ORGANIC PREPARATIONS

ORGANIC
PREPARATIONS

CONRAD WEYGAND
PROFESSOR AT THE UNIVERSITY
OF LEIPZIG

*Translated and Revised from the
German Text*

1 9 4 5

INTERSCIENCE PUBLISHERS, INC., NEW YORK

A translation of Part II, "Reaktionen," of Conrad
Weygand's *Organisch-chemische Experimentier-
kunst* (Leipzig, 1938)

PUBLISHER'S NOTE

This volume is a translation of Part II, "Reaktionen," of Conrad Weygand's *Organisch-chemische Experimentierkunst*, published in Leipzig in 1938. Parts I and III are not included for the following reasons: Part I, on materials and operations necessary for the execution of organic syntheses, deals mainly with German laboratory equipment, so that a literal translation would have limited value for the. American reader. An adaptation of the text to American equipment would have necessitated a complete rewriting of this section, a task considered beyond the scope of a translation. Part III of the German book, on the chemical and physical analyses of organic compounds, is covered by a number of excellent American texts. A translation would thus have constituted a duplication we wished to avoid.

There is one major difference between the German original and the English translation. The former contains a number of extensive literal quotations of preparations published in *Organic Syntheses;* these have been replaced in the translation by references to the corresponding volumes of *Organic Syntheses;* and wherever possible references to single volumes of *Organic Syntheses* have been replaced by references to Collective Volume I, 2nd edition, 1941, or to Collective Volume II, 1943.

In the translation of Part II, our collaborators followed the German text as closely as possible, correcting only obvious errors and taking care of a few obvious omissions. Responsibility for the content of the book rests, therefore, with Dr. Weygand. The actual work on the translation was carried out in the following sequence. A rough translation of the German text by A. Schormüller was revised from the linguistic point of view, and corrections in the German text made, by W. A. Gregory, J. E. Jones, C. J. Kibler, J. L. Leiserson, H. D. Porter, I. F. Salminen, and C. V. Wilson, all of Rochester, New York, and H. R. Rosenberg of Wilmington, Delaware. The index was compiled by Mrs. Lucia Dawe, who edited and proofread the text.

During the entire process of the translation and editing of the book we enjoyed the advice and cooperation of H. R. Rosenberg and A. Weissberger, to whom we wish to express our appreciation.

<div align="right">INTERSCIENCE PUBLISHERS, INC.</div>

October, 1945

<div align="center">v</div>

PREFACE TO THE GERMAN EDITION
(*Translated*)

Laboratory procedure in organic chemistry can be presented from various viewpoints. In this book it will be treated as an experimental art, which, in view of the wide scope of the material to be included, is the only way to organize all the pertinent facts in a restricted space.

The arrangement follows the natural course of laboratory work in organic chemistry, which usually begins with construction of apparatus and, after a variety of reactions have been investigated, concludes with analysis and physical identification.

The section dealing with chemical reactions is arranged according to one of the customary systems, whose basis is the formation of the various linkages of the carbon atom and their fission. This system is more methodical than the division according to reactive groups alone, and permits of greater elaboration. It also makes more apparent that all the basic reactions can be illustrated by simple, clear examples. Now more than ever the applications to work with complicated natural and synthetic substances must be left to the specialist, who alone is able to cover a particular field with any degree of completeness. The examples were chosen for their usefulness and with the purpose of presenting a representative view of organic chemistry. The simple precepts which are to be found in all elementary laboratory manuals are not repeated in this book.

The most important of the physical methods are included. The difficulty of their general introduction into the organic laboratory is often underrated, particularly by those organic chemists who have little experience with them. There is no lack of special treatises in this field.

The publishers have spared no pains in setting up the book in accordance with the wishes of the author.

The author wishes to thank his assistants, Dr. H. Baumgärtel, Dr. W. Lanzendorf, and Mr. Siebenmark, for their tireless collaboration.

<div align="right">C. WEYGAND</div>

Leipzig, June, 1938

CONTENTS

INTRODUCTION

Preparative organic chemistry has as its purpose the preparation from specific starting materials of compounds with carefully defined properties. In the classification of the multitude of reactions useful for the preparation of substances, the problem of starting material must be disregarded, because whatever raw material can be procured cheaply, or procured at all, depends on many conditions which are highly variable, such as the economic and geographic situation.

All organic substances have one property in common; that is, their carbon structure. In preparative organic chemistry classification can rest on the distinctions which are exemplified by the following conditions.

1. The carbon structure in the starting material is already formed. This is illustrated by the formation of benzoic acid from toluene or of acetaldehyde from ethanol.

2. The formation of the carbon structure is from 2 or more molecules with a lesser number of carbon atoms. Examples are acetophenone from benzene and acetic anhydride (2 molecules), Michler's ketone from dimethylaniline and phosgene (3 molecules), and rubber from isoprene (many molecules).

3. The carbon structure is obtained by degradation of a compound containing a greater number of carbon atoms. The formation of heptaldehyde and undecylenic acid from castor oil and of phthalic acid from naphthalene serves as examples.

4. The carbon structure is obtained by rearrangement of an existing one. This is illustrated by the pinacol-pinacolone rearrangement. These four basic types of reaction will frequently occur successively or even simultaneously and are called, respectively: (*1*) molecular change without a change in the carbon structure, (*2*) formation of a carbon structure, (*3*) degradation of the carbon structure, (*4*) molecular rearrangement of the carbon structure.

The reactions that lead to ring closure occupy a somewhat different position, but they are not different in principle from those in which bonds

1

are formed or broken. They can be classified into one or more of the four basic groups shown by the following illustrations.

1. The formation of phthalic anhydride from phthalic acid or the formation of pyrrole from ammonium mucate does not involve a change in carbon structure.

2. The formation of mesitylene from acetone and the formation of mesityl oxide are similar in nature.

3. Cyclopentanone is obtained from calcium adipate in exactly the same manner as acetone is obtained from calcium acetate.

4. The rearrangement of camphene hydrochloride to isobornyl chloride corresponds to the formation of pinacolone from pinacol.

The typical chemical processes fall very nicely into this system of classification. In Group 1 belong all reactions such as hydrogenation, chlorination, nitration, oxidation, reduction, etc. Group 2 includes those addition and condensation reactions that increase the number of carbon atoms in the molecule as well as polymerization. The separation of degradation reactions (Group 3) from the rearrangement reactions (Group 4) is novel.

The preparation of benzaldehyde (a) from toluene through benzene or benzyl chloride, (b) from benzene and hydrocyanic acid (Gatterman-Koch reaction), from bromobenzene by the Grignard reaction with formic ester, (c) from stilbene by treatment with ozone, or from diphenyl glycol treated with lead tetraacetate is not treated under one reference, "aldehydes," as is usual in the textbooks and handbooks of organic chemistry. Instead, the important reactions are discussed essentially under a single heading.

A difference of opinion about the principle of classification within the four main groups might arise. However, the characteristic common to all organic reactions is that they all consist of the breaking of existing bonds and the formation of new ones. It is advantageous, especially for the purpose of avoiding repetition, to use as the basis of classification, not the preparation of certain groups, but the formation of bonds. This book progresses from the simpler linkages to the more complex.

Most bonds can be formed by addition as well as by replacement. This creates a natural subdivision of the main chapters. The existence of few types of linkage that are of practical importance in organic chemistry simplifies the examination of the material in this manner. It is sufficient to consider the elements, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and the halogens, in their different kinds of linkage and their valences.

The preparation of an organic compound may be achieved in different ways, depending upon the starting material and upon the chemical nature of the desired product. Two special cases can be distinguished:

1. The reacting compounds in one case exhibit such preference to react with each other in only one way that the process proceeds in one direction only. Even under very different conditions, and therefore with varying velocity, the same reaction products are obtained. In this case, the success of the synthesis depends primarily on the preparation of the starting materials.

2. In the second case, several different reactions compete with each other, thus inevitably forming a mixture of reaction products. The success of the preparative work depends on directing the reaction by the choice of suitable conditions (temperature, pressure, radiation) and reagents (solvents, catalysts) so that the desired product is formed in optimum yield and is accompanied only by by-products from which it can be conveniently separated.

The reactions of the first type are marked by the presence of so called key elements which easily break their bond with carbon in favor of another, especially an ionic bond.

Formation of Carbon-Hydrogen Bonds

The reactions establishing C—H bonds are divided into two groups. The first is characterized by the fact that only hydrogen is taken up by the reacting molecule. In the second hydrogen replaces other atoms or atom groups, forming new compounds such as water, hydrochloric acid, etc. Substitution, the usual designation for reactions of the second group, proceeds primarily by way of addition compounds; but these intermediates are usually not isolated, as the purpose is to isolate the end-products. In accordance with the general plan, the only reactions that belong in this section are those in which there is no degradation of the type characterized by a breaking of C—C bonds.

In this chapter, therefore, the opening of the smaller carbon ring, which is important only from the standpoint of classification, will be described. The cleavage, by hydrogenation proper, will be dealt with in the chapter on degradation (see page 444). The only exception made here is in the treatment of the relatively unimportant transformation of acid amides into primary, secondary, or tertiary amines (see page 226).

I. FORMATION OF C—H BONDS BY ADDITION

A. Addition of Hydrogen to Unsaturated Carbon Bonds

General Aspects

The addition of hydrogen to unsaturated carbon bonds is effected by means of a great number of reactions which can be divided into two groups. In the first group belong the reactions in which hydrogen functions in the so called nascent state; that is, in the atomic state. In the same group belong the reductions with hydrogen iodide, phosphonium iodide, and sodium hyposulfite. The second group consists of the catalytic reactions in which molecular hydrogen either adds to the substances to be reduced, or is transferred from a molecule richer in hydrogen to one poorer in hydrogen.

To date, direct hydrogenation with free, atomic hydrogen is still of no practical importance, although it may become important at some future date. Only scanty observations on this topic have been reported.

In a separate chapter, some of the most important papers on the organic chemistry of heavy hydrogen, deuterium, will be discussed.

1. Addition of Hydrogen to Ethylene Bonds and to Aromatic and Heterocyclic Systems

The reduction of aliphatic double bonds to form more saturated systems depends upon whether reducible groups other than those with one or more ethylene bonds are present in the molecule.

No generally applicable rule can be established for the reduction methods which are suitable for individual cases. The hydroxyl group, for instance, is quite resistant to many reducing agents; *e.g.*, to most catalytic ones. But this is true only for the existing hydroxyl group. Hydroxyl groups might be expected to be formed in the course of reduction of aldehydes or ketones. In many cases the carbonyl oxygen is completely replaced by hydrogen. In this chapter the methods in question are considered primarily with respect to their ability to saturate double bonds, either aliphatic, or alicyclic, or aromatic and heterocyclic, respectively. First, the methods which are generally applicable are discussed.

Preparation of Nascent Hydrogen

1. Sodium plus alcohol (ethyl, butyl, amyl, and occasionally capryl alcohols) in general is a mild reducing agent. Isolated double bonds remain intact, conjugated double bonds are reduced, but the isolated double bond thus formed remains. Ethylene bonds next to the phenyl nucleus (as in styrene and cinnamic acid derivatives) undergo reduction, although a number of exceptions exist. β,γ-Unsaturated carboxylic acids can also be reduced. The most important use is for the reduction of esters to alcohols, the method of Bouveault and Blanc.

It is comparatively easy partially to reduce condensed aromatic ring systems with sodium and alcohol. Amyl alcohol is used in most cases; naphthalene yields tetralin; phenanthrene and acenaphthene give tetrahydro compounds. When ethanol is used, naphthalene yields only dihydronaphthalene. Heterocyclic systems such as pyridine and other pyridine bases easily yield piperidine derivatives; pyrazoles change to pyrazolines. The naphthylamines are attacked very easily by sodium and amyl alcohol. In the case of α-naphthylamine only the unsubstituted nucleus is hydrogenated, while with β-naphthylamine the substituted nucleus is preferentially reduced. α- and β-naphthol act in a very similar manner. In no case does the hydrogenation proceed beyond the tetrahydro stage.

The method consists simply in adding pieces of metallic sodium to the boiling alcoholic solution. Sometimes a large excess is used, for

instance 75 g. of sodium for 20 g. of pyridine, which is more than twice the theoretical amount. The alcoholic solution may be added in certain cases to the pieces of sodium.

2. Sodium amalgam plus alcohol liberates hydrogen of about the same activity as does sodium alone. Isolated double bonds are resistant to attack, but, when next to a carbonyl group, they can be reduced. Benzalacetone, for instance, yields benzylacetone. Almost without exception, α,β-unsaturated acids are hydrogenated, especially the aromatic ones. Heat must usually be applied with aliphatic ones; *e.g.,* crotonic acid. Apparently, β,γ-unsaturated acids are not attacked directly, but when heated with sodium hydroxide they rearrange into α,β-unsaturated compounds and are then hydrogenated; γ,∂-unsaturated acids are not changed. Conjugated ethylene bonds yield isolated bonds by 1,4 addition. Kuhn and Hoffer [1] systematically studied the hydrogenation with amalgam of systems with many conjugated ethylene bonds. The addition of 1 mole of hydrogen always takes place at the ends of the conjugated system. This happens in symmetrical molecules like diphenyl polyenes, or asymmetrical compounds like polyene carboxylic acids of the type $CH_3(CH:CH)_xCOOH$. 1,10-Addition was proved in the case of diphenyldecapentene.

There seems to have been little study of this method of hydrogenation on cyclic systems. Sodium amalgam is inferior to sodium-alcohol. Anthracene is reduced to dihydroanthracene, resorcinol to dihydroresorcinol, phloroglucinol to hexahydrophloroglucinol. Depending on conditions, terephthalic acid yields isomeric dihydro-, tetrahydro-, and hexahydroterephthalic acids.

When sodium amalgam is used, the reaction conditions may be varied. Either hot or cold aqueous or alcoholic solutions may be used. The sodium hydroxide formed during the reaction may be neutralized by the addition of acids, or the solution may be kept acid during the reaction.

3. Aluminum amalgam is successfully used in moist ethereal solution for the reduction of sensitive compounds. It has the advantage that the solution may be kept neutral. Conjugated double bonds are partially reduced, *e.g.* fulvenes, but exceptions are known. The method is used for the reduction of unsaturated esters when saponification might result in an alkaline solution.[2]

4. The reduction with zinc and glacial acetic acid or sulfuric acid is better in some cases than reduction with amalgam or metallic sodium; *e.g.,* for α,β-unsaturated acids (zinc and sulfuric acid). The method offers no advantage with unsaturated ketones. Under some circumstances it is convenient because of the non-alkaline reaction condition.

[1] R. Kuhn and M. Hoffer, *Ber.,* 65, 170 (1932).
[2] H. Wislicenus and L. Kaufmann, *Ber.,* 28, 1323 (1895); *J. prakt. Chem.,* 54, 18–65 (1896).

Zinc dust and glacial acetic acid, with the addition of platinum chloride, reduce pyrrole to pyrrolidine. Hydrochloric acid is substituted for acetic acid with pyrrole homologues.

Kuhn and Winterstein [3] added glacial acetic acid to a mixture of zinc dust in pyridine to hydrogenate polyene carboxylic acids. The combination is more active than zinc dust with pyridine or glacial acetic acid alone. The addition of hydrogen proceeds rapidly and at ordinary temperature. Some water or alcohol must be present, because pure glacial acetic acid does not react with zinc dust in dry pyridine. Cyanine dyes, also, are easily reduced by this method.

5. Electrolytic hydrogen is generally superior to the reagents mentioned above, because the cathode material exerts a catalytic influence. Thus, any unsaturated acid, even one with a completely isolated ethylene bond, such as oleic or erucic acids, can be readily reduced on platinized cathodes. In a very similar manner phenol is converted to cyclohexanol. Lead cathodes are suitable for the reduction of pyridine bases as well as of indole.

6. Hydriodic acid, usually combined with phosphorus to regenerate the acid from the iodine formed, is superior to all the above reducing agents. All aliphatic double bonds can be reduced by hydriodic acid. Hydroxyl or carbonyl groups are also attacked. In the reduction of cyclic compounds, hydriodic acid has little importance except that carbazole, which has so far resisted catalytic hydrogenation, yields hexahydrocarbazole when reduced with hydriodic acid.

7. Phosphonium iodide acts more strongly than hydriodic acid in some cases. It hydrogenates benzene, isomerizing it to methylcyclopentane. Toluene and xylene are partially hydrogenated; mesitylene is completely reduced.

8. Sodium hydrosulfite is suitable for the reduction of unsaturated ketones. Using hot ethanol with sodium hydrosulfite, Conant and Lutz [4] obtained from symmetrical dibenzoylethylene and its derivatives the corresponding dibenzoylethanes. The catalytic reduction of these compounds readily yields by-products.

9. Indirect methods. In some cases the reduction of double bonds may be accomplished more easily by using the hydrogen halide addition products. Thus, angelic and tiglic acids cannot be hydrogenated with sodium amalgam, but, after addition of hydrogen bromide, the bromoisovaleric acids readily yield α-methylbutyric acid with sodium amalgam on treatment in the cold and with neutralization of the sodium hydroxide formed with dilute acid. Sodium amalgam may be replaced sometimes with sodium and alcohol. For the details, see page 8.

[3] R. Kuhn and A. Winterstein, *Ber.*, **65**, 1737 (1932).
[4] J. B. Conant and R. E. Lutz, *J. Am. Chem. Soc.*, **45**, 1805 (1923).

Hydrogenation Examples

1. *Sodium and Alcohol*—The reduction with sodium and alcohol liberates such large amounts of vapor that normal reflux condensers are usually inadequate because of their small capacity. Simple metallic pipes made of brass or aluminum, equipped with appropriate jackets if water cooling is necessary, are most suitable. Glass condensers of the necessary dimensions can be manufactured, but because of their fragility they constitute a source of danger, since breakage might let water come in contact with the hot sodium metal. It is not necessary to cool with water when amyl alcohol is used and glass may be used without fear. An expensive but effective cooling is obtained by passing a strong current of carbon dioxide directly out of the cylinder downwards through the condenser jacket. This method is recommended for the short space of time that violent boiling prevails during a reaction.

For reasons of safety, the reaction vessel should be set on a sand bath and not on a steam bath or on a wire gauze.

Bamberger and Müller [5] were the first to describe the reduction of β-naphthylamine to β-aminotetralin with sodium and alcohol. A more recent method of preparation is given in *Organic Syntheses*.[6]

2. *Sodium Amalgam*—Henle [7] prepared hydrocinnamic acid according to the following procedure. 15 g. of cinnamic acid are dissolved in 75 cc. of 5% warm sodium hydroxide solution. The solution is cooled and freshly prepared 2.5% sodium amalgam is added slowly and with vigorous stirring. After addition of 300 to 350 g., the reaction product is tested. When a sample to which hydrochloric acid and an aqueous solution of sodium carbonate have been added in turn does not decolorize permanganate, the reaction is complete. The mercury is then separated by decanting through a fluted filter and washed with a small amount of water. The solution is neutralized with hydrochloric acid, filtered if necessary, and 15 cc. of concentrated hydrochloric acid added. It is then extracted with ether and the ether dried over sodium sulfate and evaporated. The oily residue solidifies. Crystallization may be initiated by scratching the walls of the vessel. The yield is about 12 g. The acid can be purified by recrystallization from a large amount of warm water. Its melting point is 48.7°C. (Henle gives 47°C.). The method is hardly practicable for the preparation of large amounts of hydrocinnamic acid. The inconvenience in preparing sodium amalgam, the necessary recovery of the mercury, and the troublesome work with large amounts of mercury make the catalytic hydrogenation procedure superior.

[5] E. Bamberger and R. Müller, *Ber.*, 21, 847 (1888).

[6] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 499.

[7] F. W. Henle, *Anleitung für das organisch-chemische Praktikum*. Akadem. Verlagsgesellschaft, Leipzig, 1927.

The preparation of sodium amalgam can be avoided by electrolyzing cinnamic acid in alkaline solution with a mercury cathode. The reduction is of course not truly an electrolytic one, but is a reduction by means of the intermediary formed, sodium amalgam. The method has many applications; for details see *Organic Syntheses.*[8]

3. Aluminum Amalgam—Thiele and Bühner [9] employed aluminum amalgam for the reduction of fulvene and indene derivatives. The amalgam is prepared according to Wislicenus [10] as follows:

Granulated aluminum is etched with a 10% sodium hydroxide solution until hydrogen is freely generated; it is then washed three times with water and, still covered with water, treated with a 1% solution of mercuric chloride. After the mercuric chloride solution has reacted for a few seconds, the sludge is washed off with water and the amalgam washed with alcohol and ether. The product thus obtained is still wet and reacts, even in dry petroleum ether, very vigorously with generation of hydrogen; therefore, it must be used immediately after preparation. Thiele and Henle [11] give the following procedure for the preparation of benzylfluorene. 5 g. of benzalfluorene are dissolved in 200 cc. of ether and treated with 30 g. of aluminum amalgam and some water. The reaction takes place at room temperature. After 24 hours the ether is filtered off and concentrated. Almost pure benzylfluorene is obtained, melting at 130° to 131°C. In a corresponding manner anisalfluorene, furfuralfluorene, and other unsaturated fluorene derivatives may be reduced.

Thiele and Bühner [12] dissolved 5 g. of benzylideneindene in ether and treated the solution with 15 g. of fresh aluminum amalgam with occasional addition of water until decoloration resulted. This took about 6 to 24 hours. Then the solution was filtered and the filter cake washed well with ether. The ether solution was dried, evaporated, and the residue fractionated. Benzylindene was obtained, boiling at 183° to 185°C. at 13 mm. pressure.

4. Zinc Dust and Glacial Acetic Acid or Hydrochloric Acid—It is quite remarkable that with zinc and glacial acetic acid the pyrrole nucleus can be partially and quite easily reduced to yield dihydropyrrole (pyrroline). Ciamician and Dennstedt [13] first carried out the reaction, which was improved later by Knorr and Rabe.[14] Andrews and McElvain [15] modified the Knorr-Rabe method.

