII

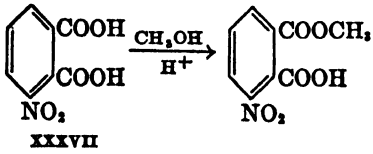


XXX

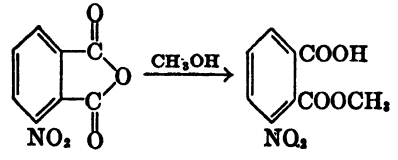


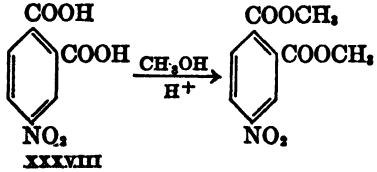
XXXVIII

quinolinic acid and 4-nitrophthalic (XXXVIII) is analogous to cinchomeronic acid. A certain steric effect will exist in the *o*-nitrophthalic acid derivative which is not found in the quinolinic acid derivative. If this is a valid comparison, it should carry over to the reactions of these compounds. The reactions of the nitrophthalic acids and anhydrides with methyl alcohol are outlined below. As seen from

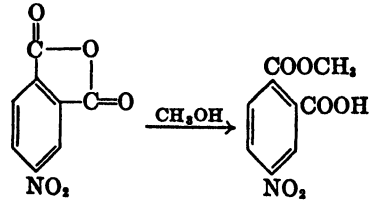


XXXVII





XXXVIII

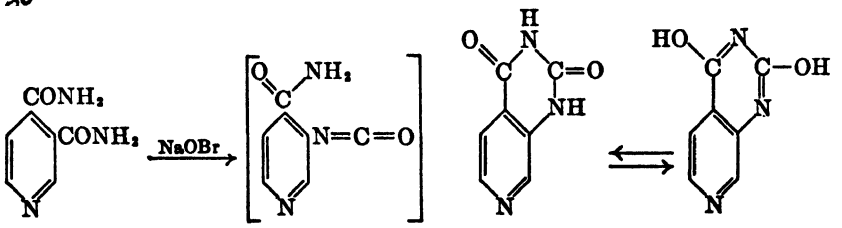


the equations, the agreement from the widely scattered reports in the literature is fair but by no means perfect, and the experimental reports in the literature must be verified before reliable theoretical conclusions can be drawn. In the four examples given, there is positive correlation in all but the first, the acid-catalyzed esterification of 3-nitrophthalic acid, and here there exists the maximum opportunity

[32] Kirpal, *Monatsh.*, **23**, 929 (1902).

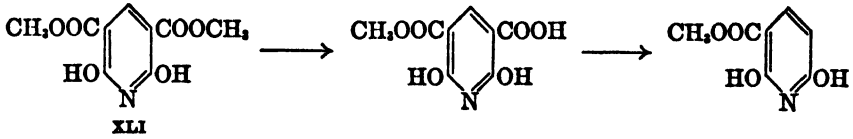
for an anomalous reaction because of the *o* positions of the nitro and carboxylic acid groups.

The diamide of the cinchomeronic acid does not give the expected diamine in the Hofmann reaction with excess sodium hypobromite but, in common with many such *o*-carboxylic acid amides, forms a fused dihydroxypyrimidine derivative. The amide group in the 3 position apparently undergoes the rearrangement most readily, giving the isocyanate intermediate (XXXIX) which spontaneously undergoes ring closure to the compound known as dioxycopazoline (XL).[33] Reider



and Elderfield [18] have observed the formation of the 6-methyl homolog of XL, in treatment of 3-cyano-6-methylisonicotinic acid with slightly more than 2 moles of sodium hypochlorite solution.

It is noteworthy that a pyridinedicarboxylic acid ester such as XLI can be half hydrolyzed and then be decarboxylated in order to remove

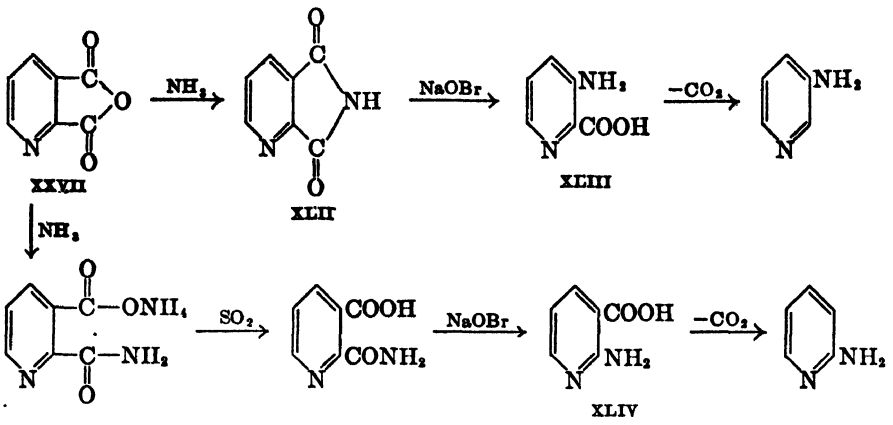


only one of the carboxyl groups, as indicated.[34] Of course, both carboxylic acid groups may be removed by complete hydrolysis and decarboxylation. The decarboxylation of nicotinic acid is the most difficult of the three pyridinemonocarboxylic acids, and yet the half ester of XLI loses carbon dioxide readily. This, however, is in accord with the great ease of decarboxylation of resorcinillic acid (2,4-dihydroxybenzoic acid) which is the benzene analog.

Aminocarboxylic Acids. The manner in which the two phthalimide analogs of the pyridine series react towards sodium hypobromite in the Hofmann reaction is worthy of some attention. Quinolinic acid imide

[33] Gabriel and Colman, *Ber.*, **35**, 2831 (1902).
[34] Errera, *Ber.*, **31**, 1241 (1898).

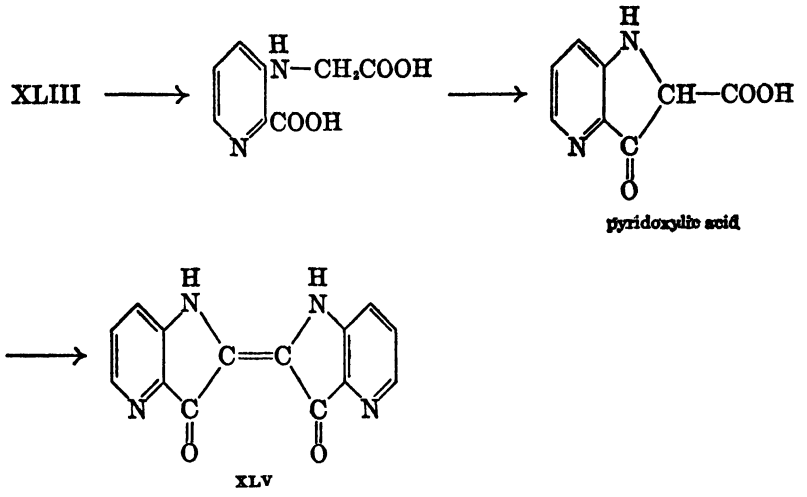
(XLII) can be made from quinolinic acid, either by conversion to the anhydride (XXVII) with acetic anhydride followed by treatment



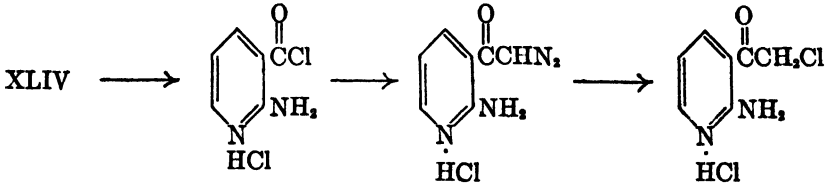
with ammonia, or by conversion to the diamide which in turn loses ammonia spontaneously when heated above its melting point.[31,35] The imide (XLII) gives a 67% yield of 3-aminopyridine-2-carboxylic acid (XLIII) in the Hofmann reaction.[17,36] Its structure is shown by the formation of 3-aminopyridine when it is heated above its melting point. Since quinolinic anhydride on treatment with an excess of dry ammonia in dry benzene gives the ammonium salt of pyridine-2-carboxamide-3-carboxylic acid, it is possible to obtain the isomeric 2-aminonicotinic acid (XLIV) from the same source by a Hofmann reaction.[37]

It is quite interesting that, of the two compounds, XLIII and XLIV, which are analogous to anthranilic acid, only the 3-aminopicolinic acid, which contains the characteristically aromatic amino group, will give an indigo-type dye (XLV) on treatment with chloroacetic acid and potassium hydroxide, followed by decarboxylation and air oxidation of the resultant pyridoxylic acid.[17] The isomeric derivatives of cinchomeronic acid undergo analogous reactions. There is complete agreement between the Hofmann reactions of the pyridine analogs of phthalimide and the corresponding nitrophthalimides,[17,38] which again indicates the value of the generalization that pyridine and its derivatives react in a manner similar to nitrobenzene and the corresponding nitrobenzene derivatives.

35 Philips, *Ber.*, **27**, 839 (1894).
36 Kirpal, *Monatsh.*, **29**, 227 (1908).
37 Philips, *Ann.*, **288**, 253 (1895).



The relatively inert nature of the amino group in 2-aminonicotinic acid is illustrated by the normal transformation of the carboxyl group in the diazomethane reaction.[38] Such reactions, of course, would not



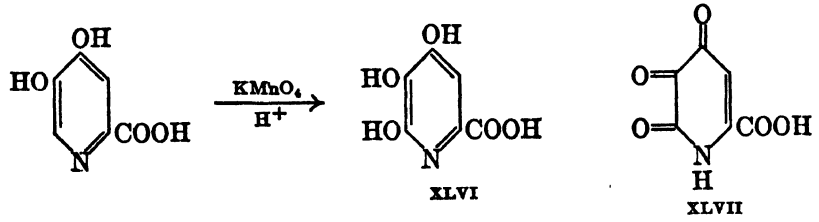
be successful with anthranilic acid because of the greater reactivity of the amino group in the benzene ring.

2-Aminopyridine-5-carboxylic acid and 2-aminopyridine-3-carboxylic acid both react with nitric acid as expected, first giving the 2-nitraminopyridine derivatives which, when warmed to 100° in sulfuric acid, are converted into 2-amino-3-nitropyridine-5-carboxylic acid and 2-amino-5-nitropyridine-3-carboxylic acid, respectively.[39] These substitution reactions take place in good yield in spite of the presence of the deactivating carboxyl acid group, the effects of which are more than overcome by the amino group. Some pyridinecarboxylic amides do not undergo a normal Hofmann reaction; for instance, 2,6-diaminopyridine-4-carboxylic acid amide with sodium hypobromite gives only a bromine-containing compound and no 2,4,6-triaminopyridine.[40]

38 Mlescher and Kägi, *Helv. Chim. Acta*, **24**, 1471 (1941).
39 Räth and Prange, *Ann.*, **467**, 1 (1928).
40 Meyer and v. Beck, *Monatsh.*, **36**, 731 (1915).

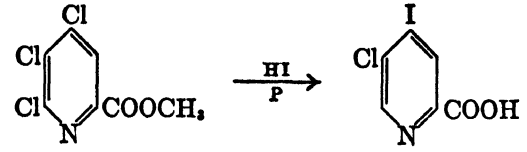
Hydroxycarboxylic Acids. Although several pyridine compounds which are analogous to salicylic acid and its derivatives such as aspirin have been prepared, there is no published information to indicate that these compounds have physiological activities comparable to those of the benzene analogs.[41] A rather large number of N-substituted 2-pyridone-3-carboxylic acid derivatives such as N-β-diethylaminoethyl-2-pyridone-3-carboxylic acid amide have been described [42,43] and are claimed to be active antiparasitic agents.

An interesting reaction of one of the hydroxy acids—3,4-dihydroxypyridine-6-carboxylic acid—is its oxidation by permanganate to a trihydroxy compound which apparently has structure XLVI.[44] This can in turn be oxidized further by nitric acid to give a carboxylic acid derivative (XLVII) of pyromecazone.[45]



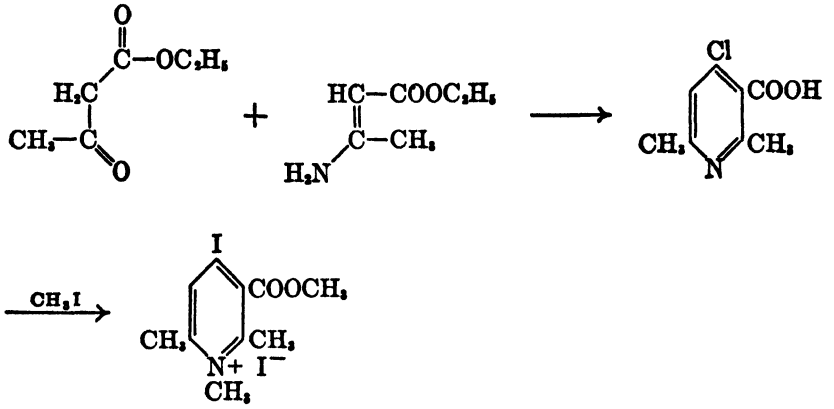
XLVI XLVII

Other Carboxylic Acids. A halogen substituted in the 2 or 4 position of a pyridinecarboxylic acid may be replaced by iodine in various reactions, as indicated in the following example.



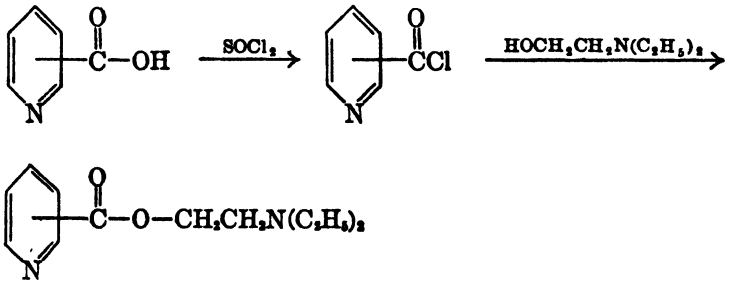
This unexpected replacement of a chlorine in the 4 position also takes place in the following methylation reaction,[46,47] in which 2,6-dimethyl-4-chloronicotinic acid (obtainable in fair yield by treatment of a mixture of ethyl acetoacetate and ethyl β-aminocrotonate with phosphorus oxychloride) is methylated with methyl iodide. A similar example was

41 Fibel and Spoerri, *J. Am. Chem. Soc.*, **70**, 3908 (1948).
42 Miescher and Urech, U. S. pat. 1,881,236 (Oct. 4, 1933) [*C. A.*, **27**, 1096 (1933)].
43 Ger. pat. 551,029 (May 30, 1932) [*C. A.*, **26**, 4343 (1932)].
44 Reibstein, *J. prakt. Chem.*, [2] **24**, 286 (1881); *Ber.*, **14**, 2692 (1881).
45 Ost, *J. prakt. Chem.*, [2] **27**, 257 (1883).
46 Michaelis and Hanisch, *Ber.*, **35**, 3156 (1902).
47 Michaelis, *Ann.*, **366**, 324 (1909).



encountered by Graf [48] in his extensive studies of the halogenated pyridinecarboxylic acids.

Several studies of the basic esters of pyridine analogs of the local anesthetics of the benzene series have been reported.[49-54] These have been made by the same methods as were employed in the benzene series. Of the three isomers of this type, only the nicotinic acid derivative



was reported to show slight local anesthetic activity,[53] and this report was not confirmed by other investigations.[52] On the other hand, a report of 2-alkoxy derivatives of basic amides and esters of isonicotinic acid,[51] which may be considered analogous to nupercaine, the diethylaminoethyl amide of 2-butoxyquinoline-4-carboxylic acid, indicated

48 Graf, *J. prakt. Chem.*, [2] **148**, 13 (1937).

49 Ingersoll and Robbins, *J. Am. Chem. Soc.*, **48**, 2449 (1926).

50 Hodnett and Stewart, *J. Am. Chem. Soc.*, **65**, 254 (1943).

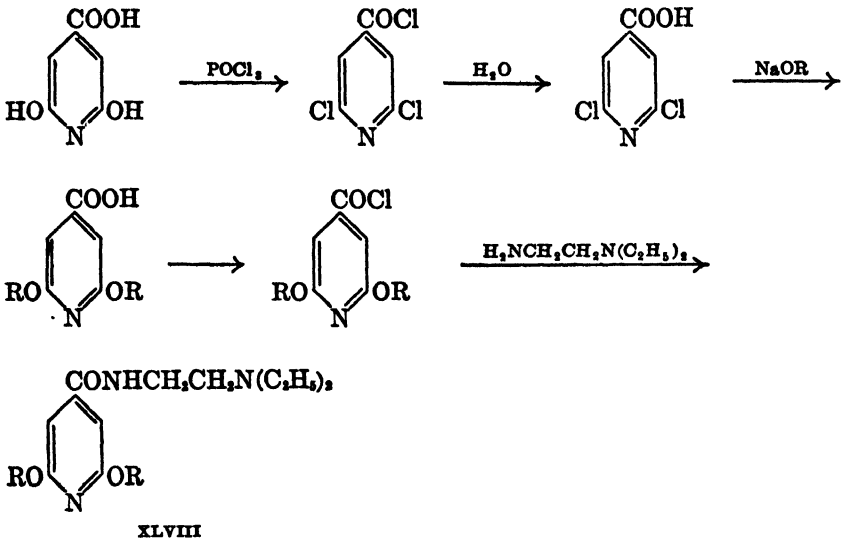
51 Buchi, Labhart, and Ragaz, *Helv. Chim. Acta*, **30**, 507 (1947).

52 Mndzhoyan, *J. Gen. Chem.* (*U.S.S.R.*), **16**, 1029 (1916); [*C. A.*, **41**, 2737 (1947)].

53 Chiang and Hartung, *J. Org. Chem.*, **10**, 26 (1945).

54 Renshaw and Dreisbach, U. S. pat. 2,194,567 (Mar. 26, 1940) [*C. A.*, **34**, 4865, (1940)].

that these compounds, especially the 2,6-dipropoxy and 2,6-dibutoxy derivatives (XLVIII, R = C_3H_7, C_4H_9) were powerful local anes-



XLVIII

thetics with anesthetic indices of 4 to 6 based on cocaine as 1. The 2-alkoxy analogs of XLVIII and the corresponding ester were made from the intermediate 2,6-dichloroisonicotinic acid by first removing one of the chlorine atoms by the method of Thielepape (p. 519).

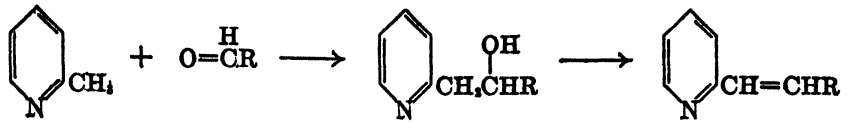
Pyridine analogs of the basic esters of *p*-aminobenzoic acid such as novocaine have also been made [55] from 2-chloropyridine-5-carboxylic acid, and they are claimed to show a high local anesthetic activity.

SIDE-CHAIN DERIVATIVES OF PYRIDINE

Alcohols

The synthesis of the pyridine derivatives which have an alcohol group in the side chain in either the 2 or 4 position is readily accomplished by condensations of the 2- and 4-methylpyridines with an aldehyde, as indicated in the first step of equations I–III. The reaction, of course, does not occur with the 3-methylpyridine derivatives. The tendency for water to split out of the alcohol (II) to form the alkene (III) depends on the nature of R and the conditions of the condensa-

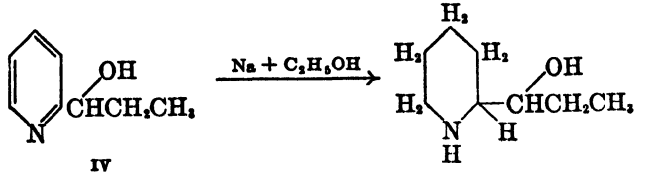
[55] Renshaw and Dreisbach, U. S. pat. 2,189,404 (Feb. 6, 1940) [*C. A.*, **34**, 4284 (1940)]; U. S. pat. 2,199,839 (May 7, 1940) [*C. A.*, **34**, 6020 (1940)].



I II III

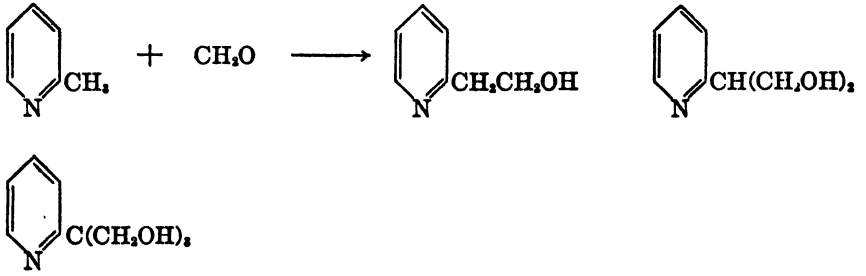
tion. In general, the condensations with aromatic aldehydes give almost exclusively the olefin, and the reaction cannot be stopped at the carbinol stage (II) (see p. 445) because of the great tendency for conjugation to take place. With an aliphatic aldehyde, it is feasible to stop at the alcohol stage, as indicated in the studies of the hemlock alkaloids. When 2-picoline is condensed with acetaldehyde, the initial product is 2-(β-hydroxypropyl)pyridine (II, R = CH_3),[1] and the final product is 2-(1-propenyl)pyridine (III, R = CH_3). This latter substance was reduced by Ladenburg with sodium and alcohol to 2-(*n*-propyl)piperidine which on resolution gave the *d* form, identical with the natural product coniine. Thus the first total synthesis of an alkaloid was achieved.

The isomeric carbinol intermediate (IV) has likewise been reduced and the resolved base shown to be identical with the alkaloid conydrine (V). When formaldehyde is used, more than one aldehyde group



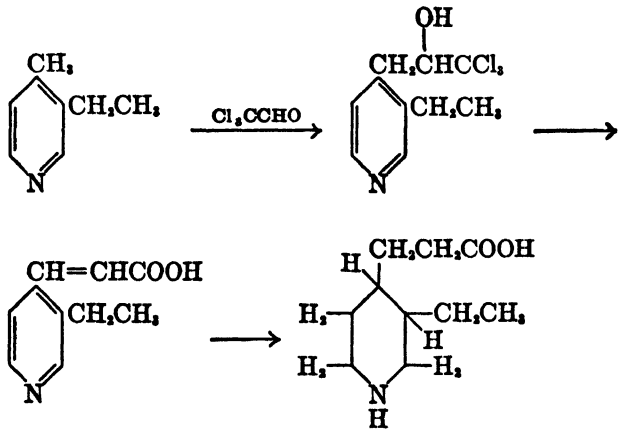
IV V

may condense with a methyl group in the 2 or 4 position, with the result that a mixture of mono-, di-, and tri-methylolpicolines can be obtained.[2,3] Similar condensations take place with 2-ethylpyridine.[4]



1 Meisenheimer and Mahler, *Ann.*, **462**, 308 (1928).
2 Koenigs and Happe, *Ber.*, **35**, 1343 (1902).
3 Lipp and Richard, *Ber.*, **37**, 737 (1904).
4 Löffler and Grosse, *Ber.*, **40**, 1325 (1907).

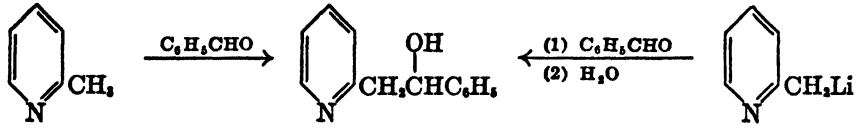
An interesting example of this same type of condensation is that between 3-ethyl-4-methylpyridine and chloral utilized by Rabe [5] in his synthesis of homocincholoipon (VI) for the ultimate synthesis of dihydroquinine. The possibility of hydrolysis of the trichloro compound to an hydroxy acid and its dehydration to an unsaturated acid de-



VI

rivative offers a method not only for the synthesis of homocincholoipon (VI) but also for a large group of 2- and 4-pyridyl-substituted lactic, acrylic, and propionic acids.[6-8]

Although the condensation of benzaldehyde and picoline in the presence of zinc chloride or acetic anhydride ordinarily gives stilbazole, in the absence of an acid catalyst and in the presence of water condensation takes place at 125° to give 2-(pyridylmethyl)phenylcarbinol (VII) [9] in poor yield. When 2-picoline is treated with phenyllithium



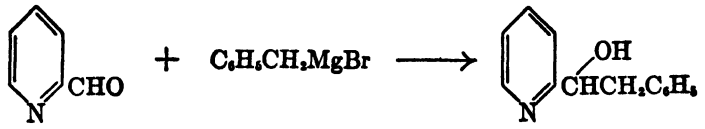
VII

and benzaldehyde is added to the resultant 2-pyridylmethyllithium, the same product (VII) is formed.[10] 2-Pyridylmethyllithium reacts with

5 Rabe et al., *Ber.*, **64**, 2487 (1931).
6 Kleiman and Weinhouse, *J. Org. Chem.*, **10**, 562 (1945).
7 Feist, *Arch. Pharm.*, **240**, 178 (1902).
8 Einhorn, *Ann.*, **265**, 208 (1891); *Ber.*, **23**, 219 (1890).
9 Räth, *Ber.*, **57**, 840 (1924).
10 Bergmann and Rosenthal, *J. prakt. Chem.*, **135**, 267 (1932).

acetaldehyde to give a 44–50% yield of 1-(α-pyridyl)-2-propanol or with ethylene oxide to give 1-(α-pyridyl)-3-propanol.[11]

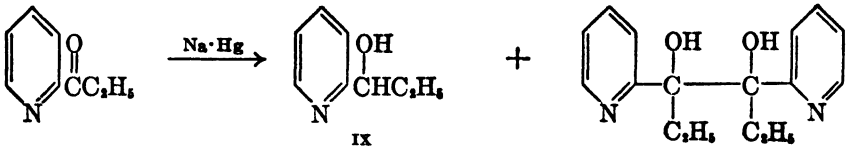
A general method that is not restricted to the synthesis of pyridine carbinols substituted in the 2 and 4 positions is the Grignard reaction on either the pyridine aldehydes, ketones, or esters. Thus, with pyridine-2-aldehyde and benzylmagnesium bromide, the carbinol (VIII) isomeric to VII is obtained.



VIII

Although the action of the Grignard reagent on the various pyridine esters does not seem to have been employed extensively, Sobecki [12] obtained a 90% yield of dimethyl-2-pyridylcarbinol by the action of three equivalents of methylmagnesium bromide on ethyl picolinate. The excess Grignard reagent is essential since one equivalent apparently is coordinated with the nitrogen atom of the pyridine ring and is therefore not available for addition to the ester. In a similar and expected manner, the action of Grignard reagents on the pyridine ketones results in the corresponding pyridine alcohols.

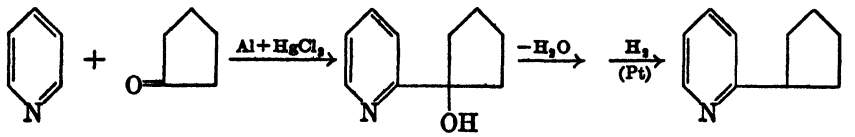
The pyridine aldehydes and ketones can be reduced normally to the alcohols by the accepted procedures. Sodium amalgam reductions of the ketones may produce, along with the normal product IX, the corresponding pinacol X by a bimolecular reduction.[13]



IX X

A unique substitution reaction which has led to several pyridine carbinols was discovered by Emmert et al.[14,15] and used by Lochte et al.[16] in the synthesis of 2-cyclopentylpyridine. The reaction gave a

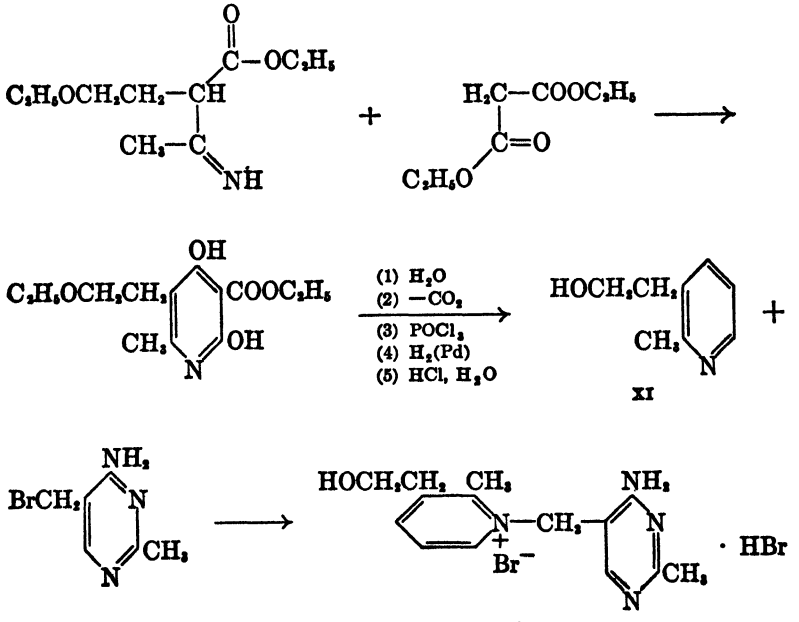
11 Walter, *Org. Syntheses*, **23**, 83 (1943).
12 Sobecki, *Ber.*, **41**, 4103 (1908).
13 Engler et al., *Ber.*, **24**, 2530, 2536 (1891).
14 Emmert and Asendorf, *Ber.*, **72**, 1188 (1939).
15 Emmert and Pirot, *Ber.*, **74**, 714 (1941).
16 Lochte, Thomas, and Truitt, *J. Am. Chem Soc.*, **66**, 550 (1944).



small yield (5%) of 2-pyridylborneol when camphor was the ketone, but no substitution was observed if 2,6-dimethylpyridine was employed instead of pyridine.

Several pyridine derivatives which may be considered pyridine isosters of vitamin B_1, in which the pyridine ring is substituted for the thiazole ring of the vitamin, have been prepared by Elderfield and co-workers.[17,18]

The structure of vitamin B_1 is most closely approximated when the pyridine moiety is derived from 2-methyl-3-(β-hydroxyethyl)pyridine (XI). The synthesis of this intermediate has been accomplished



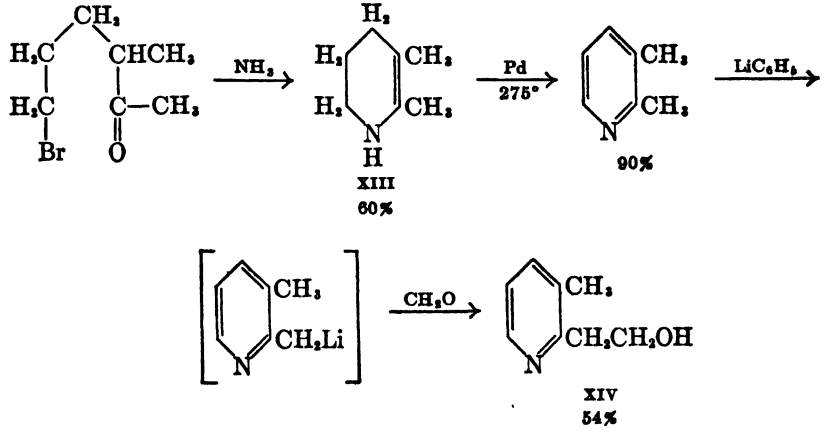
17 Tracy and Elderfield, *J. Org. Chem.*, **6**, 54 (1941). The substance prepared by these workers and named pyrathiamine by Wooley and White [*J. Biol. Chem.*, **149**, 285 (1941)] has been shown to be a mixture of presumably polymeric materials by Wilson and Harris [*J. Am. Chem. Soc.*, **71**, 2231 (1949)]. Wilson and Harris succeeded in preparing a substance the structure of which is represented truly by XII by a modification of the experimental conditions used in passing from XI to XII. To this the name neopyrathiamine was given.

18 Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).

through an initial condensation of aliphatic components in a manner related to the method of building up the pyridine ring in most of the pyridoxine syntheses.

The ester group in the initial pyridine compound was removed by the conventional processes of hydrolysis and decarboxylation, followed by replacement of the hydroxyl groups in the 2 and 4 positions with chlorine atoms and reductive cleavage of the chlorine atoms with hydrogen over palladium.

The isomeric thiamine analog made from 2-(β-hydroxyethyl)-3-methylpyridine (XIV) was also prepared. The pyridine intermediate was synthesized from a tetrahydropyridine compound (XIII) in the following interesting fashion.

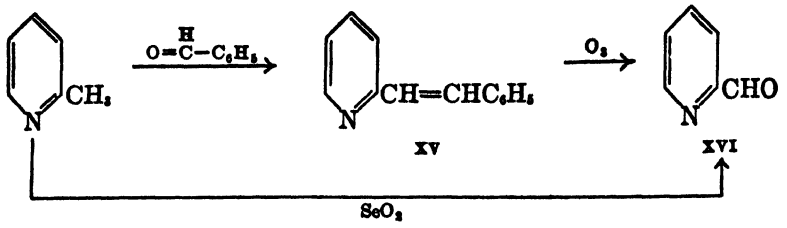


The vitamin B_1 analog (XII) (pyrathiamine) showed no curative action on polyneuritis in rats but gave approximately the same response as thiamine in the yeast growth test.

Aldehydes

None of the pyridine aldehydes is readily available by methods which give satisfactory yields. Starting materials have been the 2- and 4-picolines which, either by condensation with benzaldehyde and ozonolysis of the resulting stilbazole (XV) [19–21] or by direct oxidation with selenium dioxide,[22] are converted to the aldehydes (XVI) in poor and not always reproducible yields.

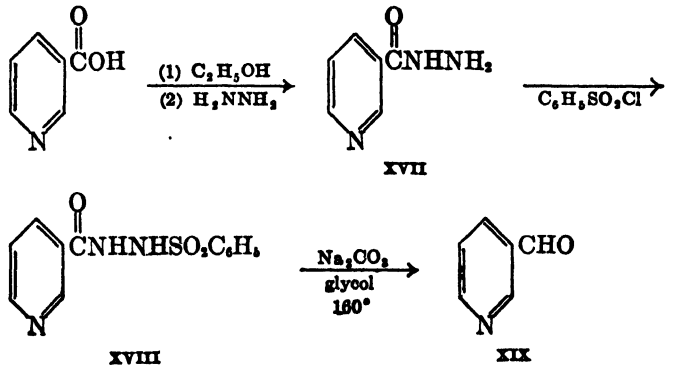
19 Wibaut et al., *Rec. trav. chim.*, **64**, 30 (1945).
20 Craig and Hixon, *J. Am. Chem. Soc.*, **53**, 4869 (1931).
21 Kaslow and Stayner, *J. Am. Chem. Soc.*, **67**, 1716 (1945).
22 Henze, *Ber.*, **67**, 750 (1934).



XV XVI

Ozonolysis of 2-vinylpyridine was studied by Ernsdorf,[23] but it gave no 2-pyridinealdehyde. Only picolinic acid and formaldehyde were isolated. 2-Pyridinealdehyde has been obtained by treating picoline with chlorine to obtain 2-trichloromethylpyridine which is partially reduced to 2-dichloromethylpyridine and then hydrolyzed with silver nitrate solution to the aldehyde.[24] The over-all yield, however, was only 5%.