500 cc. of 20% hydrochloric acid are cooled to 0°C. in a large flask by means of an ice and salt mixture, and 200 g. of zinc dust are added with vigorous stirring. 50 g. of pyrrole are then added slowly from a dropping funnel. If the temperature initially exceeds 10°C., the speed of reaction will increase uncontrollably. After all the pyrrole has been added (about 1 hour), 300 cc. of concentrated hydrochloric acid are added and

[8] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, pp. 311, 554.
[9] J. Thiele and A. Bühner, *Ann.*, 347, 249 (1906).
[10] Wislicenus, *J. prakt. Chem.*, 54, 54 (1896).
[11] J. Thiele and F. Henle, *Ann.*, 347, 298 (1906).
[12] J. Thiele and A. Bühner, *Ann.*, 347, 260 (1906).
[13] G. L. Ciamician and M. Dennstedt, *Ber.*, 16, 1536 (1883).
[14] L. Knorr and P. Rabe, *Ber.*, 34, 3491 (1901).
[15] Andrews and McElvain, *J. Am. Chem. Soc.*, 51, 889 (1929).

the stirring continued for 2 additional hours. The temperature is kept at 15° to 25°C. during this time. The cooling bath is then removed and the mixture stirred for 4½ hours at room temperature. The remaining zinc is filtered off and washed with a little water. The filtrate is made sufficiently alkaline to dissolve the precipitated zinc hydroxide and then steam-distilled until the distillate is no longer alkaline to litmus. The distillate is made acid with hydrochloric acid and evaporated on a steam bath. The gummy residue is treated with 40% sodium hydroxide solution and extracted twice with ether, and the extract dried with sodium sulfate and distilled. Thus 28.5 g. of pyrroline are obtained, boiling at 89° to 92°C. The crystalline hydrochloride prepared from the pyrroline fraction melts at 162° to 163°C. The yield is 56% of theory. The by-products are high boiling fractions.

5. Electrolytic Reduction of Pyridine—This was described for the first time by Ahrens.[16]

Pyridine is dissolved in 10 times its weight of 10% sulfuric acid. The solution is put as a cathode liquid into a porous cell containing a lead electrode. The porous cell is set into 10% sulfuric acid as an anode liquid. For the electrolysis, an electrode surface of 100 sq. cm. is used with a 12 amperes current. No evolution of hydrogen can at first be noticed, but towards the end the reaction becomes quite violent and the temperature increases to about 55°C. It is possible to isolate piperidine in a 95% yield.

The same paper describes the reductions of quinoline to tetrahydroquinoline and of quinaldine to tetrahydroquinaldine. Some details are given for the reduction of quinoline.

The cathode current amounts to 17 amperes per 100 sq. cm.; the voltage to 5.5 volts. The temperature rises to 53°C. and the reaction takes about 2 hours. The cathode which is lead and the anode (two platinum electrodes of 30 sq. cm. surface each) dip into 10% sulfuric acid. The cathode liquid contains 5% quinoline.

Marie and Lejeune [17] reinvestigated Ahrens' method and published additional data. A British patent [18] deals with the same subject.

2. Catalytic Hydrogenation

General Aspects

The catalytic hydrogenation of the ethylene linkage serves as an example for all similar methods of hydrogenation. The hydrogenation process requires equipment and preparation.

1. Sources of Hydrogen. For almost all laboratory hydrogenation methods, electrolytic hydrogen in cylinders is the most convenient starting material. Oxygen content is not harmful unless the water formed at the catalyst causes a harmful secondary reaction, which is observed

[16] F. Ahrens, *Z. Elektrochem.*, 2, 577 (1896).
[17] C. Marie and G. Lejeune, *J. chim. phys.*, 22, 59 (1925); *Chem. Abstracts*, 19, 1708 (1925).
[18] British Patent, 395,741; *Chem. Abstracts*, 28, 421 (1934).

only in rare cases. Electrolytic hydrogen may ordinarily be used without special purification. Frequently cylinders with hydrogen of other origin can be used, but only after ascertaining in every instance whether purification is necessary. The most convenient method for determining the need for purification is by hydrogenation of a suitable test substance with a good catalyst. In any case it is advisable to learn from the supplier the origin of the hydrogen.

A laboratory apparatus for the preparation of electrolytic hydrogen cannot be recommended. If hydrogen in cylinders cannot be obtained, the gas generated in a Kipp apparatus from zinc and mineral acids can generally be used after a washing with permanganate and silver nitrate.

2. Storage and Measurement of Hydrogen. Whenever an excess of hydrogen is not harmful, it may be drawn directly from the cylinder. Often it may be desirable to observe the progress of the hydrogenation qualitatively or quantitatively. If less than 1 to 2 liters of hydrogen is used in the reaction and if it is performed at atmospheric pressure (or at several centimeters mercury pressure), the hydrogen consumption is determined volumetrically. For several atmospheres and high pressure hydrogenations, a manometer is used.

A simple apparatus for hydrogenation with several liters of hydrogen is shown in Fig. 1.
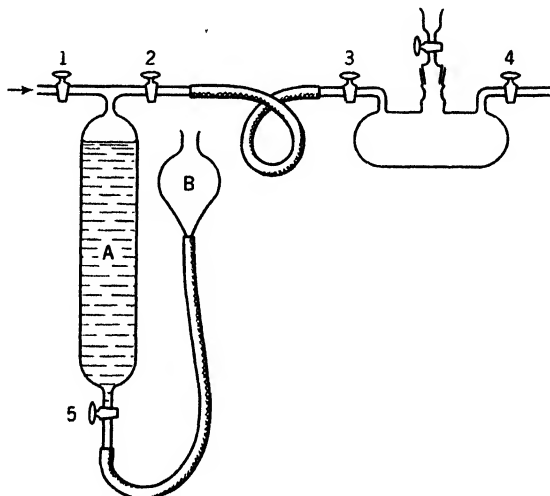
Fig. 1.—Hydrogenation apparatus for ordinary pressure.

The cylindrical vessel *A*, equipped with cocks *1* and *2*, is connected with the leveling bulb *B* by means of rubber tubing. It holds 1000 cc. between the top and bottom markings and is graduated accurately to suit the purpose. It is sufficient for most purposes to fill the vessel with water and to drain 50 cc. at a time into a good graduate; the sub-

division into 10 cc. may be marked.   A more accurate measurement is never necessary for preparative purposes.   At the start of the process, A is filled with water close to the horizontal part of the upper T-piece, then the apparatus is flushed with hydrogen, while cocks *1* to *5* are open.   Cocks *4*, *3*, and *2* are closed in succession, the leveling bulb is lowered, and hydrogen is admitted to the bottom marking.   Finally, cocks *1* and *5* are closed.   In order to bring the pressure in the whole system to atmospheric, cocks *2* and *3* may now be opened and the excess pressure relieved by a short opening of cock *4*.   Cock *5* is opened, the leveling bulb B raised 10 to 20 cm. above the lower liquid level, and the reaction started by shaking or by adding the catalyst.   For precautions during later addition of the catalyst, see page 20.

When the supply in A is used up, cocks *2* and *3* are closed, the shaking discontinued, and the water level read after equalizing to atmospheric pressure with the leveling bulb B.   Then A is again filled with hydrogen.   If it is desirable, for the sake of convenience, to fill A again exactly to the starting level, cock *2* is made a 3-way cock and the excess pressure relieved through cock *2* after the water level is brought to the bottom marking and after cocks *2* and *5* are closed.   Otherwise, the system has to be adjusted to atmospheric pressure with leveling bulb B after cock *1* has been closed and the water level noted.

For larger scale hydrogenations, with 5 to 10 liters of hydrogen, an apparatus may be set up according to *Organic Syntheses*.[19]

With the apparatus described above and in *Organic Syntheses*, all laboratory preparations can be carried out as long as higher pressures are unnecessary.   In laboratories in which no special catalytic operations are carried out, no instruments will be available for measuring the amount of hydrogen for pressure hydrogenations.   It will suffice then to observe the reduction of pressure, but no quantitative conclusions can be drawn because of the inaccuracy of the manometers.

3. Catalysts.   The efficiency of certain hydrogenation catalysts is no longer a subject of debate.   Practically the only elements which possess catalytic power are platinum, palladium, and nickel.   Great importance, however, has recently been attached to many mixed catalysts, the preparation and action of which are frequently kept secret.   Whether to use a colloidal or a crystalloidal catalyst depends upon the nature of the preparation and the experience of the investigator.   The crystalloidal catalysts and the ones precipitated onto carriers work most cleanly and in the last analysis most cheaply.

(a) Nickel Catalysts

In the preparation of nickel catalysts nickel oxide is frequently prepared first.   The effectiveness of the nickel catalyst depends substantially on its degree of dispersion.   The oxalate and nitrate are used as starting materials.   These must be as pure as possible.

1. The nickel oxide is placed in a combustion tube and heated in a stream of hydrogen to 300° to 320°C.   After the substance has reacted

[19] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 61.

completely, it is cooled in a stream of hydrogen. Nickel which has been reduced at low temperature is easily oxidized and is therefore best stored in an inert atmosphere or in a vacuum. There is no reason for reducing the nickel oxide at a lower temperature than that at which the hydrogenation is to be performed.

Sabatier performed the hydrogenation of the benzene nucleus with nickel which was reduced at red heat, below 700°C. Other sources state that the nickel is not very active if reduced at a temperature higher than 450°C. It is quite remarkable, though not surprising, that especially active nickel catalysts also promote side reactions.

Covert, Connor, and Adkins [20] recommend the following method. 58 g. of nickel nitrate hexahydrate, dissolved in 80 cc. of distilled water, are ground for 30 to 60 minutes in a mortar with 50 g. of kieselguhr (extracted with hydrochloric acid) until the mixture is apparently homogeneous and flows as freely as heavy oil. It is then slowly added to a solution prepared of 34 g. of ammonium carbonate monohydrate in 200 cc. of distilled water. The precipitate is filtered with suction, washed with 100 cc. of water in two portions, and dried at 110°C. Just before use, the product is reduced for 1 hour at 450°C. in a stream of hydrogen flowing at the rate of 10 to 15 cc. per minute.

2. A method for the preparation of very finely dispersed nickel which is quite reliable is as follows: Nickel formate is suspended in the same weight of paraffin oil and heated to 260°C. while being stirred and while carbon dioxide is passed through. The nickel formed is filtered, decanted with petroleum ether, and stored under petroleum ether. It is a highly active catalyst for pressure hydrogenations.

3. The so called Raney nickel is prepared according to Covert and Adkins [21] by combining equal parts of nickel and aluminum in an alloy and dissolving the aluminum with an aqueous solution of sodium hydroxide. The authors recommend that the commercial Raney nickel suspended in water should not be used if a highly active catalyst is desired. They suggest the following procedure. 300 g. of the finely powdered nickel-aluminum alloy are slowly added (2 to 3 hours) to a solution of 300 g. of 80% sodium hydroxide in 1200 cc. of water contained in a large beaker cooled in ice. The mixture is then heated with occasional stirring for 4 hours to 115° to 120°C. Then 400 cc. of a 19% solution of sodium hydroxide are added and the heating continued for 3 hours, or until hydrogen is no longer evolved. The solution is diluted with water to a volume of 3 liters, the clear solution of sodium aluminate decanted from the nickel, and the metal powder washed six times with water by decantation. Then the nickel is separated on a Büchner funnel and washed with water until the filtrate is neutral to litmus. Finally, the nickel is washed three times with 95% ethanol and stored under ethanol in glass-stoppered bottles.

[20] L. Covert, R. Connor, and H. Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932).
[21] L. Covert and H. Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).

Nickel prepared in this way is so reactive that nitrobenzene and its derivatives are converted into azo and azoxy compounds, respectively, even at room temperature.

(b) Noble Metal Catalysts

The metal catalysts in element form, such as platinum or palladium black, were used with great success some time ago, but they have been replaced for practical purposes by the oxides which can be prepared much more conveniently. But since it is occasionally (see page 20) necessary to use perfectly dry catalysts, the methods for their preparation are described briefly.

1. Platinum Black, According to Willstätter and Waldschmidt-Leitz [22]— 80 cc. of chloroplatinic acid containing 20 g. of platinum and a little excess of hydrochloric acid are mixed with 150 cc. of 33% aqueous formaldehyde. The mixture is cooled to $-10°C$. and a 50% potassium hydroxide solution added dropwise with thorough stirring. The temperature must never exceed 6°C. The stirring is continued for 30 minutes, and the temperature raised to 55° to 60°C. The platinum is allowed to settle, and then washed by decantation until the chloride ions and the alkalinity have disappeared. The product is collected under water on a Büchner funnel, sucked dry rapidly, and pressed between filter paper. After several days in a desiccator with a high vacuum, the product becomes dust-dry. The vacuum is replaced by carbon dioxide and the catalyst stored in this atmosphere. Willstätter and Bommer [23] state that, after several days storage, platinum black forms water from occluded hydrogen and oxygen if these gases are not removed by keeping the catalyst for some time in a high vacuum.

Platinum black is always activated in the shaking flask with air or oxygen before hydrogen is admitted.

2. Palladium Black, According to Willstätter and Waldschmidt-Leitz [24]— An acidified solution of palladium chloride (100 to 150 cc.) containing 4.25 g. of palladium is mixed with 50 cc. of a 33% aqueous solution of formaldehyde and cooled to $-10°C$. While the solution is stirred vigorously, 100 g. of a 50% potassium hydroxide solution are added within 10 minutes. The temperature must not exceed 3°C. After the solution has been heated for 15 minutes to 60°C., the brown color disappears, and the palladium black settles to the bottom. It is washed and recovered as described above for platinum black.

3. Platinic Oxide—This is the starting material used most frequently for producing a platinum catalyst for hydrogenations. Adams and co-

[22] R. Willstätter and E. Waldschmidt-Leitz, *Ber.*, 54, 113 (1921).
[23] M. Bommer, quoted in R. Willstätter and D. Jaquet, *Ber.*, 51, 770 (1918).
[24] R. Willstätter and E. Waldschmidt-Leitz, *Ber.*, 54, 123 (1921).

workers give a method for its preparation in *Organic Syntheses*.[25] The platinic oxide prepared according to these directions can be used directly or dried. The product dried in a desiccator is best stored in small portions in evacuated glass tubes. When Adams' method is used, the yield of catalyst is 95 to 100% of the theoretical amount.

Adams' platinic oxide catalyst may be prepared advantageously from ammonium chloroplatinate, according to Bruce.[26] A mixture of 3 g. of ammonium chloroplatinate and 30 g. of sodium nitrate is heated in a porcelain crucible, slowly at first, until the evolution of gases quiets down. Then the temperature is raised over a period of 15 minutes to 500°C. No spattering occurs. The temperature is kept for 30 minutes at 500° to 520°C. The fused mixture is allowed to cool, and the catalyst purified as described in Adams' method. The yield is 1.5 g. of platinic oxide which is similar in general appearance and activity to the product prepared from chloroplatinic acid.

RECOVERY OF CATALYSTS

The catalyst is dissolved in a small amount of aqua regia and the solution evaporated to dryness. The residue is dissolved in a little water and fused with sodium nitrate as above. If a platinum catalyst is recovered repeatedly according to this method, a poisoning of the catalyst may occur, in which event the catalyst must be purified thoroughly in another manner. Wichers [27] recommends a method for this purpose, but since his method is troublesome and elaborate, it is preferable to follow the instructions given in *Organic Syntheses*.[28] Platinum oxide is reduced to platinum black in the hydrogenation flask proper; when shaken with hydrogen, the compound turns black and forms a fine suspension. The time required for this reduction varies from a few seconds to several minutes, depending on reaction conditions. If the solvent only is present, the reaction is rapid in most cases. If the oxide is reduced along with the substance to be reduced, the duration of the reaction, ranging from 10 to 15 minutes, depends on the nature of the substance. When admixtures are used to maintain activation or to overcome partial inhibition, the reduction period may be prolonged still further; for example, all the oxide is reduced after 40 to 60 minutes in the presence of a small amount of sodium nitrite and an alcoholic solution of benzaldehyde.

[25] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 463.
[26] W. Bruce, *J. Am. Chem. Soc.*, **58**, 687 (1936). H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 466.
[27] Wichers, *J. Am. Chem. Soc.*, **43**, 1268 (1921).
[28] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 466.

Catalysts which have been used once can, under certain conditions, be reactivated with air or oxygen. Occasionally, reactivation has to be carried out while hydrogenation is still in progress in order to complete the reaction or to increase the diminished rate of hydrogen absorption. This procedure, however, sometimes inactivates the catalyst completely. If the catalyst conglomerates during the course of hydrogenation, especially towards the end, it must be reworked. If it settles after shaking has been stopped, it is not spoiled so long as it can be easily shaken into a suspension.

As far as the influence of the solvent is concerned, absolute or 95% ethanol seems to be the best medium; in some cases, ethyl acetate and glacial acetic acid are advantageous. When aldehydes are being reduced, a reduction of the platinum oxide along with the aldehyde is recommended, because very finely divided platinum black is produced.

4. Palladium Oxide—Shriner and Adams [29] and Starr and Hixon [30] give detailed descriptions for the preparation of this compound.

5. Osmium—Zelinskii and Turowa-Pollak [31] describe the specific properties of an osmium catalyst. Hydrogenations with osmium catalysts generally proceed at lower temperatures than with platinum, palladium, or nickel catalysts. Osmium on asbestos may be used several months without losing its activity. As a dehydrogenation catalyst, osmium is less active than platinum and palladium. It is a disadvantage that osmium catalysts which are not precipitated onto carriers must be regenerated more often and, furthermore, that at temperatures above 150°C. they cause decomposition of the substance to be hydrogenated.

6. Platinum and Palladium Precipitated on Carrier Substances—Suitable metallic carriers are magnesium, nickel, and cobalt; equally good are their oxides, hydroxides, and carbonates. Other inert carriers are calcium carbonate, barium sulfate, animal charcoal, diatomaceous earth, and silica gel.

Palladium Precipitated on Barium Sulfate—This is one of the most convenient and cleanest of hydrogenation catalysts. Paal [32] gives the following instructions. Barium sulfate is precipitated cold by adding 6.084 g. of sodium sulfate to a solution containing 10.44 g. of barium chloride dihydrate. A solution of 1.7 g. of palladium chloride is then added. The palladium is precipitated by adding, while shaking, a small excess of sodium carbonate solution. The palladium hydroxide is allowed to settle, and is then decanted, filtered, and, after thorough washing, dried in a desiccator.

[29] Shriner and Adams, *J. Am. Chem. Soc.*, **46**, 1684 (1924); **47**, 1147 (1925).
[30] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 566.
[31] N. Zelinskii and M. Turowa-Pollak, *Ber.*, **62**, 2865 (1929).
[32] German Patents, 236,488 and 265,500.

Schmidt [33] recommends another method: To 400 parts of an aqueous suspension of 20 parts of barium sulfate, which has been precipitated hot, is added a solution of 1.7 parts of palladium chloride in 50 parts of water and 1 part of 50% aqueous formaldehyde. The mixture is made alkaline to litmus with sodium hydroxide solution and boiled for a short time. The gray precipitate is filtered, washed with hot water until the alkalinity disappears, dried over potassium hydroxide, and finely powdered.

Palladium on Calcium Carbonate and Magnesium Oxide According to Paal—Palladium chloride solutions are treated with calcium carbonate or magnesium oxide which become coated with palladium hydroxide. Before use these catalysts, as well as palladium-barium sulfate catalysts, are reduced with hydrogen.

Platinum on Charcoal [34]—To a suspension of 10 to 12 g. of activated charcoal in a little water is added, while stirring, a solution of platinum chloride containing the desired percentage of platinum. The mixture is kept at 50°C. for several hours. After cooling, the solution is made alkaline with a concentrated solution of sodium carbonate. Then hydrazine hydrate is added dropwise until a drop of permanganate solution shows an excess of hydrazine. The reduced solution is stirred again for several hours at 50°C. The filtered precipitate is washed free of chlorides and alkali, pressed between filter paper, and dried.

Palladium on Charcoal [35]—Activated charcoal (5 g.) is shaken with 25 cc. of a 0.2 to 0.6% palladium chloride solution, while hydrogen is being admitted. The catalyst is filtered, washed, and dried over phosphorus pentoxide *in vacuo*. When the vacuum is released, hydrogen is again admitted to saturate the catalyst.

(c) Colloidal Substances

The colloidal hydrogenation catalysts are historically of great importance. By means of these catalysts, Paal first succeeded in performing catalytic hydrogenations at room temperature, a procedure which has become a versatile laboratory method. Currently, colloidal hydrogenation catalysts are of little practical importance, but because reference occasionally will be made to the methods in the following chapters, the most important original publications are mentioned here.

1. The reduction method of Paal,[36] noble metals with protective colloids, preparation of sodium protalbinate and lysalbinate; platinum and palladium colloids.[37] These catalysts are stable only in alkaline or neutral solutions. Kelber and Schwarz [38] describe an acid-resistant catalyst, with degraded gelatin as protective colloid.

2. The reduction method of Skita,[39] gum arabic as protective colloid.

[33] E. Schmidt, *Ber.*, **52**, 409 (1919).
[34] H. Kaffer, *Ber.*, **57**, 1263 (1924).
[35] C. Mannich and E. Thiele, *Arch. Pharm.*, **253**, 183 (1915). Gadamer, *ibid.*, **255**, 294 (1917); *Ber. deut. pharm. Ges.*, **26**, 37 (1916). H. Wienhaus, *Ber.*, **53**, 1658 (1917).
[36] C. Paal, *Ber.*, **35**, 2197 (1902).
[37] C. Paal, *Ber.*, **37**, 131 (1904).
[38] C. Kelber and A. Schwarz, *Ber.*, **45**, 1946 (1912).
[39] A. Skita and W. A. Meyer, *Ber.*, **45**, 3584 (1912). A. Skita, *Ber.*, **57**, 1977 (1924).

(d) Copper Chromium Oxide Catalysts

Connor, Folkers, and Adkins [40] give the following instructions for the preparation of the catalyst. 900 cc. of an aqueous solution containing 261 g. of copper nitrate trihydrate and 31.3 g. of barium nitrate were heated to 80°C. and run into 720 cc. of an aqueous solution (25%; 30°C.) of 151.2 g. of ammonium bichromate and 150 cc. of 28% aqueous ammonia. The precipitate was filtered and sucked as dry as possible. After the material was dried at 75° to 80°C. and pulverized, the product weighed 234 g. It was decomposed in three portions in a porcelain crucible over a free flame. The powder was stirred with a spatula from the start of the heating. As soon as decomposition started, the flame was removed. After a little more stirring, a sudden evolution of gases occurred, and the entire mass became black. The powder was stirred thoroughly, then removed from the hot crucible, and allowed to cool. The three portions were combined, extracted for 30 minutes with 600 cc. of 10% acetic acid, filtered, washed with 600 cc. of water in six portions, dried overnight at 125°C., and pulverized. The product weighed 149.5 g.

The presence of barium protects the catalyst from being reduced by hydrogen. The reduction can be noted by a change of color from black to a reddish hue. The catalysts then completely lose their ability to activate hydrogen. But other catalytic processes, as in the rearrangement of aldehydes to esters, are especially accelerated by such catalysts which probably contain monovalent copper.

The hydrogenation catalysts are not improved by substituting magnesium or calcium for barium.

For other mixed chromium oxide catalysts, see page 186.

3. Hydrogenation Procedures

(a) The oldest of all hydrogenation procedures, that of Sabatier and Senderens, has lost much of its significance for laboratory use. Therefore, the following brief description will suffice.

The reaction takes place in the gaseous phase and thus can be used only for substances which volatilize without decomposition. The vapors, mixed with hydrogen, pass over the catalyst, which is usually nickel. For the use of other metals, see page 221. Detailed descriptions by Sabatier may be found in an earlier publication. [41]

If the hydrogen used is generated from zinc and sulfuric acid in a Kipp apparatus, it must be purified by washing with a solution of potassium permanganate and potassium hydroxide, and with concentrated sulfuric

[40] R. Connor, K. Folkers, and H. Adkins, *J. Am. Chem. Soc.*, **54**, 1138 (1932).
[41] P. Sabatier, *Catalysis in Organic Chemistry*. Van Nostrand, New York, 1923.

acid. The residual oxygen must be removed by red hot copper, and the hydrogen must be dried over potassium hydroxide. Hydrogen taken from cylinders need only be passed over red hot copper and dried over potassium hydroxide.

To prepare the catalyst for use at ordinary pressure, pure nickel oxide, hydroxide, or basic carbonate is best reduced at 300° to 320°C. For use at higher pressures, lower temperatures are sufficient; the catalyst obtained is more active.[42] The freshly reduced nickel is pyrophoric because it contains a considerable amount of hydrogen. The catalyst may be stored in carbon dioxide; it loses its reactivity very rapidly when exposed to air. Especially active catalysts are not always convenient, because they promote side reactions such as the removal of water from the molecule, dehydrogenations, and rupture of molecules.

As is the case with noble metals, nickel precipitated onto carriers is frequently more active than the pure metal; it is also more resistant to inhibition. Reduction may be carried out at a higher temperature. It is preferable to reduce the catalyst immediately before use in the same container in which the hydrogenation is to be performed, usually a combustion tube. Foremost among catalyst inhibitors are the halogens, even in the smallest traces, and also substances containing sulfur. Therefore, benzene containing thiophene cannot be reduced according to the method of Sabatier and Senderens. In contrast to noble metal catalysts the activity of which often decreases within a short period of time, a nickel catalyst, when carefully handled, may be used in continuous operations for many days.

"Activators" is a term applied to promoters. Their activity is probably due to a number of different causes. Specific activators are metals such as copper, palladium, etc. Small amounts of alkalies, aluminum oxide, magnesium oxide, and alkali silicates are effective probably because they neutralize catalyst inhibitors. They are fundamentally no different from carrier substances. No sharp line can be drawn between carrier substances and activators. For the details, see Sabatier.[43]

The temperature at which the hydrogenation is carried out depends on the compound being reduced. For the reduction of aldehydes and ketones to alcohols, a temperature of 100° to 150°C. is sufficient; for double bonds, 180° to 200°C.; for the hydrogenation of carbonyl groups to methylene groups, temperatures as high as 250° to 270°C. are necessary.

This method is in principle superior to the methods in which noble metals and low temperatures are used. It is true that the methylene bond

[42] A. Grün, *Chem.-Ztg.*, **47**, 880 (1923).
[43] P. Sabatier, *Catalysis in Organic Chemistry*. Van Nostrand, New York, 1923, pp. 180s–180u.

is more easily attacked than the carbonyl groups, but the latter are reduced to a degree never experienced when noble metals are used as catalysts. An especially great difference seems to exist between the perhydrogenation of carbonyl oxygen and the nuclear hydrogenation; ketones like acetophenone and benzil can easily be reduced to ethylbenzene and diphenylethane, respectively, without an attack on the aromatic nucleus. In this respect, the action is similar to the one observed in Clemmensen's method. Also, according to Sabatier and Senderens, aliphatic and aromatic bound halogen can easily be replaced; chlorine most easily, and bromine with greater difficulty. Hydroxyl groups are eliminated only when formed during the hydrogenation. Hydroxyl groups already present remain intact; an exception is p-tolylisopropanol which is changed to cymene. The exact measurement of hydrogen and the control of other reaction conditions is more difficult than with noble metal catalysts. The method has been of outstanding value for the hydrogenation of aromatic systems.

(b) Especially important for industrial use is the reduction method of Normann-Ipatieff-Schröter. Normann[44] was the first to show that reductions can be performed in liquid phase at ordinary temperature and pressure with catalysts very similar to those used for the reductions by the method of Sabatier and Senderens. The amount of catalyst employed is rather large: 30 to 40% nickel catalyst (precipitated on diatomaceous earth or on burned and ground clay) is used in the same amount as, or in larger amounts than, the substance to be reduced. The reaction takes place in aqueous or aqueous alcoholic solution, occasionally with the addition of ethyl acetate. Unsaturated carboxylic acids are used in the form of their salts. The method became important when higher pressures and temperatures were employed, without a change in the other conditions of the reaction.

(c) The method of hydrogenation with noble metal catalysts has been simplified for laboratory use. Information on the equipment has already been given above (see page 11).

A certain amount of care is necessary when the catalyst and hydrogen are brought in contact. Certain oxide or hydroxide catalysts (palladium hydroxide) must not be used with pure hydrogen, because the formation of water proceeds so violently that the mixture may ignite while the air in the hydrogenation flask is being replaced by hydrogen. These catalysts must therefore be reduced under suitable liquids. If the solvent used later in the process can be employed for this purpose, the method is greatly simplified. Otherwise, the catalysts (palladium hydroxide, barium sulfate) are reduced under ether, for instance, until the color of the

[44] Normann, British Patent, 1515 (1903).

product changes to a gray-black. The ether is then evaporated in a stream of hydrogen. The solution to be hydrogenated is added through the funnel of the hydrogenation flask without interrupting the stream of hydrogen. However, the air can be replaced just as well by carbon dioxide before the hydrogen is admitted.

It is unnecessary to reduce the catalyst prior to the reducing process if the amount of hydrogen consumed for the reduction of the catalyst is insignificant; the reaction can be carried out easily according to the instructions given above. It is necessary to take into consideration the fact that a small amount of water is always formed when oxide or hydroxide catalysts are used; but this is never a disturbing factor, especially if water is used as a sealing liquid and if the vessels of the reaction are not thoroughly dried.

4. Specific Effects of Hydrogenation

Whenever there is competition within a molecule among the several reducible groups for the catalytically activated hydrogen, a certain sequence of reactions is observed. First, the double bond and the nitro group are attacked almost simultaneously, then the carbonyl group, the cyano group, the hydroxyl group, the carbocyclic systems, the heterocyclic systems, and the very resistant carboxyl group.[45]

Isolated double bonds are more easily reduced catalytically than are conjugated bonds, the reverse of hydrogenation with nascent hydrogen. Consequently, the reaction can nearly always be directed in multiple reducible systems in such a way that $C:C$ double bonds are saturated first. Only when nitro groups are also present is this not possible. The difficulty is of little importance, because it is rarely the case that the saturated compounds cannot be prepared, by a different method, more easily than the unsaturated nitro compounds. This is also true for nitroso compounds.

As pointed out above, after the double bond the carbonyl group is the most easily attacked. If, however, hydrogenation is interrupted as soon as the calculated amount of hydrogen has been absorbed, good results are nearly always obtained.

Attempts have been made to influence the hydrogenation catalysts so that the carbonyl group remains intact; but apparently such experiments as the theoretically important quantitative hydrogenation of polyenes of relatively high molecular weight did not meet with complete success.[46] If a compound containing a double bond and a carbonyl group lends itself to hydrogenation, but if it is difficult or impossible to isolate

[45] F. Diwoky and H. Adkins, *J. Am. Chem. Soc.*, **53**, 1868 (1931).
[46] R. Kuhn and E. F. Möller, *Angew. Chem.*, **47**, 149 (1934).

the saturated carbonyl compound, it is advisable to allow the hydrogenation to proceed until the saturated hydroxyl compound is obtained. The latter is relatively easy to isolate, and the carbonyl group can be regenerated by dehydrogenation. In any case, aromatic and heterocyclic nuclei are attacked later than other unsaturated groups, the only exceptions being hydroxyl and carboxyl groups.

Recently it was shown that the hydrogenation may be directed selectively by the addition of certain catalysts.

Adams and Garvey [47] used the platinum oxide-platinum black catalyst with the addition of small amounts of ferrous sulfate and zinc acetate. In the non-catalytic hydrogenation of citral, $(CH_3)_2 \cdot C:CH \cdot CH_2 \cdot CH_2 \cdot C(CH_3):CH \cdot CHO$, first the ethylene bond next to the aldehyde group, then the aldehyde group, and finally the second ethylene bond are reduced. Under the influence of catalysts, however, the hydrogenation attacks the carbonyl group first, and exclusively. After 1 mole of hydrogen is consumed, geraniol, $(CH_3)_2 \cdot C:CH \cdot CH_2 \cdot CH_2 \cdot C(CH_3):CH \cdot CH_2OH$, is found as the main reaction product. After another mole of hydrogen is consumed, citronellol, $(CH_3)_2C:CH \cdot CH_2 \cdot CH_2 \cdot CH(CH_3) \cdot CH_2 \cdot CH_2OH$, and finally tetrahydrogeraniol are obtained. Thus, the catalysts increase the reaction rate of the first step. In other words, the formation of geraniol from citral proceeds faster than the formation of dihydrocitral, but the reaction rate of the second and third steps (geraniol → citronellol → tetrahydrogeraniol) is decreased.

Tuley and Adams [48] obtained a complex mixture from cinnamic aldehyde when hydrogenated with platinum black in a slow reaction, but, after adding 0.01 to 0.02 millimole of ferrous chloride, they readily introduced 1 mole of hydrogen, thus forming cinnamic alcohol. Especially conspicuous was the effect of ferrous chloride plus zinc acetate: the hydrogenation proceeded well until 1 mole of hydrogen was used up; then the reaction slowed down considerably and finally stopped. The cinnamic alcohol thus obtained was practically free from aldehyde. By adding ferrous chloride alone, hydrogen was taken up further and phenylpropyl alcohol readily obtained. The pressure during these hydrogenations was 2 to 3 atmospheres.

Similar observations are reported by Adams and coworkers,[49] who found that α-furfuracrolein is hydrogenated in the presence of ferrous sulfate and zinc acetate to yield furfurylallyl alcohol with the double bond intact and furyl-*n*-propyl alcohol by addition of a further mole of hydrogen. Furfurylallyl alcohol cannot be reduced further in the presence of zinc acetate; in the presence of ferrous sulfate alone the furan nucleus

[47] R. Adams and B. Garvey, *J. Am. Chem. Soc.*, **48**, 477 (1926).
[48] W. Tuley and R. Adams, *J. Am. Chem. Soc.*, **47**, 3061 (1925).
[49] R. Adams *et al.*, *J. Am. Chem. Soc.*, **47**, 3061 (1925); **48**, 477 (1926); **49**, 2101 (1927).

is attacked, forming tetrahydrofurylallyl alcohol, which finally yields tetrahydrofuryl-*n*-propyl alcohol. By opening the ring, small amounts of a heptanediol are formed as a by-product. A total of 4.4 moles of hydrogen is absorbed in the presence of ferrous sulfate.

Few directions well worked out for such selective hydrogenations are found in the literature, despite the fact that, or because, this possible procedure is undoubtedly used frequently in industrial practice.

By using suitable catalysts, Sauer and Adkins [50] succeeded in reducing the esters of unsaturated aliphatic carboxylic acids to unsaturated alcohols with yields of more than 60%.

Thus, the butyl ester of oleic acid yielded an octadecenol at 300°C. and 200 atmospheres. A zinc-chromium oxide catalyst was used, the preparation of which is described below. Yields of 65% are reported. Accordingly, butyl erucate and butyl undecenoate could be reduced to the unsaturated alcohols, though in the latter case a yield of only 37% of the theoretical amount was obtained. (The butyl esters were used because they could be separated by distillation more easily than could the ethyl esters from the corresponding higher alcohols formed from the esters.)

Preparation of Zinc-Chromium Oxide Catalyst—To a solution of 250 g. of ammonium dichromate in 600 cc. of water are added about 400 cc. of concentrated ammonium hydroxide until the color changes to yellow. When a solution of 379 g. of zinc nitrate in 800 cc. of water is added to this mixture, a yellow precipitate is formed which is filtered, washed, and dried overnight at 85°C. It weighs 333 g. The product is decomposed in four portions according to Adkins and coworkers [51] by heating over a free flame while being stirred with a spatula. As soon as the decomposition is well under way, the flame is removed; on further stirring, gases are rapidly evolved and the whole mass turns black. In this state, the product is again stirred thoroughly and allowed to cool, and then washed with 5% acetic acid for several minutes, filtered, and dried overnight at 85°C. Thus, 220 g. of a brown colored catalyst are obtained.

On analysis the reduction products always contain several per cent of saturated alcohols as impurities. The method is not very satisfactory, because the amounts of catalyst used are very large (1 part of catalyst to 2 parts of ester), and the saturated alcohols cannot readily be separated from the unsaturated alcohols by fractional distillation. The products obtained, however, may be of interest for some purposes.

EXAMPLES OF CATALYTIC HYDROGENATION

(a) *Ethylene Bonds*

The catalytic reduction of ethylene bonds generally presents no difficulties. For preparational purposes it is immaterial whether *cis*- or *trans*-ethylene compounds are used. Paal and Schiedewitz [52] state that *cis* compounds are usually hydrogenated faster than *trans* compounds.

[50] J. Sauer and H. Adkins, *J. Am. Chem. Soc.*, **59**, 1 (1937).
[51] H. Adkins *et al.*, *J. Am. Chem. Soc.*, **54**, 1138 (1932).
[52] C. Paal and H. Schiedewitz, *Ber.*, **60**, 1221 (1927).

The differences are not great enough to be considered seriously. The amounts reduced in the same intervals under the same conditions show, for instance, a ratio of 3 : 1 when maleic-*n*-fumaric acids are used, and a ratio of 2 : 1 for *cis-* and *trans*-cinnamic acids. For details, see the original paper.

For hydrogenation of the olefinic double bond, especially active catalysts are not necessary. The methods chosen depend essentially on the amounts of material to be worked with. Ordinary experiments in the laboratory with 20 to 30 g. or less can be conducted most conveniently in one of the laboratory hydrogenation vessels described above (see page 11). In many cases it will prove necessary to control the hydrogen consumption, for it is only in rare cases that an excess of hydrogen does no harm. Good hydrogenation catalysts usually attack even aromatic nuclei after some time. With small amounts of preparations, hydrogen consumption is best observed volumetrically, and with larger ones, manometrically; the necessary directions have already been given. Pressure hydrogenation of the ethylene bond, which is used to a very large extent for hardening fats, can be dispensed with in the laboratory. A simple example may give an idea of the developments leading to the method in current use.

Reduction of the ethylene bond of α,β-unsaturated ketones may be chemically effected with nascent hydrogen. Schneidewind [53] treated benzalacetophenone in boiling glacial acetic acid with zinc dust to prepare benzylacetophenone. The experimental details are not very exact. It proved necessary to separate a high melting condensation product; the benzylacetophenone crystallized only after fractional distillation. The yields obtained are not given.

Later, Harries and Hübner [54] described the reduction of benzalacetophenone with sodium amalgam: 100 g. of benzalacetophenone are dissolved in 5 liters of ethanol; 1750 g. of 2.5% sodium amalgam are added; during the reaction the solution is kept slightly acid at all times by the addition of 5% sulfuric acid. When the reduction is completed, the solution is filtered. The alcohol is evaporated from the filtrate. The liquid residue is then diluted with water and the oil extracted with ether. The precipitate obtained by filtration (sodium sulfate?) is dissolved in water and this aqueous solution also extracted with ether. Upon evaporation of the combined ether extractions a residue is obtained which crystallizes only partially. The oily portion of the residue is dissolved in alcohol. On fractional distillation *in vacuo*, the alcoholic solution yields two fractions: one boiling at 200° to 220°C. at 20 mm.; the other above 360°C. The low boiling portion represents a reduction product of benzylacetophenone, 1,3-diphenyl-1-propanol. The crystals remaining after treatment with alcohol are a condensation product. It is thus evident that a useful method for the preparation of benzylacetophenone had not been devised.

Still later, Straus and Grindel [55] for the first time studied the catalytic reduction of benzalacetophenone for purposes of preparation. Their procedure is also cumbersome.

[53] W. Schneidewind, *Ber.*, 21, 1325 (1888).
[54] C. Harries and F. Hübner, *Ann.*, 296, 325 (1897).
[55] F. Straus and H. Grindel, *Ann.*, 439, 276 (1924).

They use as a catalyst colloidal palladium prepared by a method similar to those given by Skita (see page 17). Straus and Grindel have succeeded in defining the conditions necessary for the formation of benzylacetophenone as the main product. They obtained in 90 minutes from 10 g. of benzalacetophenone in 80 cc. of acetone, with the calculated amount of hydrogen, an almost quantitative yield of benzylacetophenone, containing only a small amount of 1,3-diphenyl-1-propanol.

The most modern and most convenient method for the catalytic reduction of benzalacetophenone is described in *Organic Syntheses.*[56]

The description of other examples may be omitted, because the essential operations remain the same in every case.

Bound Hydrogen (Hydrogen Transfer)

Because all hydrogenation catalysts, in the last analysis, add as well as remove hydrogen, it is possible under the influence of such catalysts to transfer hydrogen from an easily dehydrogenated to a readily hydrogenated compound. Kindler and Peschke[57] employed this principle when they used tetralin as a donator and palladium black as the catalyst (see page 14). Because such hydrogenations are mild, it is possible to produce specific, selective effects: cinnamic nitrile can be reduced almost quantitatively to hydrocinnamic nitrile, the cyano group thus remaining intact; *p*-chlorocinnamic acid yields *p*-chlorohydrocinnamic acid, the chlorine atom not being in the least affected. It may thus be seen that tetralin can produce special effects whenever it is used for catalytic hydrogenation. Thus far, little use has been made of this method. The tetralin is purified by shaking with dilute hydrochloric acid, washing with water, drying with calcium chloride, and finally by distillation. The palladium black is purified by heating in tetralin to boiling, the water formed by the reduction of palladium oxide being distilled off.

In the hydrogenation of *p*-chlorocinnamic acid, a solution of 5 g. of *p*-chlorocinnamic acid in 180 cc. of tetralin containing 1 g. of palladium black is boiled under a reflux for 90 minutes in a Kjeldahl flask. The hydrogen chloride set free is absorbed in silver nitrate solution and is less than 0.1%. On the other hand, the side chain is completely hydrogenated. The catalyst is filtered off and the filtrate extracted with a solution of sodium carbonate to remove the hydrogenated acid. The alkaline extract is freed from the tetralin by shaking with ether. The solution is acidified with hydrochloric acid and the separated *p*-chlorohydrocinnamic acid collected in ether. After evaporation of the ether, 4.8 g. of pure *p*-chlorohydrocinnamic acid are obtained. The melting point and the mixed melting point are 123°C.

(b) Aromatic Systems

The difficulties involved in the hydrogenation of purely aromatic systems were formerly exaggerated. When catalysts now in common use, *e.g.* platinum oxide, are used the reduction can be accomplished in most cases even at room temperature and at atmospheric pressure.

[56] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 101.
[57] K. Kindler and W. Peschke, *Ann.*, **497**, 193 (1932).

Of the aromatic compounds, the hydrocarbons are the most difficult to hydrogenate; the phenols and amines are easily reduced. Pyridine is more readily hydrogenated than benzene, but pyrrole is reduced with greater difficulty.

The direct hydrogenation of aromatic compounds is not always of importance. Thus cyclohexane (hexalin) may be prepared by the method of Sabatier and Senderens by passing a mixture of hydrogen and benzene vapors over nickel, but in this case it is more convenient to hydrogenate the easily accessible phenol. From the cyclohexanol thus formed, water is split off, and the resulting cyclohexene is hydrogenated to cyclohexane. If this process is properly performed, it is not necessary to isolate the intermediary compounds.