Attempted direct oxidation of 2-picoline by chromic anhydride in acetic anhydride in an attempt to obtain the diacetate of 2-pyridinealdehyde was also unsuccessful.[19] The other possible starting materials are the acids which, through either the Stevens method or the Rosenmund method, can be converted to the aldehyde but in poor yields. Panizzon [25] and Niemann,[26] by the method of McFadyen and Stevens,[27] converted nicotinic acid into the hydrazide (XVII); decomposition of the pyridylbenzenesulfonylhydrazide (XVIII) with sodium



XVII

XVIII XIX

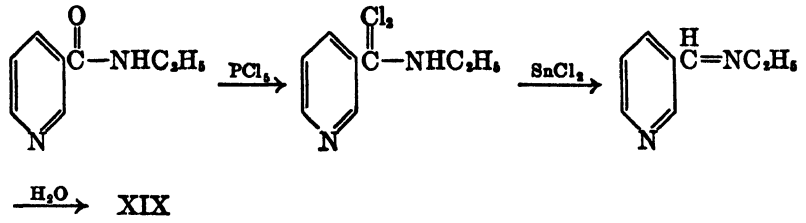
carbonate in glycol gave pyridine-3-aldehyde (XIX) in 23–36% yields. Ernsdorf [23] also found that this was the best method of syn-

23 B. P. Ernsdorf, Ph.D. Thesis, Stanford University, 1946.
24 Dyson and Hammick, *J. Chem. Soc.*, 781 (1939).
25 Panizzon, *Helv. Chim. Acta*, **24**, 24E (1941).
26 Niemann, Lewis, and Hays, *J. Am. Chem. Soc.*, **64**, 1678 (1942).
27 McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).

thesis but obtained only a 16% yield of purified aldehyde. He observed that nicotinic acid and 3-pyridylcarbinol were by-products in the reaction.

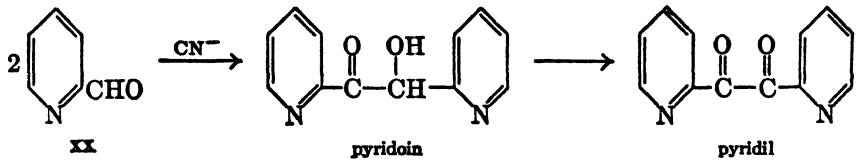
Although the unsubstituted pyridinecarboxylic acid chlorides have been reported to give no aldehyde in the Rosenmund method, Graf and co-workers [28,29] have found that several chloro-substituted pyridine acid chlorides—4,5,6-trichloropicolinoyl chloride, 5-chloronicotinoyl chloride, and 2,6-dichloroisonicotinoyl chloride—do give the aldehydes on catalytic reduction by the Rosenmund procedure.

Application of the Sonn-Müller [30] reduction of the pyridylimido dichloride by Work [31] gave pyridyl-3-aldehyde. The several steps re-



quired and the yield of about 40% in the last two steps render it a poor procedure for synthesis.

As far as they have been studied, the pyridine aldehydes show the characteristic reactions of aromatic aldehydes. Pyridine-2-aldehyde (XX) gives a bisulfite derivative, a hydrazone, reduces Fehling's and Tollen's reagents, and takes part in a typical benzoin condensation [15] to give 2-pyridoin, which in turn has been oxidized to the pyridine

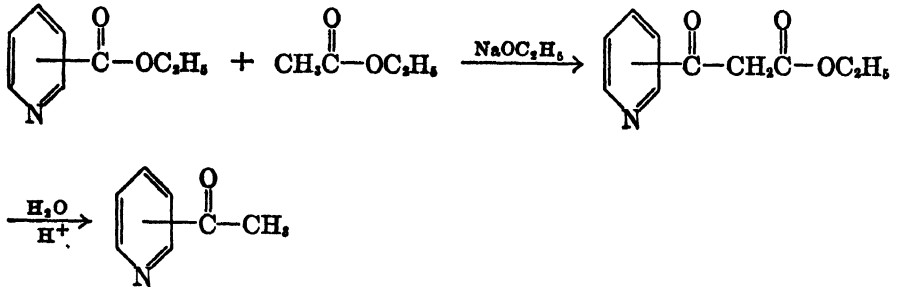


analog of benzil. Pyridine-4-aldehyde on treatment with sodium hydroxide undergoes the Cannizzaro reaction. Pyridine-3-aldehyde condenses with malonic acid in a typical Knoevenagel reaction to give pyridine-3-acrylic acid. Pyridine-2-aldehyde fails, however, in the azlactone synthesis.

28 Graf and Weinberg, *J. prakt. Chem.*, **134**, 177 (1932).
29 Graf and Lasszlo, *J. prakt. Chem.*, **138**, 231 (1933).
30 Sonn and Müller, *Ber.*, **52**, 1927 (1919).
31 Work, *J. Chem. Soc.*, 429 (1942).

Ketones

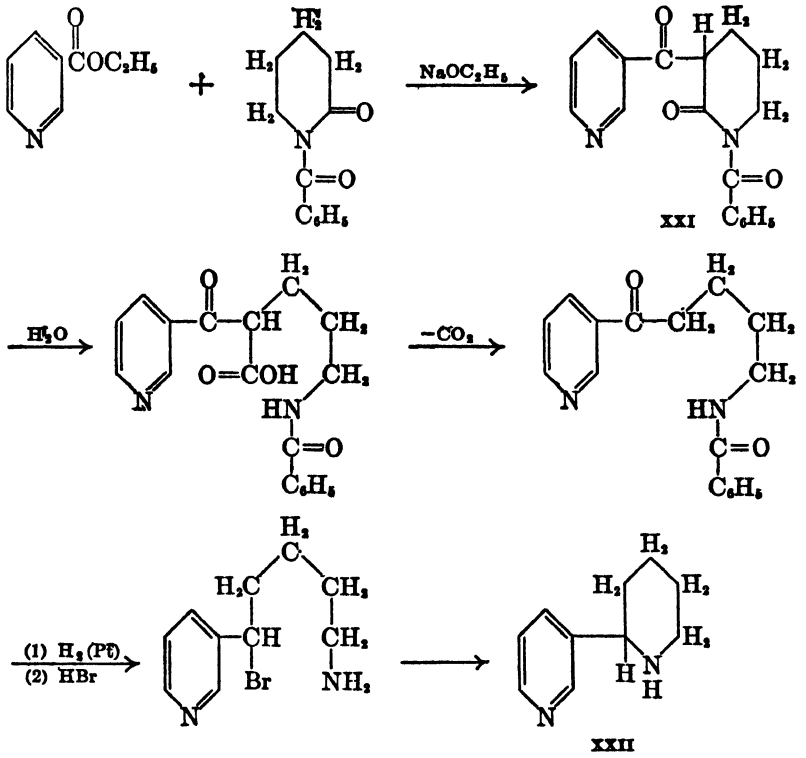
The three methyl pyridyl ketones are all readily available in good yield by the Claisen ester condensation.[32-34] The yields of the β-keto



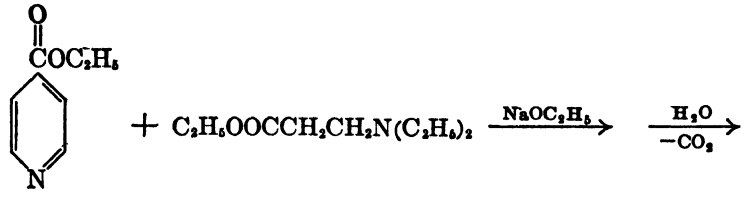
esters in the pyridine series are often superior to those obtained with many other classes of compounds. Koelsch [32] has published a useful review of the many Claisen condensations of the pyridine esters. Not only do the simple pyridine esters successfully undergo the Claisen reaction, but so also do various alkylpyridine esters such as ethyl 2,6-dimethylpyridine-3-carboxylate, ethyl 3,5-dimethylpyridine-2-carboxylate, etc. Condensation takes place with such diversified carbonyl compounds as acetone, acetophenone, butyrolactone, succinimide, N-methyl-pyrrolidone, and N-benzoyl-2-piperidone to give a variety of substituted pyridyl ketones. When ethyl nicotinate is condensed with acetone in the presence of sodium ethoxide, an 82% yield of the diketone, 3-acetoacetylpyridine, is obtained.[35] If the condensation is with N-benzoylpiperidone, then the intermediate XXI is formed from which the alkaloid anabasine (XXII) can be produced in 52% yield.[36]

An especially interesting example of the Claisen reaction is illustrated below in the condensation of ethyl isonicotinate (XXIII) and β-diethylaminopropionate (XXIV).[37] The resulting amino ketone (XXV) can be catalytically reduced to the corresponding carbinol. It is interesting that the α-diethylaminoacetate and γ-diethylaminobutyrate gave very poor yields in the same condensation.

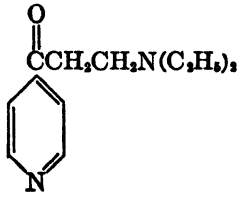
32 Koelsch, *J. Org. Chem.*, **10**, 34 (1945).
33 Burrus and Powell, *J. Am. Chem. Soc.*, **67**, 1468 (1945).
34 Kolloff and Hunter, *J. Am. Chem. Soc.*, **63**, 490 (1941).
35 Clemo and Holmes, *J. Chem. Soc.*, 1739 (1934).
36 Späth and Mamoli, *Ber.*, **69**, 1082 (1936).
37 Robert B. Taylor, Ph.D. Thesis, The Pennsylvania State College, 1945.



XXI XXII

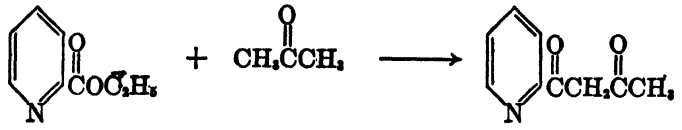


XXIII XXIV



XXV

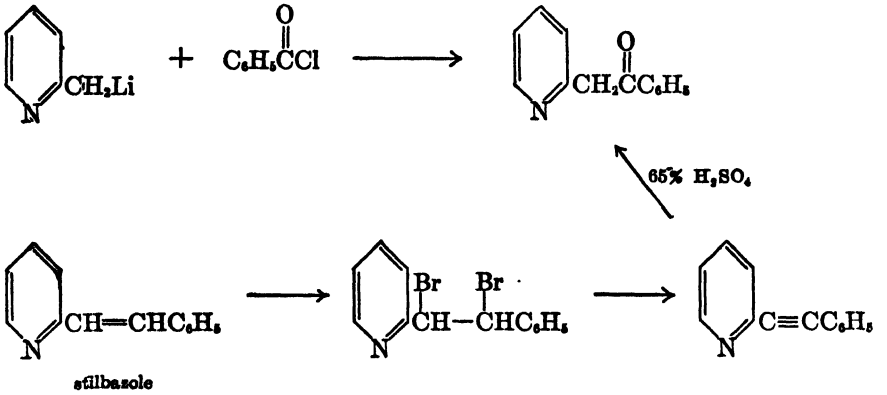
Ethyl picolinate condenses with acetone in the presence of sodium ethoxide to form 2-acetoacetylpyridine in good yield.[32] The product



shows the typical properties of a 1,3-diketone as illustrated by its reaction with phenylhydrazine to give 1-phenyl-3-(2′-pyridyl)-5-methylpyrazol.

The three isomeric phenyl pyridyl ketones have all been made; the 2- and 3-pyridyl phenyl ketones by the Friedel-Crafts reaction of picolinoyl and nicotinoyl chlorides on benzene in the presence of aluminum chloride,[38] and the 2- and 4-pyridyl phenyl ketones (90% yields) by the permanganate oxidation of the corresponding benzylpyridines.[39]

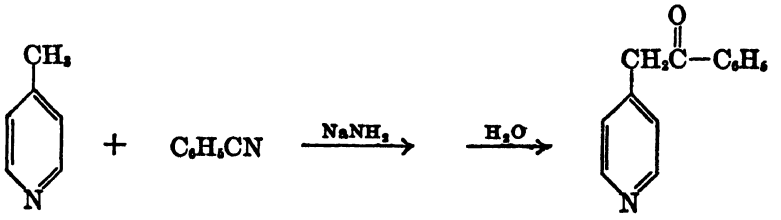
In addition to these unsubstituted compounds, various other more complex substances have been made by the same reactions, indicating the general applicability of these methods. Benzene, pyridine-2, 6-dicarboxylic acid chloride, and aluminum chloride give 2,6-dibenzoylpyridine, and the oxidation of such compounds as 4-(*p*-nitrobenzyl)pyridine give *p*-nitrophenylpyridyl ketone.[40–42] 2-Picolylphenyl ketone can be formed either by a coupling reaction between 2-picolyllithium and benzoyl chloride [43] or from stilbazole by the series



stilbazole

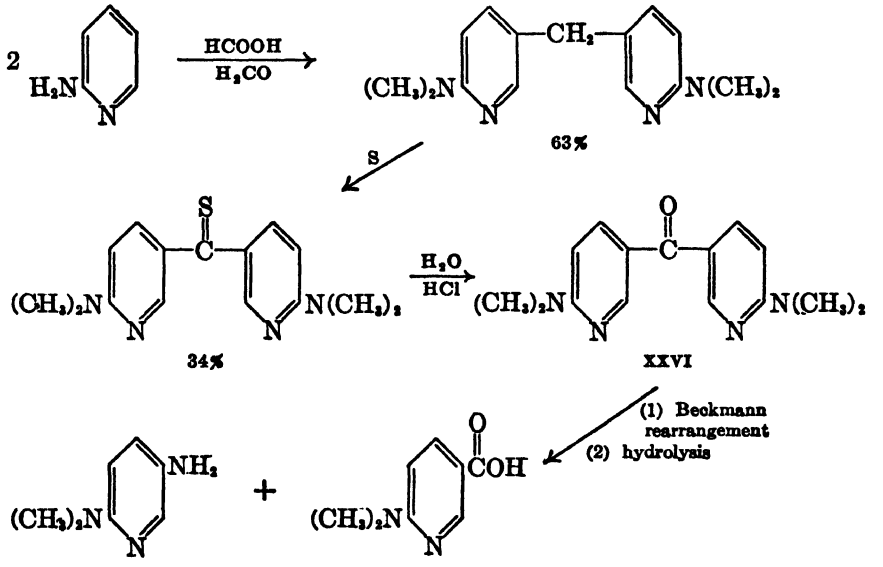
38 Wolffenstein and Hartwich, *Ber.*, **48**, 2043 (1915).
39 Chichibabin, *J. Russ. Phys. Chem. Soc.*, **33**, 700 (1901); *Chem. Zentr.*, **1902**, I, 206.
40 Chichibabin et al., *Ber.*, **58**, 1580 (1925).
41 Koenigs et al., *Ber.*, **59**, 1717 (1926).
42 Wilson, *J. Chem. Soc.*, 1936 (1931).
43 Bergmann and Rosenthal, *J. prakt. Chem.*, [2] **135**, 267 (1932).

of reactions indicated above.[44] Use has also been made of the active hydrogens in 4-picoline to bring about a condensation with benzonitrile.[45]



A very poor yield of 3,3′-dipyridyl ketone has been obtained[46] by passing nicotinic acid over thoria catalyst at 300°; other dipyridyl ketones have not been reported.

An interesting series of reactions employed by Chichibabin[47,48] which has led to the pyridine analog (XXVI) of Michler's ketone is illustrated by the following equations.



The structure of the product is indicated by conversion to the oxime from which, on Beckmann rearrangement, 2-dimethylamino-5-amino-

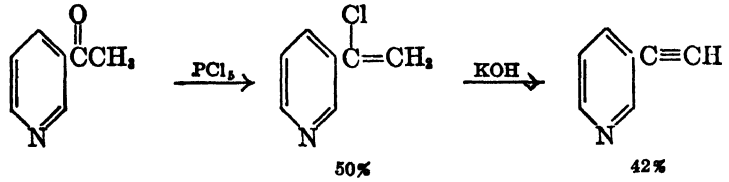
44 Boehringer, Brit. pat. 311,387 (Apr. 4, 1930) [*C. A.*, **24**, 919 (1930)].
45 Chichibabin, *Rec. trav. chim.*, **57**, 582 (1938).
46 Linsker and Evans, *J. Am. Chem. Soc.*, **68**, 907 (1946).
47 Chichibabin and Knunyantz, *Ber.*, **62**, 3048 (1929).
48 Kahn and Petrow, *J. Chem. Soc.*, 858 (1945).

pyridine and 6-dimethylaminonicotinic acid were obtained after hydrolysis. 2,6-Diaminopyridine gives similar reactions with formaldehyde and with other aldehydes.[49]

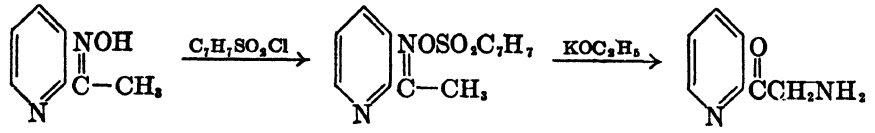
The analog of Michler's ketone (XXVI) has been reduced to the carbinol with sodium amalgam and this product treated with aniline, methylaniline, and dimethylaniline to give a series of compounds analogous to the triphenylmethane dyes.[48]

The pyridyl methyl ketones show the anticipated reactions of an active methyl group. Accordingly methyl 2-pyridyl ketone condenses with benzaldehyde to give the product analogous to benzalacetophenone.[50]

3-Pyridylacetylene has been prepared from methyl 3-pyridyl ketone by treatment with phosphorus pentachloride in benzene, followed by dehydrohalogenation with alcoholic potassium hydroxide.[51]



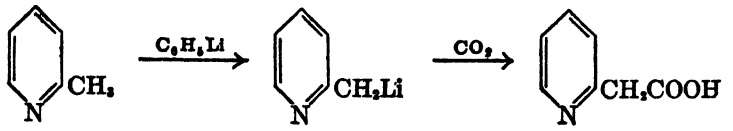
The method of Neber and Huh [52] for the preparation of α-amino ketones has been applied to 2-acetylpyridine [53] to give 2-pyridyl aminomethyl ketone in good yield.



Side-Chain Acids

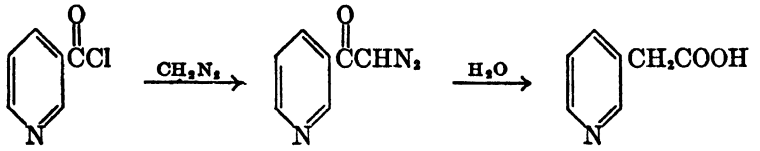
All the isomeric unsubstituted pyridylacetic acids are known. Bills [54] made a study of the various methods for the synthesis of 2-pyridylacetic acid (XXVII) and found that carbonation of 2-picolyllithium gave 44–45% yields and was superior to all other methods available.

49 Schoeller and Schickh, Ger. pat. 563,132 (Feb. 11, 1932) [*C. A.*, **27**, 1093 (1933)].
50 Engler and Engler, *Ber.*, **35**, 4061 (1902).
51 Alberts and Backman, *J. Am. Chem. Soc.*, **57**, 1284 (1935).
52 Neber and Huh, *Ann.*, **515**, 283 (1935).
53 Clemo, Holmes, and Leitch, *J. Chem. Soc.*, 753 (1938).
54 J. Bills, Ph.D. Thesis, Stanford University, 1947.



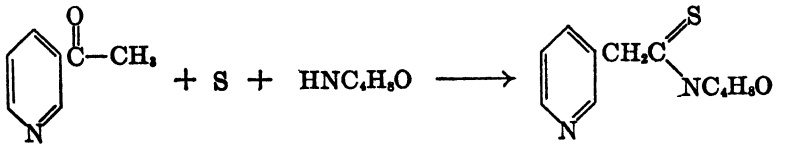
XXVII

This method has also been independently applied to the reaction of both α- and γ-picolines by Woodward.[55] Because of the ease of decarboxylation, it is preferable to isolate the acid in the form of its ethyl ester. 3-Pyridylacetic acid cannot, of course, be made by this method but is prepared either by the Willgerodt reaction [56] from 3-acetylpyridine or by the Arndt-Eistert reaction on nicotinoyl chloride.[57,58] 4-Pyridylacetic acid has also been made by the Willgerodt



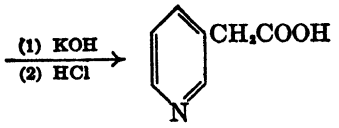
reaction [56] in an over-all yield of 60%, but when this reaction was extended to 2-pyridylacetic acid the yield was very poor.

The most interesting difference in the chemical reactivity of 2- and 3-pyridylacetic acids is their ease of decarboxylation. 3-Pyridylacetic acid is stable up to its melting point of 144–146°, whereas 2-pyridylacetic acid readily loses carbon dioxide at 90° to give α-picoline. It is for this reason that only slight yields of 2-pyridylacetic acid have been obtained by the hydrolysis of the 2-pyridylthioacetmorpholide (the 2 isomer of XXVIII) in the Willgerodt reaction. The reason for



XXVIII

80%



74%

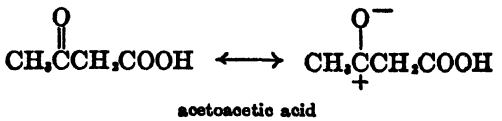
55 Woodward, private communication.

56 Malan and Dean, *J. Am. Chem. Soc.*, **69**, 1797 (1947).

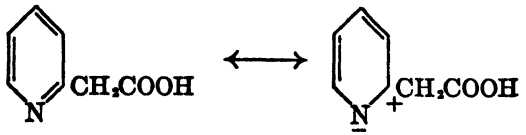
57 Miescher and Kägi, *Helv. Chim. Acta*, **24**, 1471 (1941).

58 Winterfeld and Cosel, *Arch. Pharm.*, **278**, 73 (1940).

this ease of decarboxylation is the attachment of the α carbon of the 2-pyridylacetic acid to the "positive" 2-carbon atom of pyridine. This is essentially the same situation that exists in acetoacetic ester, and



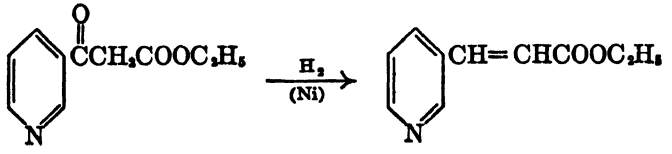
acetoacetic acid



pyridylacetic acid

therefore the reasons for the similar reactions with respect to ease of decarboxylation are quite apparent. The resonance of the pyridine ring reduces the polarization of the carbon-nitrogen bond to a value considerably less than that of the carbon-oxygen bond of the carboxyl group in acetoacetic acid, and the pyridine derivative is therefore the more stable of the two.

The β-(2- and 4-pyridyl)propionic acids have been made by reduction of the corresponding pyridineacrylic acids [25] which are obtained either from the aldehyde by a Knoevenagel condensation or from the derivative which is prepared by the condensation of 2- or 4-picoline with chloral. It is surprising that attempted catalytic reduction with nickel of nicotinoylacetic ester (XXIX) [59] produces, instead of the expected hydroxy ester, the β-(3-pyridyl)acrylic ester (XXX). This

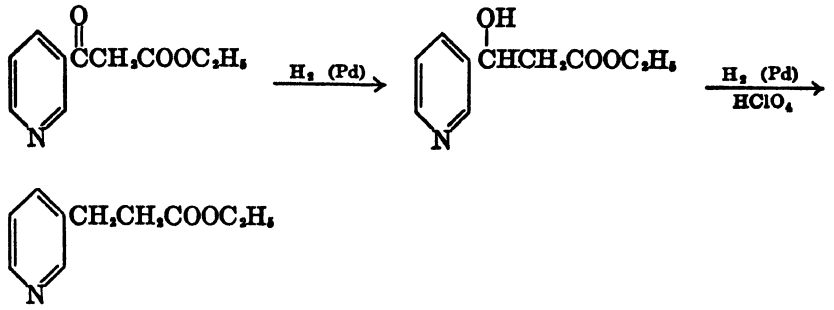


XXIX XXX

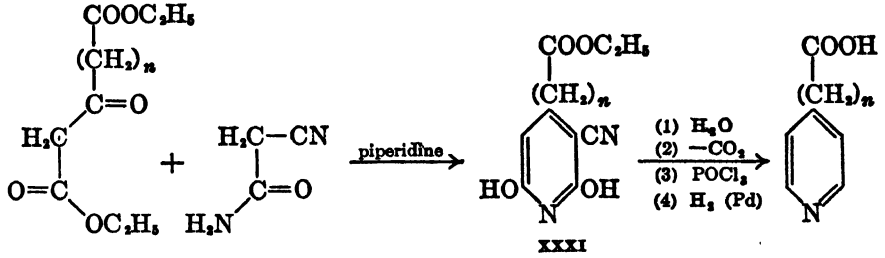
is but another example of the great tendency of organic molecules to assume a conjugated structure whenever possible. Rosenmund and Karg [60] observed that an hydroxyl group adjacent to a benzene ring could readily be replaced by hydrogen on catalytic reduction with palladium on barium sulfate in the presence of a catalytic amount of perchloric acid. Graef, Fredericksen, and Burger [61] have applied this

[59] Adkins et al., *J. Am. Chem. Soc.*, **66**, 1293 (1944).
[60] Rosenmund and Karg, *Ber.*, **75**, 1850 (1942).
[61] Graef, Fredericksen, and Burger, *J. Org. Chem.*, **11**, 257 (1946).

reduction to nicotinoylacetic ester to obtain β-(3-pyridyl)propionic ester in an over-all yield of 92%.



β-(4-Pyridyl)propionic acid has been synthesized from aliphatic components by the condensation of the appropriate β-keto ester and cyanoacetamide,[62] as indicated in the following equations.



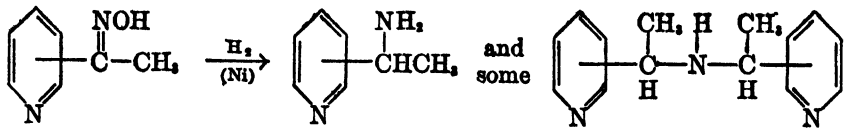
XXXI

In the initial condensation, the yields obtained were 35%, 31%, and 36%, respectively, when n was 0, 1, and 2. The conversion of XXXI, ($n = 2$) to the unsubstituted β-(4-pyridyl)propionic acid by the processes of hydrolysis, decarboxylation, treatment with phosphorus oxychloride, and removal of the chlorine atoms in the 2 and 6 positions by catalytic reduction takes place in an over-all yield of about 27%.

Side-Chain Amines

Various side-chain amines of the pyridine series have been made by methods completely analogous to those used in the benzene series and thus require only passing comment. Catalytic reduction with Raney nickel of any one of the three cyanopyridines produces a mixture of the respective picolinylamine and the di-(picolinyl)amine. In a similar manner, the reduction of the oximes of the pyridine aldehydes [63] or the three acetylpyridines gives the expected primary and

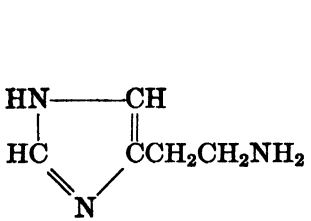
[62] Stevens and Beutel, *J. Am. Chem. Soc.*, **65**, 449 (1943).
[63] Craig and Hixon, *J. Am. Chem. Soc.*, **53**, 4367 (1931).



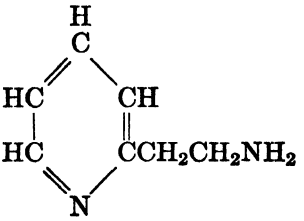
XXXII XXXIII

secondary amines (XXXII and XXXIII).[64,65] The yields of the primary amines are from 40% to 65% and undoubtedly could be considerably increased if the reduction were conducted in the presence of ammonia.[64,65]

Many pyridine amines have been studied because of their close analogy to various interesting and physiologically important benzene derivatives. These include such compounds as the pyridine analogs of the pressor amines. Several studies have been made on the physiological activity of various pyridylethylamines, pyridylpropylamines, and pyridylethanolamine derivatives.[33,59,66,67] Most of the methods employed are completely comparable to those applicable in the benzene series, such as reduction of the oximes of the acetylpyridines or substituted isonitroso ketones. Others were made from the corresponding β-(2-pyridyl)alanines by decarboxylation or from the β-(2-pyridyl)propionamides by the Hofmann reaction. The published pharmacological results indicate that the pyridine compounds with a β-aminoethyl radical substituted in the 3 or 4 position have properties qualitatively similar to the comparable pressor amines of the aromatic series, whereas β-(2-pyridyl)ethylamine (XXXV) has an histamine-like activity. This physiological resemblance to histamine (XXXIV) is reflected in a structural similarity.



XXXIV



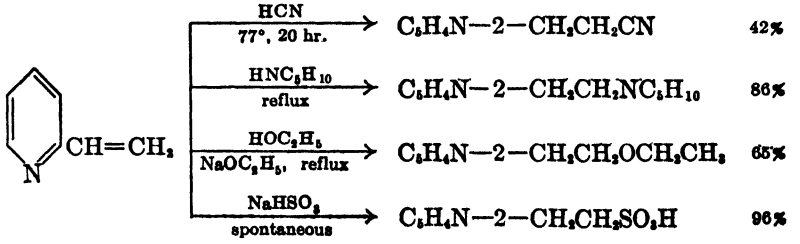
XXXV

Pyridinium analogs of the pressor amines in which a pyridinium group replaces the amino group have also been made,[68] but their activities have not been reported.

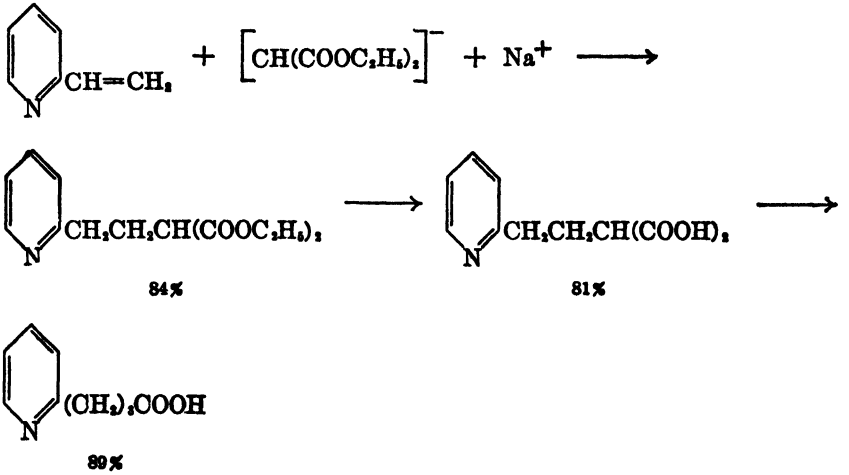
64 Schwoegler and Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939).
65 Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).
66 Walter, Hunt, and Fosbinder, *J. Am. Chem. Soc.*, **63**, 2771 (1941).
67 Niemann and Hays, *J. Am. Chem. Soc.*, **64**, 2288 (1942).
68 Riegel and Wittcoff, *J. Am. Chem. Soc.*, **68**, 1805, 1913 (1946).

Addition Reactions of 2-Vinylpyridine

A variety of 2- and 4-pyridyl side-chain derivatives can be prepared from the commercially available 2-vinylpyridine and its 4 isomer.[69] As indicated previously (p. 445), 2-vinylpyridine and its 4 isomer (but not 3-vinylpyridine) show reactions comparable to those of acrylonitrile. Thus, a series of pyridine derivatives with a variety of different substituents on the side chain is available by addition reactions to 2-vinylpyridine. As may be suspected from the added resonance stability of the pyridine ring, these reactions take place with somewhat more difficulty than do those of acrylonitrile. In addition, 2-vinylpyridine should be more reactive than 4-vinylpyridine. This is confirmed by the experiments of Doering and Weil which are outlined in the following equations.



β-(2-Pyridyl)propionitrile can be hydrolyzed very readily (75% yield) into β-(2-pyridyl)propionic acid. 2-Vinylpyridine also participates in a typical Michael condensation with malonic ester. This



[69] Doering and Weil, *J. Am. Chem. Soc.*, **69**, 2463 (1947).

is an excellent method for the preparation of γ-(2-pyridyl)butyric acid. 1-(2-Pyridyl)-4-pentanone is made in an over-all yield of 49% by the same type of reaction starting with acetoacetic ester.

Pyridoxine

Long before the isolation and identification of crystalline vitamin B_1, it was realized that the crude water-soluble vitamin concentrate, called vitamin B, was in reality a complex mixture. As early as 1926, Goldberger and Lillie had postulated a special dietary factor, the deficiency of which was responsible for a condition in rats characterized by a dermatitis called *acrodynia*. The isolation in a crystalline state from rice bran (the same original source of vitamin B_1 and nicotinic acid) of the responsible vitamin was reported by several different groups in 1938.[70-73] In 1932, Ohdake[74] had actually isolated from rice bran a crystalline substance which had the empirical formula ($C_8H_{11}O_3N \cdot HCl$) of pyridoxine, but he failed to recognize its vitamin nature. Since its discovery, pyridoxine has developed to the point where 4200 lb. were produced in 1944 at a price of approximately $450 per pound.

The elucidation of the structure of vitamin B_6 is the most interesting piece of chemical research in the field of pyridine compounds in recent years. The structure of this vitamin, called pyridoxine by most of the American workers and Adermine by the German group, was deduced both by Stiller, Keresztesy, and Stevens,[75] and by Kuhn and Wendt[76] on the basis of analysis, certain chemical reactions of the vitamin, and comparison with model substances.

Elementary analysis of the hydrochloride gave the empirical formula $C_8H_{12}NO_3Cl$. Titration of the hydrochloride electrometrically showed only one break in the titration curve, strongly indicating that it was a monobasic substance and that the empirical formula also represented the molecular formula. Tests for $-OCH_3$, $-NCH_3$, water of crystallization, and optical activity were negative, and the vitamin was stable to hydrolysis in both acid and basic solution, to nitrous

70 Lepkovsky, *Science*, **87**, 169 (1938).

71 György, *J. Am. Chem. Soc.*, **60**, 983 (1938).

72 Keresztesy and Stevens, *Proc. Exptl. Biol. Med.*, **38**, 64 (1938); *J. Am. Chem. Soc.*, **60**, 1267 (1938).

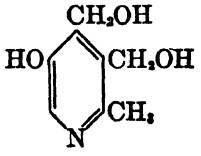
73 Kuhn and Wendt, *Ber.*, **71**, 780, 1118 (1938).

74 Ohdake, *Bull. Agr. Chem. Soc. Japan*, **8**, 111 (1932).

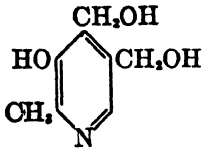
75 Stiller, Keresztesy, and Stevens, *J. Am. Chem. Soc.*, **61**, 1237 (1939).