For the preparation of partially or completely hydrogenated condensed aromatic ring systems, it is not necessary to go through such a series of steps, because these hydrocarbons are reduced more easily than benzene. Though it is hardly economical to prepare tetralin or decalin in the laboratory by hydrogenation of naphthalene, brief directions are given below for a laboratory method for the preparation of tetralin, as worked out by Schröter.[58]

The naphthalene to be used for hydrogenation must be pure, and above all free from all sulfur-containing impurities which inhibit the catalyst. In an autoclave of 4 liters capacity, equipped with a stirrer, 512 g. of naphthalene (4 moles) are melted with 15 to 20 g. of a suitable nickel compound (basic carbonate, oxide). The autoclave is first closed and tested for tightness by filling at 12 to 15 atmospheres of pure hydrogen. Stirring is started and the temperature raised to 180° to 200°C. The pressure at first increases, and then decreases at a rate of 1 atmosphere per 45 to 60 seconds; as soon as the pressure has decreased to 5 to 8 atmospheres, the autoclave is filled again with hydrogen up to 12 to 15 atmospheres. This operation is repeated until the required amount of 178 liters is absorbed. After the tetralin is formed, the rate of hydrogen absorption decreases; in about 1 minute the pressure is reduced by 1 atmosphere. When the end of the reaction approaches, the hydrogen addition is interrupted and the reduction allowed to proceed until almost all the hydrogen present has been absorbed. The total time required for the experiment is about 1 hour or a little longer. The tetralin formed is distilled under a vacuum directly from the autoclave. The catalyst is left behind. Immediately following the distillation, a second and equal quantity of naphthalene may be hydrogenated with the same catalyst; the time required for a second reduction is somewhat less than for the first. Schröter was able to make up to twenty-five runs without opening the autoclave, by introducing the new charge in a molten state into the evacuated autoclave following the distillation. The tetralin thus obtained boils at 206° to 208°C. and contains only a small amount of impurities. To effect complete purification, it is sulfonated.[59] The sodium salt of the sulfonic acid is recrystallized and decomposed in 72% sulfuric acid with superheated steam.

Crude naphthalene is purified by being melted together with finely dispersed metals and then distilling in vacuo. No details of this purification are given.

[58] G. Schröter, Ann., 426, 13 (1922).
[59] G. Schröter, Ann., 426, 83 (1922).

The catalytic hydrogenation of anthracene proceeds in a complicated manner. The so called octhracene (1,2,3,4,5,6,7,8-octahydroanthracene) is an intermediate in this hydrogenation and can be isolated. Fries and Schilling [60] ascertained that the hydrogen addition proceeds by a number of different routes, but all lead to the production of octhracene. 9,10-Dihydroanthracene and 1,2,3,4-tetrahydroanthracene, this latter compound corresponding to tetralin, are supposed to be intermediates. Perhydroanthracene, or the different anthracene perhydrides, melting at 61.5° and 93°C., respectively, are formed, depending upon the solvent, temperature, pressure, and catalyst used. Since octhracene is a completely compensated, aromatic compound, its hydrogenation to perhydroanthracene proceeds much more slowly than the addition of the first 8 hydrogen atoms to anthracene. This is analogous to the hydrogenation of naphthalene.

A process still more complicated than the hydrogenation of anthracene is the hydrogenation of chrysene. According to Braun and Irmisch [61] the first product which can be isolated upon hydrogenation of chrysene with nickel is dodecahydrochrysene, $C_{18}H_{24}$. This can be dehydrogenated with sulfur or selenium to an octahydrochrysene. The constitution of these hydrogenation products is deduced by the authors from the degradation of the dodecahydro compound to 1,2,3,4-benzenetetracarboxylic acid. According to these findings, dodecahydrochrysene has the probable con-
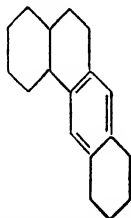
Dodecahydrochrysene

stitution given in the accompanying formula. According to this proposed structure, dodecahydrochrysene contains a compensated, aromatic system.

(c) Heterocyclic Systems

The catalytic hydrogenation of pyridine with platinum asbestos according to Sabatier and Senderens is quite erratic; the old method of Ladenburg (sodium and alcohol reduction, see page 8) is probably preferable. Recently Adkins and coworkers [62] conducted an extensive research on the usefulness of Raney's nickel as a hydrogenation catalyst

[60] K. Fries and K. Schilling, *Ber.*, 65, 1494 (1932).
[61] J. v. Braun and G. Irmisch, *Ber.*, 65, 883 (1932).
[62] H. Adkins *et al.*, *J. Am. Chem. Soc.*, 56, 2425 (1934).

(see page 13). The conditions for the hydrogenation of pyridine, its homologues, and other pyridine derivatives are rather similar; the reaction temperatures lie between 100° and 200°C.   It is significant that the reduction with Raney's nickel can be performed successfully at lower temperatures than with nickel precipitated on diatomaceous earth.   Ethanol, methylcyclohexane, and dioxane were used as solvents; the hydrogen pressure was 150 to 300 atmospheres.   Pyridine was hydrogenated at 200°C. without a solvent.   For a run of 610 g., with 25 g. of catalyst, a 83% yield was obtained in 7 hours.   Substituted pyridines, especially those substituted in the 2 or 6 positions, are reduced much more readily than pyridine.

The catalytic hydrogenation of pyrrole was formerly considered extremely difficult.   Neither Padoa [63] nor Willstätter and coworkers [64] obtained satisfactory results.   Zelinskii and Jurjev [65] also obtained poor yields when hydrogenating with palladium asbestos.   Andrews and McElvain [66] were able to obtain better results with platinum oxide.   They recommend the following procedure.

18 g. of pyrrole, twice distilled from sodium, are dissolved in 60 cc. of glacial acetic acid and hydrogenated with 0.5 g. of platinum oxide.   The absorption of hydrogen is quite slow and may stop entirely, but by shaking the reaction mixture with oxygen the catalyst can be reactivated.   After 45 hours, another 0.3 g. of platinum oxide is added. After the mixture is shaken for 96 to 100 hours, the theoretical amount of hydrogen is absorbed.   The platinum is allowed to settle, and the dark colored solution decanted. The acetic acid is neutralized with a concentrated solution of sodium hydroxide.   This operation is carried out in a vessel equipped with a reflux condenser, in order to avoid the loss of the highly volatile pyrrolidine.   Then an excess of sodium hydroxide is added and the mixture steam-distilled until the distillate is no longer alkaline to litmus.   The distillate (about 1 liter) is acidified with hydrochloric acid and evaporated to dryness on a steam bath.   The dark, viscous residue is treated with 40% sodium hydroxide and extracted with ether.   The ether solution is dried over sodium sulfate and yields on fractionation 12 g. of pyrrolidine boiling at 85° to 88°C.   This corresponds to a yield of 63%.

A little later, Craig and Hixon [67] described a very similar method in which, instead of atmospheric pressure, a pressure of 6 atmospheres was used.

The hydrogenation apparatus (Fig. 1) is so modified that all connections and pipes are made of metal, with the exception of a rubber gasket at the pressure flask.   Freshly distilled pyrrole (10 cc.) which was dried over calcium chloride is dissolved in 100 cc. of absolute ethanol and shaken with slightly more than the equivalent amount of concentrated hydrochloric acid (6 cc.) and 0.2 g. of platinum oxide.   Hydrogen is immediately

[63] Padoa, *Chem. Zentr.*, 1906, I, 1436.
[64] R. Willstätter *et al., Ber.*, 45, 1478 (1912); 54, 113 (1921).
[65] N. Zelinskii and J. Jurjev, *Ber.*, 62, 2589 (1929); 64, 101 (1931).
[66] L. Andrews and McElvain, *J. Am. Chem. Soc.*, 51, 889 (1929).
[67] L. Craig and R. Hixon, *J. Am. Chem. Soc.*, 52, 804 (1930).

absorbed at 6 atmospheres pressure, and the reaction is complete in 6 hours. Then the catalyst is allowed to settle and the liquid decanted, and a new quantity of pyrrole, dissolved in alcoholic hydrogen chloride, is added. A third amount could be hydrogenated without noticeably decreasing the reducing efficiency of the catalyst provided the pyrrole used is sufficiently pure. The alcohol is removed by distillation under diminished pressure. Unchanged pyrrole is extracted with ether, and the residue made alkaline with potassium hydroxide. When the pyrrolidine which has been set free is distilled, the fraction boiling from 86° to 88°C. is collected. Higher boiling fractions are present only in small amounts. No yields are given.

Finally, Signaigo and Adkins [68] studied the behavior of pyrrole with Raney's nickel and copper chromium oxide catalysts. Favorable conditions could not be found. The papers here compiled contain numerous references to methods suitable for the reduction of pyrrole derivatives.

Generally speaking, pyrroles with substitutions at the nitrogen can be reduced more easily than unsubstituted ones, even when the substituent is not of an aliphatic nature. Thus Craig and Hixon [69] succeeded in readily reducing N-phenylpyrrole to N-cyclohexylpyrrolidine. According to Signaigo and Adkins [70] N-substituted pyrroles could also be reduced well with Raney's nickel. Some C substitution products, *e.g.* 2-, 3-, 4-, or 5-carbethoxypyrroles, are very resistant. For details see the original papers.

The catalytic hydrogenation of furan with nickel at 170°C. has been carried out by the method of Sabatier. Cloke and Ayers [71] used Raney's nickel at 50°C. They give the following directions.

Furan (100 g.) is dissolved in 100 g. of *n*-butanol and 10 g. of Raney's nickel (see page 13) are added. The mixture is shaken with hydrogen in an electrically heated pressure flask until no further decrease in hydrogen pressure occurs. The yield of tetrahydrofuran usually amounts to 80% of the theoretical. The compound boils at 63° to 67°C.

Starr and Hixon [72] have described the reduction of furan with palladous oxide as the catalyst and without the use of a solvent. For details of the procedure see *Organic Syntheses.*[73]

5. Addition of Hydrogen to Acetylene Bonds

General Aspects

The hydrogenation of the acetylene bond is usually of importance only in the preparation of ethylene derivatives by partial reduction of acetylenes. With nascent hydrogen, mainly stable ethylene stereoisomers

[68] F. Signaigo and H. Adkins, *J. Am. Chem. Soc.*, **58**, 709 (1936).
[69] L. Craig and R. Hixon, *J. Am. Chem. Soc.*, **52**, 804 (1930).
[70] F. Signaigo and H. Adkins, *J. Am. Chem. Soc.*, **58**, 709 (1936).
[71] J. B. Cloke and O. Ayers, *J. Am. Chem. Soc.*, **56**, 2144 (1934).
[72] D. Starr and R. Hixon, *J. Am. Chem. Soc.*, **56**, 1595 (1934).
[73] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 566.

are obtained, while catalytically activated hydrogen frequently effects a good yield of the metastable isomers which are richer in energy.

Ott and Schröter [74] reported their findings on this subject in recent publications. According to these investigators, the addition of hydrogen to the acetylene bond, and generally to all unsaturated bonds, is an energy problem rather than a stereochemical one. Depending upon the activity of the catalyst, catalytically activated hydrogen produces varying amounts of both the ethylene isomers. Additional complications caused by hydrogenation of the newly formed ethylene bonds to an ethane linkage being disregarded, the yield of the isomers richer in energy increases with the reaction velocity and therefore with the activity of the catalyst. However, it is not necessarily the *cis* forms that are obtained, but, rather, the less stable forms which are richer in energy no matter what steric configuration they may have. Especially active catalysts are not advantageous in every case, because the hydrogenation might then proceed further to form the ethane derivative before all the acetylene bonds are reduced. Under certain conditions, isolation of the reduction products may become troublesome. Thus, in the case of the cinnamic acids, the metastable *cis*-cinnamic acid forms with the hydrocinnamic acid a low melting eutectic mixture which separates consistently as an oil during the recrystallization (Weygand). The reduction of tetramethylbutynediol to tetramethylbutenediol serves as an example.

With Palladium Chloride—A solution of 1 mg. of palladium foil in 2 drops of aqua regia is boiled down to dryness and then twice evaporated with hydrochloric acid. The palladium chloride thus obtained is dissolved in a few cubic centimeters of methanol and reduced by shaking with 0.2 g. of charcoal in a hydrogen atmosphere. To this mixture are added 1.42 g. of the butynediol in 18 cc. of methanol. 260 cc. of hydrogen are absorbed in 55 minutes. When evaporated under diminished pressure, the solution yields 1.2 g. of the reduction product, which is taken up in petroleum either (boiling between 30° and 50°C.). Even when the petroleum ether solution is concentrated to a very small volume, the compound proves to be very readily soluble; it does not crystallize when the concentrated petroleum ether solution is seeded with crystals of the needle form (*cis* form). Slowly, however, the characteristic prisms of the labile *trans* form begin to crystallize.

With Cobalt Nitrate—An aqueous solution of 15 g. of pure, nickel-free, crystalline cobalt nitrate is mixed with 13 g. of pure charcoal and the mixture dried on a steam bath. 6 g. of this product are reduced in pure hydrogen at about 400°C. During this operation, water vapor and nitrogen oxides are evolved and, as the reduction progresses, ammonia is given off. After 1 to 2 hours, the apparatus is allowed to cool under a slight hydrogen pressure and the catalyst is transferred under an atmosphere of hydrogen into the reaction vessel. A solution of 4.26 g. of butynediol dissolved in 60 cc. of ether, 10 cc. of ethanol, and 2 cc. of water absorbed hydrogen very slowly when shaken in an atmosphere of hydrogen. After 52 hours, the reduction product is isolated. A considerable amount of unreduced starting material is still present. The solution is extracted several times

[74] E. Ott and R. Schröter, *Ber.*, **60**, 624 (1927); **61**, 2119 (1928).

with cold petroleum ether. The extract yields only the stable *cis* form; no *trans* form can be isolated.

(a) Addition of Nascent Hydrogen

The various methods for the production of nascent hydrogen, as described on pages 5 *et seq.*, may be used for the reduction of acetylene derivatives. Reduction with nascent hydrogen deserves preference over catalytic hydrogenation only if it is desirable to obtain the stable of the two isomeric ethylene compounds and in the event that this can be produced from the metastable isomer only with difficulty. But in almost all cases the stable ethylene derivatives can be obtained more easily in other ways or can be prepared conveniently from the labile isomer obtained through catalytic hydrogenation.

(b) Catalytic Hydrogenation

Obviously, catalytic procedures should be recommended for the hydrogenation of acetylene compounds which are usually not readily accessible and require gentle handling and the application of procedures which give high yields. As shown above, it is not necessary to use especially active catalysts. The barium sulfate-palladium catalyst, first described by Paal, has proved to be well suited for such purposes. Also, the platinum catalyst of Adams may well be used. However, since in partial hydrogenations a measured amount of hydrogen must be used, it is advisable to reduce platinum oxide separately and then to add the substance to be hydrogenated. The same procedure should be followed whenever palladium hydroxide precipitated on barium sulfate is used.

Cis-cinnamic acid from phenylpropiolic acid, for instance, can, according to Paal, be prepared in the following manner.

Halogen-free phenylpropiolic acid (15 g.) is dissolved in the calculated amount of sodium carbonate solution and made up to 100 cc. with water. This solution is added to 2 g. of palladium-barium sulfate catalyst (see page 16) in a shaking flask. The air in the flask is displaced by hydrogen without shaking, the apparatus closed, and the calculated amount of hydrogen (2420 cc. at 20°C. and 773 mm.) allowed to be absorbed by shaking under slight pressure. The aqueous solution is filtered from the catalyst and the *cis*-cinnamic acid liberated with dilute hydrochloric acid; the cinnamic acid is extracted with ether, and the ethereal solution washed with water and then dried over sodium sulfate; finally, the ether is evaporated. Stoermer [75] recommends preparation of the aniline salt in order to separate the *trans*-cinnamic acid simultaneously formed and which does not yield an aniline salt because of its low acidity. For this purpose, the residue from the ether extract is dissolved in 3 times its volume of benzene. Freshly distilled aniline is added in small portions until the precipitation is complete. After several hours, the precipitate is filtered off and recrystallized from methanol or acetone until the correct melting point of 86° to 87°C. is obtained. The pure aniline salt is either decomposed with hydrochloric acid and extracted with ether or petroleum ether, or is

[75] R. Stoermer, *Ber.*, **50**, 978 (1917).

dissolved in ether, the cinnamic acid extracted from the ether solution with sodium carbonate solution, and the cinnamic acid isolated from the carbonate solution by treating as described above for the hydrogenation liquid. Depending upon the circumstances, the product obtained by this purification process shows varying melting points. If traces of the stable allocinnamic acid are in the air of the laboratory, the melting point is usually 64°C., but quite frequently it is found to be 58°C., and in rare cases 42°C. The reason for the existence of the different metastable modifications has not been established definitely. The modification with the melting point of 42°C. probably appears when the material is seeded with *trans*-cinnamic acid. However, the *trans*-cinnamic acid should have been removed by purification through the aniline salt. The modification with the melting point of 58°C. is frequently encountered. This form may possibly originate through traces of β-truxinic acid, the dimer formed from *cis*-cinnamic acid by the action of light. If crystals of the stable allocinnamic acid (m.p. 64°C.) are available, they are used for seeding. The suitable solvent for recrystallization is petroleum ether of a boiling point of about 45°C. The solubility of *cis*-cinnamic acid in hot petroleum ether is rather high, but it is best not to use too concentrated solutions, because these tend to become cloudy and oily when cooled, even when seeded with solid material. Under certain conditions, it might be advisable first to cool the solution prepared for the recrystallization to about 10°C. The opalescent and cloudy solution is clarified with diatomaceous earth, filtered, and crystallization finally initiated. The yield of the aniline salt is about 60% of the theoretical; the conversion into free *cis*-cinnamic acid is almost quantitative.

The complete reduction of the acetylene bond always proceeds through the corresponding ethylene compound; therefore, no further comment is necessary.

B. Addition of Hydrogen to Radicals and to Alicyclic Systems

It is not easy to add hydrogen to radicals. In the preparation of triphenylmethane, for example, Gomberg [76] succeeded with triphenyl-methyl as the initial material, using zinc and glacial acetic acid; Schlenk, Mair, and Bornhardt,[77] however, experienced difficulties with hexaphenyl-ethane as the initial material when sodium and aluminum amalgams were used. Schmidlin and Garcia-Banùs [78] obtained a quantitative reduction of triphenylmethyl by the use of the Fokin-Willstätter method. It can readily be seen that this reaction is of little practical importance, but the directions of Wieland and Müller [79] may be given as an example.

40 cc. of a 7.5% solution of triphenylmethyl (complete dissociation of hexaphenyl-ethane being assumed) in thiophene-free benzene are hydrogenated with 0.2 g. of palladium black. After 90 minutes at 24°C., about 225 cc. of hydrogen are absorbed. Triphenylmethyl can no longer be detected. A yield of 3 g. of triphenylmethane is obtained.

Cyclopropane, cyclobutane, and cyclopentane, as well as their derivatives, add hydrogen by opening the rings and thus changing to compounds

[76] M. Gomberg, *Ber.*, **36**, 381 (1903).
[77] W. Schlenk, L. Mair, and C. Bornhardt, *Ber.*, **44**, 1174 (1911).
[78] J. Schmidlin and A. Garcia-Banùs, *Ber.*, **45**, 3190 (1912).
[79] H. Wieland and C. Müller, *Ann.*, **401**, 240 (1913).

of the paraffin series. This reaction also is of little practical importance; but the conditions for the opening of the various rings by hydrogenation may be briefly discussed. Willstätter and Bruce [80] reduced cyclopropane by the method of Sabatier, using as a catalyst nickel precipitated on pumice. The reaction started at 80°C. and was complete at 120°C., after two passages over the catalyst. Later, Boeseken [81] succeeded, by the method of Fokin and Willstätter, in reducing cyclopropane to propane at room temperature, with platinum black as the catalyst. He observed that, under the same conditions, cyclopropane is only a little more slowly attacked than ethylene.

Cyclobutane was quantitatively hydrogenated to butane by Willstätter and Bruce [82] by Sabatier's method. Using a temperature of 200°C. and a nickel catalyst, they followed the procedure described for the hydrogenation of cyclopropane.

Under similar conditions, cyclopentane is stable towards hydrogen; at higher temperatures, fundamental changes in structure occur, which may or may not be preceded by rearrangements of the cyclopentane ring (see page 491).

C. Atomic Hydrogen

Atomic hydrogen has been known for some time, and frequent attempts have been made to use it for hydrogenations. Only some of the more important recent publications will be discussed. Urey and Lavin [83] describe a relatively simple apparatus for its preparation. They find it is a rather mild reducing agent which partially reduces azoxybenzene through known intermediates to aniline. (Certain solid dyes are decolorized.) Benzoic acid and benzamide accelerate the formation of the hydrogen molecule from the atoms, but they, in turn, are not affected.

Bogdandy, Polanyi, and Veszi [84] describe an apparatus which they call the "molecular mixer." Because of its construction, only liquids with low vapor pressure could be tested for their behavior towards atomic hydrogen. Olive oil, oleic acid, cresol, quinoline, nitrobenzene, cinnamic aldehyde, and cinnamic acid ester were examined. The paper contains few experimental details; worthy of mention are the observations that, during hydrogenation with atomic hydrogen, acetylene is apparently always formed as a by-product, and that, concurrent with hydrogenation, polymerization nearly always occurs. Examination of the reaction mixtures showed that for each oleic acid molecule hydrogenated to stearic acid 2 other molecules are polymerized. The same conclusions had been

[80] R. Willstätter and J. Bruce, *Ber.*, **40**, 4459 (1907).
[81] J. Boeseken, *Rec. trav. chim.*, **35**, 283 (1916).
[82] R. Willstätter and J. Bruce, *Ber.*, **40**, 3979 (1907).
[83] H. C. Urey and G. J. Lavin, *J. Am. Chem. Soc.*, **51**, 3286 (1929).
[84] St. v. Bogdandy, M. Polanyi, and G. Veszi, *Angew. Chem.*, **46**, 15 (1933).

reached earlier by Nagel and Tiedemann.[35]   In the latter publication are pictures and a description of an apparatus for preparing atomic hydrogen in the laboratory.   Kroepelin and Vogel [36] later performed hydrogenation experiments with atomic hydrogen, and confirmed the observations of Nagel and Tiedemann on oleic acid, but rejected the explanations of Bogdandy, Polanyi, and Veszi.   Furthermore, they confirmed the earlier observation that atomic hydrogen is suitable not only for hydrogenations but also for dehydrogenations.   The molecular weight of paraffin oil increases under the influence of atomic hydrogen from an average of 380 to an average of 535.   At the same time, the iodine value increases considerably, corresponding to one double bond for each 3 molecules of the paraffin, the iodine value of which was extremely low at the beginning. Kroepelin and Vogel could not confirm the claim of a French patent [37] that atomic hydrogen very gently reduces the carboxyl group.