76 Kuhn and Wendt, *Ber.*, **72**, 305 (1939).

acid, and to Fehling's solution. It gave, however, a positive ferric chloride test indicating a phenolic hydroxyl group, and the differences of the ultraviolet absorption spectra in acid and basic solution indicated that the vitamin was amphoteric. It contained three active hydrogen atoms as determined by the Zerewitinov method. The absorption spectra closely resembled that of 3-hydroxypyridine and some of its derivatives. Finally, methylation with diazomethane gave a methyl ether which, on oxidation with barium permanganate, was converted into a dicarboxylic acid, $C_9H_9O_5N$. This acid did not give a color with ferrous sulfate (p. 569), and therefore it was unlikely that a carboxyl group occupied the α position. In addition, this dicarboxylic acid formed a phthalein dye when fused with resorcinol indicating an *o*-dicarboxylic acid. All these reactions pointed toward a pyridine derivative, probably containing an —OH, a $-CH_3$, and two $-CH_2OH$ groups, in which the arrangement of the atoms was represented by one of the formulas I and II. The dicarboxylic acid obtained when

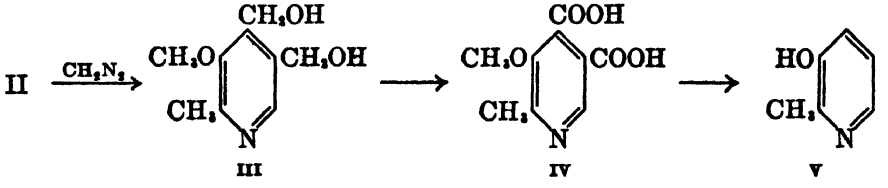


I



II

the methyl ether was oxidized gave, on decarboxylation of its sodium salt, a new substance which analyzed for an hydroxypicoline. This was not the known 5-hydroxy-2-picoline and the above deductions, if correct, indicated that structure II was that of the vitamin. These reactions can thus be interpreted as follows.



III IV V

These conclusions were completely confirmed, first by comparison of the dicarboxylic acid (IV) with a synthetic specimen made according to Chart 1, and finally by the brilliant total synthesis by Harris and Folkers (Chart 2).[77]

[77] Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 1245 (1939).

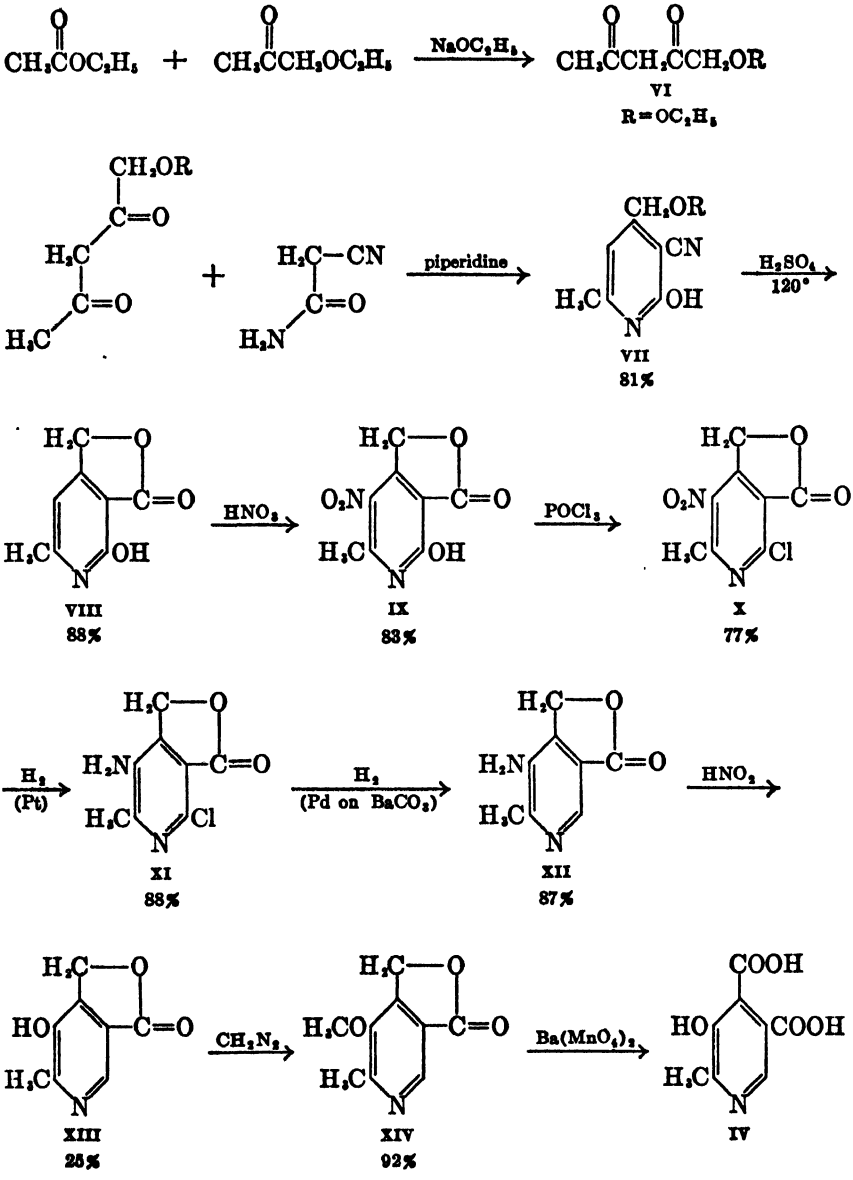

CH3COC2H5 + CH3CCH3OC2H5
NaOC2H5
CH3CCH2CCH2OR
VI
R=OC2H5
piperidine
H2SO4
120°
VII
81%
HNO2
VIII
88%
IX
83%
POCl3
X
77%
H2
(Pt)
XI
88%
H2
(Pd on BaCO3)
XII
87%
HNO2
CH2N2
XIII
25%
XIV
92%
Ba(MnO4)2
IV

CHART 1

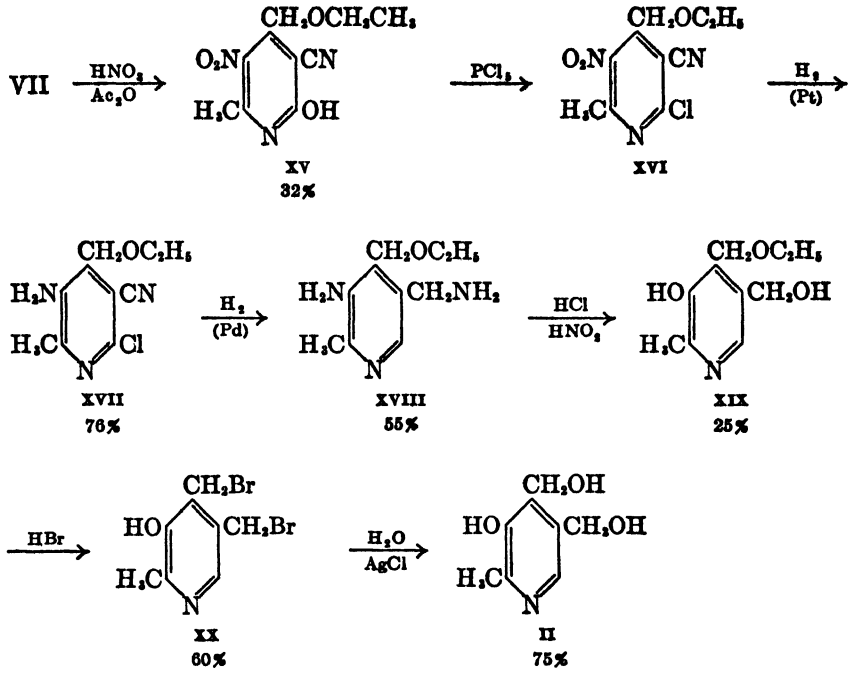


CHART 2

Subsequent publications by Harris and Folkers [78] have added some refinements to this synthesis. Most important of these has been the direct hydrolysis of XVIII with 2.5 *N* hydrochloric acid at 175° under pressure to obtain 2-methyl-3-amino-4-hydroxymethyl-5-aminomethylpyridine dihydrochloride in 77% yield. When treated with nitrous acid, this is converted directly into pyridoxine hydrochloride in 45% yield, thus obviating the hydrolysis of the dibromide XX.

Various other alternate steps have been studied which are based on the same fundamental reactions.[79–82] Variations of this basic method have employed the methyl ether (VI, R = CH_3, R′ = H),[83 85] the benzyl ether (VI, R = $CH_2C_6H_5$; R′ = H),[86] and the phenyl

78 Harris and Folkers, *J. Am. Chem. Soc.*, **61**, 3307 (1939).

79 Stiller, U. S. pat. 2,372,690 (Apr. 3, 1945) [*C. A.*, **39**, 4199 (1945)].

80 Harris, U. S. pat. 2,248,078 (July 8, 1941) [*C. A.*, **35**, 6741 (1941)].

81 Harris, U. S. pat. 2,266,754 (Dec. 23, 1942) [*C. A.*, **36**, 2378 (1942)].

82 Merck and Co., Brit. pat. 543,615 (Mar. 6, 1942) [*C. A.*, **36**, 5957 (1942)].

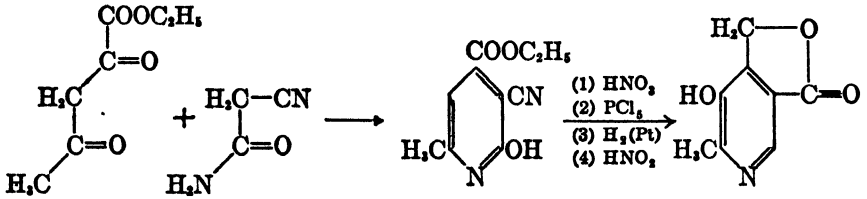
83 Keresztesy and Stevens, U. S. pat. 2,280,831 (Apr. 28, 1942) [*C. A.*, **36**, 5618 (1942)].

84 Morii and Makino, *Enzymologia*, **7**, 385 (1939) [*C. A.*, **34**, 6279 (1940)].

85 Harris, *J. Am. Chem. Soc.*, **62**, 3203 (1940).

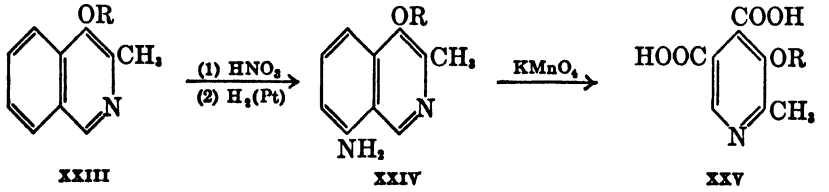
86 Hoffmann-La Roche, Ger. pat. 732,238 (1943) [*C. A.*, **38**, 1251 (1944)].

ether (VI, R = C_6H_5; R′ = H),[87] by starting with the appropriate ether of acetylacetone. All these methods are fundamentally a modification of the reactions of a β-diketone with the amide of a β-keto acid or its equivalent. Stiller [79] has described a synthesis in which an acetylamino group is incorporated into the ethoxyacetylacetone molecule, thus eliminating the steps of nitration and reduction later in the process. In addition, malononitrile has been substituted for cyanoacetamide [88] and acetylpyruvic acid (XXI) has been used to synthesize a lactone (XXII) isomeric with XII which also is effective

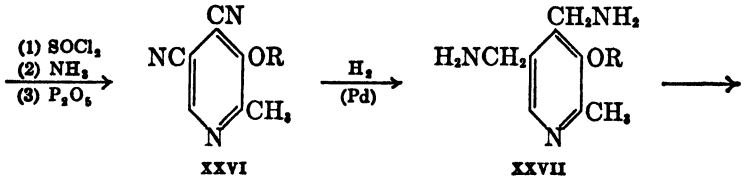


XXI XXII

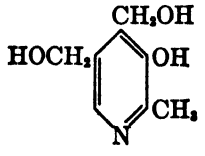
in promoting growth and preventing anemia in chicks.[89] In almost all these conversions, the key intermediate is 2-methyl-3-amino-4-ethoxymethyl-5-aminomethylpyridine (XVIII) or its equivalent.



XXIII XXIV XXV



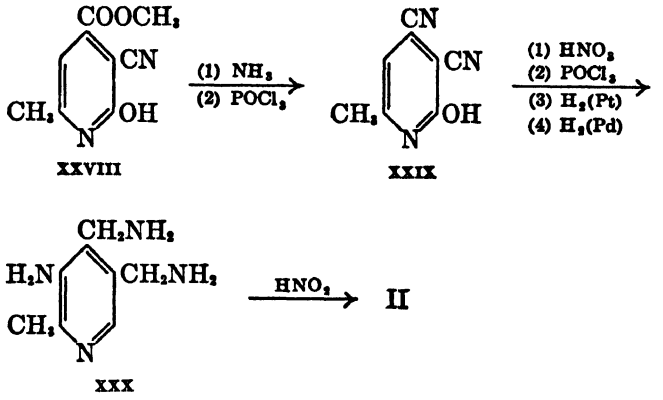
XXVI XXVII



II

[87] Hoffmann-La Roche, Brit. pat. 570,365 (July 4, 1945) [*C. A.*, 40, 5210 (1946)].
[88] Schnider, U. S. pat. 2,353,367 (July 11, 1944) [*C. A.*, 38, 6501 (1944)].
[89] Scott et al., *J. Am. Chem. Soc.*, 67, 157 (1945).

Another type of synthesis depends on obtaining a suitable derivative of 3,4-dicyanopyridine. This has been accomplished [90-92] by the oxidation of the appropriate isoquinoline derivative. The introduction of an amino group into the benzene portion of the isoquinoline ring (XXIV) facilitates the attack of the oxidizing agent on this portion of the molecule. Salzer [93] has developed a similar but longer synthesis from the oxidation of a quinoline derivative. Carlson [94,95] prepared XXX by converting methyl 2-hydroxy-3-cyano-6-methyl isonicotinate to the dinitrile through the conventional steps of amide formation and dehydration with phosphorus oxychloride. Following logical steps,



XXVIII XXIX XXX

an amine group was introduced in the 5 position by nitration and reduction, and the hydroxyl group in the 2 position was removed by conversion to the corresponding chloro compound and reduction. The resulting triamino compound was converted into pyridoxine by appropriate treatment with nitrous acid.

Finally, it has been possible to reduce the lactone XIII (p. 602) directly with sodium amalgam in acetic acid to pyridoxine.[80,96]

The compounds that are analogous to pyridoxine but which contain an ethyl, chloro, or bromo group in place of the methyl group in the α position have been made by similar methods [97,98] and have been

90 Westphal and Andersag, U. S. pat. 2,302,903 (Nov. 24, 1943) [*C. A.*, **37**, 2390 (1943)].

91 Westphal, U. S. pat. 2,349,318 (May 23, 1944) [*C. A.*, **39**, 1513 (1945)].

92 Szabo, U. S. pat. 2,359,260 (Sept. 26, 1944) [*C. A.*, **39**, 1965 (1945)].

93 Salzer, U. S. pat. 2,250,396 (July 22, 1941) [*C. A.*, **35**, 7123 (1941)].

94 Carlson, U. S. pat. 2,310,167 (Feb. 2, 1943) [*C. A.*, **37**, 4207 (1943)].

95 Lederle Laboratories, Brit. pat. 567,611 (Feb. 23, 1945) [*C. A.*, **41**, 2755 (1947)].

96 Merck and Co., Brit. pat. 534,916 (Mar. 21, 1941) [*C. A.*, **36**, 1739 (1942)].

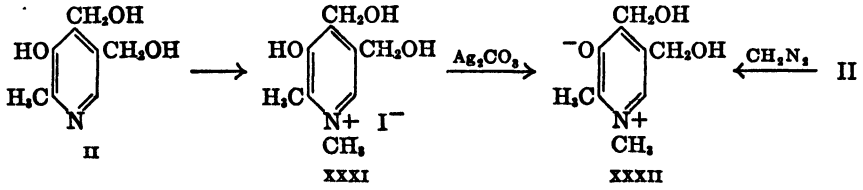
97 Harris and Wilson, *J. Am. Chem. Soc.*, **63**, 2526 (1941).

98 Merck and Co., Ger. pat. 707,266 (1943) [*C. A.*, **37**, 502 (1943)].

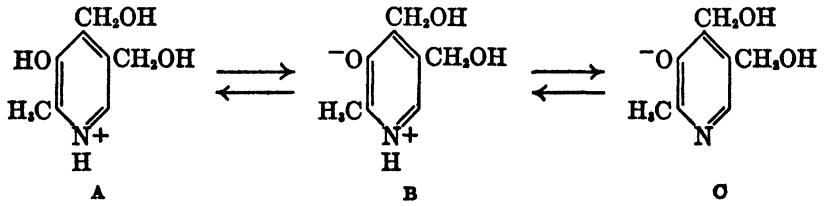
found to possess only a small fraction (about 2%) of the activity of pyridoxine itself. It has been shown that the pyridoxine-like compound, 2,4-dimethyl-3-hydroxy-5-hydroxymethylpyridine, is a potent inhibitor of the vitamin as tested in chicks.[99]

One of the important chemical reactions of pyridoxine is the characteristic color developed in the Gibbs color test [100,101] with 2,6-dichloroquinone chlorimide which has been developed into a quantitative colorimetric method for the estimation of the vitamin.[102] This reaction is characteristic of phenols, unsubstituted in the *p* position.

Pyridoxine forms a normal methiodide (XXXI) [103] when refluxed with methyl iodide in benzene-methanol solution. This methiodide no longer gives the color reaction with 2,6-dichloroquinone chlorimide, nor does it condense with *p*-dimethylaminobenzaldehyde, a reaction usually characteristic of 2-methylpyridine methiodides. When treated



with silver carbonate, XXXI is converted into the N-methylpyridoxine betaine (XXXII). The betaine XXXII is formed in a minor amount by treatment of pyridoxine with diazomethane.[104] The formation of the betaine in neutral solution is indicative of the zwitterion nature of pyridoxine in neutral solution. The structures of pyridoxine in acid, neutral, and basic solution are illustrated by the formulas, A, B, and C, respectively. Snell [105] reported observations in 1944 which could



99 Ott, *Proc. Soc. Exptl. Biol. Med.*, **61**, 125 (1946).

100 Gibbs, *J. Biol. Chem.*, **72**, 649 (1927).

101 Theriault, *Ind. Eng. Chem.*, **21**, 343 (1929).

102 Scudi, Koones, and Keresztesy, *Proc. Soc. Exptl. Biol. Med.*, **43**, 118 (1940).

103 Harris, Webb, and Folkers, *J. Am. Chem. Soc.*, **62**, 3198 (1940).

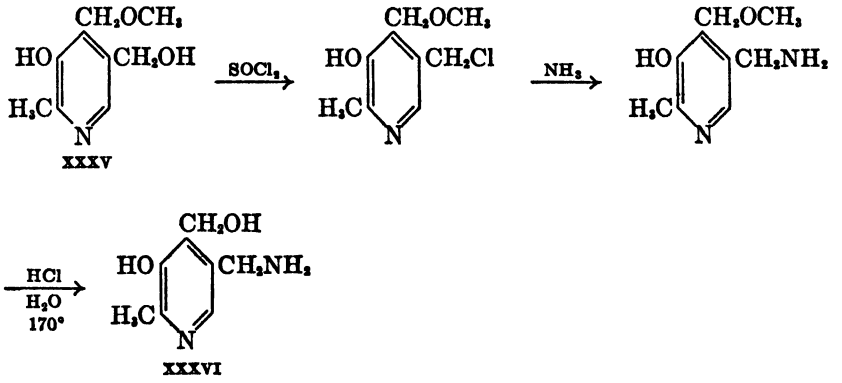
104 Ichiba and Michi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **35**, 73 (1938) [*C. A.*, **33**, 3430 (1939)].

105 Snell, *J. Biol. Chem.*, **154**, 313 (1944).

best be explained on the assumption that there were pyridoxine-like but distinct substances in natural materials which had a high growth promoting action for *Lactobacillus casei* and for *Streptococcus fecalis* under special conditions. By a series of brilliant microbiological experiments, Snell [106] was able to deduce that there were two substances —one, an aldehyde which he named pyridoxal (XXXIII), and the other an amine, pyridoxamine (XXXIV)—which were interconvertible by a transamination reaction in the following sense where glutamic acid acts as the source for the transfer of the amine group.

$$\underset{\text{XXXIII}}{\text{pyridoxal}} + \text{glutamic acid} \rightleftarrows \underset{\text{XXXIV}}{\text{pyridoxamine}} + \alpha\text{-ketoglutaric acid}$$

It was logical to postulate that amine and aldehyde groups replaced the hydroxymethyl groups of pyridoxine in either or both the 3 and 4 positions. These possibilities were investigated synthetically by Harris, Heyl, and Folkers [107] who first undertook to synthesize the analog having the aminomethyl group in the 3 position by the following sequence.



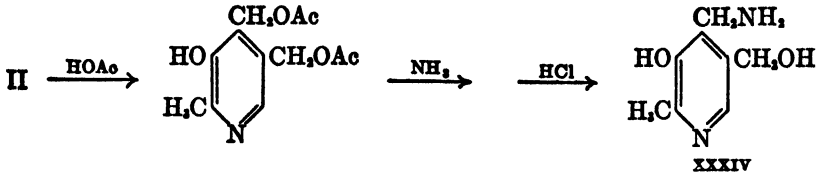
XXXV XXXVI

The product, concerning the structure of which there could be no doubt, was devoid of growth-promoting properties for several test organisms.

Direct treatment of the acetate of pyridoxine (or better, the 4-methoxymethyl derivative of pyridoxine) with ammonia gave an amine (XXXIV) which is isomeric with XXXVI but which possesses all the activity expected of the product, pyridoxamine. Since the struc-

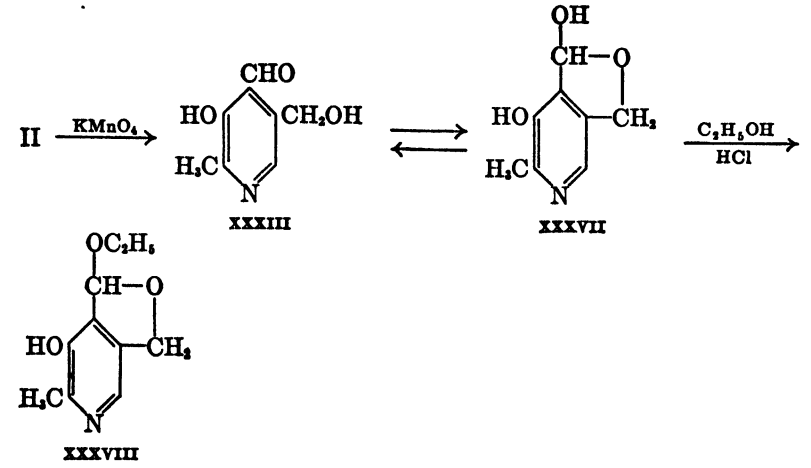
[106] Snell, *J. Am. Chem. Soc.*, **66**, 2082 (1944).

[107] Harris, Heyl, and Folkers, *J. Am. Chem. Soc.*, **66**, 2088 (1944).



XXXIV

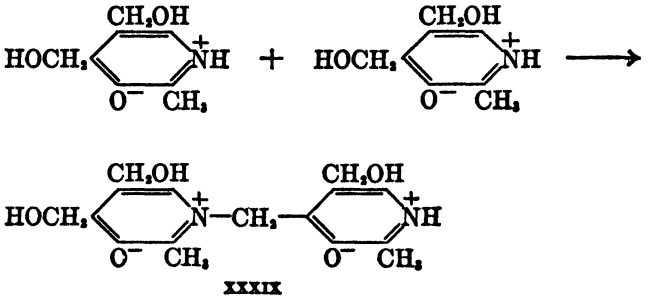
ture of XXXVI is known by synthesis and the new product was chemically different and isomeric, the latter must have the indicated structure (XXXIV). This was confirmed by synthesis from the known 4-methoxymethyl derivative. It was found that the aldehyde, pyridoxal XXXIII, could also be made directly from pyridoxine by careful permanganate oxidation. The aldehyde may actually have the cyclic



XXXIII XXXVII XXXVIII

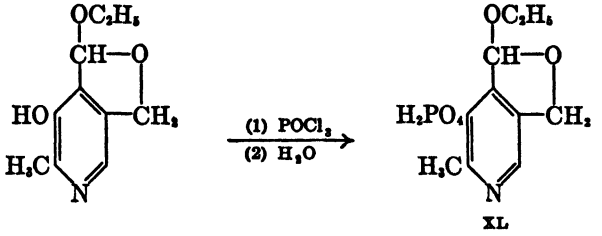
structure XXXVII; it is readily converted to an acetal XXXVIII by treatment with hydrogen chloride and ethanol. The structure of pyridoxal was proved among other ways by conversion to pyridoxamine through the oxime and reduction. In addition, the isomeric aldehyde with the formyl group in the 6 position was synthesized and found to be devoid of the growth-promoting properties of pyridoxal. This preferential attack on the 4 position of pyridine is further illustrated by the polymerization of pyridoxine [108] to a dimer XXXIX. Since the polymer forms only in neutral water solution, its formation probably occurs through the reaction of the zwitterion (p. 606) as indicated. Considerable evidence has been gathered by Harris in favor of such a formulation.

[108] Harris, *J. Am. Chem. Soc.*, **63**, 3363 (1941).



XXXIX

Starting with pyridoxal acetal, Karrer and Viscontini [109] succeeded in preparing a crystalline phosphoric acid ester (XL) of pyridoxine which had all of the activity of natural codecarboxylase.



XL

The role of pyridoxine and its related compounds, pyridoxal and pyridoxamine, in human nutrition has not yet been clarified. Use of pyridoxine in treating radiation sickness, agranulocytosis, and nausea and vomiting during pregnancy has met with indications of slight success. The actual human symptoms of a pyridoxine deficiency have not yet been clearly defined, although the appearance of certain skin conditions has been suspected.[110]

SULFUR DERIVATIVES OF PYRIDINE

Mercaptopyridines

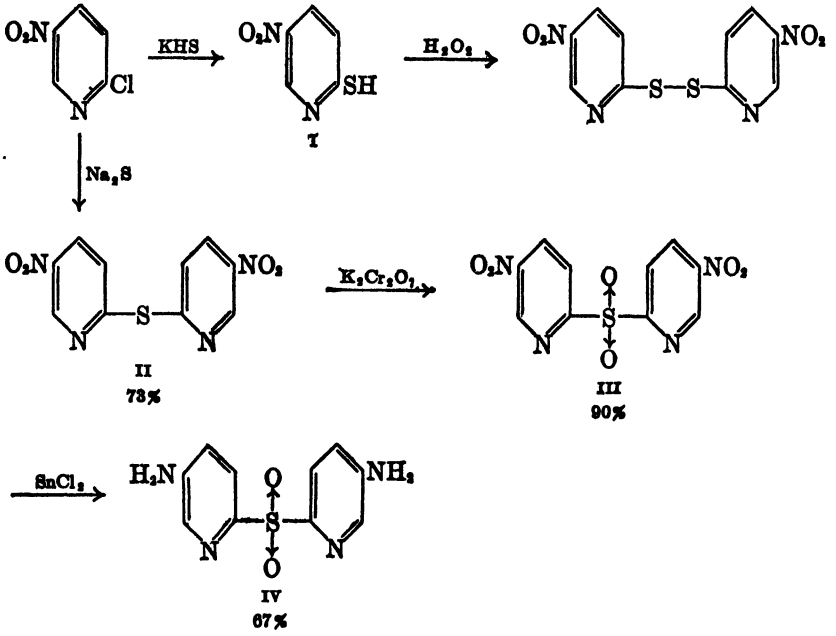
2-Mercapto- and 4-mercapto-pyridine and their derivatives are made in excellent yields by the reaction of the corresponding 2- or 4-halopyridine with potassium hydrogen sulfide. 2-Bromopyridine is thus converted into 2-mercaptopyridine in 83–87% yield when it is refluxed

109 Karrer and Viscontini, *Helv. Chim. Acta*, **30**, 52 (1947).

110 For a review of the clinical uses of pyridoxine, refer to Merck Service Bulletin *Vitamin B_6 (Pyridoxine Hydrochloride)*, April 1943, supplement January 1947, Merck and Co., Rahway, N. J.

(170°) in propylene glycol for 20 hr.[1] When a *m*-directing group is situated in the *o* or *p* position, the replacement reactions take place with even greater ease. Accordingly, it is only necessary to mix a methanolic solution of potassium hydrogen sulfide with 2-chloro-5-nitropyridine and warm it slightly in order to obtain a 90% yield of 2-mercapto-5-nitropyridine (I) (p. 524).[2, 3]

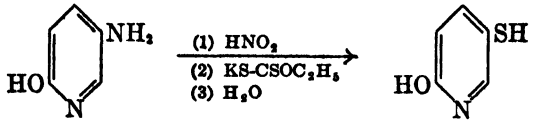
If, instead of potassium hydrogen sulfide, sodium sulfide is used in the reaction with the requisite amount of 2-chloro-5-nitropyridine, di-(5-nitro-2-pyridyl)sulfide (II) is formed.[4] The sulfide (II) may be



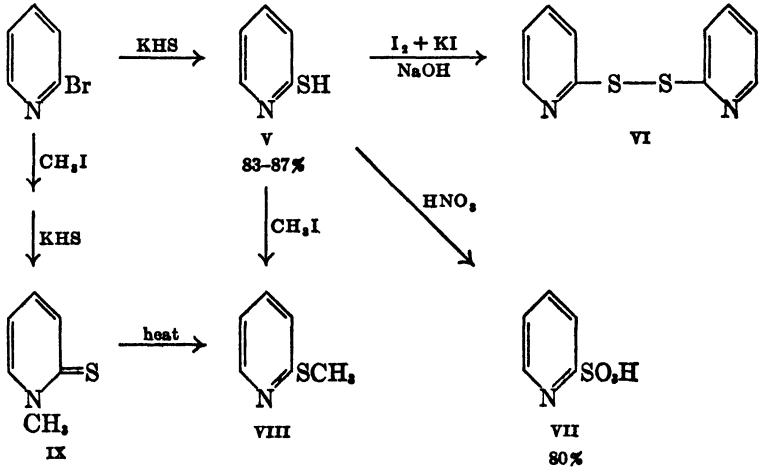
oxidized to the sulfone (III) with dichromate in acid solution, and III in turn has been reduced to the corresponding diamino compound (IV) with stannous chloride. These compounds are of considerable interest because of their relationship to the therapeutically active *p,p*-diaminodiphenyl sulfone which shows some activity in the chemotherapy of tuberculosis.[5]

1 Thirtle, *J. Am. Chem. Soc.*, **68**, 342 (1946).
2 Räth, *Ann.*, **487**, 105 (1931).
3 Colonna, *Boll. Sci. facolta chim. ind., Bologna*, **1941**, 145 [*C. A.*, **37**, 4399 (1943)].
4 Surrey and Lindwall, *J. Am. Chem. Soc.*, **62**, 173 (1940).
5 Burton and Davy, *J. Chem. Soc.*, 52 (1947).

The halogen atom in the 3 or 5 position is usually not reactive enough to allow direct substitution in a similar manner, but 3-chloropyridine-2-carboxylic acid can be converted into 3-mercaptopyridine-2-carboxylic acid by direct substitution because of the activating carboxylic acid group in the *o* position.[6] In special cases, the 3-mercapto derivative may be prepared from the corresponding amine through the



diazo reaction as illustrated for 2-hydroxy-5-mercaptopyridine.[7] Most of the reactions of the mercaptopyridines proceed as expected; 2-mercaptopyridine, the best-known and most widely studied derivative of this type, undergoes oxidation with iodine in potassium iodide to the disulfide (VI) [8] or with nitric acid to the sulfonic acid (VII).[9] Methylation with methyl iodide in basic solution results in the 2-methylmercaptopyridine (VIII) with no indication of the isomeric



N-methyl-2-thiopyridone.[8] The methyl thio ether (VIII) is oxidized in the normal manner with potassium permanganate and acetic acid to

6 Sucharda and Troszkiewicz, *Roczniki Chem.*, **12**, 493 (1932) [*C. A.*, **27**, 5076 (1933)].

7 Kochendoerfer, U. S. pat. 1,753,658 (Apr. 8, 1930) [*C. A.*, **24**, 2471 (1930)].

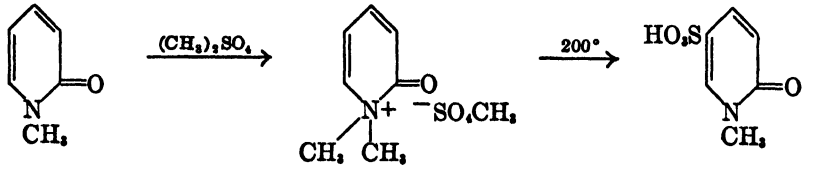
8 Marckwald, Klemm, and Trabert, *Ber.*, **33**, 1556 (1900).

9 van Gastel and Wibaut, *Rec. trav. chim.*, **53**, 1031 (1934).

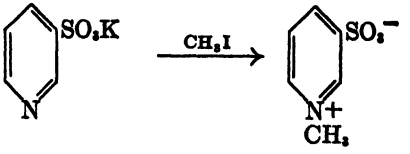
the sulfone.[8] N-Methyl-2-thiopyridone (IX) is not formed by direct methylation but results from treatment of the 2-iodopyridine methiodide with potassium hydrogen sulfide.[10]

Pyridinesulfonic Acids

The sulfonation of pyridine and its various derivatives has been considered under the substitution reactions of pyridine and picoline. A wide variety of pyridinesulfonic acids are available by this route. Direct sulfonation almost always introduces the sulfonic acid group in the 3 or 5 position. An *o,p*-directing group in the 2 or 4 position invariably facilitates this substitution. The pyridine derivatives with an amino or hydroxyl group in the 3 position may substitute in the 2 or 6 position. Other than the relatively few pyridine-2-sulfonic acid derivatives made by this method, the 2- and 4-pyridinesulfonic acid derivatives are available by oxidation of the corresponding mercaptans, e.g., the oxidation of 2,6-dimercaptopyridine-4-carboxylic acid with nitric acid to pyridine-2,6-disulfonic-4-carboxylic acid.[11] When N-methyl-2-pyridone is converted to the methosulfate with dimethyl sulfate and then heated to 200°, rearrangement takes place to give N-methyl-2-pyridone-5-sulfonic acid.[12]

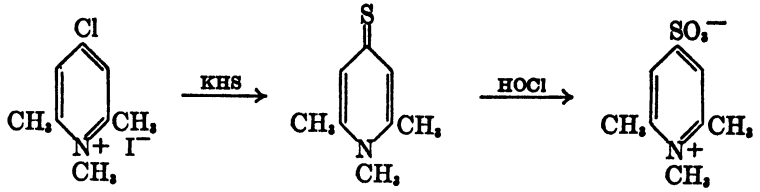


Just as the pyridinecarboxylic acids form betaines, pyridinesulfonic acids give sulfonic acid inner salts. The tendency to form these inner salts is greater than with the carboxylic acids. It is sufficient to treat the potassium salt of the sulfonic acid with methyl iodide at 150° to produce the methyl betaine of the sulfonic acid directly.[13] Such



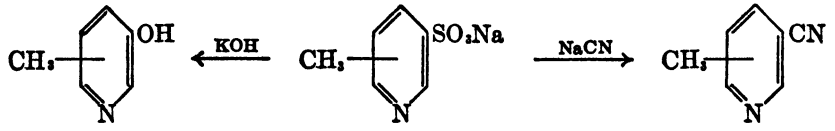
10 Michaelis and Hölken, *Ann.*, **331**, 245 (1904).
11 Bittner, *Ber.*, **35**, 2933 (1902).
12 Haack, Ger. pat. 597,452 (May 24, 1934) [*C. A.*, **28**, 5083 (1934)].
13 Meyer, *Ber.*, **36**, 616 (1903).

betaines may be made directly by oxidation of a thiopyridone as illustrated in the following example.[10]



The sulfonic acids of the pyridine series show the normal reactions of typical aromatic sulfonic acids in so far as these reactions have been studied. They are converted to the sulfonyl chlorides by treatment with phosphorus oxychloride, and the chlorides react with ammonia to give the sulfonamides. Much of the work on the pyridinesulfonic acids has been stimulated by the discovery of the sulfa drugs and resulting investigations of pyridine analogs. As yet, none of the analogs of sulfapyridine which have been reported appear to be of any clinical worth.[14–17] Pyridine-3-sulfonic acid occupies a position of special importance among the pyridinesulfonic acids because of its relationship to the vitamin, nicotinic acid.[18] Under certain conditions, pyridine-3-sulfonamide shows the same physiological inhibitory action towards nicotinic acid as sulfanilamide shows towards *p*-aminobenzoic acid.[19]

Two replacement reactions of the sulfonic acids have been employed for the synthesis of hydroxy- and cyano-pyridines. Fusion of the sodium salt of the sulfonic acid with sodium cyanide gives the corresponding nitrile, and fusion with alkali gives the hydroxypyridine.[20,21]



These reactions are most valuable for the synthesis of the 3-substituted pyridines, since the other reactions commonly employed for ob-

14 Caldwell and Kornfeld, *J. Am. Chem. Soc.*, **64**, 1696 (1942).

15 Bernstein et al., *J. Am. Chem. Soc.*, **69**, 1158 (1947).

16 Belg. pat. 445,915 (July 31, 1942) [*C. A.*, **39**, 784 (1945)].

17 Caldwell, Tyson, and Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).

18 Erlenmeyer, Block, and Kiefer, *Helv. Chim. Acta*, **25**, 1066 (1942).

19 For a review of the question of metabolic antagonism, see Roblin, *Chem. Revs.*, **38**, 255 (1946).

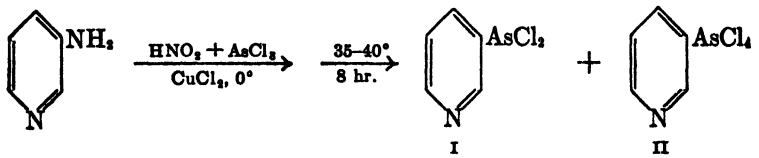
20 Webb and Corwin, *J. Am. Chem. Soc.*, **66**, 1456 (1944).

21 Wulff, Ger. pat. 541,681 (Nov. 27, 1928) [*C. A.*, **26**, 2471 (1932)].

taining cyano- and hydroxy-pyridines cannot always be applied to the synthesis of the 3 isomers.

ARSENIC DERIVATIVES OF PYRIDINE

Arsenic compounds of the pyridine series have been made and studied because of their relationship to the very valuable benzene arsenicals, Arsphenamine, Salvarsan, Mapharsen, Atoxyl, etc., which are used in the treatment of spirochetal infections. Binz and his coworkers [1] have been responsible for the major portion of these investigations on the pyridine analogs of the therapeutically active benzene arsenicals. In all the work on the pyridine arsenicals, pyridine-3-arsonic acid and its derivatives are the key intermediates. In fact, no compound of pyridine in which the arsenic atom is attached to the 2, 4, or 6 position has yet been reported. Pyridine-3-arsonic acid has been made in 6% yield by the Bart diazo reaction.[2] Binz has improved on this fundamental reaction by application of the Scheller modification in which arsenic trichloride is employed instead of potassium arsenite.[3,4] The pentavalent arsenic compound (II) can be converted into the trivalent derivative (I) by treatment with potassium iodide and sulfur dioxide. 3-Pyridylchloroarsine can be hydrolyzed to 3-arsenopyridine (80% over-all yield) or oxidized with peroxide to



I II

pyridine-3-arsonic acid (77% over-all yield). This reaction is applicable to 2-hydroxy-5-aminopyridine and 2-chloro-5-aminopyridine. 3-Pyridylchloroarsine (I) as the hydrochloride can also be made by refluxing 3-pyridylmercuric chloride with arsenic trichloride.[2]

A more direct synthesis of the hydroxyarsonic acids is by fusion with arsenic acid according to the method of Bechamp. Fair yields of 2-hydroxypyridine-5-arsonic acid (mixed with a small amount of the 2,3 isomer) have been obtained by this method. 4-Hydroxypyri-

1 A review of the accomplishments of Arthur Binz in this field is to be found in *Z. angew. Chemie*, **51**, 779 (1938).

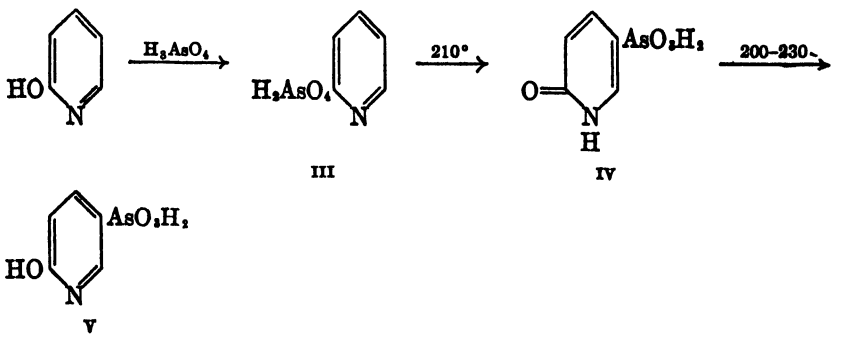
2 McCleland and Wilson, *J. Chem. Soc.*, 1497 (1932).

3 Binz and Schickh, *Ber.*, **69**, 1527 (1936).

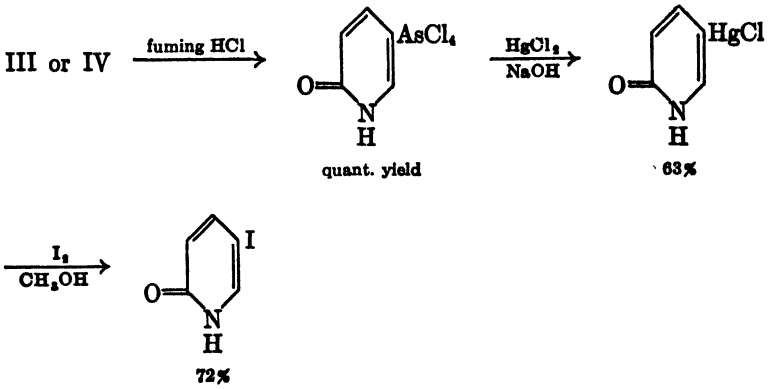
4 Ishikawa, *J. Chem. Soc. Japan*, **63**, 801 (1942) [*C. A.*, **41**, 3463 (1947)].

dine-3-arsonic acid, 2-aminopyridine-5-arsonic acid,[5,6] and 2-hydroxy-3-aminopyridine-5-arsonic acid [7,8] have also been made by this method.

A very interesting case of isomerism has been observed in the Bechamp reaction on 2-hydroxypyridine.[8] Depending on the time of heating the fusion mixture, two different substances were formed. When the fusion was conducted at 130–140° for 3 hr. and the mixture was then heated at 210° for 5 hr., a substance was obtained (28% yield) which was very difficultly soluble in water, had no melting point, and was the same as the product obtained by the Bart reaction on 2-hydroxy-5-aminopyridine. If the fusion was prolonged for 24 hr. at 210°, the product (16% yield) had the same composition as before but melted between 200 and 230° and showed a greater water solu-



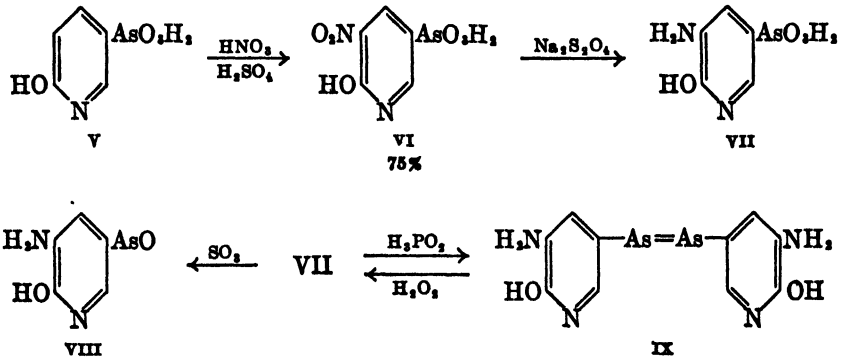
bility. The evidence that the two substances are not position isomers is good and is based on the following reactions.



5 Binz, Maier-Bode, and Rost, *Z. angew. Chem.*, **44**, 835 (1931).
6 Binz and Räth, Ger. pat. 587,896 (Nov. 7, 1931) [*C. A.*, **26**, 1301 (1932)].
7 Binz, Räth, and Urbschat, *Ann.*, **475**, 136 (1929).
8 Binz, Räth, and Maier-Bode, *Ann.*, **478**, 22 (1930).

Accordingly, Binz, Räth, and Maier-Bode [8] have considered IV and V pyridone and hydroxypyridine tautomers. The substance with the greater water solubility and lower melting point was assigned the hydroxypyridine structure.

The intermediate (V) serves for the synthesis of the pyridine analog of Salvarsan (IX).[9,10]



Mapharsen (*m*-amino-*p*-hydroxyphenylarsine oxide) is the arsenical of choice in the treatment of syphilis. The pyridine isoster is prepared by the reduction of the corresponding arsonic acid with sulfur dioxide.[7]

The pharmacology of these pyridine arsenic compounds has been published,[11] and the results indicate that compounds such as IX show a remarkable activity in experimental spirochetal infections. However, the advantages apparently are not sufficient to outweigh the increased difficulties of production, and the drugs therefore have not been employed clinically.

9 Binz and Räth, Ger. pat. 546,144 (Apr. 13, 1929) [*C. A.*, **26**, 3335 (1932)].
10 Binz and Räth, U. S. pat. 1,802,073 (Apr. 21, 1931) [*C. A.*, **25**, 3361 (1931)].
11 Schlossberger and Schüffner, *Z. angew. Chem.*, **47**, 768 (1934).

CHAPTER 9

PIPERIDINES AND PARTIALLY HYDROGENATED PYRIDINES

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CONTENTS

INTRODUCTION

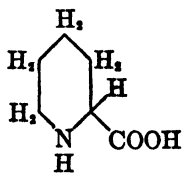
The study of piperidine chemistry has been closely associated throughout its development with the alkaloids. Piperidine is present as the amide of piperic acid in the alkaloid piperine from commercial pepper. The piperidine nucleus also occurs throughout the areca, hemlock, lobelia, and pomegranate alkaloids. In addition, it is present in a fused state in many other alkaloids such as the coca, solanaceae, lupine, and even morphine groups. Much of the work in the piperidine series has been aimed at the synthesis of these alkaloidal products or the preparation of synthetic substances with similar properties. A very large number of compounds have been made for testing as local anesthetics, the structures of which were patterned after cocaine and

contained the piperidine nucleus. Compounds patterned after the belladonna alkaloids have been made and tested as mydriatics. Since the discovery of Demerol, there have been several studies of piperidine compounds as simpler models of the morphine structures.

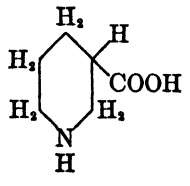
The subject of the alkaloids has been adequately treated by Henry [1] and Small,[2] and it is therefore unnecessary to consider extensively this phase of piperidine chemistry in the following pages.

The numbering in the piperidine system is the same as that in the pyridine types. The radical ($C_5H_{10}N$) is known as the piperidyl radical. A compound such as $C_5H_{10}NCH_3$, in which the substituent is on the nitrogen atom, can be named 1-piperidylmethane or piperidinomethane. The *-ino* ending is reserved for piperidine derivatives substituted on the nitrogen atom. The names of piperidine derivatives are often derived from those of the corresponding pyridine compound simply by inserting *-pe-* after the first syllable; accordingly, 2-methylpiperidine may be referred to as 2-pipecoline.

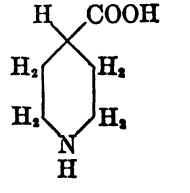
The chemistry of the pyridines and piperidines differs widely. In a very broad sense, pyridine is related to piperidine as benzene is to cyclohexane. The chemistry of pyridine is dominated by its "aromatic" character, whereas the chemistry of piperidine is primarily that of a secondary amine. Since the six-membered ring in piperidine is saturated, there exist all the possibilities of optical and geometrical isomers that are found in the cyclohexane series. Because the piperidine ring is not completely symmetrical, the position of the groups on the ring is also important in determining the number of such isomers. Accordingly, pipecolinic acid possesses an asymmetric carbon atom and can exist in *d* and *l* forms. Both of these have been obtained. The



pipecolinic acid



nipecotinic acid



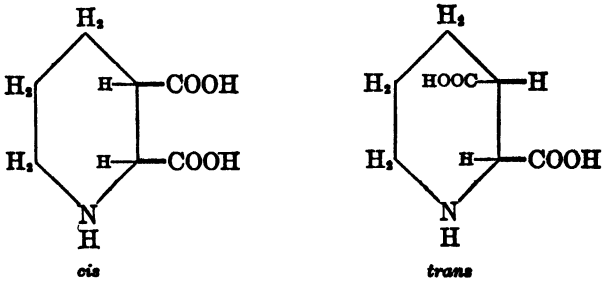
isonipecotinic acid

same consideration applies for the isomeric nipecotinic acid, but the isonipecotinic acid molecule contains a plane of symmetry. In the

1 Henry, *The Plant Alkaloids*, 4th ed., Blakiston Co., Philadelphia, 1949.

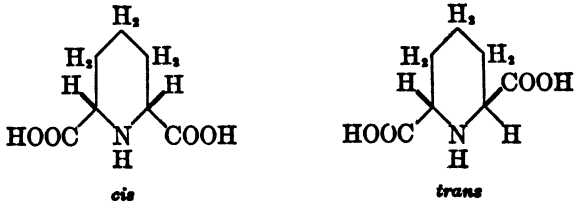
2 Small, "Alkaloids," in Gilman's *Organic Chemistry*, Vol. II, 2nd ed., John Wiley & Sons, 1943, pp. 1166–1258.

case of piperidine-2,3-dicarboxylic acid (hexahydroquinolinic acid), not only are there two asymmetric carbon atoms, but the ring also allows the existence of *cis,trans* isomers. It therefore exists in two stereochemical modifications, both of which have been resolved. A



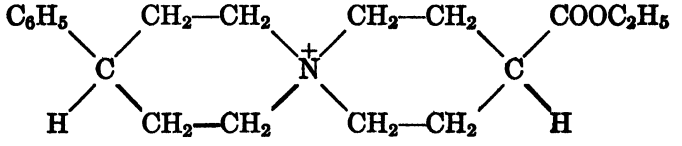
piperidine 2, 3-dicarboxylic acids

similar argument applies to the isomeric piperidine-3,4-dicarboxylic acid, but piperidine-2,6-dicarboxylic acid contains two identical asymmetric centers and therefore exists in *cis* and *trans* forms, only the latter of which may be resolved, since the *cis* form is a *meso* modification.



piperidine-2, 6-dicarboxylic acids

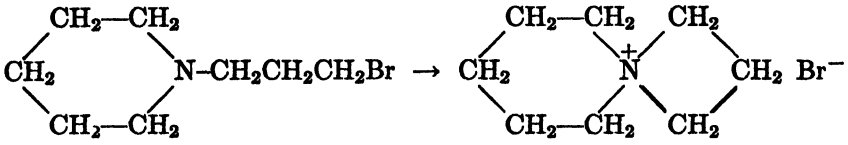
Special piperidine compounds have been of great value in the development of our knowledge of the stereochemistry of the nitrogen atom. Mills and Warren [3] prepared and resolved the following spiropiperidinium compound.



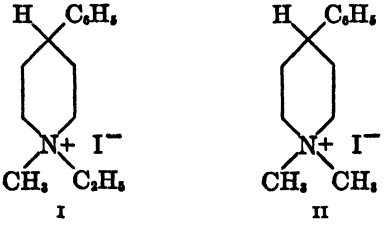
These results confirm the tetrahedral nature of the nitrogen atom and are incompatible with the pyramidal structure. Similar spiran-type

[3] Mills and Warren, *J. Chem. Soc.*, **127**, 2507 (1925).

piperidinium compounds have been obtained with three- and four-membered rings [4–6] and even with three consecutive rings.[7]



Another interesting example is the *cis,trans* isomerism of a quaternary compound such as I and the lack of such isomerism in II in which the two alkyl groups on the nitrogen atom are identical.[8] The stereo-



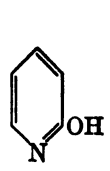
I II

chemical considerations for the quaternary nitrogen atom are therefore the same as for the carbon atom.

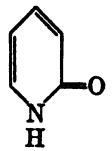
DIHYDROPYRIDINES

Frequently the difference between a pyridine compound and dihydro- or tetrahydro-pyridine derivative is merely a matter of definition. Thus, 2-pyridone may be considered as a 1,2-dihydropyridine derivative, but in its enol form, 2-hydroxypyridine, it is a true pyridine compound. From the previous discussion of such compounds, it is obvious that such a division in this and similar instances is highly artificial and undesirable. Therefore, the pyridones have been discussed in the pyridine section under the designation of hydroxypyridine compounds. There can be no doubt, however, that a compound such as N-methyl-4-pyridone is a true dihydropyridine derivative.

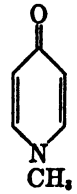
4 Gabriel and Colman, *Ber.*, **39**, 2875 (1906); **40**, 424 (1907).
5 v. Braun, *Ber.*, **39**, 4347 (1906).
6 Albert, *Ber.*, **42**, 545 (1909).
7 Scholtz, *Ber.*, **44**, 480 (1911).
8 Mills, Parkin, and Ward, *J. Chem. Soc.*, 2613 (1927).



2-hydroxypyridine

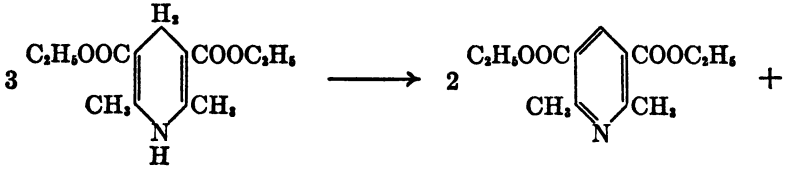


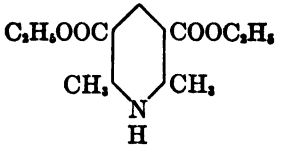
2-pyridone
(1, 2-dihydro-2-pyridone)



N-methyl-4-pyridone
(1, 4-dihydro-1-methyl-4-pyridone)

Because of their close relationship to the hydroxypyridines, however, these substances have also been described in the previous chapter. The Hantzsch synthesis from an aldehyde, acetoacetic ester, and ammonia (p. 462) leads to 1,4-dihydrolutidinedicarboxylic esters, and many variations of this reaction are possible. These compounds are valuable primarily because of their ready oxidation to pyridine derivatives, and, in fact, in certain cases the excess aldehyde in the reaction mixture accomplishes the in situ oxidation of the intermediate dihydropyridine to the true pyridine derivative. Such oxidation is sometimes accomplished at the expense of another molecule of the dihydropyridine which is in turn reduced.[9] This behavior is com-



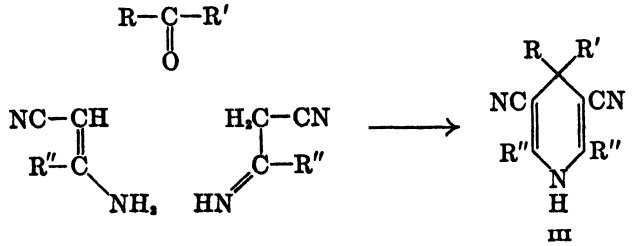


pletely analogous to the disproportionation of cyclohexene into a mixture of benzene and cyclohexane in the presence of hydrogenation catalysts.[10]

The reaction of "dinitriles" with ketones is another very successful method for obtaining dihydropyridines. Meyer[11] has made a large

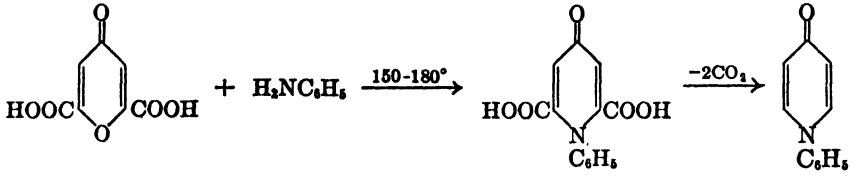
9 Knoevenagel and Fuchs, *Ber.*, **35**, 1788 (1902).
10 Zelinsky and Pawlow, *Ber.*, **66**, 1420 (1933).
11 Meyer, *J. prakt. Chem.*, [2] **92**, 174 (1915).

number of 4,4-dialkyl-1,4-dihydropyridines (III) in excellent yields by the following general reaction.

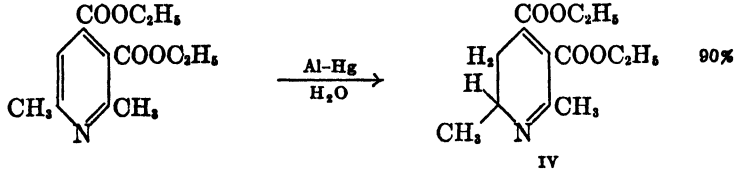


III

Dihydropyridines are also formed by the action of primary amines on pyrones such as chelidonic acid,[12] as illustrated in the formation of N-phenyl-4-pyridone.



It has been possible to accomplish the direct reduction of certain pyridine compounds, usually carboxylic acids or esters, to dihydropyridines.[13] Mumm and Beth used amalgamated aluminum in moist ether as the reducing agent. The position of the saturated bond is in



IV

some doubt, but it apparently does not involve the nitrogen atom since repeated acylation and arylation experiments of varied nature failed. The product of the reduction is characterized by its ready oxidation back to the original pyridine compound, either with chromic anhydride in acetic acid at room temperature or even by the action of the air. Although IV is stable to aqueous alkali at room temperature, cold sodium ethoxide solution or hot hydrochloric acid solution splits the ring with the liberation of ammonia. The aluminum reduc-

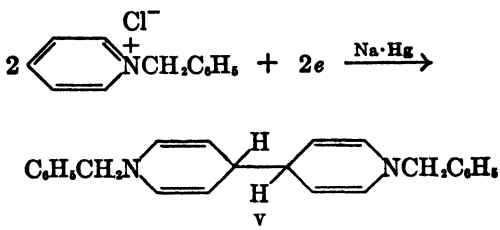
12 Smirnoff, *Helv. Chim. Acta*, **4**, 599 (1921).

13 Mumm and Beth, *Ber.*, **54**, 1591 (1921).

tion of 2,6-dimethylpyridine-3,5-dicarboxylic ester (lutidinedicarboxylic ester) gives a bright yellow dihydro compound (m.p. 136°, yield 60%) which is not the same as the dihydrolutidinedicarboxylic ester (m.p. 176–183°) obtained by the Hantzsch synthesis (p. 462). Reduction of collidinedicarboxylic ester and phenyllutidinedicarboxylic ester by this method gives products identical with those obtained in the Hantzsch synthesis.

Sodium hydrosulfite or sodium amalgam also serve for the partial reduction of pyridine compounds;[14] the former reagent was used by Karrer and Blumer (p. 564) for their synthesis of model substances related to coenzymes I and II.

A variety of reduction methods produce tetrahydrobipyridyls when applied to pyridine and pyridine derivatives. The formation of bipyridyls by the action of the alkali metals on pyridine (p. 407) passes through such tetrahydrobipyridyls. In addition, the zinc dust and acetic anhydride reduction of pyridine (pp. 407, 502) gives the stable 1,1′-diacetyl-1,1′,4,4′-tetrahydrobipyridyl, and the action of sodium amalgam on a quaternary salt such as benzylpyridinium chloride gives 1,1′-dibenzyl-1,1′,4,4′-tetrahydrobipyridyl (V).[15–25]

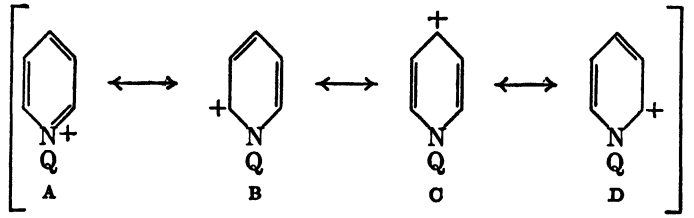


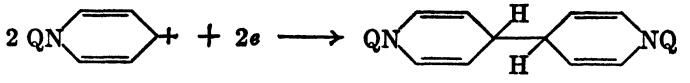
V

All reactions which produce bipyridyl derivatives by reduction of pyridines can probably be generalized as follows. The first step is the formation of a pyridinium ion with contributions from resonance states such as A, B, C, and D. Q may be a benzyl group, as given

14 Mumm and Diederichsen, *Ann.*, **538**, 195 (1939).
15 Emmert and Parr, *Ber.*, **54**, 3168 (1921).
16 Emmert, Jungck, and Häffner, *Ber.*, **57**, 1792 (1924).
17 Emmert and Varenkamp, *Ber.*, **56**, 491 (1923).
18 Emmert, *Ber.*, **52**, 1351 (1919); **53**, 370 (1920).
19 Mumm, Roder, and Ludwig, *Ber.*, **57**, 865 (1924).
20 Mumm and Ludwig, *Ber.*, **59**, 1605 (1926).
21 Weitz and König, *Ber.*, **55**, 2864 (1922).
22 Weitz and Ludwig, *Ber.*, **55**, 395 (1922).
23 Weitz and Fischer, *Ber.*, **59**, 432 (1926).
24 Weitz and Nelken, *Ann.*, **425**, 187 (1921).
25 Weitz, Roth, and Nelken, *Ann.*, **425**, 161 (1921).

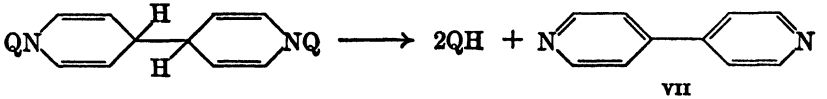
in the previous equation; it may also be an acetyl or benzoyl group; or it may be a metal such as sodium. In a reducing environment, the pyridinium ion may accept electrons in states B, C, or D, as illustrated for the 4,4′ isomer. The 1,1′,4,4′-tetrahydropyridyl (VI) may be





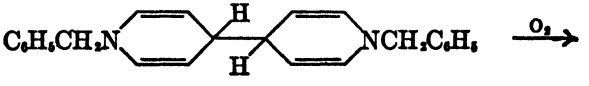
C VI

stable or it may spontaneously lose QH (C_6H_5CHO, NaH, $C_6H_5CH_3$, etc.) to give a bipyridyl.

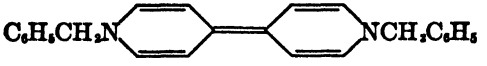


VII

The conversion to a bipyridyl may also occur by oxidation either with chromic anhydride in acetic acid or by air. When a limited amount of air is used for the oxidation of 1,1′-dibenzyl-1,1′,4,4′-tetrahydrobipyridyl (V) a deep blue solution is formed from which red crystals separate. Weitz [21,25] interprets the reaction in terms of free radical formation, but subsequent work [26,27] seems definitely to indicate that the product is the quinoid-like compound VIII.



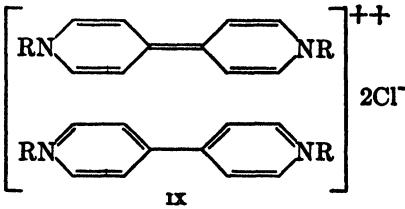
V



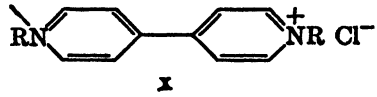
VIII

26 Müller and Wiesemann, *Ber.*, **69**, 2157 (1936).
27 Schwab, Schwab-Agallidis, and Agliardi, *Ber.*, **73**, 279 (1940).

The product (VIII) reacts with chlorine to give N,N′-dibenzyl-4,4′-bipyridinium dichloride. If VIII and N,N′-dibenzyl-4,4′-bipyridinium dichloride are heated in alcoholic solution, a violet salt (IX) is formed

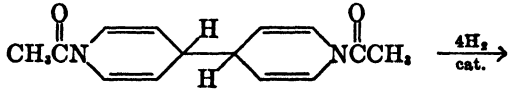


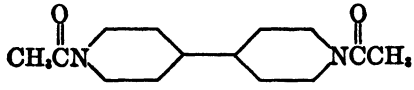
IX



X

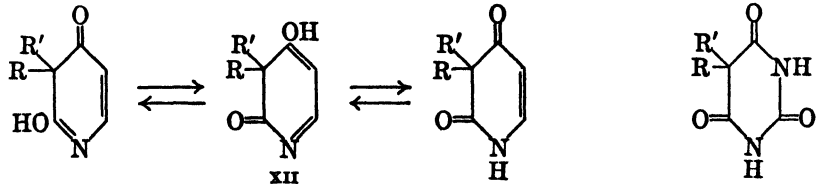
which apparently is analogous to quinhydrone and cannot have the free radical structure (X) originally assigned by Weitz. The tetrahydrobipyridyls can also be reduced to 4,4′-bipiperidyls (XI).[28]





XI

A series of 3,3-dialkyl-4-hydroxy-2,3-dihydro-2-pyridone compounds (XII) has been reported and patented as soporifics (p. 538).[29-32]



XII XIII

The relationship to the 5,5′-dialkylbarbiturates (XIII) is quite apparent. The compound (XIV) that is isosteric with barbital has been

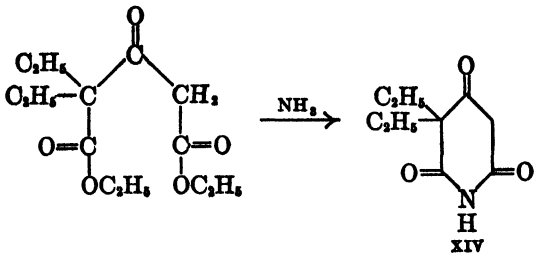
[28] Emmert and Wolpert, *Ber.*, **74**, 1015 (1941).

[29] Hoffmann-La Roche and Co., Ger. pat. 637,875 (Nov. 5, 1936) [*C. A.*, **31**, 5381 (1937)].

[30] Hoffmann-La Roche and Co., Ger. pat. 653,307 (Nov. 22, 1937) [*C. A.*, **32**, 1868 (1938)].

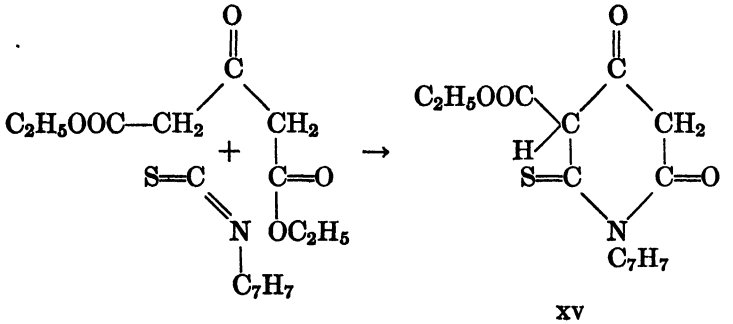
[31] Preiswerk and Schnider, U. S. pat. 2,151,047 (Mar. 21, 1939) [*C. A.*, **33**, 4744 (1939)].

[32] Kubli and Schmid, *Helv. Chim. Acta*, **28**, 213 (1945).



XIV

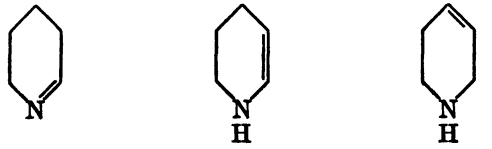
synthesized from a substituted acetonedicarboxylic ester.[33] A related compound (XV) is formed from acetonedicarboxylic ester and *p*-tolylisothiocyanate.[34]



XV

TETRAHYDROPYRIDINES

There are three possible tetrahydropyridines (called piperideines), depending on the position of the double bond. Although derivatives



2, 3, 4, 5- (Δ^1-) | 1, 2, 3, 4- (Δ^2-) | 1, 2, 3, 6- (Δ^3-)

tetrahydropyridines

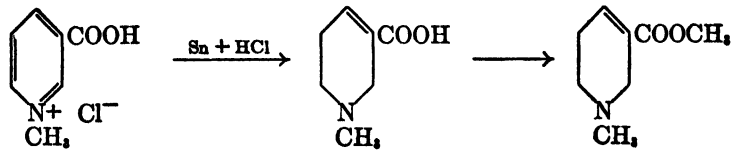
of all three types are known, only the Δ^3 compound itself has been made with any certainty. Tetrahydropyridines are formed in small amounts by the sodium and alcohol reduction of pyridines.[35-37] Since

[33] Erlenmeyer and Meyenburg, *Helv. Chim. Acta*, **20**, 1388 (1937).
[34] Worrall, *J. Am. Chem. Soc.*, **61**, 2966 (1939).
[35] Koenigs and Bernhart, *Ber.*, **38**, 3042, 3928 (1905).
[36] Koenigs, *Ber.*, **40**, 3199 (1907).
[37] Chichibabin, *Ber.*, **38**, 3834 (1905).

these tetrahydropyridines boil at approximately the same temperature as the corresponding piperidine compounds, they cannot be separated by distillation. They add bromine very readily and can, therefore, be separated in this form. The resulting dibromide is reconverted to the tetrahydropyridine by treatment with zinc dust. Since the product can be acetylated, the double bond is not in the 1,2 position and probably occupies the 3,4 position. A tetrahydropyridine is also formed by the removal of water from N-hydroxypiperidine (p. 666) [38] and by fusion of a piperidine sulfonic acid with lime (p. 676). 1,2,3,6-Tetrahydropyridine has been made from 4-bromopiperidine by treatment with base (p. 674).[39] The 4-bromopiperidine is made from 4-hydroxypiperidine; therefore, there is no doubt about the structure of this product. N-Phenyl-1,2,3,6-tetrahydropyridine has been made in an exactly analogous manner.[40]

Δ^3-Tetrahydropyridine is readily methylated to the quaternary salt with methyl iodide, and the quaternary salt is rapidly reduced by hydrogen in the presence of Adams catalyst. It has been reported that the Δ^3-tetrahydropyridines themselves are difficult to reduce.[36,41] Arecoline is the best-known example of the Δ^3-tetrahydropyridines and the most important of the alkaloids found in the fruit of the betel palm. Chewing the betel nut promotes a feeling of mild euphoria, which accounts for its use by the natives of the Philippines, other Pacific islands, and India.