D. Addition of Hydrogen to C=O Bonds

General Aspects

The object in adding hydrogen to $C:O$ bonds is the preparation of primary alcohols from aldehydes or secondary alcohols from ketones. The formation of pinacols from ketones according to the equation

$$2R \cdot CO \cdot R \longrightarrow R_2 : COH \cdot COH : R_2 \qquad (1)$$

occurs as a side reaction and will be discussed in the chapter on condensation (see page 343).

Since the $C:O$ bond readily absorbs hydrogen, especially active reducing agents are not required.   Frequently, nascent hydrogen is sufficient.   The catalytic methods sometimes permit retaining other easily reducible groups, such as double bonds.   Electrochemical methods are used advantageously for the reduction of ketones.

Special conditions exist in the $C:O$ groups of the β-diketones and β-ketocarboxylic esters.

For reductions with nascent hydrogen, sodium amalgam and glacial acetic acid together with zinc dust or iron are used primarily; sometimes sodium in moist ether is employed.

A reduction method which has recently become very important proceeds according to the equation

$$R_2 \cdot CO + R' \cdot CH_2OH \rightleftharpoons R_2 \cdot CHOH + R' \cdot CHO \qquad (2)$$
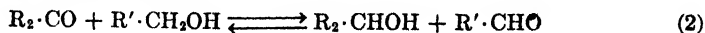
Hydrogen is transferred from 1 molecule to another by means of aluminum

[35] W. Nagel and E. Tiedemann, *Wiss. Veröffentl. Siemens-Konzern*, **8**, 187 (1930).
[36] H. Kroepelin and E. Vogel, *Ber.*, **68**, 684 (1935).
[37] French Patent, 728,893.

or magnesium alcoholates; aldehydes are reduced to primary alcohols, and ketones to secondary alcohols.

1. Reduction of Aldehydes to Primary Alcohols

Aliphatic aldehydes can be readily reduced to primary alcohols. Practically, however, this reaction is important only when the alcohol is difficult to obtain by other methods. The choice of reducing agent depends upon the solubility characteristics of the aldehyde. Aldehydes readily soluble in water may be reduced conveniently with amalgam. If the aldehyde is not water-soluble, glacial acetic acid and a suitable metal are used. Frequently, through secondary reactions, acetates of the alcohols are obtained. Aromatic aldehydes tend to undergo condensations more readily than aliphatic aldehydes; the conditions can be so adjusted that hydrobenzoins, which correspond to the pinacols, are formed almost exclusively. Sometimes these are the only products which can be isolated, as in the case of phenol aldehydes. Often, the aromatic alcohols can be prepared from aldehydes more conveniently by dismutation than by reduction (see page 153).

2. Reduction of Ketones to Secondary Alcohols

For the reduction of ketones to secondary alcohols, alkaline reducing agents are recommended; pinacols are formed easily in an acid medium. The reductions of aliphatic, mixed, or purely aromatic ketones are essentially the same. In every case it must be decided whether or not the secondary alcohol can be prepared more easily by nuclear synthesis.

For instance, the two isomeric alcohols, p-tolylethylcarbinol ($CH_3\cdot C_6H_4\cdot CHOH\cdot C_2H_5$) and p-ethylphenylmethylcarbinol ($C_2H_5\cdot C_6H_4\cdot CHOH\cdot CH_3$), are worth considering. The ketone, $CH_3\cdot C_6H_4\cdot CO\cdot C_2H_5$, can be prepared by the Friedel-Crafts reaction from toluene and propionyl chloride, but propionyl chloride is quite expensive. More convenient in this case is a Grignard synthesis, which yields the carbinol directly. In one method p-tolualdehyde and ethyl magnesium halide are used as starting materials; in another, propionaldehyde and p-tolyl magnesium halide. Only the first method, of course, is practical. The ketone, $C_2H_5\cdot C_6H_4\cdot CO\cdot CH_3$, is obtained in excellent yield from ethylbenzene and acetic anhydride; should one attempt to obtain the corresponding carbinol by direct synthesis, either p-ethylbenzaldehyde or p-bromoethylbenzene would be required. But both of these substances are difficult to obtain. In this particular case, in contradistinction to the previously discussed example, reduction of the ketone is the best method for obtaining the carbinol.

Of the chemical reducing agents, the following will be discussed: sodium amalgam; sodium and alcohol, especially for acetophenones; zinc dust in aqueous alcoholic alkaline solution, and aluminum amalgam.

3. Catalytic Reduction of the C═O Group

As mentioned above, it is easy to obtain a hydroxyl group by catalytic hydrogenation of a carbonyl group. This is true for nearly all hydrogenation procedures, including Sabatier's method. All in all, the catalytic methods are often superior to the chemical.

Examples of Reduction of Carbonyl Compounds

(a) **Glacial Acetic Acid-Iron.** As an example of the preparation of a primary alcohol from an aldehyde, see *Organic Syntheses*[88] for instructions for the preparation of *n*-heptanol from heptaldehyde.

(b) **Sodium and Moist Ether.** The directions of Wislicenus and Hentschel [89] are given as an example of the preparation of an alcohol by the reduction of a keto group with sodium in moist ether.

Cyclopentanone is mixed with an equal volume of ether and the mixture is then saturated with water by shaking with an equal volume of water. Metallic sodium is added, a few small pieces at a time. In order to avoid losses of ether, the operation is carried out in a flask provided with a reflux condenser. After the pieces of sodium have disappeared, the mixture is shaken again to saturate the ether layer with water. This is continued until an amount of sodium has been added equal to the weight of the ketone. The ether layer is separated from the aqueous sodium hydroxide solution, dried with potassium carbonate, and fractionated. The main fraction boils between 135° and 140°C., a second fraction between 145° and 230°C. After redistillation of the two fractions, the pure cyclopentanol, boiling at 139°C., is obtained.

(c) **Aluminum Alcoholate and Magnesium Chloroethylate.** The very versatile reduction method of Meerwein and Schmidt,[90] in which aluminum alcoholate is employed warrants a more thorough discussion. It is particularly useful when the molecule contains other groups which might be simultaneously reduced, if other reducing agents were used. Thus carbonyl compounds such as nitro ketones, halogen ketones, and unsaturated ketones are reduced to the corresponding alcohol without affecting the other reaction points. An interesting example of this is found in the final step of the synthesis of vitamin A. Kuhn and Morris,[91] employing aluminum isopropylate, were able to prepare vitamin A alcohol without reducing any of the double bonds present (see page 436). If aldehydes or ketones are heated with aluminum alcoholate in suitable solvents, an exchange of hydrogen occurs between the alcohol of the

[88] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 304.
[89] Wislicenus and Hentschel, *Ann.,* 275, 322 (1893).
[90] Meerwein and Schmidt, *Ann.,* 444, 221 (1925).
[91] R. Kuhn and C. Morris, *Ber.,* 70, 853 (1937).

aluminum alcoholate and the carbonyl group, leading to an equilibrium. If the newly formed carbonyl compound has a boiling point lower than all the other reaction components (a condition which can be brought about by careful selection of the reacting substances), it can be removed by continuous distillation; thus the reaction is, for practical purposes, quantitative.

Instead of aluminum ethylate, magnesium chloroethylate may be used. Directions for the preparation of aluminum ethylate and magnesium chloroethylate, respectively, are as follows:

100 g. of aluminum powder are covered with 650 cc. of xylene. To the mixture, while boiling vigorously under a reflux, a solution of 0.5 g. each of mercuric chloride and iodine in 440 cc. of absolute ethanol is added slowly. The reaction starts immediately. After a short time, the heating may be discontinued. Ethanol is added only as fast as it is used up to prevent the formation of an insoluble alcoholate. If a crystalline precipitate is formed, the addition of ethanol is interrupted until the precipitate disappears. When, after 40 minutes, 320 cc. of alcohol have been added, the mixture is heated again, because the speed of reaction decreases. After a total of about 90 minutes the remaining alcohol should have been added. The boiling is continued for an additional 15 minutes until the evolution of hydrogen has ceased. The hot solution is filtered through a heated fluted filter. The xylene is removed from the filtrate by distilling first at ordinary pressure and then *in vacuo*. The yield is 400 g. of pure, colorless, molten aluminum ethylate.

To prepare magnesium chloroethylate,[92] a mixture of 10 g. of magnesium turnings, 100 cc. of absolute ethanol, 20 cc. of xylene, and a trace of mercuric chloride and iodine is heated to gentle reflux. A constant vigorous evolution of hydrogen starts and large amounts of crystalline magnesium ethylate are formed on the magnesium particles; the entire flask becomes filled with the product which has the appearance of boiled rice. After about 5 hours, when all the magnesium has disappeared, the xylene and excess ethanol are removed by distillation from the reaction flask, or by filtering the product in a dry atmosphere. The loosely bound alcohol of crystallization is removed by heating. Thus, magnesium ethylate is obtained as a colorless, amorphous powder which is practically insoluble in alcohol. Magnesium chloroethylate is obtained from magnesium ethylate by treating with the calculated amount of alcoholic hydrochloric acid or alcoholic magnesium chloride solution. The colorless, clear crystals thus obtained may be recrystallized from hot ethanol, but in this process the chloroethylate is partially disproportionated, forming a mixture of magnesium ethylate and magnesium chloride. The product is then of varying composition. When magnesium chloroethylate is used as a reducing agent, it is not always necessary to isolate it. In that event, it may be prepared from magnesium powder and alcoholic hydrochloric acid (see page 38).

As an example of the reduction of aldehydes with aluminum ethylate at room temperature, the preparation of furfuryl alcohol [93] is given.

Freshly distilled furfural (150 g.) boiling at 162°C. is dissolved in 350 cc. of absolute ethanol, and 45 g. of molten aluminum ethylate are added. The mixture becomes cloudy and the precipitate increases upon standing for some time at 25°C. After several hours,

[92] Meerwein and Schmidt, *Ann.*, **444**, 236 (1925).
[93] Meerwein and Schmidt, *Ann.*, **444**, 232 (1925).

the odor of ethyl acetate is noticed. From time to time, tests are made with aniline acetate for the presence of furfural. After 5 days all the furfural disappears. Then the excess ethanol, the ethyl acetate, and a small amount of acetaldehyde are removed by distillation, a bath heated to 120°C. being employed. The residue is steam-distilled. The distillate is saturated with potassium carbonate, the furfuryl alcohol is extracted with ether, and the ethereal solution is dried with potassium carbonate. Distillation yields 138 g. of a furfuryl alcohol fraction, boiling from 172° to 173°C., which contains several per cent of an ester, presumably pyromucic acid ethyl ester. In the residue remain 3.5 g. of furfuryl pyromucate. The furfuryl alcohol fraction may be freed from the ester contamination by saponification. The yield is 88% of the theoretical.

In a similar manner, benzyl alcohol, anisyl alcohol, p-chlorobenzyl alcohol, p-nitrobenzyl alcohol, and cinnamic alcohol are obtained in yields of 82 to 92% of the theoretical.

Instead of isolation of the alcohol by steam distillation, the reaction product, after the ethanol and the ethyl acetate have been removed by distillation, may be decomposed with dilute sodium hydroxide or with dilute sulfuric acid, and the alcohol obtained by ether extraction.

The procedure for reducing at higher temperatures is well illustrated by the preparation of trichloroethanol from chloral.[94]

The optimum yield is obtained by using a column by means of which acetaldehyde and alcohol can be separated completely. According to the directions recommended by Hahn,[95] a column heated by boiling methanol should be used. A modern laboratory column like the one described by Widmer-Schenk will probably serve the purpose.

By a similar method Meerwein and Schmidt [96] obtained tribromoethyl alcohol in a yield of 69%, 1,1,1-trichloroisopropyl alcohol in a yield of 67%, and trichloromethylphenylcarbinol in a yield of 68.5%. As an example of their procedure, the authors describe the preparation of β,β,γ-trichlorobutyl alcohol from butyl chloral. Details are also given for the reduction of benzoin to hydrobenzoin.

The directions for the reduction of cinnamaldehyde to cinnamic alcohol with magnesium chloroethylate, as given by the same authors,[97] are as follows:

A solution of 3 g. of dry hydrogen chloride in 75 cc. of absolute ethanol is added to 2 g. of magnesium filings. After the initial vigor of the reaction has subsided somewhat, the mixture is heated under a reflux on a steam bath for an additional 2 hours until all the magnesium has dissolved. Then 175 cc. of ethanol and 100 cc. of cinnamaldehyde are added. The magnesium chloroethylate which may have precipitated again goes into solution. The mixture is boiled under nitrogen or hydrogen with the column

[94] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 598.
[95] J. Houben, *Die Methoden der organischen Chemie*. Vol. I, Thieme, Leipzig, 1925, p. 595.
[96] Meerwein and Schmidt, *Ann.*, **444**, 234 (1925).
[97] Meerwein and Schmidt, *Ann.*, **444**, 237 (1925).

described in *Organic Syntheses* [98] for the preparation of trichloroethyl alcohol. An amorphous precipitate is formed and the liquid turns a yellowish brown. After about 9 hours the odor and the taste of cinnamaldehyde disappear. The alcohol is removed by distillation, the residue treated with dilute sulfuric acid, and the aqueous solution extracted with ether. The ether solution is dried over potassium carbonate, the ether evaporated, and the residue fractionally distilled. The weight of the first fraction is 6.6 g.; the second fraction, boiling at 126° to 130°C. at 7 mm. pressure, weighs 75.5 g.; and the last fraction weighs 3.2 g. The total yield thus amounts to 85.3 g., which is approximately 80% of the theoretical. The main fraction solidifies at 27°C. The other two fractions also consist of almost pure cinnamic alcohol.

Following the same procedure, benzyl alcohol, anisyl alcohol, *p*-nitrobenzyl alcohol, crotonyl alcohol, and citronellol may be prepared in yields ranging from 60 to 80%. Aliphatic alcohols containing halogen are decomposed by magnesium chloroethylate, yielding chloroform and formic acid ester, or carbon monoxide, respectively.

The reverse of Meerwein's method can be used conveniently for the preparation of carbonyl compounds from hydroxy compounds (see page 142).

Lund [99] recommends the general use of aluminum alcoholate for the reduction of ketones. The aluminum isopropylate he uses is prepared as follows:

In a 2 liter flask 55 g. of clean, freshly prepared aluminum turnings are heated under a reflux with 0.2 g. of mercuric chloride and 1 liter of isopropanol distilled from quicklime. At the beginning the reaction flask is cooled, but finally the solution is heated until all the aluminum has dissolved. After the flask has stood overnight at 70°C., a gray precipitate settles to the bottom. The liquid is decanted and made up to 2 liters with dry isopropanol. Thus an approximately 1 *M* solution is obtained from which, upon cooling, aluminum isopropylate crystallizes.

For carrying out the reduction, a bulb condenser is set up as follows:

The bulbs are filled with Raschig rings, and the jacket is filled to two-thirds of its capacity with methanol. Through the lower inlet of the jacket a capillary tube is introduced through which air is blown in order to facilitate boiling of the methanol. The outlet at the upper end of the jacket is connected to an ordinary reflux condenser. The top of the bulb condenser is equipped with a thermometer and a tube for removing the acetone formed during the reaction by distillation. The reaction proper is carried out exactly as described above. The isopropanol solution of aluminum isopropylate may be used as well as a toluene or benzene solution of the crystalline substance. An excess of from 50 to 100% of aluminum isopropylate is always used. Progress of the reaction is checked by analyzing the distillate for acetone. For this purpose, a few drops of distillate are mixed with 5 drops of a solution of 1 g. of 2,4-dinitrophenylhydrazine in 1 liter of 2 *N* hydrochloric acid. The reduction is considered complete when acetone-dinitrophenylhydrazone is no longer formed. To be sure that the reduction is actually finished, the reaction mixture is heated under a complete reflux for an additional 10

[98] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 598.
[99] H. Lund, *Ber.*, 70, 1520 (1937).

minutes. Then the distillation is started again and the first drops coming over are tested for the presence of acetone. In most cases, the yields amount to 90% of the theoretical.

II. FORMATION OF C—H BONDS BY EXCHANGE

A. Replacement of Halogen by Hydrogen

General Aspects

It is a general rule that iodine can be replaced by hydrogen more easily than bromine, and bromine more easily than chlorine; therefore it is sometimes advisable to convert chlorides or bromides into iodides before attempting reduction. The reduction methods to be considered may again be grouped into methods using nascent hydrogen and those employing catalytic procedures. The halogen atom to be removed may be attached to carbon, in either a saturated or an unsaturated aliphatic compound, or it may be a substituent in an aromatic or heterocyclic ring. In the first case any one procedure may be employed unless other easily reducible groups are present in the molecule; in the second case the choice of the procedure depends upon whether the ethylene bond should remain intact or is to be reduced; in the third case the possibility of a simultaneous nuclear hydrogenation must be considered.

Outside this classification are a few special cases; *e.g.*, the halogen of carboxylic acid halides or of imide chlorides.

In addition to the direct reduction methods, according to the equation $RX + H_2 \rightarrow RH + HX$, indirect procedures may be used. The most important one of these proceeds through the Grignard reagent in the following manner: $RX \xrightarrow{Mg} RMgX \xrightarrow{H_2O} RH + MgXOH$.

The replacement of halogen by hydrogen is of little practical importance. Naturally occurring substances and their derivatives, *e.g.* coal tar products, contain, with few exceptions, no carbon-bound halogen. Most halogen-containing organic compounds are prepared by replacement of a hydrogen and there is, usually, no reason for reversing this reaction. But the replacement of the alcoholic hydroxyl group by hydrogen may proceed often through the halide.

1. Halogen on a Saturated C—C Bond

(a) Direct Exchange

As mentioned above, of the halides, iodine can be replaced most easily by hydrogen. Ethyl iodine can be reduced to ethane by zinc dust in aqueous alcoholic suspension. Also chloroform is converted to methane under these conditions. Occasionally, however, condensation reactions may occur, as with triphenylchloromethane, which yields hexaphenylethane.

Straus [100] used coppered zinc as the reducing agent. 10 g. of zinc dust are added in one portion to 250 cc. of a 4% copper sulfate solution; after the material is shaken thoroughly, the powder is allowed to settle and is repeatedly washed with water by decantation. When an alcoholic solution of methyl iodide is dropped on the powder, methane is generated.

More active than zinc is aluminum amalgam, but the latter does not possess any outstanding advantages. When sensitive substances such as optically active compounds which might racemize at higher temperatures are being used, the halide is reduced in a solution of hydrogen iodide in glacial acetic acid and zinc dust is added during cooling. Another useful combination is hydrogen chloride in glacial acetic acid and zinc dust or turnings.

Sodium amalgam, an almost universally suitable reagent, is also appropriate, but it should be remembered that under certain conditions (see page 8) sodium amalgam also hydrogenates ethylene bonds. For instance, glycerol monochlorohydrin is converted to propylene glycol, bromohydroxyisobutyric acid to hydroxyisobutyric acid, mono-, di-, and triiodobenzene to benzene, and the three isomeric chlorobenzoic acids to benzoic acid. If sodium amalgam fails, the reduction can sometimes be accomplished by zinc and potassium hydroxide in the presence of a small amount of iron filings. By the use of this procedure halogen bound to an aromatic nucleus can be replaced by hydrogen.

Finally, nearly all reducing agents which yield nascent hydrogen may be used for eliminating halogen. Mention may be made of sodium and alcohol, zinc and hydrochloric acid, iron and acetic or sulfuric acid. Only this short summary is given here, since the reaction is not frequently used and since, in most cases, a suitable catalytic method (see below) serves equally well.

A few examples for the replacement of several halogen atoms on a single carbon atom by hydrogen were mentioned above. However, 2 halogen atoms on adjacent carbon atoms cannot usually be directly replaced by hydrogen, for, in this case, the reducing agent removes molecular halogen, yielding the corresponding ethylene compound. Since often these dihalides are prepared from the ethylene compounds, the removal of the halogens by hydrogen is of little importance. Sometimes, however, the halides are used for the purpose of purification.

An application of the replacement of halogen by hydrogen is found in the preparation of an aliphatic hydrocarbon from a carboxylic acid of the same number of carbon atoms, as described by Levene in *Organic Syntheses*.[101] Palmitic acid is used as the starting material, and its ester is

[100] Straus, *Ann.*, 342, 238, foot-note (1905).
[101] P. Levene in *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 320.

reduced to cetyl alcohol by the method of Bouveault and Blanc. The hydroxyl group of the latter is replaced by iodine to yield cetyl iodide. The reduction of the iodide to *n*-hexadecane is carried out in acetic acid solution by means of zinc dust and hydrochloric acid.

Almost universally suitable for substitution of halogen by hydrogen are the catalytic methods with noble metals or nickel. Busch and Stöve [102] used palladium precipitated on calcium carbonate. The reaction was carried out in 10% alcoholic potassium hydroxide in order to bind the hydrogen halide which forms during the reduction. Otherwise the reduction slows down. Kelber [103] employed a nickel catalyst made from basic nickel carbonate by reduction at 310° to 320°C.; also, in this case the reaction is carried out in an alcoholic solution in the presence of alkali. It is not surprising that frequently double bonds are hydrogenated simultaneously. Thus dibenzyl is obtained from dichlorostilbene and from tetrachlorotolane. Halogen bound to an olefin can be substituted in several cases by means of catalytic methods while keeping the double bond intact; special precautions, however, have to be taken in such cases (see page 44).