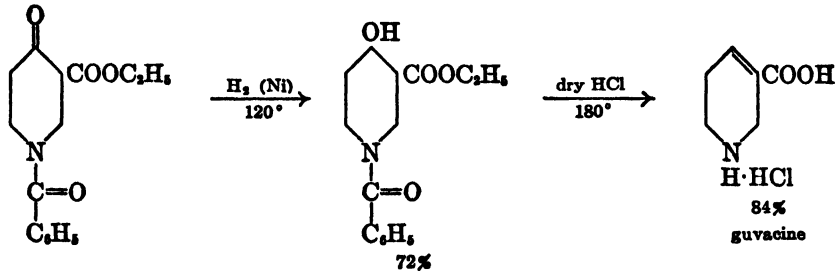
Arecoline ($C_8H_{13}O_2N$) is readily hydrolyzed into methyl alcohol and an amphoteric alkaloid arecaidine ($C_7H_{11}O_2N$), also found in the areca nut. The nitrogen atom in both arecoline and arecaidine is methylated, as indicated by liberation of methyl chloride on treatment with hydrochloric acid at 250°. It was postulated early that arecaidine was a partially saturated N-methylpyridinecarboxylic acid. Jahns [42] confirmed this theory by the synthesis of arecaidine from nicotinic acid methochloride by reduction with tin and hydrochloric acid.[42]



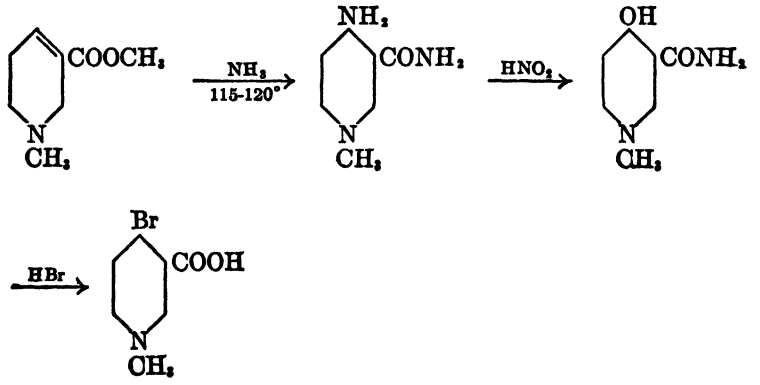
arecaidine arecoline

38 Sobecki, *Ber.*, **41**, 4107, 4109 (1908).
39 Renshaw and Conn, *J. Am. Chem. Soc.*, **60**, 745 (1938).
40 Hahn, Cerkovnikov, and Prelog, *Ber.*, **74**, 1658 (1941).
41 Winterstein and Weinhagen, *Z. physiol. Chem.*, **100**, 170 (1917).
42 Jahns, *Ber.*, **21**, 3404 (1888); **23**, 2972 (1890); **24**, 2615 (1891).

The position of the double bond is not established by this synthesis, but it seems logical to assume that it involves the β-carbon atom in the molecule, since the natural alkaloid is optically inactive. This would leave only the 2,3 or 3,4 positions available for the unsaturation. Many syntheses of arecoline and its derivatives [43-47] have established the position of the double bond beyond doubt. The most direct of these syntheses [47] proceeds from N-benzoyl-3-carbethoxy-4-piperidone, which is made from ethyl acrylate by reaction with ammonia followed by benzoylation and ring closure by the Dieckmann method (p. 655). Reduction and hydrolysis give guvacine (norarecaidine). Guvacine



is converted into arecaidine and arecoline by N methylation and esterification. Arecoline shows the reactions expected of an α,β-unsaturated ester.[48] An example is the reaction with ammonia to give the amino amide as well as some of the unsaturated amide and amino acid. The



43 Wohl and Johnson, *Ber.*, **40**, 4712 (1907).

44 Preobrazhenskii and Fisher, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 140 (1941) [*C. A.*, **35**, 5505 (1941)].

45 Ugryumov, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 829 (1941) [*C. A.*, **36**, 4125 (1942)].

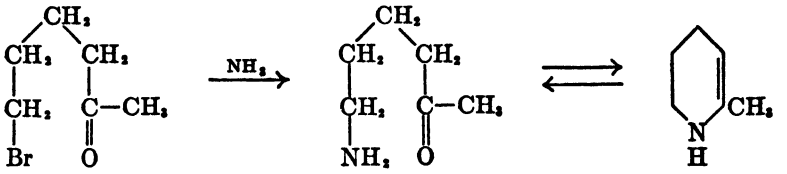
46 Dankova, Sidorova, and Preobrazhenskii, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 934 (1941) [*C. A.*, **37**, 881 (1943)].

47 McElvain and Stork, *J. Am. Chem. Soc.*, **68**, 1049 (1946).

48 Karrer and Ruckstuhl, *Helv. Chim. Acta*, **27**, 1698 (1944).

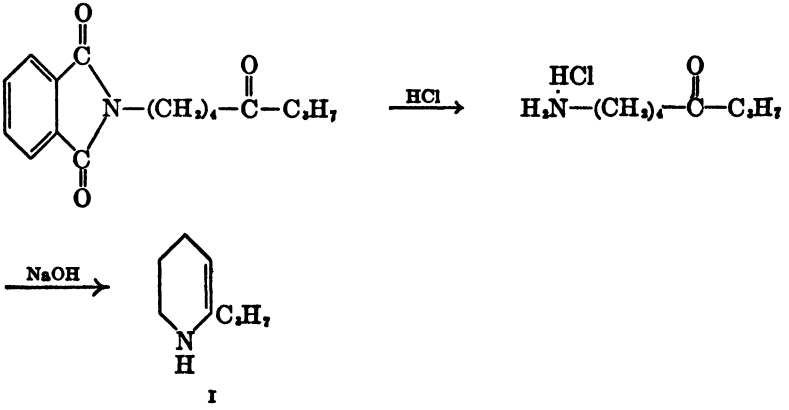
product shows the expected reactions with nitrous acid, and the resulting 4-hydroxypiperidine derivative can be dehydrated to arecaidine or treated with hydrogen bromide to give the corresponding bromo derivative.

The synthesis of 2-methyl-Δ^2-tetrahydropyridine was accomplished by Lipp [49] from δ-bromobutyl methyl ketone and ammonia. The



reaction takes the same course when a primary amine is substituted for ammonia, but a secondary amine gives the expected δ-amino ketone. From a consideration of the method of synthesis alone, the double bond could just as logically have been established from the α carbon of the ring to the nitrogen atom or to the methyl group. It appears generally accepted that the unsaturation is always in the 2,3 position.

Gabriel [50] has used the phthalimide method for the synthesis of 2-phenyl-Δ^2-tetrahydropyridine and has extended the same method to the synthesis of the alkaloid, γ-coniceine (I), which occurs naturally

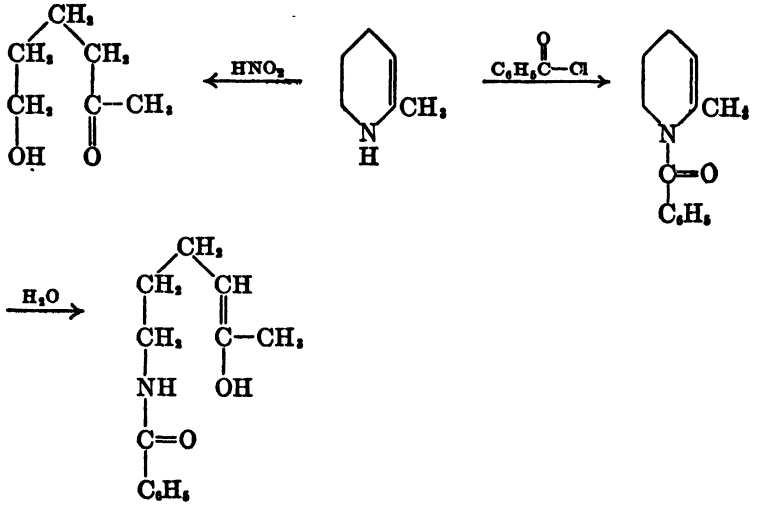


I

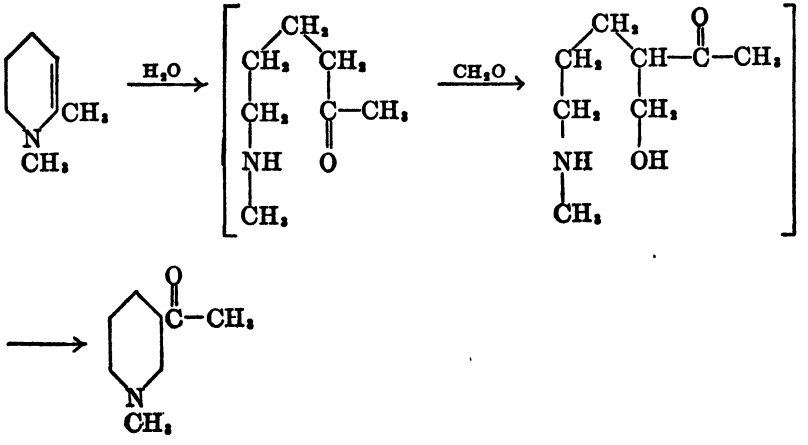
in the hemlock herb or spotted cowbane along with coniine. γ-Coniceine is also formed by bromination and dehydrohalogenation of coniine. The Δ^2-tetrahydropyridines hydrolyze readily, and, in fact,

[49] Lipp, *Ber.*, **18**, 3284 (1885); **25**, 2190 (1892).
[50] Gabriel, *Ber.*, **41**, 2010 (1908); **42**, 1242, 4059 (1909).

there is reason to believe that the 2-alkyl-Δ^2-tetrahydropyridines exist in aqueous solution to a considerable extent as the alkyl δ-aminobutyl ketones. Upon isolation, however, they readily lose water, giving back the tetrahydropyridine derivatives. The Δ^2-tetrahydropyridines are easily reduced to the piperidine derivatives and also readily undergo ring cleavage, either by benzoylation and hydrolysis or by oxidation with nitrous acid.[51] The ease of hydrolysis of the Δ^2-tetrahydropyr-



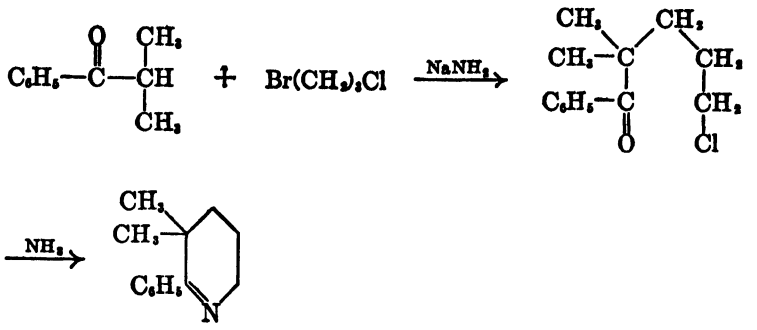
idines is further illustrated by the formation of N-methyl-3-acetylpiperidine from 1,2-dimethyl-1,2,3,4-tetrahydropyridine on treatment with formaldehyde at 0°. The reaction undoubtedly proceeds by a



[51] Lipp, *Ann.*, **289**, 173 (1896).

hydrolytic ring cleavage, followed by condensation with formaldehyde and subsequent ring closure.[52] The Δ^2-tetrahydropyridines are, in general, quite unstable as the free bases, and some can be isolated only in the form of their salts because of their tendency to polymerize.

By the simple expedient of introducing two alkyl groups in the 3 position, Haller and Ramart-Lucas [53] were able to prepare a Δ^1-tetrahydropyridine.



PIPERIDINES

Synthesis

Reduction of Pyridine Compounds. The commonest method for the synthesis of piperidine compounds is by the reduction of the corresponding pyridine derivatives. This can be accomplished by several reagents such as sodium and absolute alcohol, tin and hydrochloric acid, or hydrogen, in the presence of either nickel or noble metal catalysts. Almost all the earlier reductions of the pyridine homologs were carried out with sodium and alcohol.[54–59] A typical example is the reduction of 2,6-lutidine by sodium and alcohol to give a mixture of the racemic and *meso* forms of 2,6-dimethylpiperidine (2,6-lupetidine).[60,61] 2-Methyl-6-phenylpiperidine, obtained by the reduction

52 Lipp and Widnmann, *Ber.*, **38**, 2471 (1905).
53 Haller and Ramart-Lucas, *Ann. chim.*, [9] **8**, 5 (1917).
54 Marckwald, *Ber.*, **29**, 43 (1896).
55 Ladenburg, *Ber.*, **29**, 422 (1896).
56 Levy and Wolffenstein, *Ber.*, **28**, 2270 (1895); **29**, 1959 (1896).
57 Günther, *Ber.*, **31**, 2141 (1898).
58 Frese, *Ber.*, **33**, 3483 (1900).
59 Lipp, *Ber.*, **33**, 3513 (1900).
60 Hohenemser and Wolffenstein, *Ber.*, **32**, 2520 (1899).
61 Marcuse and Wolffenstein, *Ber.*, **34**, 2426 (1901).

of the corresponding pyridine compound, has been separated into two racemic modifications, both of which have been resolved.[62] Small amounts of tetrahydropyridines are formed by incomplete reduction of certain pyridines. In a few reductions, as with 3-ethylpyridine,[36,37] dealkylation takes place.

Except under special circumstances, catalytic methods have almost entirely replaced the reductions with sodium and alcohols. Piperidine itself is made commercially in high yield by the nickel-catalyzed reduction of pyridine without solvent at 170–200°. The small amount of unreduced pyridine is readily separated from the piperidine by careful fractionation or azeotropic distillation with water.[63]

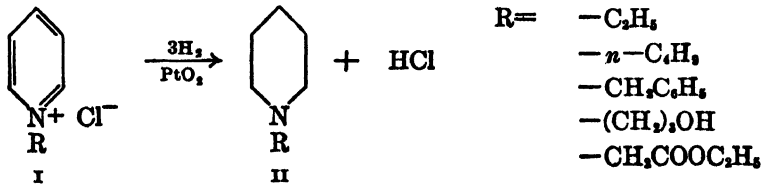
The same method is directly applicable to the reduction of the pyridine homologs.[64–66] There is generally no complication unless the temperature of reduction is raised to a point where hydrogenolysis becomes appreciable. In the reduction of pyridine at temperatures around 200° and above, amylamine, pentane, and ammonia are formed. Since active catalysts such as Raney nickel will reduce almost any pyridine compound below this temperature, this difficulty is not serious; Adkins and his students [67–70] made a study of Raney nickel as a catalyst in the reduction of pyridine compounds and found that the pyridine homologs reduce readily at temperatures from 100–200° in yields of 66–96%. The many possible methylpiperidines are readily available by this procedure; as an example, 2,6-dimethylpyridine was reduced to 2,6-dimethylpiperidine in a yield of 92%. Although the temperature necessary for the reduction of pyridine itself, over Raney nickel catalyst, is higher than that for benzene, under comparable conditions the pyridine ring in 2-phenylpyridine, 2-benzylpyridine,[70,71] and quinoline (p. 407) is preferentially reduced, whereas the benzene ring is unaffected.

A study made of the reduction of the phenylpyridines [65] revealed that 2- and 3-phenylpyridines were readily reduced with hydrogen in the presence of platinum oxide catalyst to the 2- and 3-phenylpiperi-

62 Scholtz and Müller, *Ber.*, **33**, 2842 (1900); **34**, 1616 (1901).
63 Stasse, U. S. pat. 2,363,157; 2,363,158 (Nov. 21, 1944) [*C. A.*, **39**, 3310 (1945)].
64 Adkins, *Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts*, University of Wisconsin Press, Madison, 1947, p. 66.
65 Overhoff and Wibaut, *Rec. trav. chim.*, **50**, 957 (1931).
66 Palfray, *Bull. soc. chim. France*, [5] **7**, 430 (1940).
67 Kulck and Adkins, *J. Am. Chem. Soc.*, **57**, 143 (1935).
68 Winans and Adkins, *J. Am. Chem. Soc.*, **55**, 4167 (1933).
69 Paden and Adkins, *J. Am. Chem. Soc.*, **58**, 2487 (1936).
70 Adkins et al., *J. Am. Chem. Soc.*, **56**, 2425 (1934).
71 Anker, Cook, and Heilbron, *J. Chem. Soc.*, 917 (1945).

dines but that 4-phenylpyridine was recovered unchanged. 2,6-Diphenylpyridine was reduced under the same conditions to 2,6-dicyclohexylpiperidine, but pentaphenylpyridine gave tetracyclohexylpiperidine; one molecule of benzene was removed by hydrogenolysis during the reduction. In general, the pyridine derivatives are more readily reduced than pyridine itself, and the substances with a substituent in the 2 position generally are reduced the most readily. Thus, 2-benzylpyridine is reduced to 2-benzylpiperidine in 96% yield at 100°, whereas pyridine requires a temperature approaching 200° with the same catalyst. Studies made on the velocities of reduction of the pyridine homologs by Ushakov [72,73] indicate that reduction occurs more easily as additional methyl groups are introduced into the pyridine ring, and the nearer the substituent is to the ring nitrogen, the more pronounced the effect. The nitrogen bases are strongly adsorbed by the hydrogenation catalysts; it is possible that the steric effect of the substituents adjacent to the nitrogen atom reduces this strong adsorption and resultant poisoning of the catalyst.

Platinum oxide catalyst has been used with a greater variety of pyridine compounds than has nickel. Platinum catalysts are generally poisoned by pyridine bases, but the hydrochlorides are readily reduced at room temperatures and 2–3 atm. of pressure with Adams catalyst.[74] It is not necessary, of course, to isolate the hydrochloride derivative of the base, but the equivalent procedure of reduction in a solvent to which dry hydrogen chloride (or other acid) has been added is usually just as satisfactory. Absolute ethanol and dioxane are equally successful as solvents, but 95% ethanol and commercial methanol are occasionally unsatisfactory. With acetic acid as solvent, it becomes unnecessary to convert the base to the hydrochloride. Pyridinium salts as well as the hydrochlorides are readily reduced. Hamilton and Adams [74] have reported quantitative reduction of the following substances.



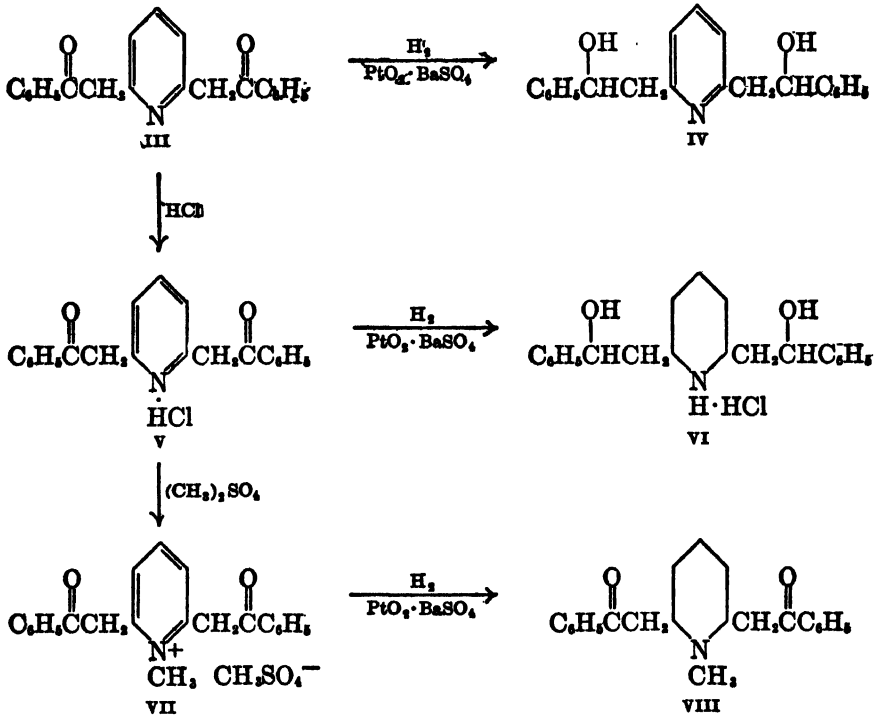
72 Ushakov and Bronevskii, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 750 (1937) [*C. A.*, **31**, 5799 (1937)].

73 Ushakov and Yakovleva, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 753 (1937) [*C. A.*, **31**, 5799 (1937)].

74 Hamilton and Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).

Without exception, the reduction of these pyridinium compounds was more rapid than the reduction of pyridine hydrochlorides under the same conditions.

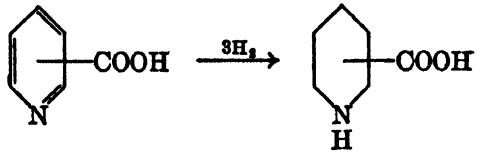
Because the reduction is applicable to so many different types of compounds and because of the mild conditions, the most convenient method for research purposes at present is catalytic hydrogenation, over platinum catalyst in acetic acid. A typical example is the reduction of 2-methyl-5-ethylpyridine (aldehyde collidine) to 2-methyl-5-ethylpiperidine (copellidine) in 80% yield.[75] Since the reduction of the pyridine ring over a noble metal catalyst proceeds very slowly except in acid solution, it is usually possible to reduce various substituents on the pyridine nucleus selectively. Scheuing and Winterhalder[76] found that, in the presence of platinum on barium sulfate, 2,6-diphenacylpyridine (III) absorbed two molar equivalents of hydrogen, at which point the reduction stopped and the product isolated was the dicarbinol (IV); but when the hydrochloride (V) was reduced under the same conditions, reduction proceeded to norlobelanidine (VI), in



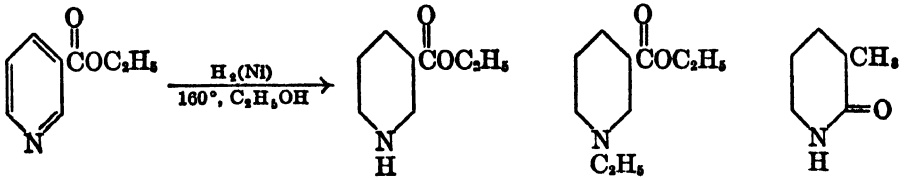
[75] Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939).
[76] Scheuing and Winterhalder, *Ann.*, **473**, 126 (1929).

which both the carbonyl groups and the pyridine ring were reduced. With the methosulfate (VII) under the same conditions, it was even possible to reduce the pyridine ring in preference to the carbonyl group with the formation of lobelanin (VIII). Either by methylation of VI or by further reduction of VIII, the alkaloid lobelanidine was obtained. These reactions illustrate the possibilities of controlled and selective reductions in the pyridine series.

Picolinic, nicotinic, and isonicotinic acids are reduced to the corresponding piperidinemonocarboxylic acids—pipecolinic, nipecotinic, and isonipecotinic acids. The reduction has been accomplished in the past with sodium and alcohol but proceeds equally as well or better with platinum catalyst in aqueous or acetic acid solution.[44,77-79] The



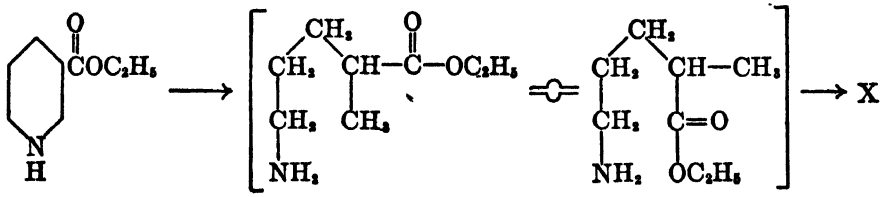
products are very soluble in water, giving neutral solutions. They are also soluble in alcohol, from which they can be crystallized by the addition of ether. These acids are reasonably stable to oxidation by acid permanganate and are sublimed without decomposition in vacuum. Pipecolinic and nipecotinic acids are asymmetric and have been resolved into *d* and *l* modifications. Since nickel reacts with acids, such catalysts cannot be used with the pyridine acids themselves, but reduction of the esters proceeds normally.[64] Reduction of ethyl nicotinate over Raney nickel catalyst in ethanol solution at 160° leads to formation of certain interesting by-products. In addition, the product contains unreduced ethyl nicotinate. The presence of ethyl N-ethyl-



nipecotinate (IX) results from alkylation by the ethanol solvent. This by-product is not formed in methylcyclohexane or dioxane, and

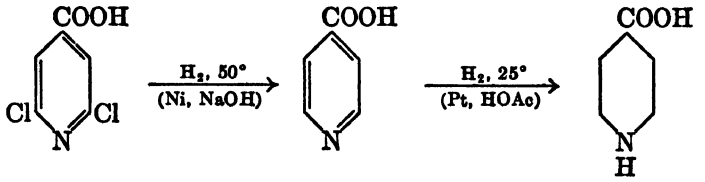
[77] Wibaut, *Rec. trav. chim.*, **63**, 141 (1944).
[78] Hess and Leibbrandt, *Ber.*, **50**, 385 (1917).
[79] McElvain and Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923).

the reduction proceeds more nearly to completion in these solvents. 3-Methyl-2-piperidone (X) must be formed by hydrogenolysis of the carbon-nitrogen bond, followed by ring closure with the elimination of

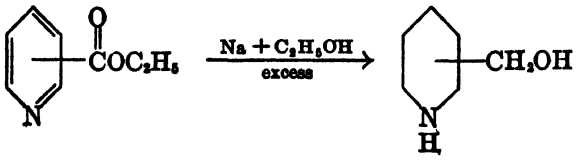


ethanol. With a kieselguhr-supported nickel catalyst in this reduction, the formation of X is greatly increased. The methyl betaine, trigonelline, is readily reduced in the presence of platinum to N-methyl nipecotinic acid.[80]

An interesting example of reduction is that of 2,6-dichloroisonicotinic acid; in very dilute sodium hydroxide solution with Raney nickel catalyst at 50° and 4 atm. of hydrogen, the reduction stops after the halogens have been removed, giving isonicotinic acid. Isonicotinic acid in glacial acetic acid with platinum catalyst at 1 atm. of hydrogen gives isonipecotinic acid. On reduction of the esters of the isomeric



pyridinemonocarboxylic acids with sodium and alcohol, both the ester group and the pyridine ring are reduced.[81–83] The two pyridine-

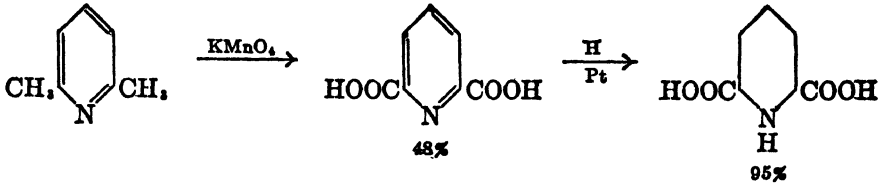


Isomer	Yield
2	28%
3	40-43%
4	42% (two steps)

dicarboxylic acids, quinolinic acid and cinchomeronic acid, have been reduced to the corresponding piperidine acids. Each has been obtained in two stereoisomeric (*cis,trans*) modifications, each of which

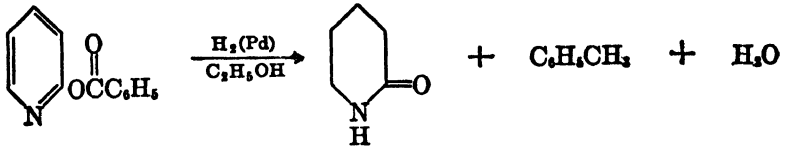
80 Winterstein and Weinhagen, *Z. physiol. Chem.*, **100**, 174 (1917).
81 Sandborn and Marvel, *J. Am. Chem. Soc.*, **50**, 563 (1928).
82 Renshaw et al., *J. Am. Chem. Soc.*, **61**, 638 (1939).
83 Clemo and Metcalfe, *J. Chem. Soc.*, 1525 (1937).

has been resolved into *d* and *l* forms.[84] The low-melting (*cis*) form is converted into the high-melting (*trans*) form if it is heated with sodium ethoxide. Pyridine-2,6-dicarboxylic acid (lutidinic acid) is reduced in acetic acid in the presence of colloidal platinum to give almost entirely one of the stereoisomeric forms of lupetidinic acid, and sodium in alcohol reduction gives a mixture of both forms.[85]



Catalytic reduction of ethyl quinolinate (2,3-dicarbethoxypyridine) over Raney nickel is quite satisfactory in dioxane at 125° (77% yield) but gives a large amount of high molecular weight substances in other solvents or at higher temperatures; 2,6-dicarbethoxypyridine reduces more rapidly (66% yield). These acids have served as extremely valuable reference substances in studies of the oxidation products of the pyridine alkaloids.

The 3- and 4-hydroxypyridines are reduced in the expected manner to hydroxypiperidines, but 2-hydroxypyridine is reduced to 2-piperidone. Cavallito and Haskell [86] have made a study of the reduction of the hydroxypyridines and their esters. With a palladium sponge catalyst, temperatures of 25–55°, 1–3 atm. of hydrogen, and dioxane or ethanol solvent, the authors found that 2-hydroxypyridine (2-pyridone) was reduced to 2-piperidone and 3- or 4-hydroxypyridine was unchanged under the same conditions. In neutral solvent, Adams catalyst and Raney nickel were ineffective in the reduction of 2-hydroxypyridine. An extremely surprising result was the great ease of hydrogenolysis of the benzoic acid esters of 2- and 4-hydroxypyridines; 2-benzoxypyridine gave toluene and 2-piperidone, whereas the



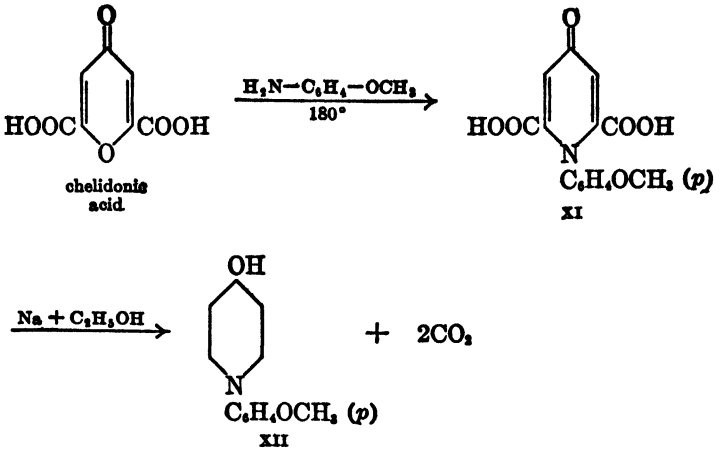
84 Besthorn, *Ber.*, **29**, 2665 (1896).
85 Hess and Wissing, *Ber.*, **48**, 1909 (1915).
86 Cavallito and Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).

isomeric 4-benzoxypyridine underwent hydrogenolysis without reduction of the pyridine ring, giving 4-hydroxypyridine and toluene. 3-Benzoxypyridine was unaffected.

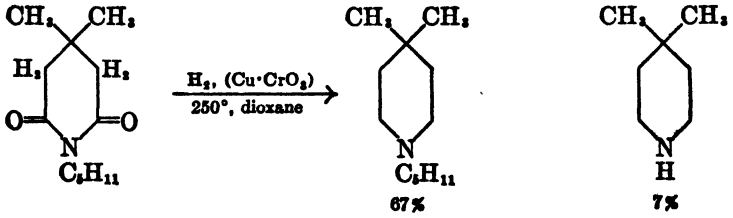
4-Hydroxypyridine is reduced with sodium and absolute ethanol to give a 30% yield of 4-hydroxypiperidine and a 50% recovery of the starting pyridine compound.[89,87,88] Renshaw and Conn [89] were unable to obtain any reduction of 4-hydroxypyridine over Adams catalyst under a variety of conditions, although Emmert has claimed to have successfully achieved the reaction with a large amount of platinum black as catalyst. Sodium and alcohol reduction of 4-methoxypyridine gave mostly piperidine and a small amount of a substance considered to be a 4-hydroxytetrahydropyridine.[87] The catalytic reduction of 3-hydroxypyridine and 5-hydroxy-3-methylpyridine over platinum catalyst has been described in the patent literature.[89,90]

All attempts to prepare 2-hydroxypiperidine have led to failure.[91] Catalytic reduction of 2-pyridone stops when 2 moles of hydrogen have been absorbed, and the only product that has been isolated is 2-piperidone. If the reduction is forced beyond this stage, hydrogenolysis takes place with cleavage of the piperidine ring and liberation of ammonia. N-Methyl-2-pyridone behaves in a similar fashion—N-methyl-2-piperidone is formed very readily, but reduction beyond this point results in rupture of the piperidine ring. The reduction of 2-methoxypyridine by all the catalytic methods gives methyl alcohol and piperidine. Sodium or sodium amalgam reduction splits the ring and liberates ammonia. It is thus apparent that the reduction of 2-hydroxypyridine is unique among the hydroxypyridines and that 2-piperidone, because of its inner amide structure, is fundamentally different from either the 3 or 4 isomer. A dihydropyridone such as N-(*p*-methoxyphenyl)chelidamic acid (XI), which is readily prepared from chelidonic acid, has been reduced to the piperidine derivative.[92] During the reduction, decarboxylation takes place and 1-(*p*-methoxyphenyl)-4-hydroxypiperidine (XII) results (51% yield). By electrolytic reduction, chelidamic acid has been reduced to 4-hydroxypiperidine-2,6-dicarboxylic acid without decarboxylation. Glutarimides (2,6-dihydroxydihydropyridines) are reduced by hydrogen over copper

87 Emmert and Dorn, *Ber.*, **48**, 687 (1915).
88 Koenigs and Neumann, *Ber.*, **48**, 961 (1915).
89 Nicodemus and Wulff, Ger. pat. 571,227 (Apr. 7, 1933); [*C. A.*, **27**, 4253 (1933)].
90 Nicodemus and Wulff, Ger. pat. 568,759 (Oct. 27, 1929) [*C. A.*, **27**, 2694 (1933)].
91 Grave, *J. Am. Chem. Soc.*, **46**, 1468 (1924).
92 Hahn, Cerkovnikov, and Prelog, *Helv. Chim. Acta*, **26**, 1132 (1943).



chromite at 250–260° and 200–400 atm. to the corresponding oxygen-free piperidine compounds.[69,93]

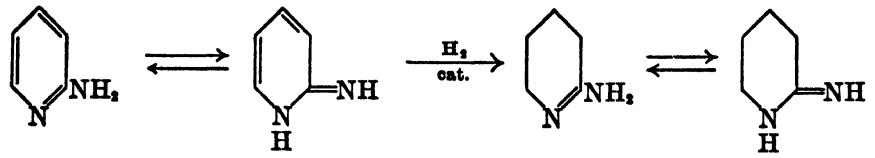


The results of the reduction of the hydroxypyridines and the aminopyridines parallel each other. 4-Aminopyridine, on reduction with sodium and alcohol,[86,87] gives a 50% yield of 4-aminopiperidine isolated as the hydrochloride, but the catalytic reduction has not been reported. 3-Aminopiperidine results from reduction of 3-aminopyridine by either sodium and alcohol or platinum and hydrogen.[94] Sodium and alcohol reduction of 2,5-diaminopyridine results primarily in the formation of 3-aminopyridine and ammonia.[95]

In complete analogy with 2-hydroxypyridine, 2-aminopyridine has not been successfully reduced to 2-aminopiperidine. It has been shown [96] that the product previously reported as 2-aminopiperidine [95] was probably pentamethylenediamine resulting from hydrogenolysis of the ring. In the platinum-catalyzed reduction of 2-aminopyridine

93 Ref. 64, pp. 117–119.
94 Nienburg, *Ber.*, 70, 635 (1937).
95 Chichibabin and Gertschuk, *Ber.*, 63, 1155 (1930).
96 Kirsanov and Ivastchenko, *Bull. soc. chim. France*, [5] 3, 2279 (1936).