The stepwise replacement of halogen by hydrogen in polyhalides is of practical importance in the manufacture of halogen compounds of the type $RCHX_2$. These may easily be obtained from the corresponding aldehydes provided the latter are conveniently accessible, but they cannot be prepared in a simple manner by direct halogenation of a side chain methyl group, since halogenation does not stop at the $RCHX_2$ stage. However, the trihalogeno compounds are readily accessible, so that the dihalogeno compounds are frequently best prepared by substituting hydrogen for one of the formers' halogens. The best reducing agent for this purpose is sodium arsenite. Methylene bromide, for instance, can be prepared from bromoform according to the directions of Gutmann,[104] described in detail by Hartmann and Dreger in *Organic Syntheses*.[105]

In a similar manner methylene iodide can be prepared from iodoform according to the directions given by Adams and Marvel.[106]

Side Reactions Occurring during Replacement of Halogen

Busch and Weber [107] recently called attention to a side reaction occurring during the catalytic hydrogenation of halides. This reaction is

[102] M. Busch and H. Stöve, *Ber.*, **49**, 1063 (1916).
[103] C. Kelber, *Ber.*, **54**, 2255 (1921).
[104] A. Gutmann, *Ber.*, **52**, 212 (1919).
[105] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 357.
[106] R. Adams and C. Marvel in *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 358.
[107] M. Busch and W. Weber, *J. prakt. Chem.*, **146**, 1 (1936).

comparable to the Wurtz-Fittig synthesis and proceeds according to the equation, $2RX + H_2 \rightarrow R \cdot R + 2HX$.

The authors discuss in detail the conditions under which this side reaction becomes marked or even predominant. The method may actually be considered of practical importance. The lowest yield of condensation products is obtained by using molecular hydrogen. Through the use of atomic hydrogen the yield is increased to 80% in the case of the preparation of diphenyl from bromobenzene. Atomic hydrogen is generated by decomposing hydrazine with palladium. Depending upon the experimental conditions, this reaction yields ammonia in addition to hydrogen and nitrogen. It is important that, according to Busch,[108] the halogen of many different halides can be replaced quantitatively by hydrogen without any side reaction, and that with almost identical reagents, by merely changing the conditions, a condensation can be successfully effected.

The application of this method to m- and p-dihalogenobenzene leads to chain formations to an extent previously unknown; m-dibromobenzene, for instance, yields a sedeciphenyl, $C_{96}H_{66}$ (see also page 354).

(b) Indirect Exchange through Grignard Compounds

Organic magnesium halides react with water and hydroxyl-containing substances according to the equation

$$R \cdot MgX + R' \cdot OH \longrightarrow RH + MgXOR'$$
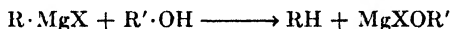
This method is the basis for the well known procedure of Tschugaeff and Zerewitinoff for the quantitative determination of the hydroxyl group. But even in this analytical procedure the reaction does not proceed uniformly; in addition to methane, hydrocarbons of high molecular weight are formed. According to Gilman and Fothergill,[109] these side reactions occur during the preparation of the Grignard compounds and, therefore, cannot be avoided. Nevertheless, the lower hydrocarbons of the aliphatic series can be prepared quite readily from their iodides or bromides through the Grignard compounds.

Side reactions often occur when aromatic Grignard compounds react with hydroxyl compounds, the corresponding diphenyl derivatives being formed. Ammonia and primary and secondary amines decompose Grignard compounds in a manner analogous to the action of water and alcohols. According to Houben [110] the best method for the preparation of saturated hydrocarbons from Grignard compounds is the reaction with ammonium chloride.

[108] M. Busch, Angew. Chem., 38, 519 (1925); 47, 536 (1934).
[109] H. Gilman and R. Fothergill, J. Am. Chem. Soc., 50, 3334 (1928).
[110] J. Houben, Ber., 38, 3017 (1905).

2. Halogen on an Unsaturated C—C Bond

Generally speaking the statements made above in regard to the replacement of halogen by hydrogen also apply when the halogen is bound to an unsaturated carbon to carbon linkage. Compounds of this type are usually obtained from ethylene compounds by adding halogen, thus forming dihalides, followed by removing hydrogen halide; or from acetylene compounds by adding halogen or hydrogen halide. There is no point in reconverting the unsaturated halide, obtained from an ethylene compound, into the starting material by replacing the halogen with hydrogen. If it is desired to convert an acetylene compound into an ethylene derivative, partial hydrogenation (see page 31) of the acetylene compound is usually a better method than addition of halide or hydrogen halide followed by exchange of the halogen for hydrogen. Yet the reaction is of importance because it can be used for the determination of the configuration of stereoisomeric ethylenes, since it is possible to substitute hydrogen for halogen bound to an unsaturated linkage without change in the stereoisomeric configuration of the double bond.

Normally the action of zinc dust will bring about the conversion of an unsaturated halogen compound in alcoholic or acetic acid solution to the corresponding unsaturated hydrocarbon. The normal β-bromocinnamic acid (m.p. 133°C.), for instance, yields on heating with zinc dust and absolute alcohol the normal high melting cinnamic acid, while from the so called β-bromoallocinnamic acid (m.p. 159°C.) the lower melting allocinnamic acid is obtained in almost quantitative yield.

In place of zinc dust, Wislicenus used aluminum amalgam for substituting halogen with hydrogen without affecting the double bond (see page 9). There are, however, compounds in which the halogen cannot be replaced by hydrogen without simultaneous hydrogenation of the double bond.

Occasionally, catalytic hydrogenation of compounds having a halogen bound to an unsaturated linkage leaves the double bond intact; see Rosenmund and Zetzsche,[111] and Paal, Schiedewitz, and Rauscher.[112]

3. Halogen Bound in Other Ways

The catalytic reduction of acid chlorides yielding aldehydes, as suggested by Rosenmund and Zetzsche, is not of practical importance. Palladium and platinum in colloidal solution as well as precipitated on carrier substances [113] have been used in this procedure.

A more recent observation on the reduction of acid chlorides of dibasic

[111] K. W. Rosenmund and F. Zetzsche, *Ber.*, 51, 578 (1918).
[112] C. Paal, H. Schiedewitz, and K. Rauscher, *Ber.*, 64, 1561 (1931).
[113] K. W. Rosenmund and F. Zetzsche, *Ber.*, 54, 425 (1921); 56, 1481 (1923).

acids has been reported by Fröschl and Maier.[114] The inhibitors of catalysts recommended by Rosenmund and Zetzsche proved to be effective only for retarding the hydrogenation without changing the relative yields of the reaction products. Benzene and tetralin were used as solvents; palladium-barium sulfate and osmium precipitated on carbon as catalysts.

Numerous compounds of trivalent nitrogen in which the nitrogen atom is 1 atom removed from oxygen react in tautomeric forms, as, for instance, cyanuric and isocyanuric acids. Similarly, from the substituted acid amides, $R \cdot CO \cdot NH \cdot R$, the most varied derivatives of the tautomeric formula, $R \cdot C(OH):N \cdot R$, can be derived. This makes possible, among other things, the transformation of acid amides into Schiff bases, according to the scheme, $R \cdot C(OH):N \cdot R \rightarrow R \cdot CCl:N \cdot R \rightarrow R \cdot CH:N \cdot R'$ ($R' =$ aryl). From the acid amides with phosphorus pentachloride the imide chlorides are obtained, which in many cases can be isolated pure, but which may be processed further as crude substances.

The transformation into Schiff bases can be performed successfully according to Sonn and Müller [115] by reduction with stannous chloride and hydrochloric acid. Thus earlier, more cumbersome methods (see Sonn and Müller) can be dispensed with. The Schiff bases can be hydrolyzed to the corresponding aldehydes, the preparation of which is the real purpose of the method, as the Schiff bases are much more conveniently prepared according to the method of Reddelien (see page 252). However, the reduction with stannous chloride and hydrochloric acid frequently fails with unsaturated aliphatic imide chlorides. Braun and Rudolph [116] have, therefore, developed a generally applicable procedure involving the use of chromous chloride as reducing agent. Chromous chloride is used as a suspension and is obtained from freshly prepared chromous acetate which is washed with methanol and ether. If necessary, the chromous acetate can be stored in a desiccator which is first filled with carbon dioxide and is then evacuated. For the preparation of chromous chloride, the chromous acetate is suspended in a 2 to 3 N solution of hydrogen chloride in ether containing twice the theoretically required amount of hydrogen chloride; e.g., 55 g. of chromous acetate, containing water of crystallization, are suspended in 19 g. of hydrochloric acid in 250 cc. of dry ether. When hydrogen chloride is passed through the agitated suspension, a fine almost colorless precipitate of chromous chloride is formed. To this suspension is added a solution of the imide chloride in benzene or ether (one-half of the amount calculated on the

[114] N. Fröschl and A. Maier, *Monatsh.*, **59**, 256 (1932).
[115] A. Sonn and E. Müller, *Ber.*, **52**, 1927 (1919).
[116] J. v. Braun and W. Rudolph, *Ber.*, **67**, 269, 1735 (1934).

basis of the chromous acetate). The chromous chloride changes color and usually dissolves when the mixture is stirred. The entire solution then becomes red. After 90 minutes dilute hydrochloric acid is added and the solvent removed by distillation, if necessary, under reduced pressure. The aldehyde formed in the reaction $R \cdot CH : N \cdot R' + H_2O \rightarrow R \cdot CHO + R'NH_2$ passes over into the distillate. If the Schiff's base is desired, details for its isolation can be found in the papers cited.

As an example, the directions of Kuhn and Morris [117] are given below. A suspension of chromous chloride in ether is prepared in the quantities given above. The imide chloride solution is prepared and reacts as follows:

β-Ionylideneacet-o-toluidide (21 g.) is mixed at 0°C. with 50 cc. of dry benzene and 13.6 g. of phosphorus pentachloride. The benzene is removed by vacuum distillation under nitrogen and the residue twice treated in the same manner with 50 cc. of benzene. The resulting dark reddish brown imide chloride is dissolved in 30 cc. of dry ether and added slowly to the chromous chloride suspension under nitrogen with vigorous stirring. During 90 minutes stirring the reaction mixture warms up, becomes dark, and a clear solution is formed. The reaction mixture is shaken four times with water and the ether evaporated *in vacuo* under nitrogen. To the dark brown, oily, crude product a 10% solution of oxalic acid is added and the mixture steam-distilled under carbon dioxide. The colorless distillate is extracted with ether and dried with sodium sulfate under nitrogen. After removal of the ether 3.9 g. of β-ionylideneacetaldehyde remains as a thin, faintly yellow liquid. The aldehyde boils at a bath temperature of 110°C. at 0.0001 mm. with partial decomposition. It was characterized by semicarbazone formation.

B. Replacement of Oxygen by Hydrogen

1. Replacement of Hydroxyl Group

The direct substitution of hydrogen for the hydroxyl group is of practical importance only in a few special but very important cases. Different procedures, involving additional steps, are more convenient for replacing primary and secondary hydroxyl groups by hydrogen. Primary hydroxyl groups are best replaced by hydrogen through the corresponding halides and secondary alcohols are best reduced by way of the unsaturated compounds obtained therefrom. In general, tertiary hydroxyl groups can be replaced directly by hydrogen.

Frequently it is unnecessary to prepare the pure halides, especially if the substituting reagent is also the reducing agent, as, for instance, hydriodic acid. Since, however, hydriodic acid is one of the strongest reducing agents known, it is obvious that a number of side reactions might occur whenever other reducible groups are present. This reaction is discussed with the direct substitution methods.

[117] R. Kuhn and C. Morris, *Ber.*, **70**, 857 (1937).

The catalytic substitution of hydrogen for the hydroxyl group is so difficult to achieve that the reaction cannot be used for practical purposes.

(a) Direct Reduction with Hydriodic Acid

Instead of using hydrogen iodide alone, frequently a mixture of hydrogen iodide and phosphorus is employed. The phosphorus reacts with the iodide formed during the reaction and regenerates hydrogen iodide in the presence of water. Phosphorus with a small amount of iodine may also be used in this reaction. In the latter case, the phosphorus is the reducing substance proper.

A good example for the use of phosphorus and iodine is the reduction of benzilic acid, $(C_6H_5)_2COH \cdot COOH$, in acetic acid to biphenylacetic acid, as described in *Organic Syntheses*.[118]

(b) Direct Reduction with Nascent Hydrogen

(a) Alcoholic Hydroxyl Group. Hydroxyl groups next to unsaturated and aromatic bonds can be reduced with alkaline or acid substances which provide nascent hydrogen. An example (not important for preparational work) is the reduction of cinnamyl alcohol with sodium and alcohol according to Klages.[119] The reaction mixture contains, mainly, propylbenzene and a little propenylbenzene, $C_6H_5 \cdot CH:CH \cdot CH_3$. Propylbenzene cannot have been formed from phenylpropyl alcohol, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_2OH$, because the latter remains completely intact under the conditions of the reaction.

Cumic alcohol, $(CH_3)_2CH \cdot C_6H_4 \cdot CH_2OH$, yields cymene when boiled for a long period of time with zinc dust.

Carbonyl groups next to the hydroxyl radical also have a similar effect. Thus, acetoins such as benzoin can be reduced with zinc and alcoholic hydrogen chloride, giving good yields of desoxyacetoins; that is, saturated ketones. Desoxybenzoin can be prepared, for instance, according to Stobbe's method,[120] but in this case the nuclear synthesis from phenylacetic chloride and benzene is preferable (see page 388). When tin or stannous chloride is used in place of zinc, a glycol is formed, hydro- or isohydrobenzoin, respectively.

Since tertiary hydroxyl groups are readily removed by nascent hydrogen generated with zinc dust, the method is of importance whenever unsaturated bonds must also be preserved. Thus linaloöl, $(CH_3)_2C:CH \cdot CH_2 \cdot CH_2 \cdot C(CH_3)OH \cdot CH:CH_2$, the tertiary hydroxyl group of which is next to the double bond, changes to linaloölene when boiled with zinc dust; see Semmler.[121]

[118] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 224.
[119] A. Klages, *Ber.*, **39**, 2587 (1906).
[120] H. Stobbe, *Ber.*, **35**, 911 (1902).
[121] F. W. Semmler, *Ber.*, **27**, 2520 (1894).

Occasionally one can deduct from the course of the reaction whether the hydroxyl group exists as a tertiary, secondary, or primary hydroxyl group; see Semmler.[122]

The hydroxyl group of the triarylcarbinols can generally be exchanged for hydrogen by boiling with zinc in glacial acetic acid. Kauffmann and coworkers [123] state that methoxytriphenylcarbinols can be reduced in the presence of hydrogen chloride by means of warm ethanol to triphenylmethanes; the reaction presumably proceeds through the carbinol chloride. Thus triphenylmethane is obtained according to Schmidlin and Garcia-Banùs [124] from a solution of 10 g. of triphenylcarbinol in 100 cc. of ethanol with the addition of 100 cc. of sulfuric acid. The temperature is not allowed to exceed 70° to 80°C.; the yellow color of the carbinol sulfate soon disappears. Finally the mixture is heated on a steam bath for 15 minutes. After it is cooled, triphenylmethane crystallizes. The crystals are filtered off, dried, and recrystallized from benzene. The melting point is 92°C. For the preparation of larger amounts, triphenylchloromethane is the best starting material.

The phthaleins react in a quite similar manner; thus, according to Baeyer [125] phthalophenone yields triphenylmethane-o-carboxylic acid on boiling with sodium hydroxide and zinc dust.
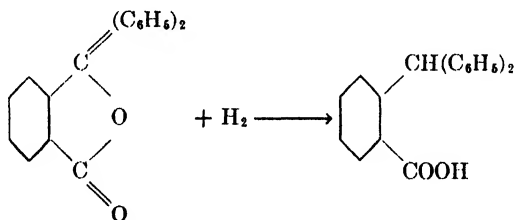
According to Vorländer [126] the reduction succeeds also with enolic hydroxyl, as shown in the transformation of indoxyl into indole with sodium amalgam.

The lactones of the γ- or δ-hydroxy acids may be reduced by sodium amalgam in acid solution. Valerolactone yields valeric acid; caprolactone, caproic acid. Contrariwise the lactones of polyhydroxy acids, especially of the sugar series, are attacked at the carboxyl group first.

Frequently polyhydroxycarboxylic acid lactones with hydriodic acid give lactones of monohydroxy fatty acids first. Thus, from gluconic acid

[122] F. W. Semmler, *Ber.*, **33**, 776 (1900).
[123] H. Kauffmann *et al.*, *Ber.*, **38**, 2702 (1905); **41**, 4423 (1908).
[124] J. Schmidlin and A. Garcia-Banùs, *Ber.*, **45**, 3188 (1912).
[125] Baeyer, *Ber.*, **12**, 644 (1879); *Ann.*, **202**, 52, 80 (1880).
[126] D. Vorländer, *Ber.*, **37**, 1134 (1904).

lactone, caprolactone is obtained first; only at a higher temperature in a sealed tube is caproic acid formed; see Kiliani and Kleemann.[127]

Whenever carboxyl and hydroxyl compete, it is generally immaterial whether the hydroxyl group is part of a purely aliphatic or an alicyclic system.

An amino group next to a hydroxyl group almost always stays intact. Glucosaminic acid gives aminocaproic acid when treated with hydriodic acid.

(b) Phenolic Hydroxyl Group. The reaction is seldom of preparative importance but is used for the elucidation of structure. The method in general use is carried out by mixing the substance with zinc dust and distilling dry, or by passing the vapors over heated zinc dust; see Baeyer.[128]

Phenol, cresols, hydroquinone, dihydroxybiphenyl, and many others, when thus treated, give the mother hydrocarbons. Alkoxy groups usually remain unchanged when subjected to distillation over zinc dust; aldehydes, ketones, etc., are, under certain conditions, drastically changed.

Specific methods for the reduction of phenolic hydroxyl groups do not exist. Very strong reducing agents such as phosphorus trisulfide usually effect further changes.

With aromatic systems containing several hydroxyl groups some of the latter can be successfully eliminated. Worthy of mention is purpurin which loses the hydroxyl in the 2 position when treated with zinc dust and glacial acetic acid and forms quinizarin; on the other hand, with sodium hyposulfite it yields purpuroxanthin. The same effect is produced with alkaline reducing agents in general; see Rosenstiehl.[129]

In rare cases even aromatically bound alkoxy groups are replaced by hydrogen when these groups accumulate in the same nucleus.

2. Replacement of Carboxyl Oxygen

(a) Direct Replacement

Clemmensen Reduction—The method consists of the reduction by nascent hydrogen of carbonyl compounds: $RCOR + 2H_2 \rightarrow RCH_2R + H_2O$. Mild reducing agents form pinacoles from ketones by condensation, while the monomolecular reduction is apparently favored more the higher the potential of the generated hydrogen. According to Clemmensen [130] the best combination is amalgamated zinc-concentrated hydrochloric acid, whereby use is made of the high potential of hydrogen on mercury.

[127] Kiliani and Kleemann, *Ber.*, **17**, 1300 (1884).
[128] A. v. Baeyer, *Ann.*, **140**, 295 (1866).
[129] Rosenstiehl, *Compt. rend.*, **79**, 764 (1874).
[130] Clemmensen, *Ber.*, **46**, 1837 (1913); **47**, 51, 681 (1914).

Zinc shavings as well as zinc granules may be used. They are treated with 2 parts of 5% aqueous mercuric chloride solution during 1 hour and then rinsed. When thin sheets of zinc are used, the amalgamation is finished in shorter time. Clemmensen recommends diluting crude hydrochloric acid with 1 to 2 parts of water. In order to bring the reacting substances into close contact it is advisable to stir well. Hydrochloric acid is added as fast as it is used up. As the reduction is carried out with boiling hydrochloric acid, it is best to use a 3-necked flask with a reflux condenser, dropping funnel, and a mercury seal for the stirrer.

The transformation of fatty aromatic ketones into the corresponding hydrocarbons proceeds very smoothly. However, the resulting products are not always of a very high purity because of side reactions. Thus Steinkopf and Wolfram,[131] when reducing acetophenone, isolated styrene as well as ethylbenzene and hydrocarbons of higher molecular weight. Clemmensen himself [132] realized and correctly explained the difficulties occasionally encountered. He found that acetophenone treated with an excess of hydrochloric acid and amalgamated zinc gives ethylbenzene in an 80% yield; but if too little hydrochloric acid is used, so that not enough hydrogen is generated for complete reduction, the main portion of the reaction product consists of styrene.

As an example of the reduction of aliphatic ketones to paraffin hydrocarbons, the following directions of Clemmensen [133] for the preparation of *n*-undecane from methyl *n*-nonyl ketone are given.

Methyl *n*-nonyl ketone (50 g.), boiling at 224° to 226°C., is refluxed for 24 hours with 300 g. of amalgamated zinc and 300 cc. of a mixture of equal parts of concentrated hydrochloric acid and water. Concentrated hydrochloric acid is added several times to maintain a strong generation of hydrogen. After cooling, the oil layer is separated from the aqueous solution, washed with water, and dried. On fractionation 40 g. of *n*-undecane boiling at 193° to 195°C. are obtained.

The method for the reduction of fatty aromatic ketones is quite similar. For instance, *n*-propylbenzene [134] is obtained as follows: Propiophenone (25 g.) is heated with 100 g. of amalgamated zinc and a mixture of equal parts of concentrated crude hydrochloric acid and water. After 5 minutes a vigorous reaction starts; then the heating is continued for 4 hours while concentrated hydrochloric acid is added. *n*-Propylbenzene (20 g.), boiling at 155° to 160°C., can be isolated; this is a yield of 90% of the theoretical.

If the method is used with substances of a more complicated structure, many side reactions, of course, are to be expected. Thus with benzoin the hydroxyl group is also reduced, yielding dibenzyl, which is not surprising, since benzoin is changed to desoxybenzoin with ordinary zinc and hydrochloric acid.

[131] Steinkopf and Wolfram, *Ann.*, **430**, 113 (1923).
[132] Clemmensen, *Ber.*, **46**, 1838 (1913).
[133] Clemmensen, *Ber.*, **46**, 1841 (1913).
[134] Clemmensen, *Ber.*, **46**, 1839 (1913).

Phenolic hydroxyl, when present, remains intact, as might be expected; thus from salicylaldehyde pure o-cresol is obtained.

The usually excellent results with Clemmensen's method may presumably be traced to the fact that the intermediate carbinol never accumulates in high concentrations; therefore no water or only a negligible amount of it (see above) is split off. This theory is supported by the fact that di- and triarylcarbinols (benzhydrol, triphenylcarbinol) which cannot undergo an intramolecular dehydration are especially easily reduced to hydrocarbons (see page 48).