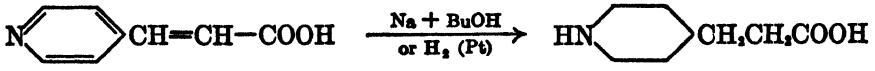
in the presence of acetic acid and acetic anhydride, it has been reported that the diacetyl derivative of 2-aminopiperidine is formed, but attempts to hydrolyze the product resulted in the formation of a polymer.[97] The catalytic reduction of 2-aminopyridine over platinum black or colloidal platinum gives 2-iminopiperidine, a cyclic amidine.[91]



Attempts to carry the reduction of 2-iminopiperidine further with sodium and alcohol or catalytically with Adams catalyst result primarily in the formation of piperidine and ammonia. Birkofer[98] has studied the reduction of 1-benzyl-2-pyridoneimine and 2-(benzylamino)pyridine. The former compound gave as primary products 2-iminopiperidine and toluene; from 2-(benzylamino)pyridine, since the benzyl group was not removed by hydrogenolysis, the product was 2-(benzylimino)piperidine. Hydrolysis of either 2-iminopiperidine or 2-(benzylimino)piperidine with 2 *N* sodium hydroxide gives 2-piperidone.

The successful reduction of any of the halogenated pyridines to halogen piperidines has not been reported. It has been adequately demonstrated with 2- and 4-chloropyridine derivatives that the first step in the reduction is removal of the halogen by hydrogenolysis and that reduction of the pyridine ring is a subsequent step.

Many pyridine side-chain compounds have been reduced to the corresponding piperidine derivatives. The reduction of β-(3-ethyl-4-pyridyl)acrylic acid to homocincholoipon (p. 584) by Rabe has already been mentioned. The similar reduction of β-(4-pyridyl)acrylic acid (XIII) (p. 494) with sodium and butanol to β-(4-piperidyl)propionic acid (XIV) gives a 22% yield,[99] but, if the reduction is conducted with hydrogen and platinum oxide catalyst in dilute hydrochloric acid solution, a quantitative yield of XIV may be obtained.[100]

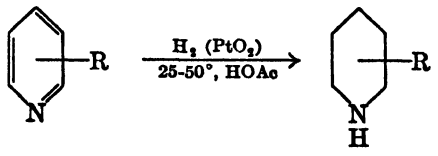


XIII XIV

97 Ivastchenko and Kirsanov, *Bull. soc. chim. France*, [5] **3**, 2289 (1936).
98 Birkofer, *Ber.*, **75**, 429 (1942).
99 Koelsch, *J. Am. Chem. Soc.*, **65**, 2460 (1943).
100 Kleiman and Weinhouse, *J. Org. Chem.*, **10**, 562 (1945).

γ-(2-Pyridyl)butyric acid was reduced in this same manner to γ-(2-piperidyl)butyric acid in 97% yield.[101] This product is of interest because of its conversion to the cyclic amide, norlupin-4-one on distillation.

A large number of pyridine side-chain alcohols have been catalytically reduced to the corresponding piperidine alcohols. The yields seem to be the best when platinum oxide in acetic acid is employed. The reductions were conducted at about 3 atm. of hydrogen and usually required from 8–10 hr.[102,103] Since most of these pyridine alcohols

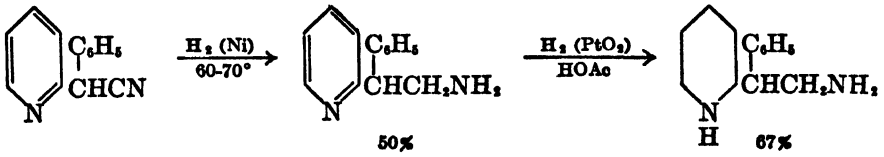


R	Yield(%)
2—CH_2CH_2OH	82
2—$CH_2CH_2CH_2OH$	89
4—CH_2CH_2OH	59
4—$CH_2CH_2CH_2OH$	83
4—$CH_2CH_2CH_2CH_2OCH_3$	94
4—$CH_2CH_2CH_2OCH_3$	87–5

are easily obtained by methods already outlined, the piperidine alcohols are likewise readily available starting materials. Their diphenylacetic acid esters and diphenyleneacetic acid esters have been studied as antispasmodics. The alcohol can be methylated prior to reduction, and the product is then an N-methylpiperidine derivative, or the piperidine alcohols can be readily methylated in good yields if heated with formaldehyde and formic acid at 140°.

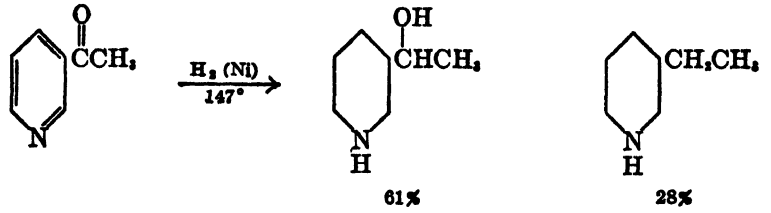
2-Cyanopyridine is reduced to 2-aminomethylpiperidine (61% yield),[104,105] and δ-(3-pyridyl)butylamine is reduced to the corresponding piperidine derivative (65% yield) [106] by catalytic reduction over platinum oxide in acid solution.

An example of the selective reduction of a pyridine compound is illustrated by the following stepwise reactions.[107]

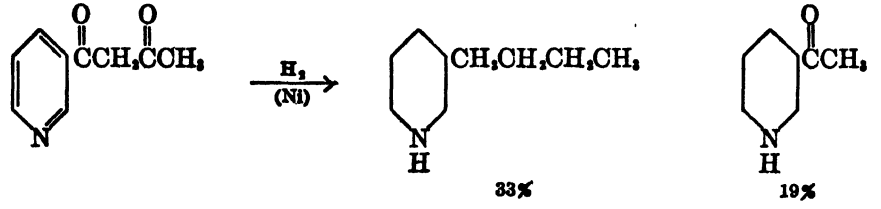


101 Doering and Weil, *J. Am. Chem. Soc.*, **69**, 2464 (1947).
102 Burtner and Brown, *J. Am. Chem. Soc.*, **69**, 630 (1947).
103 Norton et al., *J. Am. Chem. Soc.*, **68**, 1572 (1946).
104 Reihlen et al., *Ann.*, **493**, 20 (1932).
105 Norton et al., *J. Am. Chem. Soc.*, **68**, 1330 (1946).
106 Haines, Eisner, and Woodward, *J. Am. Chem. Soc.*, **67**, 1258 (1945).
107 Panizzon, *Helv. Chim. Acta*, **29**, 324 (1946).

Kuick and Adkins[67] have obtained very interesting results on the reduction of 3-acetylpyridine, over Raney nickel catalyst. Although a 61% yield of methyl-3-piperidylcarbinol, the expected product, was obtained, some 3-ethylpiperidine was also formed. Methyl-3-pyridyl-



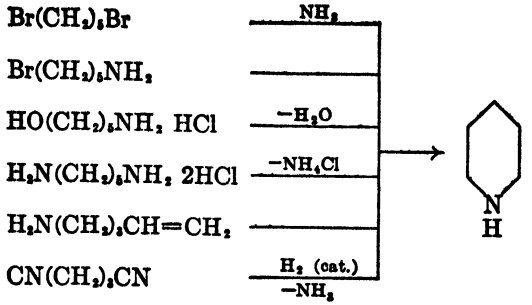
carbinol could not be isolated, although the carbonyl group is usually reduced with much greater ease than the pyridine ring. In addition, the reduction of the β-diketone, 3-acetoacetylpyridine, with Raney nickel catalyst at 150–160° in dioxane gives not only 3-butylpiperidine but also 3-acetylpiperidine in which the pyridine ring is reduced in



preference to the carbonyl group. This illustrates further possibilities in selective reduction with different catalysts and conditions and also indicates the impossibility of predicting the course of a selective reduction with certainty on the basis of the ease of reduction of the respective groups separately.

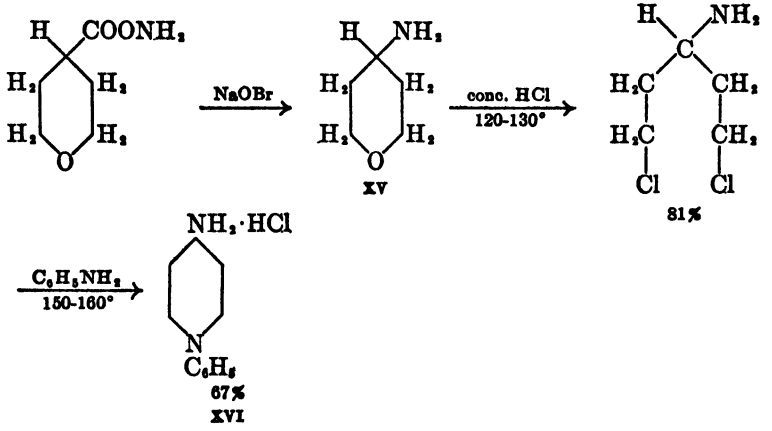
Ring-Closure Reactions at the Nitrogen Atom. A large variety of methods are available for building up the piperidine ring from aliphatic compounds. Most, but not all, of these have as their last step the closing of the piperidine ring at the nitrogen atom and therefore depend on obtaining as the starting material a suitable 1,5-dihalide, 1,5-aminohalide, 1,5-amino alcohol, 1,5-diamine, 4,5-unsaturated amylamine, 1,3-dinitrile, etc. The reactions are exemplified by the following equations.[108]

[108] These reactions have been reviewed by Hollins in *Nitrogen Ring Compounds*, Van Nostrand Co., London, 1924, pp. 187–238.



Usually the major portion of the synthetic problem is the preparation of the desired aliphatic starting material. It is not the purpose of this review to go into the synthesis of these starting materials, but an attempt will be made to indicate the availability or method of synthesis of some of the more important of these.

From 1,5 Dihalides. If an ammoniacal ether solution of 1,5-dibromopentane is refluxed, piperidine is formed; with a primary amine, an N-substituted piperidine is the product.[109] Until about 1940, the best method of obtaining 1,5-dibromopentane was from piperidine (p. 669), and this particular synthesis is, therefore, of only theoretical interest. The method does have very distinct advantages in the synthesis of some special piperidine derivatives. Hahn, Cerkovnikov, and Prelog [92] have prepared 1-phenyl-4-aminopiperidine (XVI) by this method, as indicated in the following sequence of reactions.

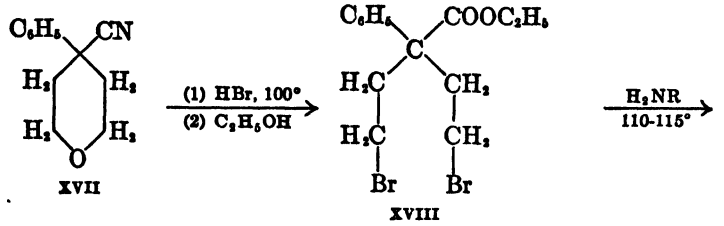


4-Aminotetrahydropyran (XV) was also converted to 4-dimethylaminotetrahydropyran by methylation with formaldehyde and formic

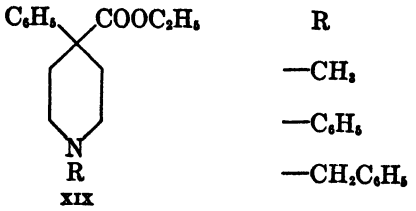
[109] v. Braun, *Ber.*, **41**, 2156 (1908).

acid, and this was likewise changed via the dichloride to 1-phenyl-4-dimethylaminopiperidine in slightly better yields. These final compounds show powerful spasmolytic activity.

The cleavage of a pyran ring has also been used by Walton and Green [110] to obtain a valuable 1,5-dibromo derivative for the synthesis of the analgesic, Demerol (XIX, R = CH_3) (see p. 658).

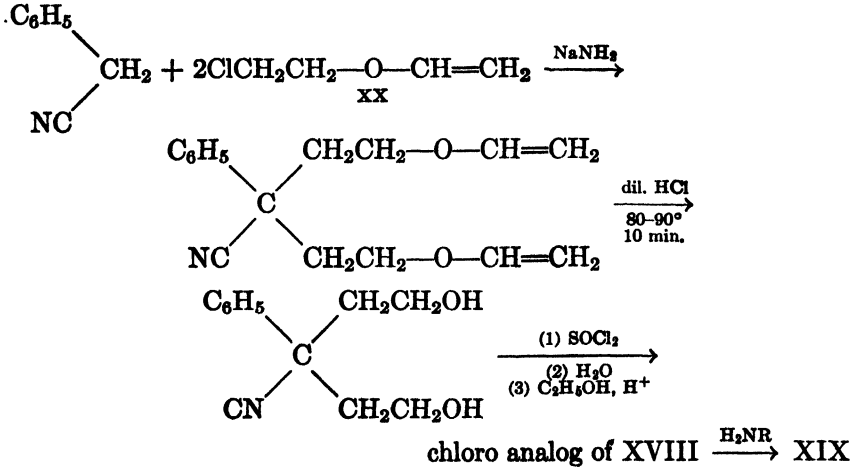


XVII XVIII



XIX

Similar reactions have been patented by Bergel et al.[111] The 1,5 dihalide was prepared from β-chloroethyl vinyl ether (XX), as indicated in the following equations.

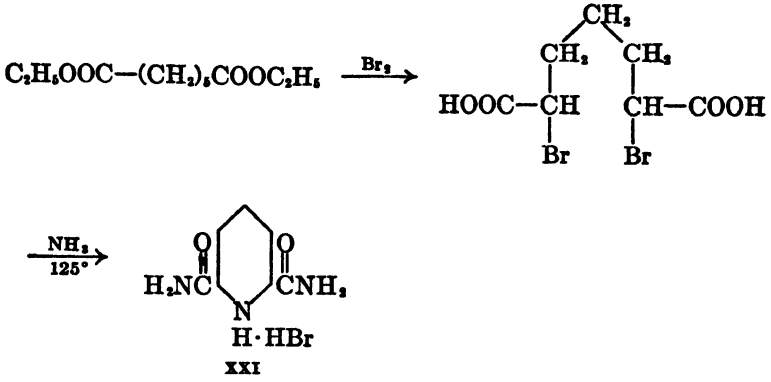


chloro analog of XVIII $\xrightarrow{H_2NR}$ XIX

[110] Walton and Green, *J. Chem. Soc.*, 815 (1945); Brit. pat. 566,307 (Dec. 21, 1944).

[111] Bergel et al., U. S. pat. 2,398,575 (Apr. 16, 1946) [*C. A.*, **40**, 4396 (1946)]; Brit. pat. 550,963 (Feb. 2, 1943) [*C. A.*, **38**, 1752 (1944)].

Ethyl pimelate gives ethyl α,α'-dibromopimelate on bromination, and this 1,5-dibromo compound is converted into a mixture of the two stereoisomeric modifications of piperidine-2,6-dicarboxylic acid amide (XXI) on treatment with ammonia,[85,112] and into N-substituted derivatives on treatment with primary amines.[113] The product (XXI)



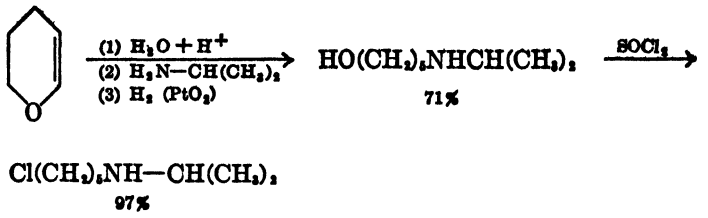
XXI

is prepared more readily by catalytic reduction of pyridine-2,6-dicarboxylic acid, obtained by the oxidation of 2,6-lutidine,[85] and subsequent conversion to the amide.

If a limited amount of a secondary amine is used in the reaction with 1,5-dibromopentane, ring closure still takes place, forming a piperidinium bromide,[109,114] but, with an excess of the secondary amine, a substituted 1,5-diaminopentane results.

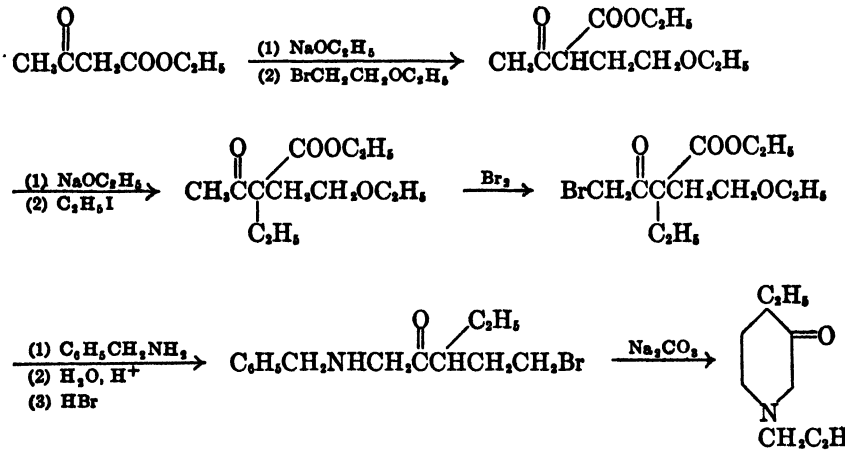
From 1,5-Aminohalides. The difference between the reactions of ammonia with a 1,5-dihalide and the reaction of a 1,5-aminohalide to give piperidines is only a matter of definition, since the 1,5-aminohalides are undoubtedly formed as intermediates in the reactions which have just been considered. ϵ-Chloroamylamines are completely stable in the form of their hydrochlorides but are immediately converted into piperidines upon neutralization.[108] The synthesis of ϵ-chloroamylamines and β-alkyl-ϵ-chloroamylamines can be accomplished by the condensation of γ-phenoxypropyl chloride with malonic ester or alkylmalonic esters. These syntheses, however, are not of preparative value, except for very special compounds. A superior synthesis for the preparation of ϵ-chloroamylisopropylamine [115] proceeds from the readily available dihydropyran (p. 348).[116] This 1,5-aminohalide is per-

112 Fischer, *Ber.*, **34**, 2543 (1901).
113 Braun and Leistner, *Ber.*, **59**, 2323 (1926).
114 Scholtz and Wolfrum, *Ber.*, **43**, 2317 (1910).
115 Drake et al., *J. Am. Chem. Soc.*, **68**, 1530 (1946).
116 Schniepp and Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946).

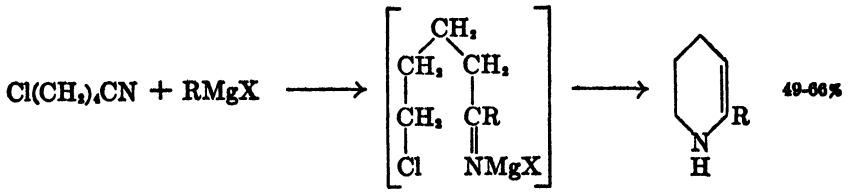


fectly stable as the hydrochloride but readily cyclizes to N-isopropylpiperidine on neutralization.

An example of the preparation of a special piperidine from a 1,5-aminohalide is illustrated by the following synthesis of 1-benzyl-4-ethyl-3-piperidone.[117] δ-*t*-Aminoamyl halides slowly cyclize in the

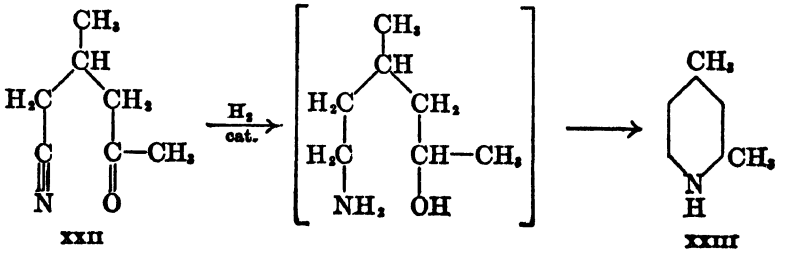


form of the free bases to give quaternary piperidinium salts.[118] A closely related piperidine synthesis is the reaction of Grignard reagents upon δ-chlorovaleronitrile.[119] The products are readily reduced to the saturated piperidine compounds.



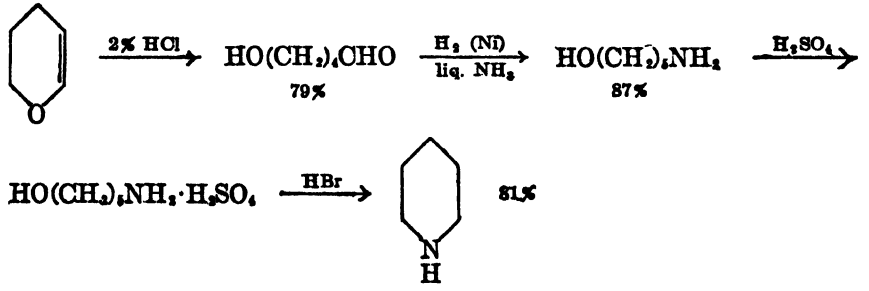
117 Work, *J. Chem. Soc.*, 194 (1946).
118 Mannich and Lesse, *Arch. Pharm.*, 271, 92 (1933).
119 Salathiel, Burch, and Hixon, *J. Am. Chem. Soc.*, 59, 5361 (1937).

From 1,5-Amino Alcohols. It was at one time thought that 1,5-amino alcohols were incapable of existence in the free state but immediately underwent internal condensation to form piperidines. The formation of 2,4-dimethylpiperidine XXIII, instead of the amino alcohol, by reduction of the keto nitrile (XXII) and other similar results led to



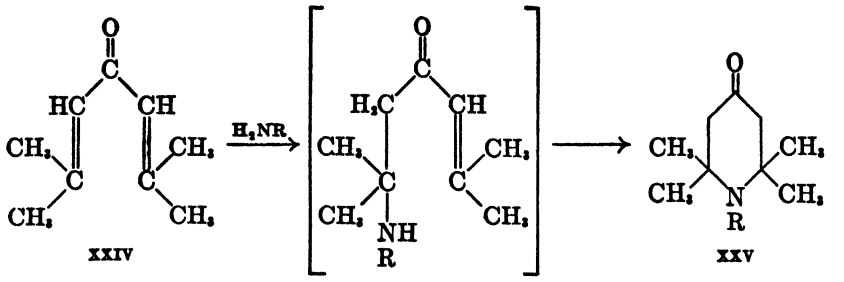
XXII XXIII

this belief.[120,121] However, 1-amino-5-pentanol has been made from dihydropyran[122] and is stable to distillation. It is converted into piperidine in good yield if its acid sulfate is refluxed with constant boiling hydrobromic acid.

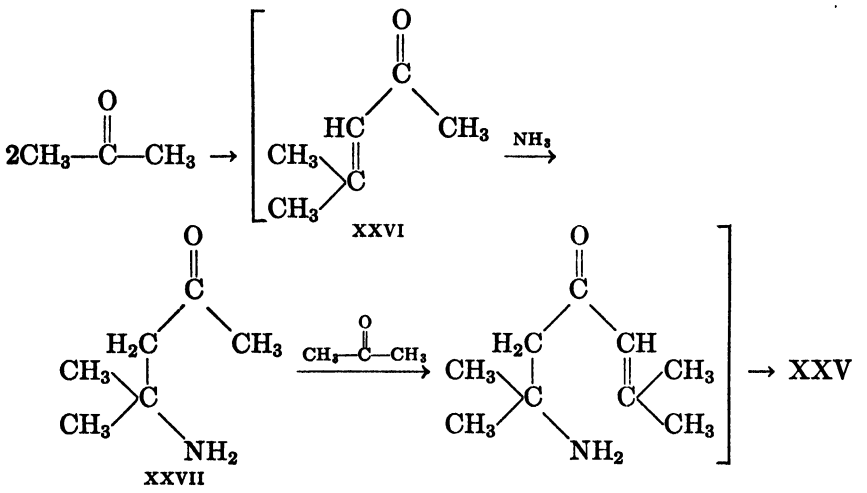


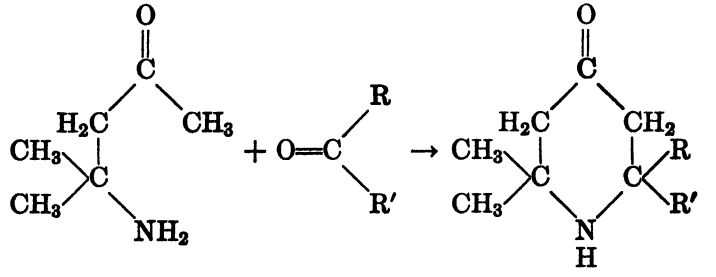
From 4,5-Unsaturated Amines. Phorone (XXIV), or similar compounds such as benzalmesityl oxide, reacts with ammonia or primary amines to give piperidine derivatives (XXV).[123–126] Although the intermediate has not been separated, the reaction is assumed to take place, as indicated, by the addition of a molecule of the primary amine to the α,β-unsaturated carbonyl compound followed by a second intramolecular addition to form the piperidine derivative.

120 Rupe and Stern, *Helv. Chim. Acta*, **10**, 859 (1927).
121 Wohl and Maag, *Ber.*, **43**, 3280 (1910).
122 Woods and Sanders, *J. Am. Chem. Soc.*, **68**, 2111 (1946)
123 Ref. 108, pp. 209–210.
124 Harries and Lehmann, *Ber.*, **30**, 231, 2735 (1897).
125 Pauly, *Ber.*, **32**, 2244 (1899).
126 Nazarov and Khomenko, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, **1944**, 137, 226 [*C. A.*, **39**, 1621 (1945)].



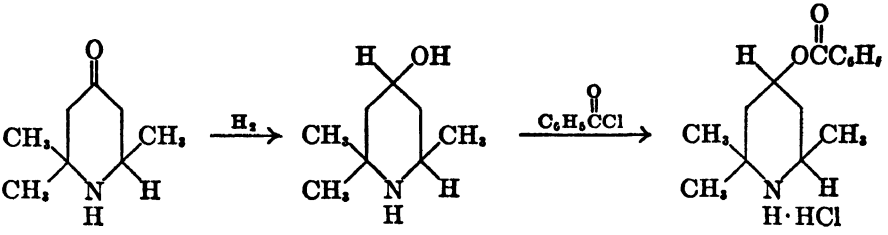
When ammonia is added to acetone under proper conditions, a very small yield (approximately 1%) of the piperidine compound, triacetonamine (XXV, R = H), is obtained.[123,127] This condensation takes place through the intermediates, mesityl oxide (XXVI) and diacetonamine (XXVII). With diacetonamine (XXVII) and an aldehyde or ketone, a large variety of piperidine derivatives can be formed in



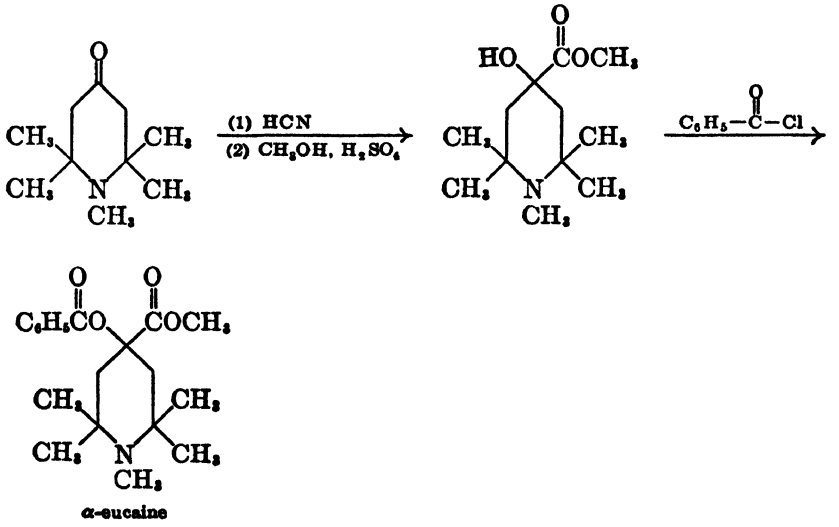


127 See also Bradbury, Hancox, and Hatt, *J. Chem. Soc.*, 1394 (1947).

good yields.[128] The corresponding product obtained from acetaldehyde, known as vinyl diacetonamine, is formed in 90% yields. The discovery of the hypnotic properties of the alkamine reduction product (XXVIII) and the local anesthetic properties of the benzoic acid ester (XXIX) and mandelic acid ester led to extensive study of this reaction and to the issuing of many patents covering the conditions and various products.

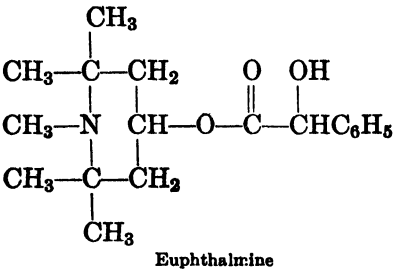


α-Eucaine was made from triacetonamine through a cyanohydrin synthesis. Although α-eucaine is approximately as effective as cocaine as a local anesthetic, its injection is accompanied by local irritation and it has been replaced by the simpler β-eucaine hydrochloride (XXIX) (Betacaine, Racemic Benzamine) which is equally active and does not show the same undesirable side effects. XXIX has the addi-

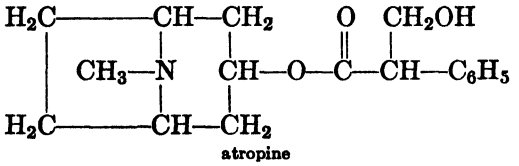


128 Fischer, *Ber.*, 16, 649, 1604 (1883); 17, 1789 (1884).

tional advantage of being stable to sterilization in boiling solution for short periods, and it has found limited use as a local anesthetic. The relationship of Euphthalmine (the mandelate ester of reduced N-methyl triacetonamine) to atropine is apparent in the two following formulas. Both compounds show marked mydriatic action.



Euphthalmine



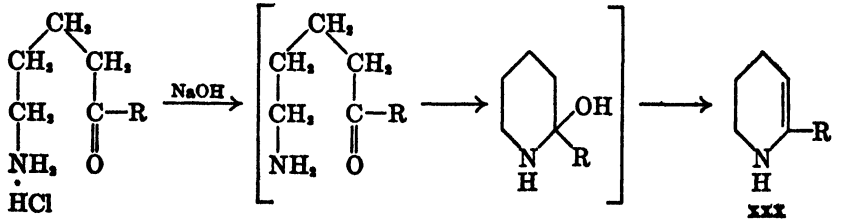
atropine

From 1,5-Diamines. Ladenburg originally prepared piperidine by heating the hydrochloride of pentamethylene diamine.[129] This reac-

$$HCl \cdot H_2N(CH_2)_5NH_2 \cdot HCl \rightarrow C_5H_{11}N \cdot HCl + NH_4Cl$$

tion is not practical because of the difficulties of obtaining the 1,5-diamines, and frequently the reactions which would be expected to give the 1,5-diamine by reduction give the piperidine derivative directly.

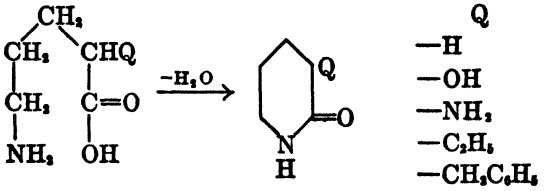
From δ-Aminocarbonyl Compounds. The ring closure of δ-amino ketones has been discussed in connection with the Δ^2-tetrahydropyridines (p. 629). This reaction is essentially the intramolecular addition of a 5,6-unsaturated amine. It is very similar to the reaction discussed earlier (p. 648), with the exception that the unsaturation is that of carbon to oxygen instead of carbon to carbon.



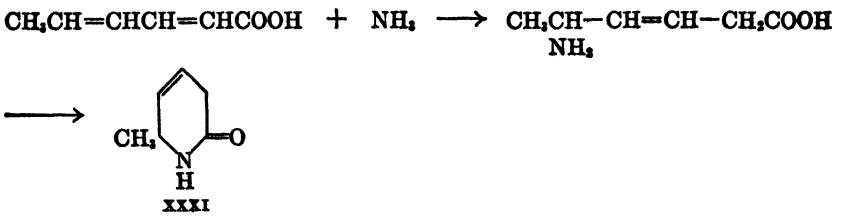
XXII

[129] Ladenburg, *Ber.*, **17**, 388, 513 (1884); **18**, 3100 (1885); *Ann.*, **247**, 1 (1888).

δ-Aminovaleric acid and its derivatives are converted into the corresponding lactam or 2-piperidone when heated.[130–132] δ-Aminovaleric

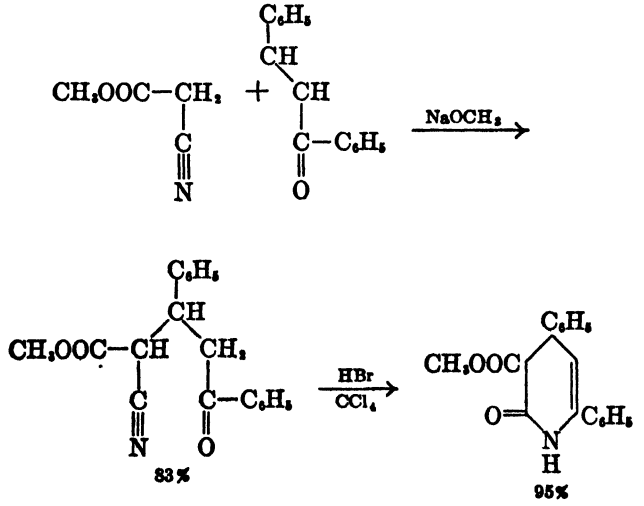


acid itself can be obtained from N-benzoylpiperidine by permanganate oxidation and acid hydrolysis; this series of reactions therefore allows 2-piperidone to be made from piperidine (see also p. 669). The commercially available sorbic acid adds ammonia to give an unsaturated lactam, XXXI, which on reduction gives 6-methyl-2-piperidone.



XXXI

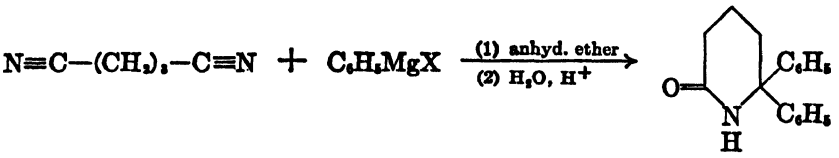
By the addition of ethyl cyanoacetate, cyanoacetamide, malononitrile, phenylacetonitrile, etc., to α,β-unsaturated ketones, it is possible



130 Ref. 108, pp. 195–197.
131 Hunter and Woodward, *Biochem. J.*, **35**, 1298 (1941).
132 Dieckmann, *Ber.*, **38**, 1657 (1905).

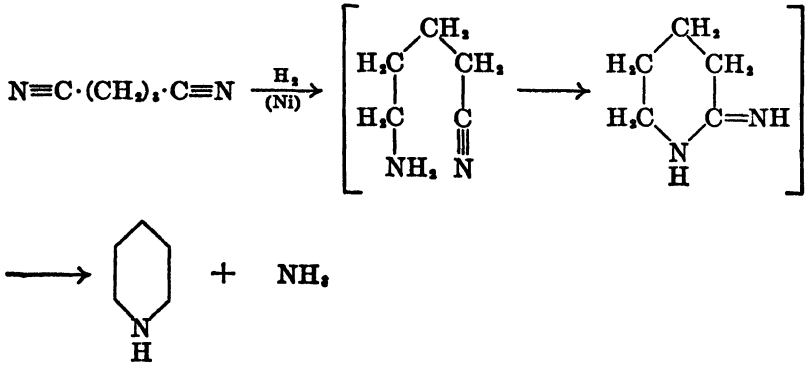
to obtain a great variety of closely related δ-ketonic nitriles which change more or less rapidly into tetrahydropyridones.[133]

A complex but related reaction is the formation of piperidines by the action of Grignard reagents on 1,3-dicyanopropane.[134] The course



of the reaction must also be related to that involved in the Grignard reaction on glutarimides (p. 672).

From the Reduction of 1,3-Dinitriles, 1,3-Cyano Esters and 1,4-Aminonitriles. The reduction of 1,3-dicyanopropane (glutaronitrile) gives only a very poor yield of the normal product, pentamethylene diamine (15–20%), the major product being piperidine (50–70%).[69] The amount of piperidine formed is reduced only slightly when the reaction is conducted in the presence of added ammonia. The inter-



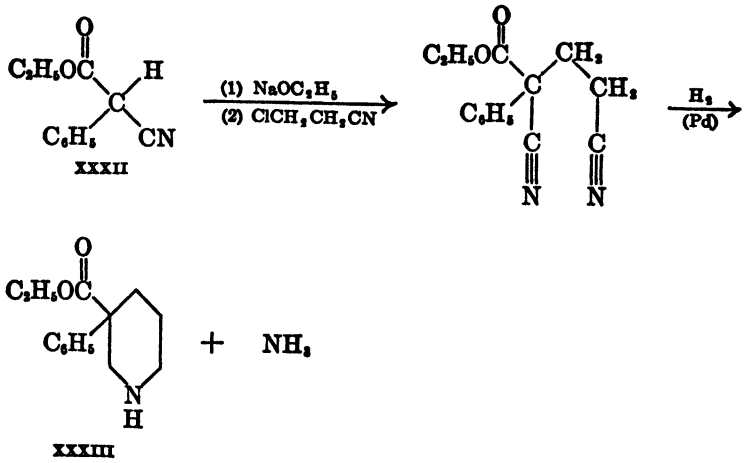
mediate probably is a δ-imino- or δ-amino-nitrile which, however, has never been isolated from the products of reduction. Considered from this viewpoint, the reduction is very similar to that of the δ-amino-carbonyl compounds just discussed. Koelsch [135] has reported that the reaction fails with phenyl- and α,β-diphenyl-glutaronitriles; however, with α-phenyl-α-carbethoxyglutaronitrile,[136] reduction gives the piperidine derivative in the expected manner. It is interesting to note that

133 Kohler, Graustein, and Merrill, *J. Am. Chem. Soc.*, **44**, 2536 (1922).

134 Bruylants and Dewael, *Bull. sci. acad. roy. Belg.*, [5] **12**, 464 (1926) [*C. A.*, **21**, 1108 (1927)].

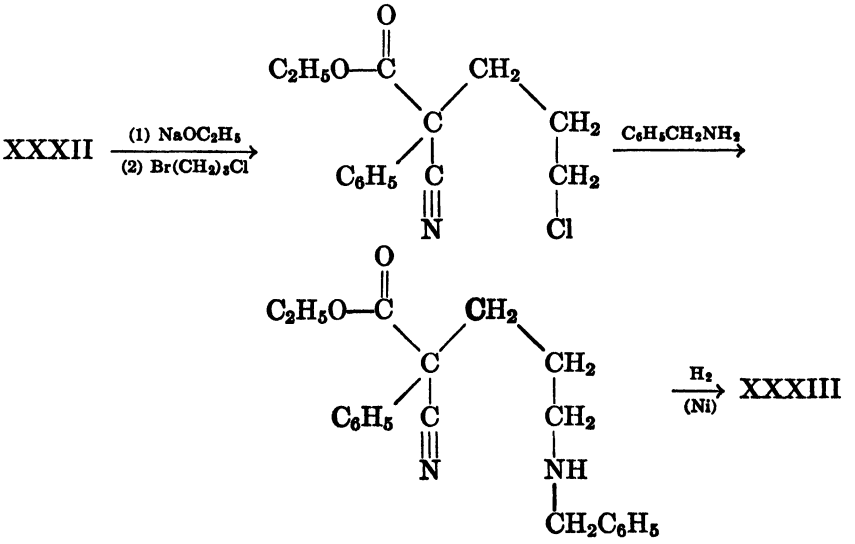
135 Koelsch, *J. Am. Chem. Soc.*, **65**, 2093 (1943).

136 Bergel, Morrison, and Rinderknecht, Brit. pat. 564,741 (Oct. 11, 1944) [*C. A.*, **40**, 4085 (1946)].



XXXII XXXIII

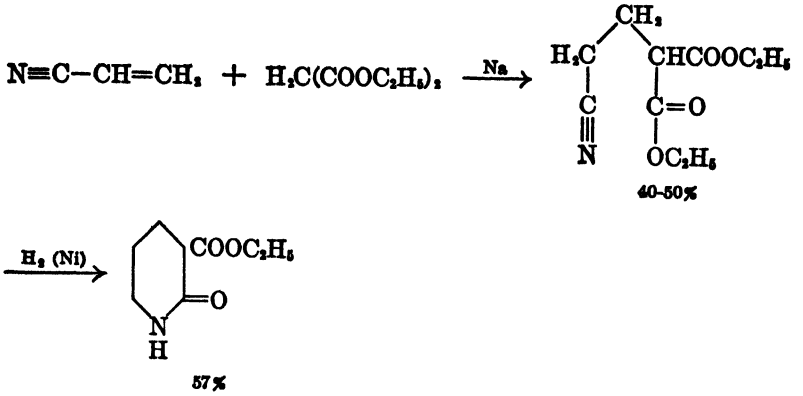
in the intermediate which is reduced both the cyano and carbethoxy groups are in the γ position to the second nitrile group. It is, therefore, possible for the condensation to proceed, involving either the cyano or ester group, giving a six-membered ring. Apparently the condensation with the nitrile group takes precedence over condensation with the carbethoxy group, since 3-cyano-3-phenyl-2-piperidone was not reported. The same product is formed in the reduction of a δ-cyanoamine.[137] In the reduction, hydrogenolysis of the benzyl group



[137] Bergel et al., *J. Chem. Soc.*, 269 (1944); Brit. pat. 563,665 (Aug. 24, 1944) [*C. A.*, 40, 3142 (1946)].

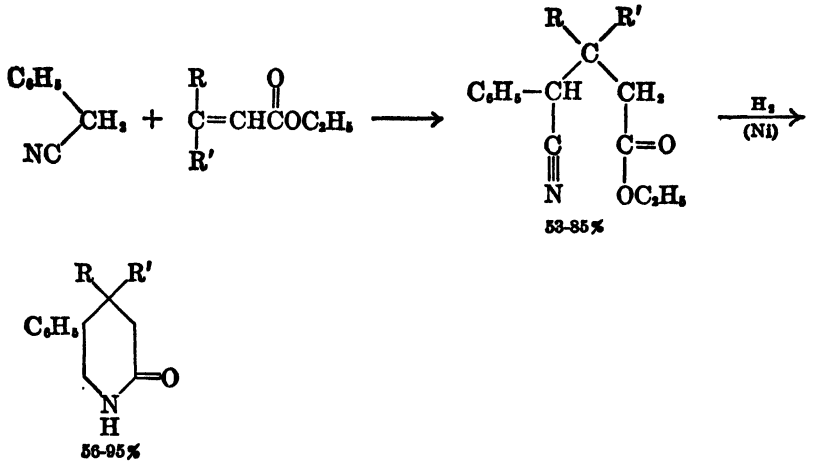
gives the aminonitrile, which then undergoes intramolecular condensation to form the piperidine derivative. With dibenzylamine both benzyl groups are removed by hydrogenolysis and XXXIII is still formed, but with methylbenzylamine the product is an N-methylpiperidine derivative.

The reduction of 1,3-cyano esters, which is very similar to the above examples, has been studied extensively by Koelsch [99] and has led to the preparation of a large number of 2-piperidones. In one of the simplest examples, the 1,3-cyano ester is prepared by a Michael condensation between acrylonitrile and malonic ester, and the subsequent reduction of the product is carried out at 140° and under 200 lb. of hydrogen in the presence of Raney nickel catalyst. From β-(methoxymethyl)-

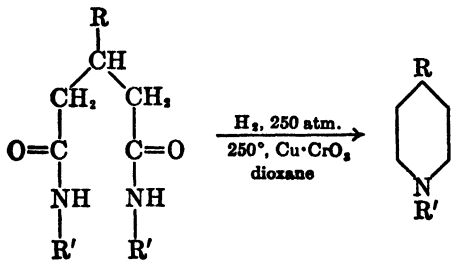


acrylonitrile, 4-methoxymethyl-3-carbethoxy-2-piperidone was formed in 77% yield. If methyl acrylate is condensed with cyanoacetic ester and the product is reduced, 5-carbomethoxy-2-piperidone is formed in excellent yield. When ethyl cinnamate replaced methyl acrylate, an 85% yield in the Michael condensation and a 67% yield of 4-phenyl-5-carbethoxy-2-piperidone on reduction were obtained.[138] By the same essential steps—a Michael condensation with a substituted acrylonitrile or acrylic ester followed by reduction—alkyl, aryl, and carbethoxy piperidines have been prepared.[135,139–141] When R and R′ are different, a mixture of *cis* and *trans* modifications is formed in the reduction.

138 Koelsch, *J. Am. Chem. Soc.*, **65**, 2459 (1943).
139 Koelsch, *J. Am. Chem. Soc.*, **65**, 437 (1943).
140 Koelsch and Raffauf, *J. Am. Chem. Soc.*, **66**, 1857 (1944).
141 Barr and Cook, *J. Chem. Soc.*, 438 (1945).



The amides of glutaric acid and substituted glutaric acids undergo ring closure on reduction at high temperatures and pressures over copper-chromite catalyst.[69] Glutaramide, itself, gives piperidine in 74% yield, and reduction works equally well for the substituted derivatives.

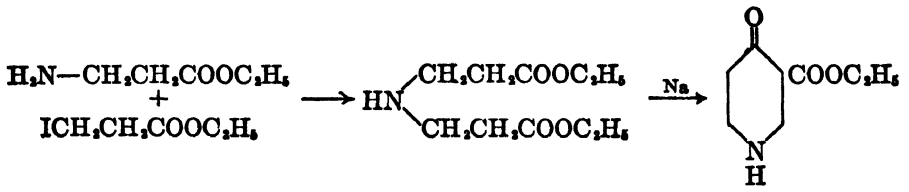


R	R′	Yield(%)
—H	—H	70
—H	$-CH_2CH_2C_6H_5$	77
$-CH_3$	$-CH_2CH_2C_6H_5$	70
$-C_6H_5$	$-CH_2CH_2C_6H_5$	70
—H	$-C_5H_{11}$	74
$-CH_3$	$-C_5H_{11}$	62
$-C_6H_5$	$-C_5H_{11}$	72
$-C_6H_5$	$-CH_2C_6H_5$	65

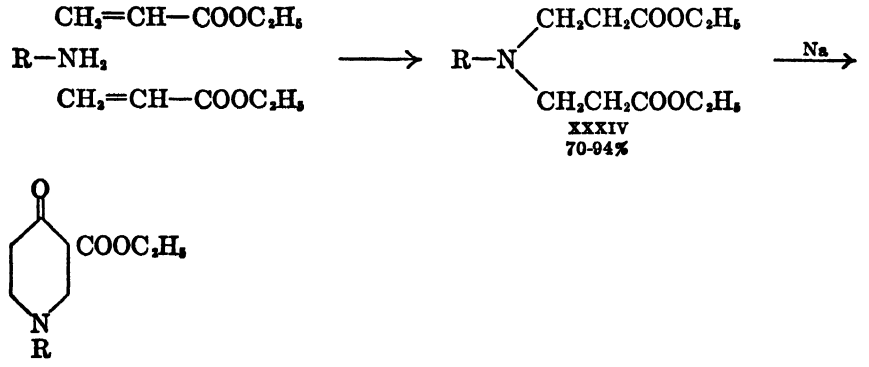
When an N,N,N′,N′-tetraalkylglutaramide is reduced under these conditions, the N,N,N′,N′-tetraalkylpentamethylenediamine is formed. Hydrogenolysis of the N-alkyl group is an important side reaction at the temperature of these reductions.

Ring Closure between Carbon Atoms. In the synthesis of *pyridine* and its derivatives from aliphatic substances, all reactions of any importance complete the ring closure at the nitrogen atom. One of the more important *piperidine* syntheses, however, involves the Dieckmann condensation of suitable dicarboxylic esters or nitriles, in which the ring closure is completed between the carbon atoms in the β,γ

positions.[142] The first of such ring closures was reported by Ruzicka and Fournasir,[143] who treated ethyl β-iodopropionate with ethyl β-aminopropionate to obtain di-(β-carbethoxyethyl)amine. On treatment with sodium, this gave a very poor yield of 3-carbethoxy-4-piperidone by an intramolecular Claisen condensation. Since the prod-



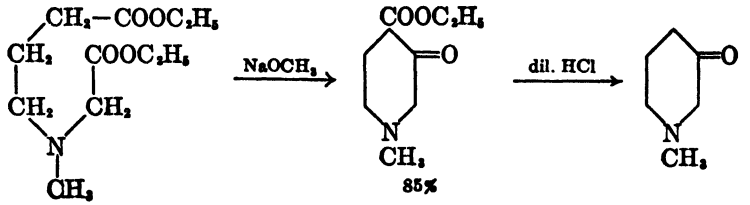
uct is a β-keto ester, it can be hydrolyzed and decarboxylated to give 4-piperidone. Although the over-all yields are quite poor, attempts to prepare 4-piperidone by either the reduction of 4-pyridone or the oxidation of 4-hydroxypiperidine have been unsuccessful. Further study of this Dieckmann reaction [144] resulted in a slightly better procedure, but the low yield is apparently inherent. However, the yields are generally good when a tertiary amine is employed.[46,47,145–151] In addition, the starting esters (XXXIV) can be made in excellent yields



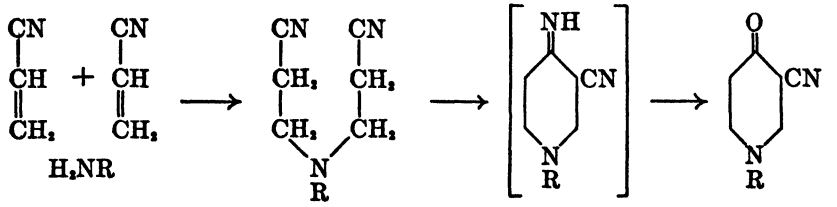
XXXIV
70-94%

142 Ref. 108, pp. 237–238.
143 Ruzicka and Fournasir, *Helv. Chim. Acta*, **3**, 806 (1920).
144 Kuettel and McElvain, *J. Am. Chem. Soc.*, **53**, 2692 (1931).
145 McElvain, *J. Am. Chem. Soc.*, **46**, 1721 (1924); **48**, 2179 (1926).
146 Thomas and McElvain, *J. Am. Chem. Soc.*, **54**, 3295 (1932).
147 Prill and McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933).
148 Thayer and McElvain, *J. Am. Chem. Soc.*, **49**, 2862 (1927).
149 Fuson, Parham, and Reed, *J. Am. Chem. Soc.*, **68**, 1239 (1946).
150 Howton, *J. Org. Chem.*, **10**, 277 (1945).
151 Ziering et al., *J. Org. Chem.*, **12**, 894 (1947).

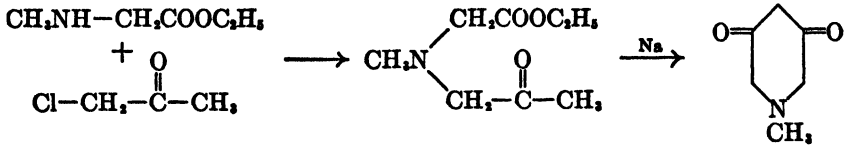
by the addition of primary amines to ethyl acrylate.[147] This reaction has been successfully conducted with compounds in which R was an alkyl group from methyl through amyl, as well as phenyl, benzyl, β-phenylethyl, and benzoyl. That the ring will form from an unsymmetrical amino diester is illustrated by the following synthesis of N-methyl-3-piperidone.



The intermediate β-keto ester may possibly have the isomeric N-methyl-2-carbethoxy-3-piperidone structure in which the ring was completed to the carbon atom attached to the nitrogen, but, from analogous reactions, the above structure seems more probable. 3-Piperidone would result from the hydrolysis and decarboxylation of either isomer. The reaction is equally successful if acrylonitrile is substituted for ethyl acrylate, the product being a 3-cyanopiperidone.[152,153]

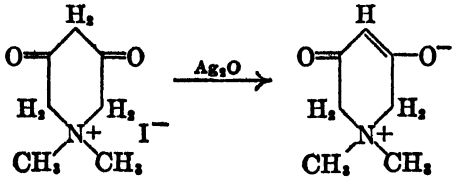


A very similar condensation is illustrated by the following synthesis of N-methyl-3,5-diketopiperidine.[154] The product shows the reactions

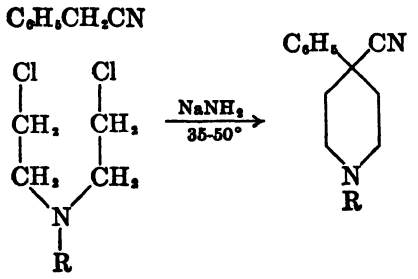


of a tertiary amine and a β-diketone. Of special interest is the formation of an enol betaine from its quaternary salt.

152 Cook and Reed, *J. Chem. Soc.*, 399 (1945).
153 Bachman and Backer, *J. Am. Chem. Soc.*, 69, 1535 (1947).
154 Gustafsson, *Ber.*, 70, 1591 (1937).



A second important reaction in which the ring is completed through establishment of a carbon-to-carbon bond was discovered by Eisleb.[155] A di(β-chloroethyl)amine derivative is condensed in the presence of sodium amide with a substance such as phenylacetonitrile bearing two active hydrogens on the α-carbon atom. Malonic ester,[71] as well as



R	Yield (%)
CH_3	66
C_6H_5	40
$CH_2C_6H_5$	60
$SO_2C_7H_7$	37

such substances as fluorene, N-methyloxindol, phenylbenzylsulfone, and methane sulfonic acid diethylamide, can be substituted for the phenylacetonitrile.

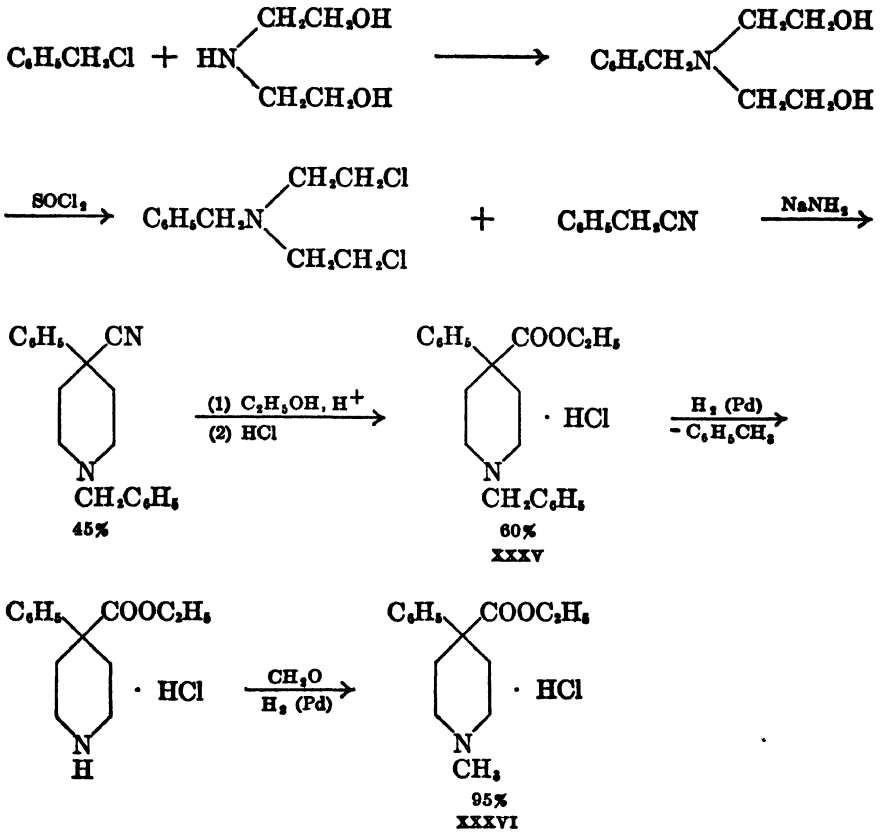
Much of the recent interest in the piperidines has been stimulated by the discovery of the drug Demerol (XXXVI) by the I. G. Farbenindustrie workers.[156,157] This substance possesses powerful analgesic properties and has found considerable application as a morphine substitute. Its synthesis can be accomplished according to the method already indicated by the condensation of phenylacetonitrile with di(β-chloroethyl)methylamine in the presence of sodium amide. However, the di-β-chloroethylamine derivative belongs to the class of compounds known as nitrogen mustards and is a potent vesicant. As a consequence, the commercial procedure starts from the much less active products, di-(β-chloroethyl)benzylamine or N,N-di-(β-chloroethyl)sulfonamide. Complete details for the commercial process using the former substance were obtained from captured German docu-

155 Eisleb, *Ber.*, **74**, 1433 (1941).

156 Eisleb and Schaumann, *Deut. med. Wochschr.*, **65**, 967 (1939) [*C. A.*, **33**, 9442 (1939)].

157 Eisleb, U. S. pat. 2,167,351 (July 25, 1939) [*C. A.*, **33**, 8923 (1939)].

ments.[158] The reaction proceeds according to the following equations, with an over-all yield of about 25% of Demerol (XXXVI).



A large number of compounds of this general type have been made in which the methyl, ethyl, and phenyl groups have been widely varied, but Demerol appears to show the maximum activity.[158]

Ring Closure from Several Fragments. An ingenious synthesis of piperidine compounds is the method developed by Petrenko-Kritschenko [159–162] in which two molecules of benzaldehyde are condensed with ammonia (or a primary aromatic or aliphatic amine) and an ester of acetonedicarboxylic acid.

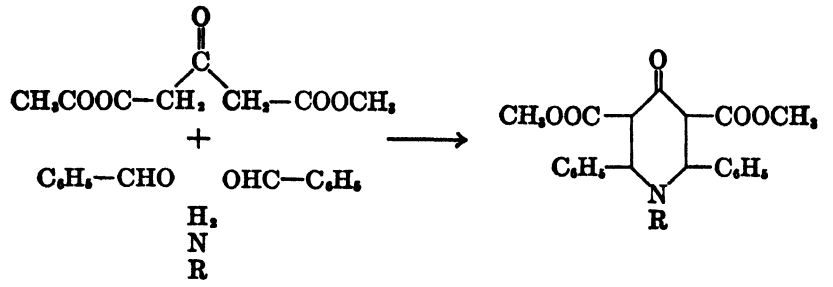
158 *U. S. Dept. Commerce, Office of Technical Services Report* PB981, pp. 85–95.

159 Petrenko-Kritschenko et al., *Ber.*, **39**, 1358 (1906); **40**, 2882 (1907); **41**, 1692 (1908); **42**, 2020, 3683 (1909).

160 Petrenko-Kritschenko, *J. prakt. Chem.*, [2] **85**, 1 (1912).

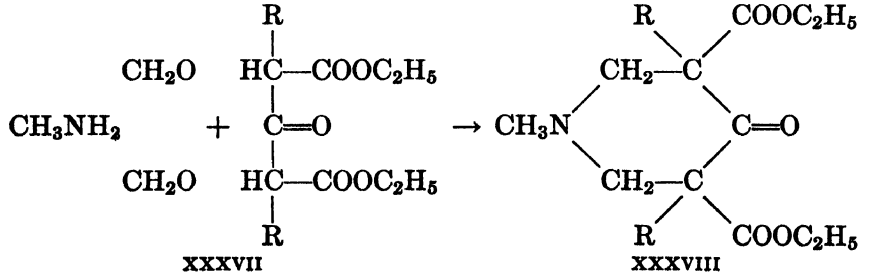
161 Mannich and Mohs, *Ber.*, **63**, 608 (1930).

162 Mannich, *Arch. Pharm.*, **272**, 323 (1934).



R	Yield (%)
—H	80
—CH_3	65
—C_2H_5	--
—C_6H_5	--
—CH_2CH_2OH	--

The reaction is successful when acetaldehyde is substituted for benzaldehyde (46% yield),[46,163,164] although it has been reported to fail with formaldehyde.[143] Ethyl α,α'-diethylacetonedicarboxylate (XXXVII, R = C_2H_5) reacts with formaldhehyde and methylamine, however, to give a piperidone (XXXVIII, R = C_2H_5, 40% yield).[165] Only two active hydrogen atoms are available on the substituted ethyl acetonedicarboxylate, and these are in the 1,3 position. Accordingly, the formation of the many possible by-products by further condensation of formaldehyde is eliminated, and the yield of piperidone is fairly good. When R in the equation is H, further condensation

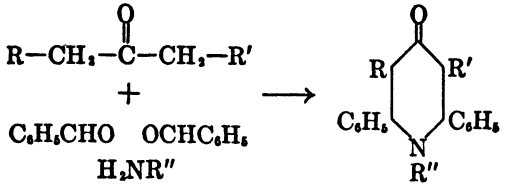


XXXVII XXXVIII

with formaldehyde and methylamine can take place to give bicyclic pyridones known as bispidins (p. 664). Attempts to conduct the same reaction on simple ketones instead of acetonedicarboxylic esters were

163 Mannich, Ger. pat. 510,184 (June 3, 1927) [*C. A.*, **25**, 1037 (1931)].
164 Mannich and Veit, *Ber.*, **68**, 506 (1935).
165 Mannich and Schumann, *Ber.*, **69**, 2299 (1936).

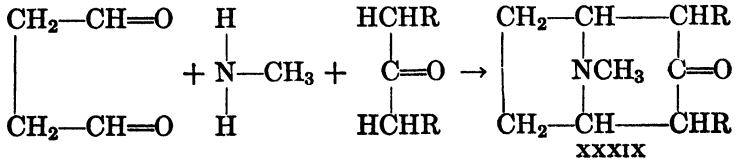
unsatisfactory until Baliaha [166,167] found that this reaction proceeds with exceptional ease when acetic acid is the solvent. The yields were



R	R′	R″	Yield (%)
$-CH_2CH_3$	$-CH_2CH_3$	$-H$	75
$-CH_2CH_3$	$-CH_2CH_3$	$-CH_3$	50
$-CH_3$	$-CH_2CH_3$	$-H$	40
$-CH_3$	$-CH_2CH_3$	$-CH_3$	40
$-C_3H_7$	$-C_3H_7$	$-H$	48
$-C_3H_7$	$-C_3H_7$	$-CH_3$	30
$-CH_3$	$-CH_2CH(CH_3)_2$	$-H$	20

highest with ammonia (R″ = H) and were poorer as the size of the R group increased. On the other hand, benzaldehyde can be readily replaced with other aromatic aldehydes such as anisaldehyde, piperonal, and veratraldehyde without substantially altering the yields. This same fundamental reaction has been employed by Böhm and Stöcker [168] in which acetoacetic ester replaces the ketone in the above equation or replaces the methyl acetonedicarboxylate in the method of Petrenko-Kritschenko. The condensation is conducted in the presence of malonic acid.[169,170] *m*-Nitrobenzaldehyde, anisaldehyde, and piperonal were also successful in this condensation.

The Petrenko-Kritschenko reaction formed the basis for Robinson's elegant and classical synthesis of tropinone (XXXIX, R = H) from acetone, succinaldehyde (as the dioxime), and methylamine in basic solution.[171] With acetone, the yields are poor, but substitution of



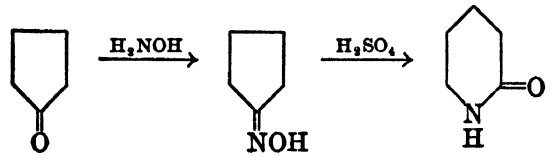
XXXIX

166 Baliaha, Ph.D. Thesis, Stanford University, 1948.
167 Dr. C. R. Noller, private communication.
168 Böhm and Stöcker, *Arch. Pharm.*, **281**, 62 (1943).
169 Mannich and Hieronimus, *Ber.*, **75**, 49 (1942).
170 Mannich and Ball, *Arch. Pharm.*, **264**, 65 (1926).
171 Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917).

methyl acetonedicarboxylate (R = $-COOCH_3$) leads to much better yields. Tropinone results on hydrolysis and decarboxylation of the diester (XXXIX, R = $-COOCH_3$).

Schöpf and Lehmann [172,173] and Keagle and Hartung [174] have investigated the conditions, yields, and versatility of this reaction further. The conditions are such that the same reaction may very possibly be the first step in the biosynthesis of the tropine portion of the Solonaceae alkaloids such as atropine and hyoscyamine and even of the coca alkaloids such as cocaine. Thus, acetonedicarboxylic acid, succinaldehyde, and methylamine hydrochloride in aqueous solution at *p*H 7 gave a 78% yield of tropinone on standing at room temperature for 3 days.[172] These are conditions which can exist in the plant tissues. The reaction is capable of considerable variation; the methylamine may be replaced by ethyl-, isopropyl-, benzyl-, or β-hydroxyethyl-amine to obtain the corresponding N-substituted tropinones in yields of 30–72%.[174] The main stumbling block in the reaction is the difficulty of obtaining the succindialdehyde itself, for which there is still no satisfactory synthesis. However, the acetal of the aldehyde is equally adaptable to the synthesis and can be readily prepared by the action of ethyl orthoformate on acetylene Grignard reagent. The acetal does not polymerize so readily as the free aldehyde. Succindialdehyde oxime may be substituted for the acetal, and the aldehyde chain may be interrupted with a nitrogen, sulfur, or selenium atom. Other dialdehydes such as adipaldehyde and glutaraldehyde [175,176] give ring homologs, and levulinaldehyde gives a side-chain homolog of tropinone.

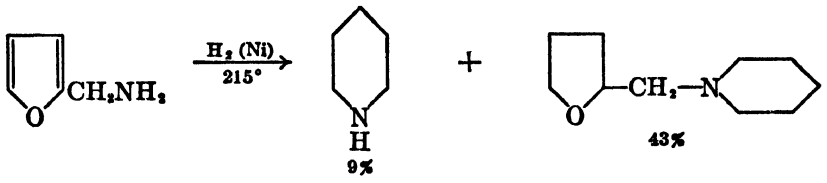
Synthesis from Other Ring Compounds. A novel and general method for making 2-piperidones is by the Beckmann rearrangement of cyclopentanone oxime and its derivatives.[177–180] In the alkyl-sub-



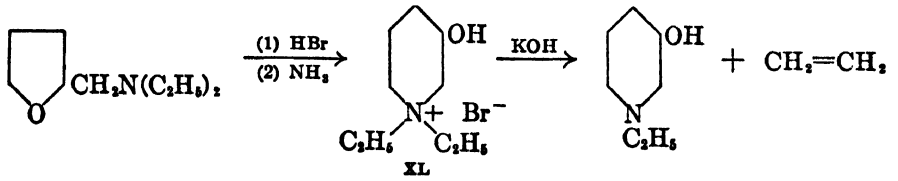
172 Schöpf and Lehmann, *Ann.*, **518**, 5 (1935).
173 Schöpf, *Z. angew. Chem.*, **50**, 779, 797 (1937).
174 Keagle and Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).
175 Menzies and Robinson, *J. Chem. Soc.*, **125**, 2163 (1924).
176 Blount and Robinson, *J. Chem. Soc.*, 1429 (1932); 1511 (1933).
177 Wallach et al., *Ann.*, **309**, 13 (1899); **312**, 179, 184 (1900); **324**, 285, 288 (1902).
178 Moncrieff and Young, Brit. pat. 563,783 (Aug. 30, 1944) [*C. A.*, **40**, 3143 (1946)].
179 Koelsch and Stratton, *J. Am. Chem. Soc.*, **66**, 1881 (1944).
180 Hildebrand and Bogert, *J. Am. Chem. Soc.*, **58**, 650 (1936).

stituted cyclopentanone oximes, both *cis* and *trans* modifications are possible and a mixture of the two possible isomeric alkyl-2-piperidones can therefore be formed.

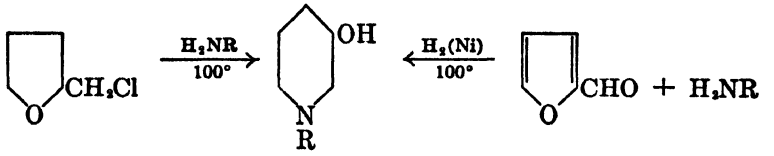
Various furan derivatives are converted into piperidines. 2-Furfurylamine on catalytic hydrogenation in the liquid state at temperatures up to 215° with Raney nickel catalyst gives piperidine and N-tetrahydrofurfurylpiperidine according to the following equation.[181]



Paul [182] found that furfuryldiethylamine on treatment with dry hydrogen bromide and then ammonia forms the quaternary piperidinium bromide (XL) which, with concentrated potassium hydroxide, loses



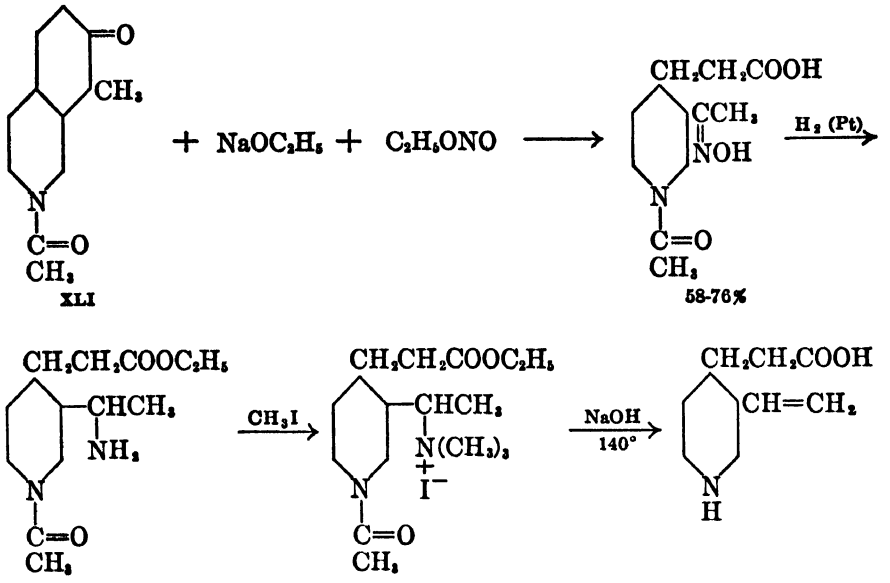
ethylene to give 1-ethyl-3-hydroxypiperidine in 77% over-all yield. Essentially the same transformation is brought about upon treatment of furfuryl chloride [183] or a derivative of furfuryl chloride [184] with a large excess of a primary amine. The catalytic reduction of a mixture of furfuraldehyde and a primary amine gives the same product.