The extent to which the method can be used is limited, because too many substances react too sluggishly owing to their insolubility in aqueous hydrochloric acid or because side reactions become predominant; in such cases the Wolff-Kishner method serves the purpose better (see page 52).

Recently Martin [135] suggested performing the Clemmensen reduction in the presence of toluene in order to facilitate reaction of substances which have relatively high melting points and are soluble in hydrochloric acid. Various substituted benzoylpropionic acids were reduced to the corresponding arylbutyric acids, which were required as starting materials for the synthesis of hydrocarbons with several rings. The general procedure is described as follows: First 100 g. of mossy zinc are shaken for 5 minutes with 10 g. of mercuric chloride, 5 cc. of concentrated hydrochloric acid, and 150 cc. of water and the aqueous layer decanted. To the amalgamated zinc were added 75 cc. of water, 175 cc. of concentrated hydrochloric acid, 100 cc. of toluene, and 50 g. of the carbonyl compound to be reduced. If necessary, to increase the solubility in the aqueous layer, 3 to 5 cc. of glacial acetic acid were added and the mixture boiled vigorously under a reflux. At intervals of 6 hours, three 50 cc. portions of hydrochloric acid were added, the boiling lasting altogether about 24 hours. In this manner β-benzoylpropionic acid, m- and p-β-toluylpropionic acid, 1- and 2-β-naphthoylpropionic acid, benzoylnaphthalene, β-naphthyl methyl ketone, and other substances were reduced with better success than without the addition of toluene. In comparative preparations without toluene the yields were 72 to 78%, while with toluene a yield of 90% was obtained.

The reduction of β-benzoylpropionic acid to γ-phenyl-n-butyric acid is described by Krollpfeiffer and Schäfer.[136] *Organic Syntheses* [137] gives directions according to both the old and the new method.

The attempt to hydrogenate the C=O group catalytically to the methylene group has thus far not been successful. From recent litera-

[135] E. L. Martin, *J. Am. Chem. Soc.*, 58, 1438 (1936).
[136] Krollpfeiffer and Schäfer, *Ber.*, 56, 620 (1923).
[137] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 499.

ture some observations of Packendorff [138] may be mentioned. He used a platinum catalyst which is surprisingly more active in acid than in alkaline solution.

Finely powdered platinized activated charcoal is added to the aqueous or alcoholic solution of the ketone to be hydrogenated. The solution also contains a small amount of chloroplatinic acid, which is reduced in a few minutes time when shaken with hydrogen. The yields of hydrocarbon are quite small. For instance, 10 g. of cyclohexanone were hydrogenated in 6% hydrochloric acid with 0.5 g. of platinized carbon and 1 cc. of a solution of chloroplatinic acid (0.05 g. of platinum). After 3 hours no more hydrogen was taken up. The addition of hydrochloric acid as well as additional amounts of chloroplatinic acid were without effect. From the reaction mixture 2 g. of cyclohexane and 6 g. of cyclohexanol could be isolated. Similar results were obtained in hydrogenating cyclopentanone.

(b) Replacement by Way of Intermediates

Wolff-Kishner Reduction of Carbonyl Compounds—The method consists of the preparation of hydrazones or semicarbazones of carbonyl compounds which are then decomposed under suitable conditions, according to the scheme, $R_2:C:N \cdot NH_2 \rightarrow R_2:CH_2 + N_2$. Wolff [139] gives the following general directions. The hydrazone to be treated is heated in a sealed tube with 7% sodium ethylate solution at about 150°C. for 6 to 8 hours. Considerable pressure has to be expected because free nitrogen is formed.

Kishner [140] used solid potassium hydroxide in place of the ethylate solution, simply heating the hydrazones with powdered potassium hydroxide. On account of the low volatility of the hydrazones frequently no sealed vessels are required.

Staudinger [141] observed an analogous reaction of free ketones when they were heated with hydrazine. He obtained from 2 g. of benzophenone and 5 g. of hydrazine at 200°C. a theoretical yield of diphenylmethane.

Schönberg [142] found that under certain conditions it is more advantageous to start with semicarbazones than with hydrazones. According to Wolff [139] the hydrazones are formed as intermediates. Apparently the result is the same when one starts with hydrazones or semicarbazones; the decisive factor is which of the two classes of derivatives of the carbonyl compound can be prepared most readily and purified best.

The Wolff-Kishner reduction accomplishes the same thing as that of Clemmensen, but in complicated cases it offers many advantages because the reduction is limited exclusively to the carbonyl group. Knorr and

[138] K. Packendorff, *Ber.*, **67**, 905 (1934).
[139] L. Wolff, *Ber.*, **44**, 2760 (1911); *Ann.*, **394**, 87 (1912).
[140] N. Kishner, *J. Russ. Phys.-Chem. Soc.*, **43**, 582 (1911); *Chem. Zentr.*, 1911, **II**, 363.
[141] H. Staudinger, *Ber.*, **44**, 2211 (1911).
[142] Schönberg, *Ber.*, **54**, 2838 (1921).

Hess [143] apparently used it for the first time in the chemistry of pyrroles for the reduction of 2,4-dimethyl-3-acetylpyrrole to dimethylethylpyrrole.

Dimethylacetylpyrrole (13.7 g.) is refluxed for 8 hours with 5 g. of hydrazine hydrate, extracted with ether, and dried over sodium sulfate. The syrupy residue left after evaporation of the ether solidified after several days; when recrystallized from alcohol, the hydrazone melted at 178° to 179°C. Portions of 2.5 g. of the hydrazone were sealed under nitrogen with a solution of 2 g. of sodium in 25 cc. of absolute ethanol and heated to 150° to 160°C. for 14 hours. After cooling, the contents of the tube, in which crystals had formed, were diluted with boiled water and steam-distilled in an atmosphere of hydrogen on account of the sensitivity of the pyrrole derivative. The dimethylethylpyrrole was salted out of the distillate with ammonium sulfate, completely extracted with ether, the ether solution washed with water to remove the alcohol, and dried over sodium sulfate.

To isolate the hemopyrrole, Piloty [144] suggests partially removing the ether by distillation under diminished pressure in a luke-warm water bath. The concentrated ethereal solution is run from a dropping funnel, the stem of which is drawn out to a capillary, into a fractionation flask so that the ether evaporates instantaneously at low heat in a vacuum. The 2,4-dimethyl-3-ethylpyrrole is obtained as a colorless liquid in the final distillation under reduced pressure; it boils at 90° to 104°C. at 11 mm.

The Wolff-Kishner method has been especially useful in the sterol series in which it, as well as the method of Clemmensen, played an important rôle. A few examples are given to illustrate the method.

To transform cholestenone into pseudocholestene (Lettré [145]) 1.5 g. of cholestenone semicarbazone are heated with a solution of 1.5 g. of sodium in 15 cc. of absolute alcohol in a sealed tube for 10 hours at 200°C. After cooling, the contents of the tube are washed out with water and ether, the ether solution washed with water, and the ether evaporated. The residue is dissolved in 200 cc. of boiling ethanol and precipitated with a solution of 1 g. of digitonin in 100 cc. of 90 per cent alcohol, the cholesterol and cholestanol, formed as by-products, being thus removed. The filtrate is evaporated to dryness in a vacuum, and the residue dissolved in ether and concentrated. When methanol is added, a crystalline product is obtained, melting at 62° to 67°C. The preparation of pure pseudocholestene was not completely successful; it was isolated from the mixture as the dibromide. For the formation of alcohols as by-products of the Wolff-Kishner reduction see Eisenlohr and Polenske.[146]

According to Cook and Haslewood [147] 0.4 g. of 12-ketonorcholanic acid in 10 cc. of ethanol is heated for 3 hours with a concentrated aqueous solution of 0.4 g. each of semicarbazide hydrochloride and sodium acetate. The semicarbazone, recrystallized from ethanol, has a melting point of 235°C. The semicarbazone (0.4 g.) is heated in a sealed tube with 0.4 g. of sodium in 6 cc. of ethanol for 3 hours at 170° to 175°C. After being cooled and diluted with water, the sodium salt of the norcholanic acid, which is difficultly soluble, is separated and decomposed in an ether suspension with dilute hydrochloric acid. The ether is evaporated and the free acid recrystallized from glacial acetic acid. The melting point is 175° to 176.5°C.

[143] L. Knorr and K. Hess, *Ber.*, **44**, 2765 (1911).
[144] O. Piloty, *Ann.*, **366**, 251 (1909).
[145] H. Lettré, *Z. physiol. Chem.*, **221**, 82 (1933).
[146] F. Eisenlohr and R. Polenske, *Ber.*, **57**, 1641 (1924).
[147] J. Cook and G. Haslewood, *J. Chem. Soc.*, **1934**, 433.

3. Replacement of Oxygen in Carboxylic Acids and Esters

The direct reduction of the carboxyl group to the methyl group was formerly performed almost exclusively with hydriodic acid and red phosphorus. From palmitic acid, by repeated heating to 210° to 240°C. with 3 to 4 parts of hydriodic acid and red phosphorus, which are renewed several times, hexadecane is finally obtained. The method can be used for fatty acids and hydroaromatic carboxylic acids. In the aromatic series there is rarely any need for this procedure, as other methods are usually more advantageous. Occasionally milder means may be used; terephthalic acid changes partially into toluic acid when treated only with zinc dust and hydrochloric acid in alcoholic solution; picolinic acid yields α-picoline with zinc and acetic acid.

The preparation by high pressure hydrogenation of hydrocarbons and alcohols from carboxylic acids or their esters respectively has only recently become important for laboratory practice, although details of technical methods had been published some time ago. Schrauth, Schenk, and Stickdorn [148] state that with suitable catalysts good yields can be obtained from fats and esters of fatty acids with monohydric alcohols, at 200 atmospheres pressure and at temperatures between 300° and 400°C.; free acids also give good yields of paraffins and primary alcohols, depending on the conditions. A little later Schmidt [149] showed that the same reactions can be performed without pressure, also, if sufficiently active catalysts are used.

Schmidt gives two examples, the preparation of octadecyl alcohol from oleic acid ethyl ester and of octadecanediol from castor oil. As a by-product of the latter reaction, octadecyl alcohol is formed. The preparation of the necessary copper chromite catalyst is as follows:

Copper nitrate trihydrate (483 g.) is dissolved in 1500 cc. of water and precipitated hot with a solution of 304 g. of ammonium chromate in 2 liters of water. The precipitated copper chromate is washed well, dried, and finely powdered. By dialyzing a solution of 45 g. of 100% formic acid and 100 g. of a 30 to 35% solution of sodium silicate in 500 cc. of water, a colloidal silicic acid solution is prepared. Dried copper chromate (130 g.) is stirred into 300 cc. of the silicic acid solution and the mixture evaporated on a steam bath with 1 liter of small glass rings. The catalyst mass thus prepared is put into the reaction space of an electrically heated oven (see Fig. 2) and reduced with hydrogen at about 300°C. to give copper chromite. The ethyl oleate is then added dropwise in a stream of hydrogen at 250° to 280°C. The reaction product is collected in well cooled receivers. The crude product contains 80 to 90% of octadecyl alcohol which can be purified by fractionation or recrystallization.

Schrauth and coworkers sometimes use 4 liter autoclaves, with stirrers, or if the pressure exceeds 100 atmospheres, steel cylinders or high pressure

[148] W. Schrauth, O. Schenk, and K. Stickdorn, *Ber.*, **64**, 1314 (1931).
[149] O. Schmidt, *Ber.*, **64**, 2051 (1931).

shaking autoclaves.   The temperature is measured with a thermocouple. As one of the many examples, the preparation of dodecyl alcohol from methyl laurate may be described.   All that is mentioned of the catalyst used is the fact that it is prepared by the reaction of an excess of sodium dichromate with 2 parts of zinc oxide and 1 part of copper oxide.

Methyl laurate (40 g.) is heated at 145 atmospheres pressure with 4 g. of the zinc-copper chromite catalyst reduced at 400°C.   Between 305° and 325°C. the pressure increases to 290 atmospheres and then goes down to 272 atmospheres where it remains constant.   The reaction time is 16 minutes.   The reaction product is saponified, separated from unchanged lauric acid, and yields 10.5 g. of pure dodecyl alcohol melting at 21° to 22°C.

The pressure hydrogenation of castor oil according to Schmidt takes place with a cobalt catalyst prepared by reduction of basic cobalt carbonate at 320° to 350°C.

Castor oil (200 g.) is mixed with 10 g. of the catalyst and treated with hydrogen in a rotating bomb of 1 liter capacity at 220°C. and 200 atmospheres until no more hydrogen is absorbed.   The colorless reaction product is filtered off from the catalyst and fractionated. Octadecyl alcohol is obtained in 17% yield calculated on the basis of the total C_{18} content of the starting material; it boils at 210°C. at 15 mm. pressure.   75% of octadecanediol, boiling at 223°C. at 9 mm., is also obtained.

Fig. 2.—Apparatus for the catalytic hydrogenation of esters.

Schrauth uses a copper-kieselguhr catalyst for the preparation of dodecane from free lauric acid; the catalyst contains 20% copper as basic copper carbonate.

Lauric acid (40 g.) and 4 g. of catalyst are heated in a shaking autoclave with hydrogen at 130 atmospheres.   When heated to 300°C. the pressure increases to 272 atmospheres, then decreases to 242 atmospheres within 4 minutes; finally it increases again to 270 atmospheres at 390°C.   The experiment is terminated after 60 minutes. The crude product boils between 95° and 125°C. at 16 mm.   On rectification, 22 g. of dodecane, boiling at 98° to 101°C. under 17 mm. pressure, are obtained.

For the catalytic reduction of the carboxyl group see also Normann.[150]

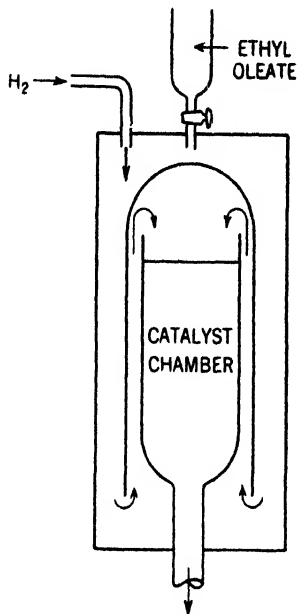[150] W. Normann, *Angew. Chem.*, **44**, 714 (1931).

C. Replacement of Trivalent Nitrogen by Hydrogen

1. Amino Groups

The replacement of the amino group by hydrogen is effected almost exclusively by way of the diazonium compounds (see page 106). The most convenient method consists of boiling the diazonium compound in alcoholic solution. The normal reaction of diazonium compounds with alcohol, however, is the formation of phenol ethers. See Hantzsch and Reddelien.[151] Therefore, the yields are frequently very unsatisfactory. Thus E. Fischer obtained from p-rosaniline only 5% of the theoretical amount of triphenylcarbinol. The following conditions influence the ratio of hydrocarbons and phenol ethers obtained: the lower alcohols, especially polyhydric, favor the formation of ethers; the higher ones, the formation of hydrocarbons. For instance, from benzenediazonium chloride with methanol only anisole is obtained; with ethanol, a little benzene together with much phenetole; with benzyl alcohol, much benzene together with very little benzyl phenyl ether.

Substituents such as the so called negative groups and the halogens on the benzene nucleus favor the formation of hydrocarbons; tribromophenyldiazonium chloride, even with highly diluted alcohol, yields tribromobenzene almost exclusively and only traces of tribromophenol; in the same manner, from nitrated diazonium compounds very good yields of nitro hydrocarbons are obtained.

When the method is not applicable because of the preponderant formation of ethers, the reaction can be directed into the desired course by reducing agents. For this purpose stannous chloride is especially suited when used in excess. An alkaline stannite solution added to the diazonium solution which has been rendered basic with sodium hydroxide is even better. Apparently the reaction proceeds according to the equation:

$$C_6H_5 \cdot NH \cdot NH_2 + C_6H_5 \cdot N_2 \cdot OH \longrightarrow 2C_6H_6 + 2N_2 + H_2O$$
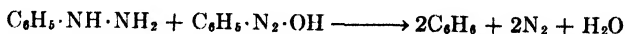
It is seen that phenylhydrazine is formed as an intermediate. It is not surprising, therefore, that hydrazines are the main by-products. Other reducing agents [152] which may be used are hydrazine, hydroxylamine, copper hydride, and hypophosphorous acid (see Mai [153]).

The above reaction of diazonium salts can be speeded up catalytically by exactly the same means as all the other Sandmeyer reactions; that is, by copper powder, copper salts, and potassium cuprous cyanide.

---

[151] A. Hantzsch and G. Reddelien, *Die Diazoverbindungen.* Springer, Berlin, 1921, p. 82.

[152] A recent addition to the list of reducing agents, whose use is sometimes advantageous, is alkaline formaldehyde; Brewster and Poje, *J. Am. Chem. Soc.*, **51**, 2418 (1939).
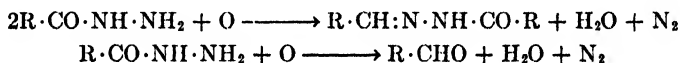
[153] I. Mai, *Ber.*, **35**, 162 (1902).

In some cases, when diazonium salts are boiled with water, hydrocarbons instead of phenols are obtained directly, supposedly with partial oxidation of part of the starting material. This may be observed especially in the case of halogenated amines and in sulfuric acid solution, for instance, with m-bromotoluidine, m-dibromoaniline, and dibromophenetidine.

The reaction cannot be used in the aliphatic series.

2. Other Compounds of Trivalent Nitrogen

Kalb and Gross [154] describe a method which makes possible the transformation of carboxylic acids, by way of their hydrazides, into the corresponding aldehydes with quite good yields. The course of the reaction can be represented schematically by the following equations.

$$2R \cdot CO \cdot NH \cdot NH_2 + O \longrightarrow R \cdot CH{:}N \cdot NH \cdot CO \cdot R + H_2O + N_2$$
$$R \cdot CO \cdot NH \cdot NH_2 + O \longrightarrow R \cdot CHO + H_2O + N_2$$

Potassium ferricyanide in ammoniacal solution proved to be an especially suitable oxidizing reagent. The conditions for the most favorable yield of aldehyde change from one case to another; frequently less than the calculated amount of 2 moles of potassium ferricyanide is used up, but sometimes an excess is favorable. The oxidation is usually run according to the second equation so that the free aldehyde and not the acylated hydrazone is obtained. As an example, the formation of m-bromobenzaldehyde is described.

m-Bromobenzhydrazide (1 g.) is dissolved in a little ethanol and added in one portion to an aqueous solution of 2 equivalents of potassium ferricyanide and 10 equivalents of ammonia in 100 cc. of water. The reaction proceeds with evolution of nitrogen. A small precipitate is filtered off, and the m-bromobenzaldehyde precipitated from the filtrate as the phenylhydrazone. The yield is 50% of the theoretical. Experiments with larger amounts are not described in the paper cited. Little attention has apparently been paid to this method so far. Considering the fact that m-bromobenzaldehyde, as usually prepared (*Organic Syntheses* [155]) from m-nitrobenzaldehyde by way of m-aminobenzaldehyde, can be obtained in a yield of only 65%, it seems worth while to check the method again.[156]

[154] L. Kalb and O. Gross, *Ber.*, 59, 727 (1926).
[155] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 132.
[156] An analogous method, discovered by McHayden and Stevens, *J. Chem. Soc.*, 1936, 584, involves the decomposition of arylsulfonylacylhydrazides in alkaline media. Further literature on both methods, neither of which is applicable to the aliphatic series, is given in a discussion of the reactions by Nieman and Hays, *J. Am. Chem. Soc.*, 65, 482 (1943).

D. Replacement of Sulfonic Group in Aromatic Substances by Hydrogen

The importance of the reaction is as follows:

Since the sulfonic acid group can be removed more easily from the aromatic nucleus than any other group, certain places in the nucleus can be blocked temporarily by sulfonation, and a new substituent may be forced to enter a position which it would not ordinarily take. The sulfonic group may then be removed to give an abnormal derivative of the parent substance.

An example for this method is the preparation of *o*-chlorophenol according to Hazard.[157]
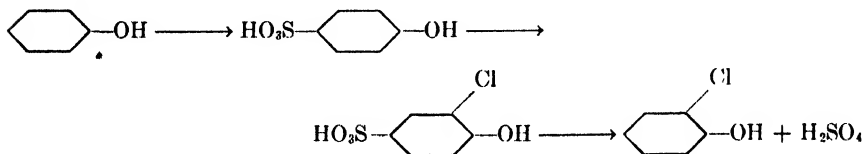
In this case, the force of the temporarily introduced substituent which directs to the *m* position joins the hydroxyl group which directs to the *o* position, thus forming the desired derivative with especial ease. Furthermore the sulfonic group is removed again especially easily from the 3-chloro-4-hydroxybenzenesulfonic acid.

The method is very simple in principle. Usually the readily soluble sulfonic acids are treated with hydrochloric acid for some time under pressure at a temperature of 200°C. Furthermore, this method may be used to separate certain substances from otherwise difficultly separated mixtures. Thus, if one constituent of a mixture is more readily sulfonated than any of the others, it may be removed with water or alkali as the sulfonic acid, from which the pure substance may be regenerated. This was the old method for the preparation of thiophene-free benzene, or conversely for the recovery of thiophene.

[157] Hazard, German Patent, 141,751.

Formation of Carbon-Halogen Bonds

General Aspects

Of all typical organic reactions the formation of carbon-halogen bonds is most similar to the ones discussed in the preceding chapter. The addition of halogen to ethylenic and acetylenic compounds is completely analogous to hydrogenation though it differs in method. The aggressive character of the lighter halogens like chlorine and fluorine causes pronounced splitting of molecules under certain conditions. The reaction of halogens with carbon-oxygen and carbon-nitrogen double bonds is completely different from hydrogenation.

Of the halogens, chlorine and bromine are almost alike in addition reactions. While iodine is somewhat similar, it differs more when substitution occurs. Fluorine is unique in its reaction pattern.

I. BY ADDITION

A. Addition of Halogen to Unsaturated Carbon Compounds

1. Addition to Ethylenic Bonds and to Aromatic Systems

The reaction proceeds in most cases at low temperature and without activation. It is used under suitable conditions for analytical determinations, for instance, the determination of the iodine value. Fluorine usually destroys this type of compounds.