Cyclopentanol reacted with ammonia over aluminum oxide at 400° to give a 9% yield of piperidine,[185] and pyran under similar conditions gave a 16% yield.

181 Wilson, *J. Am. Chem. Soc.*, **67**, 693 (1945).
182 Paul, *Compt. rend.*, **221**, 412 (1945).
183 Paul and Tchelitcheff, *Compt. rend.*, **221**, 560 (1945).
184 Leuchs and Splettstösser, *Ber.*, **40**, 304 (1907).
185 Kline and Turkevich, *J. Am. Chem. Soc.*, **66**, 1710 (1944).

The final piperidine synthesis that will be considered is the unique conversion of the decahydroisoquinoline compound (XLI, *cis* modification) by Woodward and Doering [186] into the key intermediate in their total synthesis of quinine. This resulting oxime was reduced, completely methylated with methyl iodide, and heated with 60% sodium

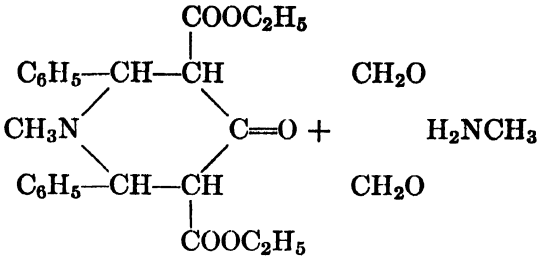


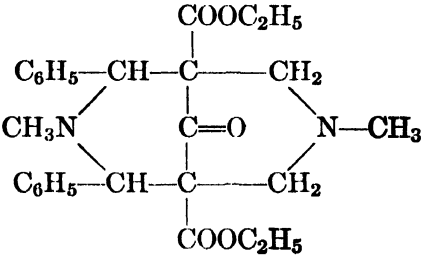
hydroxide; trimethylamine was eliminated and homomeroquinene was formed. A discussion of the mechanism of the cleavage reaction may be found in the original article.

Bicyclic Piperidine Derivatives. A series of unusually interesting bicyclic piperidine derivatives has been made by special applications of the methods just discussed. The conditions and yields usually differ only slightly from the simpler examples, and little comment will be offered. Among these derivatives may be mentioned quinuclidine, norlupinane, and similar substances. A detailed discussion of these will be found in a later volume of the present series.

Bispidins (XLII) are often formed in the Mannich reaction.[162,163] Under the proper conditions, excellent yields of these bicyclic compounds can be obtained from the piperidine compounds formed from acetonedicarboxylic esters (p. 660).[162,165]

186 Woodward and Doering, *J. Am. Chem. Soc.*, **67**, 866 (1945).





XLII

Reactions of Piperidines

Piperidine has a lower boiling point (106°) and a higher melting point (−9°) than pyridine and possesses a distinctly different odor. It is a much stronger base than pyridine and, in fact, has a basic strength rather close to that of diethylamine.

	K_B
Ammonia	1.8×10^{-5}
Diethylamine	1.2×10^{-3}
Piperidine	1.6×10^{-3}
Pyridine	2.3×10^{-9}

Normal Reactions as a Secondary Amine. The great majority of the reactions of piperidine and piperidine derivatives are those of a more or less typical secondary amine. Since these reactions are in no way peculiar to piperidine and differ only in degree from the comparable reactions of a dialkylamine such as diethylamine, they will not be discussed in any detail. These reactions are applicable to almost every piperidine derivative in which the ring nitrogen atom is not already substituted. Thus, piperidine undergoes vigorous acylation with acetyl chloride or acetic anhydride. It also reacts, but more slowly, with esters to give the amides.

$$RCOCl + 2HNC_5H_{10} \rightarrow R\overset{\overset{O}{\|}}{C}NC_5H_{10} + C_5H_{10}NH \cdot HCl$$

$$(RCO)_2O + HNC_5H_{10} \rightarrow R\overset{\overset{O}{\|}}{C}NC_5H_{10} + C_5H_{10}NH \cdot HO\overset{\overset{O}{\|}}{C}R$$

$$RCOOCH_3 + HNC_5H_{10} \rightarrow R\overset{\overset{O}{\|}}{C}NC_5H_{10} + CH_3OH$$

Piperidine reacts readily with nitrous acid to give N-nitrosopiperidine, a stable liquid. This nitroso compound can be reduced to the N-aminopiperidine (N,N-pentamethylenehydrazine) which shows characteristic hydrazine reactions. Piperidine reacts with carbon disulfide to form the dithiocarbamic acid which crystallizes as its piperidinium salt (I). With a peroxide oxidizing agent, it forms a hydroxylamine derivative. This hydroxylamine is isomeric with the N oxide. Al-

$$C_5H_{10}NH + CS_2 \rightarrow C_5H_{10}N{-}\overset{\overset{S}{\|}}{C}{-}SH \xrightarrow{HNC_5H_{10}} C_5H_{10}N{-}\overset{\overset{S}{\|}}{C}{-}SH_2NC_5H_{10}$$

I

$$C_5H_{10}NH + H_2O_2 \rightarrow C_5H_{10}NOH$$

though most amines are relatively stable to cold permanganate in acid solution, piperidine is readily oxidized under these conditions [187] and also reacts with permanganate in neutral solution to liberate ammonia.[188] It is also oxidized by dichromate in acid solution (p. 668) [189] but is stable to the oxygen of the air.

Piperidine reacts readily with sulfur, first forming N,N′-dipiperidyl sulfide, which may react further to give polysulfides.[190] It is this

$$2C_5H_{10}NH + 2S \rightarrow C_5H_{10}N{-}S{-}NC_5H_{10} + H_2S$$

ability to combine with sulfur which has led to its value in the vulcanization of rubber. The derivative from piperidine and carbon disulfide, piperidinium pentamethylene dithiocarbamate (I), has an

187 Delépine, *Comp. rend.*, **184**, 206 (1927).
188 Goldschmidt and Voeth, *Ann.*, **435**, 265 (1924).
189 Karrer and Widmer, *Helv. Chim. Acta*, **9**, 886 (1926).
190 Levi, *Gazz. chim. ital.*, **61**, 286 (1931) [*C. A.*, **25**, 4853 (1931)].

equivalent activity and is handled more readily since it is a solid. Piperidine also acts as an antioxidant for synthetic rubbers.[191]

Many derivatives of piperidine are prepared by alkylation, and the N-alkyl compounds in turn are readily converted to the quaternary salts. This reaction has served both to measure the relative reactivi-

$$C_5H_{10}NH + RX \rightarrow C_5H_{10}NR \cdot HX \xrightarrow{RX} C_5H_{10}\overset{+}{N}R_2\overset{-}{X} + HX$$

ties of various halogen compounds[192,193] and to prepare derivatives of such aromatic compounds as *o*-nitrochlorobenzene, in which the activity of the aromatic halogen has been enhanced by the presence of a *m*-directing group in the *o* or *p* position.[194] Piperidine is an especially desirable substance in this connection since it reacts with greater ease than almost any other secondary base. This greater reactivity cannot be attributed to the basic strength of piperidine since it differs only slightly from that of the much less reactive diethylamine. However, it is explainable on the basis of steric considerations. In diethylamine the ethyl groups are free to rotate (and interfere with the attack of a group on the nitrogen atom), whereas in piperidine a methylene group rigidly holds the two ethyl groups of diethylamine in a six-membered ring, thus leaving the nitrogen atom relatively unprotected from attack by other groups. These steric factors have been investigated by Singer and McElvain,[195] who found that the reactivity of piperidine, 2-methylpiperidine, and 2,6-dimethylpiperidine with butyl bromide decreased in this order. It was observed that the methyl group in the α position was found to be as effective sterically in this reaction as the α-benzyl group or α-carbethoxy group. The greater reactivity of piperidine is also demonstrated in its addition reactions to such α,β-unsaturated compounds as acrylonitrile,[196] ethyl acrylate,[197] and benzalacetone.[198] This ease of reaction and generally better yields

$$C_5H_{10}NH + CH_2{=}CHCN \rightarrow C_5H_{10}NCH_2CH_2CN$$

account for the frequent use of piperidine in the Mannich condensation.[199]

191 Whitby and Katz, *Ind. Eng. Chem.*, **25**, 1204, 1338 (1933).
192 McElvain et al., *J. Am. Chem. Soc.*, **53**, 690 (1931); **54**, 282 (1932); **55**, 1155 (1933); **56**, 697 (1934); **62**, 1435 (1940).
193 Spitzer and Wheland, *J. Am. Chem. Soc.*, **62**, 2995 (1940).
194 Seikel, *J. Am. Chem. Soc.*, **62**, 751 (1940).
195 Singer and McElvain, *J. Am. Chem. Soc.*, **57**, 1135 (1935).
196 Whitmore et al., *J. Am. Chem. Soc.*, **66**, 725 (1944).
197 Weisel et al., *J. Am. Chem. Soc.*, **67**, 1071 (1945).
198 Cromwell, Wiles, and Schroeder, *J. Am. Chem. Soc.*, **64**, 2432 (1942).
199 Fry, *J. Org. Chem.*, **10**, 259 (1945).

Substitution of alkyl groups on the nitrogen atom of piperidine can also be achieved by treatment with alcohols at elevated temperatures in the presence of a suitable catalyst [68] or by treatment with an aldehyde or ketone under reducing conditions. Mannich [200] has been

$$C_5H_{10}NH + C_2H_5OH \xrightarrow{(Ni)} C_5H_{10}NC_2H_5 + H_2O \qquad 80\%$$

$$C_5H_{10}NH + CH_3CH_2CHO \xrightarrow[(Ni)]{H_2} C_5H_{10}NCH_2CH_2CH_3 + H_2O \qquad 93\%$$

able to demonstrate that an alkylene derivative (III) can be isolated in the reaction of an aldehyde with piperidine in the presence of potassium carbonate. This or the postulated intermediate (II) undoubtedly acts as an intermediate in the reductive alkylation reactions of Winans and Adkins.

$$C_5H_{10}NH + OCHCH_2CH_3 \rightarrow \underset{\text{II}}{\left[C_5H_{10}NCHCH_2CH_3\right]} \xrightarrow{-H_2O} \underset{\text{III}}{C_5H_{10}NCH{=}CHCH_3}$$

Piperidine reacts with formaldehyde to give dipiperidinomethane (IV) [201] and with formaldehyde in ethanol to give piperidinomethyl ethyl ether (V).[202] IV is a convenient source of bound formalde-

$$2C_5H_{10}NH + CH_2O \rightarrow \underset{\text{IV}}{C_5H_{10}NCH_2NC_5H_{10}} + H_2O$$

$$C_5H_{10}NH + CH_2O + C_2H_5OH \rightarrow \underset{\text{V}}{C_5H_{10}NCH_2OC_2H_5} + H_2O$$

hyde,[203] whereas the V will substitute for a mixture of formaldehyde and piperidine in the Mannich condensation.[204,205]

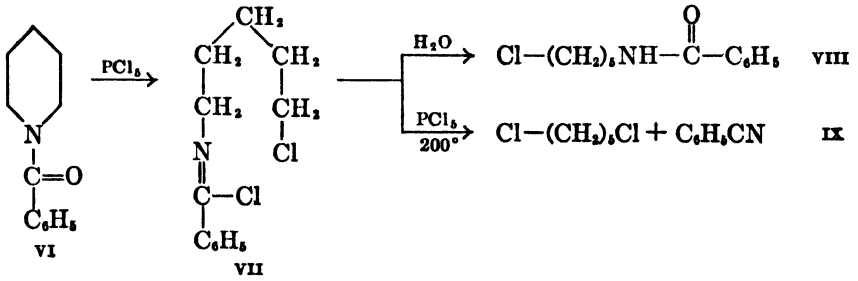
Piperidine is well known for its ability to catalyze the Michael and Knoevenagel condensations.

Ring-Opening Reactions. Some of the most interesting reactions of the piperidine series are those which result in cleavage of the ring. Karrer [189] was able to isolate β-aminopropionic acid (4% yield) from

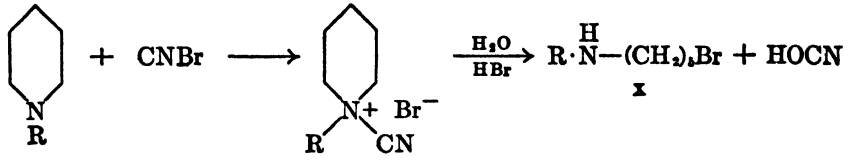
200 Mannich and Davidsen, *Ber.*, **69**, 2106 (1936).
201 Ehrenberg, *J. prakt. Chem.*, [2] **36**, 117 (1887).
202 McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).
203 McLaughlin and Wagner, *J. Am. Chem. Soc.*, **66**, 251 (1944).
204 Tseou and Yang, *J. Org. Chem.*, **4**, 123 (1939).
205 Yang, *J. Org. Chem.*, **10**, 67 (1945).

the dichromate oxidation of piperidine and γ-aminobutyric acid from the oxidation with nitric acid. In both oxidations, the conditions resulted in serious degradation of the carbon chain. When the secondary amine is protected by benzoylation, better yields of primary oxidation products may be obtained.

The action of phosphorus pentachloride on N-benzoylpiperidine (VI) results in the smooth cleavage of the piperidine ring to give an iminochloride (VII), which is easily hydrolyzed to ε-benzoylaminoamyl chloride (VIII) (50% yield).[206] Further treatment with phosphorus pentachloride gives 1,5-dichloropentane (IX) and benzonitrile.



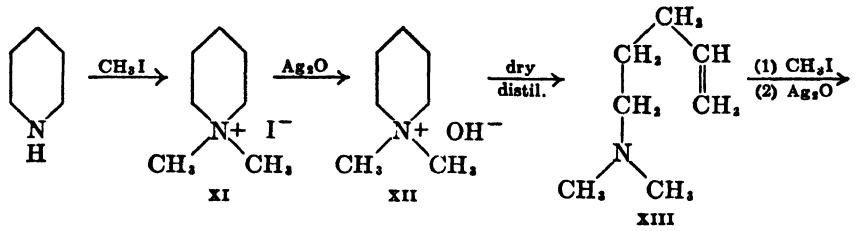
Alkyl- and aryl-piperidines react with cyanogen bromide to give quaternary derivatives which hydrolyze with the opening of a carbon-to-nitrogen bond.[207] Depending on the substituent on the nitrogen atom, the ring may open, giving an ε-aminoamyl bromide (X). The course of the reaction is as shown in the following equations when the substituent is phenyl. The tendency of the R group to be eliminated as RX without cleavage of the piperidine ring becomes progressively greater as R is changed from isopropyl to propyl, ethyl, methyl, and benzyl.

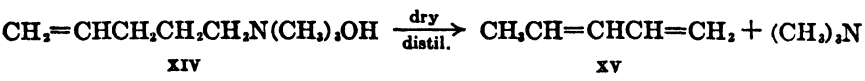


Exhaustive methylation of piperidine leads successively to dimethylpiperidinium iodide (XI), dimethylpiperidinium hydroxide (XII), 5-

206 v. Braun, *Ber.*, **37**, 2915 (1904).
207 v. Braun, *Ber.*, **40**, 3914, 3933 (1907).

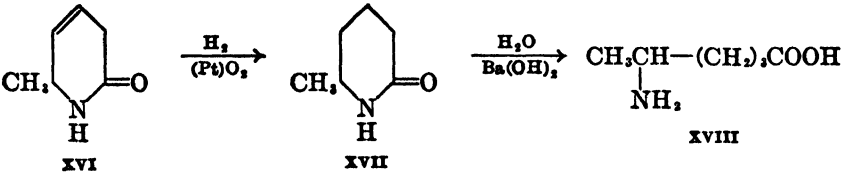
dimethylamino-1-pentene (XIII), the corresponding quaternary hydroxide (XIV), and, finally, piperylene, 1,3-pentadiene (XV). The expected 1,4-pentadiene rearranges during the final reaction to the





conjugated system. The reaction is of very limited value from the standpoint of synthesis but has been of great importance in the elucidation of the structures of various alkaloidal products.

Reactions Involving Substituents on the Piperidine Nucleus. *Piperidones.* Of all the piperidine derivatives, the piperidones have been most valuable for further syntheses. The 3- and 4-piperidones show most of the reactions typical of a basic ketone, such as addition, reduction, and condensations involving active hydrogens on the carbon atom adjacent to the carbonyl. 2-Piperidone, on the other hand, shows reactions more characteristic of a cyclic amide instead of a basic ketone, and therefore hydrolytic reactions predominate over addition reactions. A typical reaction is the hydrolysis of 6-methyl-2-piperidone (XVII) by barium hydroxide solution to δ-aminocaproic acid (XVIII).[208] This piperidone is prepared by reduction of the unsaturated lactam (XVI), which is obtained as indicated on p. 651.



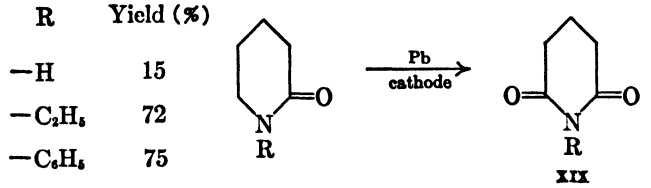
Bromination of δ-benzoylaminovaleric acid (obtained from the Beckmann rearrangement of cyclopentanone oxime in 71% yield) [209] results

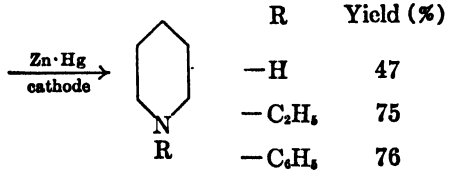
[208] Kuhn and Jerchel, *Ber.*, **76**, 413 (1943).
[209] Fox, Dunn, and Palmer, *J. Org. Chem.*, **6**, 410 (1941).

in concurrent ring closure to the 3,3-dibromo-N-benzoyl-2-piperidone. The same compound results from the direct bromination of N-benzoyl-2-piperidone.[210] 2-Piperidone, itself, can be readily converted into the 3,3-dichloro-2-piperidone by phosphorus pentachloride.[211] The activity of the α hydrogens in N-benzoyl-2-piperidone has been illustrated in the synthesis of anabasine on p. 590.

It has not been possible to reduce 2-piperidones to the corresponding hydroxy compounds. There is, therefore, no danger of also reducing the carbonyl group in the catalytic reduction of a compound such as XVI. Complete removal of the carbonyl group can be accomplished by the action of sodium and butyl alcohol,[185,179] as indicated by the reduction of the *cis* modification of 4,5-diethyl-2-piperidone to *cis*-3,4-diethylpiperidine in 85% yield.

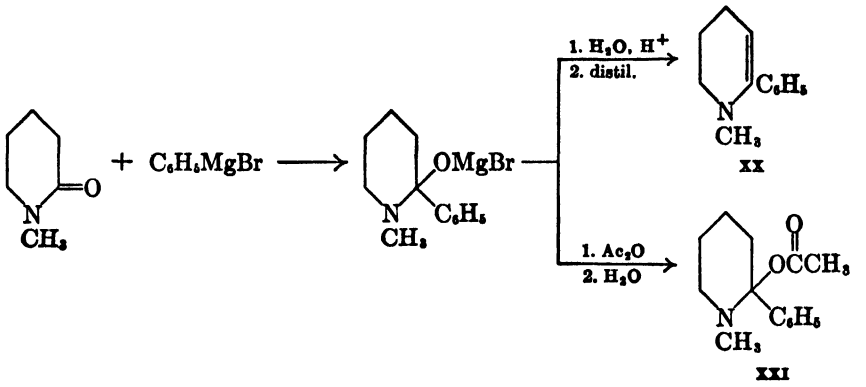
Glutarimide and N-alkylglutarimides have been reduced electrolytically, either partially to the 2-piperidone, or completely to the piperidine derivative.[212]





N-Alkyl-2-piperidones react with Grignard reagents to give magnesium halide salts of a tertiary alcohol which, on hydrolysis and attempted distillation, dehydrate to the tetrahydropyridine derivatives, such as XX. Lee and co-workers[213] were able to obtain the acetic acid ester (XXI) of the tertiary alcohol in poor yields by direct treat-

210 Schniepp and Marvel, *J. Am. Chem. Soc.*, **57**, 1557 (1935).
211 Heymons, *Ber.*, **66**, 846 (1933).
212 Sakurai, *Bull. Chem. Soc. Japan*, **13**, 482 (1938) [*C. A.*, **32**, 8281 (1938)].
213 Lee et al., *J. Org. Chem.*, **12**, 883 (1947).



ment of the Grignard complex with acetic anhydride. Occasionally reaction with lithium phenyl was somewhat more desirable. Lukeš and co-workers [214,215] studied the reaction of Grignard reagents on N-methylglutarimide and N-methyl-2-piperidone and observed essentially the same fundamental reactions but found that, in the presence of excess Grignard reagent, two alkyl groups could be introduced on the same α-carbon atom, giving a 2,2-dialkylpiperidine. The mechanism of this reaction is as yet unknown.

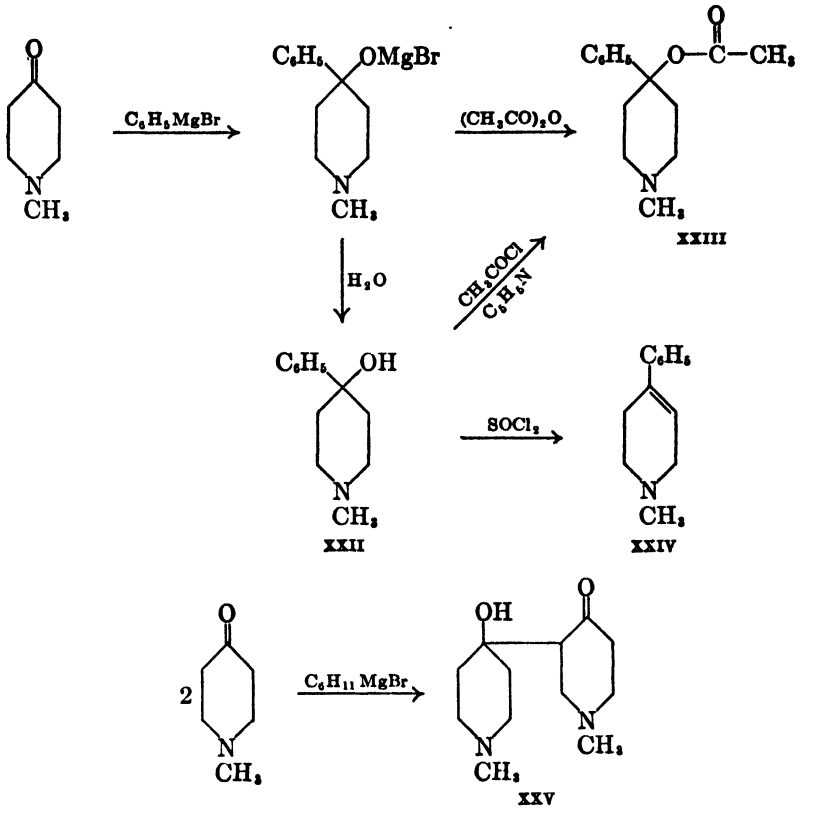
The 4-piperidones take part in many normal addition reactions; they react with Grignard reagents and, in contrast to the 2 isomers, the tertiary alcohols resulting on hydrolysis are stable.[151,216] Either the magnesium bromide salt of the alcohol or the free alcohol can be acetylated. Lee and co-workers [213] have made an extensive study of these compounds because of their analgesic properties, and certain derivatives of XXIII are claimed to be more potent than Demerol (p. 658), especially the 3-methyl homolog.

All attempts to replace the hydroxyl group with halogen resulted in the formation of the olefin (XXIV). A reaction leading to the formation of an important by-product (XXV) is catalyzed by the Grignard reagent and results from the aldol-type condensation of two molecules of the piperidone. When cyclohexylmagnesium bromide was added to N-methyl-4-piperidone, this condensation product was the only substance isolated.[151] A similar aldol-type condensation occurs with the 2-piperidones.

214 Lukeš and Gorocholinskij, *Collection Czechoslov. Chem. Communs.*, 8, 223 (1936) [*C. A.*, 30, 5989 (1936)].

215 Lukeš and Grossmann, *Collection Czechoslov. Chem. Communs.*, 8, 533 (1936) [*C. A.*, 31, 2608 (1937)].

216 Jensen et al., *Dansk Tids. Farm.*, 17, 173 (1943) [*C. A.*, 39, 2506 (1945)].



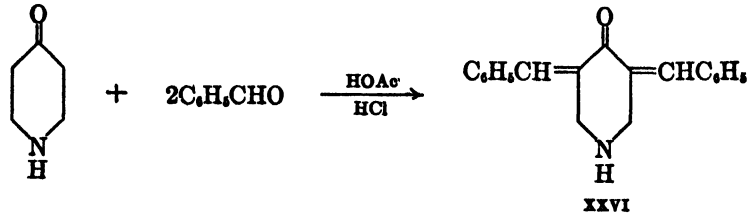
XXIII XXII XXIV XXV

The 4-piperidones give addition reactions with hydrogen cyanide to form cyanohydrins,[217] with phenylhydrazine to give phenylhydrazones,[153] and with hydroxylamine to give oximes.[218] The carbonyl group in the 4-piperidones can be converted readily into the carbinol group by catalytic reduction [148] or by the action of sodium and alcohol.[92] Catalytic reduction of N-ethyl-4-piperidone in the presence of ammonia [149] has given a mixture of 4-amino-N-ethylpiperidine (51%) and 4-hydroxy-N-ethylpiperidine (12%). The carbonyl group in 2,2-dimethyl-6-phenyl-4-piperidone has been removed completely by the Wolff-Kishner procedure, but the same conversion could not be successfully accomplished with amalgamated zinc and hydrochloric acid by the Clemmensen method.[71]

217 Lovens Kemiske Fabrik Ved A. Kongsted, Dan. pat. 62,791 (Oct. 16, 1944) [*C. A.*, **40**, 4181 (1946)].

218 Harries et al., *Ann.*, **417**, 107 (1918).

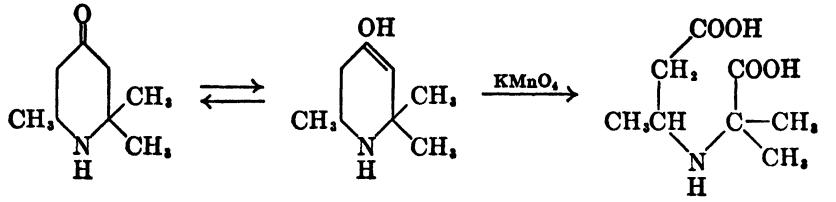
The hydrogens adjacent to the carbonyl in 4-piperidone are active and react as would be expected on this basis. Thus, two molecules of benzaldehyde will condense with 4-piperidone in glacial acetic acid in the presence of anhydrous hydrogen chloride to give a product (XXVI) completely analogous to dibenzalacetone.[143,144] A compound



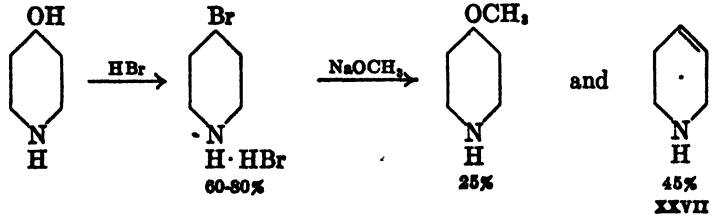
XXVI

such as N-benzoyl-3-carbethoxy-4-piperidone is a typical β-keto ester and accordingly undergoes alkylation in the same manner as acetoacetic ester and readily decarboxylates after hydrolysis.

2,2,6-Trimethyl-4-piperidone is oxidized with ring cleavage in a manner to be expected from its enol form.[219]



Halopiperidines. Only a few nuclear halogenated piperidine derivatives have been made from the corresponding hydroxypiperidines. Renshaw and Conn [39] found that treatment of 4-bromopiperidine hydrobromide with sodium methoxide gave only a 25% yield of 4-methoxypiperidine and that dehydrohalogenation with formation of 1,2,3,6-tetrahydropyridine (XXVII) was the major reaction (p. 627).

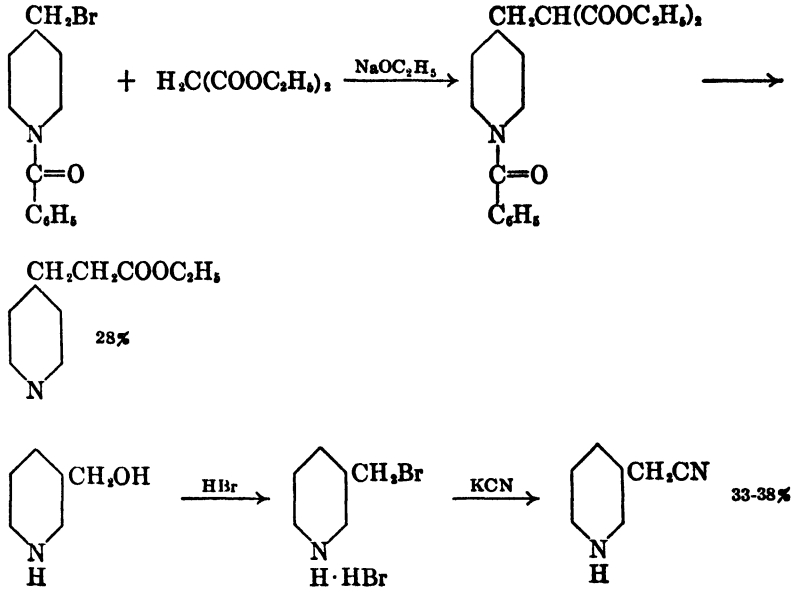


XXVII

219 Heintz, *Ann.*, **198**, 74 (1879).

Addition of bromine to XXVII reportedly gives 3,4-dibromopiperidine hydrobromide. Similar results were obtained in replacement reactions of N-phenyl-4-halopiperidines with secondary amines.[92] Thus, 4-iodo-1-phenylpiperidine, when treated with piperidine, gave a 27% yield of 4-piperidino-1-phenylpiperidine and a 47% yield of 1-phenyl-1,2,3,6-tetrahydropyridine.

Piperidine compounds in which the halogen is on a side chain react in a normal manner as shown by the following reactions.[220, 221]

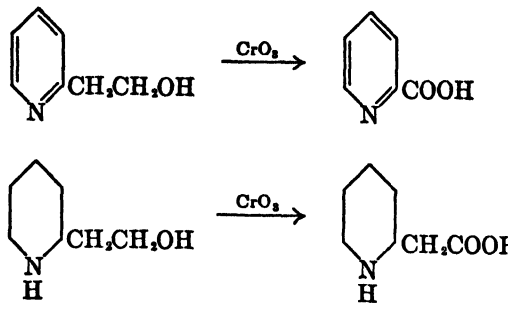


Piperidinecarboxylic Acids and Derivatives. The action of methylmagnesium iodide on piperidine esters has been studied, but the reported results indicate that it is not satisfactory.[222] However, Eisleb [223] has claimed that the Grignard reaction on 4-cyano-4-phenyl-N-methylpiperidine proceeds normally to give the expected ketone on hydrolysis. Cyanopiperidines have been reduced to the corresponding amines in good yields.[224, 225]

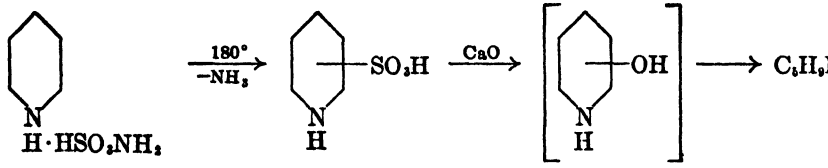
220 Koelsch, *J. Am. Chem. Soc.*, **65**, 2460 (1943); **66**, 1611 (1944).
221 Merchant and Marvel, *J. Am. Chem. Soc.*, **50**, 1197 (1928).
222 Clemo and Hogarth, *J. Chem. Soc.*, 41 (1941).
223 Eisleb, U. S. pat. 2,248,018 (July 1, 1941) [*C. A.*, **35**, 6394 (1941)].
224 Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).
225 Kwartler and Lucas, *J. Am. Chem. Soc.*, **69**, 2582 (1947).

Aminopiperidines. Several 3- and 4-aminopiperidines have been prepared. These have been made by the reduction of the corresponding 3- or 4-aminopyridine or by the reduction of the oximes of the 4-piperidones.[226] Similar methods do not lead to 2-aminopiperidine.

Miscellaneous. Both 3-benzylpiperidine and 4-phenylpiperidine have been nitrated, a nitro group being introduced into the *p* position of the benzene ring.[227] In contrast to the corresponding reaction of the pyridine series, β-(2-piperidyl)ethanol is oxidized to 2-piperidylacetic acid without alteration of the carbon skeleton.[228]



Piperidine reacts with sulfur trioxide to form an N-piperidinesulfonic acid which reacts with water to give the sulfate salt of piperidine.[229] With sulfamic acid, piperidine gives the sulfamate, which, when heated with excess piperidine, is partially converted into a nuclear sulfonated product. The product, when heated with lime, is



converted into an unsaturated derivative of piperidine, presumably through an intermediate hydroxypiperidine. Several piperidine sulfonic acids have also been reported[230] by the catalytic reduction of the corresponding pyridine sulfonic acids or their salts.

226 Orthner, *Ann.*, **456**, 225 (1927).
227 Bryans and Pyman, *J. Chem. Soc.*, 549 (1929).
228 Koenigs and Happe, *Ber.*, **36**, 2905 (1903).
229 Paal and Hubaleck, *Ber.*, **34**, 2757 (1901).
230 Nicodemus and Wulff, U. S. pat. 2,008,292 (July 16, 1935) [*C. A.*, **29**, 5864 (1935)].

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