The ease of addition advances from chlorine to iodine. Therefore, small amounts of iodine accelerate the addition of chlorine and bromine. Iodine addition compounds can react according to the following equation: $R \cdot CHI \cdot CHI \cdot R + Br_2 \rightarrow R \cdot CHBr \cdot CHBr \cdot R + I_2$.

Ingold and coworkers,[1] in a long series of papers, developed theories as to the reaction mechanism of halogen addition to unsaturated systems. They used two methods to locate the point of attack.

1. Addition of Iodine Monochloride ("Asymmetric Halogen")—The assumption was made that the position of iodine, as afterwards determined, shows the point at which the addition started.

2. Addition of Hydroxyl after One Chlorine Atom Is Added—The method simply consists of the action of halogen on the aqueous solution of un-

[1] K. Ingold *et al.*, *J. Chem. Soc.*, **1934**, 79 and 87.

saturated acids. Terry, Eichelberger, and Francis[2] found the primary product to be a cation containing a single chlorine atom which easily added a hydroxyl group from water. Thus it appears as if a hypohalous acid had been added.

For details of these interesting investigations, which as yet have not been largely exploited in the laboratory, see the original paper.

Substitution as well as the splitting off of hydrohalogen according to the equation, $R \cdot CHX \cdot CHX \cdot R \rightarrow R \cdot CH : CX \cdot R + HX$, occurs as side reactions. These reactions may be largely avoided by choosing the proper reaction conditions.

With few exceptions, all purely carbocyclic and aromatic systems as well as unsaturated compounds containing isolated or conjugated bonds will add halogen. There are a few important peculiarities.

1. Double bonds between carbon atoms bearing four aromatic substituents do not

add halogen. The group $\diagup C = C \diagdown$ also does not add halogen.

2. Conjugated systems add halogen stepwise. Usually, the addition goes 1,4 first (Thiele's rule), then in the 2,3 position. Conjugated trienes easily add 4 halogen atoms, but the last 2 with difficulty. In oleostearic acid, for instance, complete saturation is effected only under the influence of ultraviolet light.

3. Purely aromatic systems always add halogen to complete saturation. Hexabromobenzene is obtained from benzene at once, but the di- and tetrabromides are unknown. There is a different reaction with naphthalene (see page 75).

The course of stepwise halogen addition is more complicated than the simple equation would indicate: $R \cdot CH : CH \cdot R + X_2 \rightarrow R \cdot CHX \cdot CHX \cdot R$. In the first place, numerous substances give deeply colored addition products which gradually change to the normal dihalides. A very instructive example of this reaction is offered by 1,1-dianisylethylene, $CH_2 : C : (C_6H_4OCH_3)_2$, which yields a dark violet primary product when treated with bromine vapor. The theory of this phenomenon is discussed by Pfeiffer and Schneider.[3]

Further differences in the behavior of the halogens are as follows: Some unsaturated substances such as diphenylmaleic anhydride and dimethylmaleic anhydride,[4] add chlorine but not bromine or iodine. Alicyclic compounds, like cyclopropane, react with chlorine to form substitution products, but with bromine the ring is opened and addition takes place:

$$CH_2 \diagup \diagdown CH_2 \text{———} CH_2 + Br_2 \longrightarrow CH_2Br \cdot CH_2 \cdot CH_2Br$$

[2] Terry, Eichelberger, and Francis, *J. Am. Chem. Soc.*, **47**, 1067, 2340 (1925).
[3] Pfeiffer and Schneider, *J. prakt. Chem.*, **129**, 129 (1931).
[4] R. Fittig, *Ann.*, **188**, 59 (1877).

When halogen is added to systems of the type, $R' \cdot CH:CH \cdot R''$, usually mixtures of diastereomers are formed, which can be separated by fractional crystallization. This occurs when the important dibromides of cinnamic acid and of benzalacetophenone are prepared. Subsequent reactions of the diastereomers take place more or less readily (removal of halogen) or stereoisomers are formed (removal of hydrogen halide); see page 316.

The bromides are important for laboratory work mainly because of their ease of preparation and handling. The following general statements can be made concerning the addition of bromine:

In most cases the reactions are run in a solvent, such as carbon bisulfide or chloroform, both of which are excellent because of their solvent power and inert character. Carbon tetrachloride is often useful but is limited by its low solvent power. Ether can be used at low temperatures. Often it is not necessary to dissolve the substance completely if it is well dispersed mechanically. The dibromides are frequently soluble in ether; thus, after addition of bromine the unsaturated substance passes into solution before the dibromide appears as crystals.

Ultraviolet light speeds up the addition. Sunlight, daylight, or a strong incandescent lamp can be used, depending on the convenience. Heating should be avoided, because it promotes substitution and the removal of hydrogen bromide. Hydrogen bromide is sometimes split out by warming or by recrystallizing from certain solvents. An example of the latter is dibromoanisalacetophenone, which, when boiled in methanol, undergoes immediate decomposition according to the equation, $CH_3O \cdot C_6H_4 \cdot CHBr \cdot CHBr \cdot CO \cdot C_6H_5 + CH_3OH \rightarrow CH_3O \cdot C_6H_4 \cdot CH(OCH_3) \cdot CHBr \cdot CO \cdot C_6H_5 + HBr$; see Pond and Shoffstall.[5] The reaction does not consist of the replacement of bromine by methoxyl as one might surmise from the reaction equation, but of the removal of hydrogen bromide and subsequent addition of methanol. Depending on the conditions, hydrogen bromide appears either as such (aqueous methanol) or as methyl bromide. Dibromoanisalacetophenone can be recrystallized from benzene without decomposition.

A few examples are as follows:

1. The method of Grün and Janko [6] for the separation of fatty acids from linseed oil is as follows: The oil, or the mixture of the free acids obtained by saponifying the oil, is made into the methyl or ethyl esters. The ester mixture (15 to 20 g.) is dissolved in 5 times its volume of chloroform, carbon tetrachloride, or petroleum ether and cooled in ice water. Bromine is added dropwise with shaking until the color of the bromine remains, or to a slight excess, as determined by the iodine value of the mixture. If the

[5] Pond and Shoffstall, *J. Am. Chem. Soc.*, **22**, 658 (1900).
[6] A. Grün, *Analyse der Fette und Wachse.* Vol. I, Springer, Berlin, 1925, p. 223.

ester mixture is dark colored, it can be tested with potassium iodide-starch paper. The solution is allowed to stand for 30 minutes, the solvent removed by distillation, and the residue fractionated in a vacuum. The saturated fatty acid esters distil at a much lower temperature than the dibromides of the unsaturated acids. Most important of all, the dibromides remain unchanged at the boiling point of the bromine-free esters; e.g., ethyl stearate boils at 172°C. at 2 mm. but dibromoöleic acid undergoes decomposition above 190°C. It is advantageous to distil in an atmosphere of carbon dioxide.

In the case of mixtures such as the linseed oil fatty acids, which contain trienes, the hexabromides have to be removed before the distillation, because they are decomposed at the boiling temperature of the saturated esters. To accomplish this the addition of bromine is performed at −5° to −10°C. with the free fatty acids dissolved in ether. The precipitate which contains the main portion of the hexabromides is filtered off. Then the mixture of the acids remaining after the removal of the ether by distillation is esterified and distilled in a vacuum as above.

The residues from the distillation are dissolved in ether, if necessary, washed with a solution of sodium bicarbonate and water, and then dried. To reconvert the dibromides into the unsaturated esters, 10 g. portions of each are boiled with 15 cc. of ethanol and 10 g. of zinc, while 15 cc. of 5 N alcoholic hydrochloric acid are run in during 20 minutes. The mixture is boiled a total of 1 hour. The products are isolated according to the usual method. Sometimes the removal of the bromine has to be repeated. See also page 315.

2. Dibromocinnamic acid. The high melting dibromide is obtained as the main product from equimolecular amounts of bromine and ordinary *trans*-cinnamic acid. Powdered cinnamic acid is covered with 6 times its weight of ether, cooled in ice, and treated with 1 mole of bromine. After some time, the ether is partially evaporated, the mixture filtered, and the crystals dried; m.p. 203° to 204°C. with decomposition. The low melting dibromide "dibromoallocinnamic acid" is prepared by Liebermann[7] as follows: *Cis*-cinnamic acid (8 g.) dissolved in 64 g. of carbon bisulfide is added with good stirring in the dark during 2 hours to a solution of 24 g. of bromine in 50 g. of carbon bisulfide. The ordinary dibromocinnamic acid, which is only slightly soluble in carbon bisulfide, is filtered off and the low melting dibromide recovered from the solution; m.p. 91° to 93°C. Both dibromocinnamic acids have been separated into their optical isomers by means of the cinchonine salts.

3. Directions for the preparation of dibromobenzalacetophenone can be found in *Organic Syntheses*.[8]

The addition of bromine to the double bond and the subsequent removal of hydrogen bromide played a large rôle in the synthesis of unsaturated cyclic ring systems. Willstätter's[9] synthesis of tropilidene is of interest because of its importance in determining structure and in the synthesis of tropine systems. Experimental details are found on page 324.

Dibromocycloheptene was prepared in chloroform solution by adding the calculated amount of bromine with stirring and cooling; the chloroform was evaporated in a vacuum from the reaction mixture and the residue used without further purification.

[7] Liebermann, *Ber.*, 27, 2039 (1894).
[8] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 205.
[9] R. Willstätter, *Ann.*, 317, 204 (1901).

Cycloheptadiene was prepared from dibromocycloheptene by means of dimethylaniline. This, on being treated with 1 mole of bromine, yielded 1,4-dibromocycloheptene by addition to the 1,4 position as follows: A solution of 10 g. of cycloheptadiene in 100 g. of alcohol-free, dry chloroform was cooled to −5°C. Precautions were taken to exclude moisture while a solution of 17 g. of dry bromide in 68 g. of chloroform was added dropwise with stirring during 90 minutes. The bromine was used up instantaneously and only traces of hydrogen bromide appeared. The chloroform was removed *in vacuo* and the residue fractionated. After several distillations, the main fraction distilled at 123°C. at 15 mm. pressure. The yield amounted to 22 g. (85%) after the first distillation.

Dibromocholesterol is readily prepared according to Windaus [10] as follows:

A mixture of 25 g. of bromine and 250 cc. of glacial acetic acid is added to a solution of 50 g. of cholesterol in 500 cc. of ether. After several minutes, the mixture solidifies to a mass of crystals. These are filtered off and washed with acetic acid and water, giving a pure product.

The bromine addition products of easily decomposed, unsaturated hydrocarbons may still be used advantageously in the laboratory to keep available small amounts of such compounds as butadiene. Therefore, Thiele's [11] directions are given for the preparation of tetrabromobutadiene.

Butadiene is prepared by decomposing amyl alcohol vapors according to a method of Caventou.[12] According to Thiele 350 to 400 g. of amyl alcohol are distilled within 1 hour through an iron pipe of 40 mm. inside diameter, the middle section of which is heated to moderate red heat for a distance of 40 cm. The vapors formed are passed through a cooled flask, a reflux condenser, a flask cooled in ice, and finally into an adsorption bottle containing pure liquid bromine. The distillation has to be regulated so that neither carbon dust nor tar appears in the condenser. In such a case either the pyrolysis temperature is too high or the speed of distillation too low. If the iron tube should get plugged, the carbon formed may easily be pushed out without removal of the pipe from the oven, although this seldom occurs. As the absorption progresses, the volume in the absorption apparatus increases and the color changes; at the end of the reaction the color of the bromide mixture is light brown, provided the reaction is run carefully; otherwise the color is darker. The mixture is distilled in a vacuum at 20 mm., the fraction boiling up to 100°C. being separated. When the mixture cools, the residue solidifies and tetrabromobutadiene separates. If the crystals are badly contaminated with a brown oil, they are boiled with alcohol, decanted while hot from the tarry residue, and the tetrabromobutadiene allowed to crystallize. This procedure is repeated once more and the tetrabromobutadiene is steam-distilled, giving a snow-white product. If the tetrabromide is but slightly contaminated, a case which sometimes occurs, it may be steam-distilled directly after having been washed with petroleum ether.

Residues and mother liquors are concentrated and added drop by drop to a refluxed mixture of zinc dust and alcohol. The escaping gases are partially condensed in a freezing mixture and the remainder is passed through a solution of bromine in chloroform.

[10] A. Windaus, *Ber.*, **39**, 518 (1906).
[11] J. Thiele, *Ann.*, **308**, 337 (1899).
[12] Caventou, *Ann.*, **127**, 93 (1863).

Finally, the freezing mixture is removed and the condensate, boiling up to 10°C., is distilled into the solution of bromine in chloroform. After the chloroform and the excess is evaporated off, the residue is treated with petroleum ether, thus yielding another considerable amount of tetrabromide. The total yield is 3 to 3.5% of the bromine used, but this is obtained without special apparatus and with relatively cheap starting material.

For the addition of halogen to aromatic systems see pages 59 and 75.

2. Addition to Acetylenic Bonds

The addition proceeds in two steps, forming 1,2-dihalogen ethylenes first and then 1,1,2,2-tetrahalogen ethanes: $R \cdot C : C \cdot R + X_2 \rightarrow R \cdot CX : CX \cdot R + X_2 \rightarrow R \cdot CX_2 \cdot CX_2 \cdot R$. One reason why the reaction is of preparational value is that the metastable dihalogen ethylenes are frequently obtained in the first step analogous to the addition of hydrogen to the acetylenic bond. If it is not this specific modification which is desired, it may be more advantageous to prepare the ethylene derivative by removing the halogen from the tetrahalogen ethane.

There is no useful description of a laboratory method for the preparation of acetylene dichloride (sym-dichloroethylene) from acetylene and chlorine, despite the fact that the substance is manufactured commercially in large quantities.

An old method of Berthelot and Jungfleisch [13] starts with the addition product of antimony pentachloride and acetylene. To prepare this, dry acetylene is passed over antimony pentachloride and cooled sufficiently to avoid overheating yet without allowing it to solidify too much. As soon as no more acetylene is absorbed, the mixture is allowed to cool, and the excess antimony pentachloride is removed by evaporating in a stream of carbon dioxide. The addition compound is decomposed into antimony trichloride and sym-dichloroethylene, by careful heating.

Later Sabanejev [14] was not able to reproduce the observation of Berthelot and Jungfleisch. He found that acetylene is absorbed very slowly by antimony pentachloride and that despite all precaution sudden explosions occur. No acetylene dichloride was found as reaction product but instead tetrachloroethane. Data in the patent literature indicate that mixtures of acetylene dichloride and acetylene tetrachloride are obtained in this manner, but no good laboratory method could be developed. If one desires to prepare acetylene dichloride in the laboratory, it is more convenient to start from acetylene tetrachloride and remove 2 chlorine atoms.

Recently Peters and Neumann [15] found that the reaction of antimony pentachloride and acetylene proceeds in a reproducible manner when carried out under reduced pressure in a quartz flask illuminated with ultraviolet light. This cannot be made the basis of a simple laboratory method.

[13] Berthelot and Jungfleisch, *Compt. rend.*, 69, 542 (1869); *Ann., Supplement*, 7, 252 (1870).
[14] Sabanejev, *Ann.*, 216, 262 (1883).
[15] K. Peters and L. Neumann, *Angew. Chem.*, 45, 261 (1932).

The technical *sym*-dichloroethylene on the market is always a mixture of the two stereoisomers.

Bromine can be added to acetylene with comparative ease. According to Sabanejev [16] ethanol is saturated at room temperature with acetylene and the theoretical amount of bromine (6 volumes), calculated from the solubility of acetylene in alcohol, is added. Then acetylene is added anew, followed by bromine, and this process repeated several times. Water is added, precipitating the acetylene dibromide as an oil which is washed with water and fractionated. Essentially two fractions are obtained, one boiling at 50° to 80°C., and the other at 106° to 115°C. The boiling point of the two stereoisomeric forms, when pure, is 112.5°C. and 108°C., respectively. In this case, as in the case of acetylene dichloride, it seems more advantageous to use acetylene tetrabromide for the laboratory preparation of the dibromide.

Finally, acetylene diiodide can readily be prepared from elemental iodine and acetylene. According to Biltz [17] 100 g. of powdered iodine are covered with 200 g. of absolute ethanol in a wide mouthed Erlenmeyer flask. The empty space is filled with acetylene gas, after which the flask is closed with a stopper equipped with a gas delivery tube running close to the surface of the alcohol. The tube is connected with an acetylene generator and left connected for several days. The solution in the flasks which already contains crystals of acetylene diiodide is diluted with water. The residual iodine is removed by washing with sodium hydroxide and water, after which the solid mass is filtered off and recrystallized from ethanol. The yield is 85 g., m.p. 73°C. Acetylene diiodide also exists in two modifications, one of which is solid, the other liquid.

The addition of halogen to substituted acetylenic compounds proceeds with the greatest ease in the first step. Phenylacetylene readily yields phenylacetylene dibromide when treated in the cold with the calculated amount of bromine in chloroform solution (Nef [18]). According to Nissen [19] phenylpropiolic acid adds chlorine in a cold chloroform solution, the first step being the formation of α,β-dichlorocinnamic acid of the form melting at 120° to 121°C.

B. Addition of Hydrogen Halide to Unsaturated Carbon Compounds

1. Addition to Ethylenic Bonds

The addition of hydrogen halides proceeds much more slowly than the addition of halogens. It is of little preparative importance, because the

[16] Sabanejev, *Ann.*, **178**, 116 (1875).
[17] H. Biltz, *Ber.*, **30**, 1207 (1897).
[18] U. Nef, *Ann.*, **308**, 273 (1899).
[19] C. Nissen, *Ber.*, **25**, 2664 (1892).

halides concerned can usually be prepared by a more convenient method. Yet it is the best method for the preparation of β-halogenated carboxylic acids and ketones because, according to a general rule, the halogen takes the place more distant from the carbonyl group: $R \cdot CH : CH \cdot COOH + HX \rightarrow R \cdot CHX \cdot CH_2 \cdot COOH$.

Hydrogen iodide is the easiest to add, while hydrogen chloride is the most difficult. Often the reaction must be carried out at high pressure and temperature, and sealed tubes ("bomb" tubes) are required.

In general, terminal double bonds add halogen halides with greater difficulty than double bonds in the middle. This makes possible the separation of certain isomeric olefins: 2-hexene, $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH : CH \cdot CH_3$, adds hydrogen chloride from fuming hydrochloric acid at room temperature, leaving 1-hexene, $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH : CH_2$, intact; see Schorlemmer and Morgan.[20]

Markovnikov's [21] rule that the halogen of a hydrohalogen adds to the carbon atom which has the least hydrogen atoms corresponds entirely to the rule of Saytzev (see page 318) for the removal of hydrogen halide. If the double bond already carries a halogen atom, the entering halogen adds to the same carbon atom:

$$(CH_3)_2 : C : CH_2 + HBr \longrightarrow (CH_3)_2 : CBr \cdot CH_3$$
$$CH_2 : CHBr + HBr \longrightarrow CH_3 \cdot CHBr_2$$
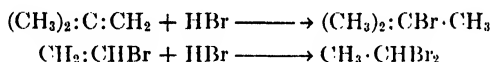
Of the two isomers, $R \cdot CBr : CH_2$ and $R \cdot CH \cdot CHBr$, the first always adds hydrogen halide much more readily than the latter, thus rendering possible the separation of mixtures in certain cases.

These rules are not without exception. The solvent often influences markedly the ratio of the reaction product. According to Michael [22] propylene adds hydrogen iodide to give but a small proportion of 1-iodopropane, the main product being 2-iodopropane, while in glacial acetic acid the formation of 1-iodopropane is greater. Erlenmeyer [23] and Reboul [24] have shown that the temperature also plays a part.

The β,γ-unsaturated acids behave like the acrylic acids in that the hydrogen is added farthest from the carboxyl group. The γ,δ-unsaturated acids add hydrogen halides in the opposite manner; that is, the halogen is added to the γ position. These generalizations are based on experiments performed with compounds of relatively short chain length; namely, with pentenoic acids. In the case of the 3-pentenoic acid, $CH_3 \cdot CH : CH \cdot CH_2 \cdot COOH \rightarrow CH_3 \cdot CHI \cdot CH_2 \cdot CH_2 \cdot COOH$, the loca-

[20] Schorlemmer and Morgan, *Ann.*, **177**, 305 (1875).
[21] Markovnikov, *Ann.*, **153**, 256 (1870).
[22] Michael, *J. prakt. Chem.*, **60**, 445 (1899).
[23] Erlenmeyer, *Ann.*, **197**, 180 (1879).
[24] Reboul, *Ann. chim. phys.*, **14**, 487 (1878).

tion of the halogen is explained by the effect of the carboxyl group. The reversal of addition in the formation of $CH_3 \cdot CHI \cdot CH_2 \cdot CH_2 \cdot COOH$ from the 4-pentenoic acid, $CH_2:CH \cdot CH_2 \cdot CH_2 \cdot COOH$, can be explained by the fact that the vinyl group at the end, as mentioned above, adds iodine at the carbon atom with least hydrogen. The reversal is not caused by the carboxyl group.

Complications enter in the reaction of unsaturated ketones with hydrobromic acid. Vorländer and coworkers [25] found that colored isomers of the normal addition products, as well as complexes containing several hydrogen halide molecules, were formed.

The addition of hydrogen halide has rarely become of preparational importance; however, an important use is found in the synthesis of tropine according to Willstätter.[26] In this synthesis bromocycloheptadiene was prepared by treating cycloheptatriene with hydrobromic acid according to the following equation.

$$
\begin{array}{ccc}
CH_2-CH=CH & & CH_2-CHBr \cdot CH_2 \\
| \qquad \qquad \quad \diagdown & & | \qquad \qquad \qquad \diagdown \\
| \qquad \qquad \quad CH + HBr \longrightarrow & | \qquad \qquad \qquad CH \\
CH=CH-CH \diagup & & CH=CH-CH \diagup
\end{array}
$$
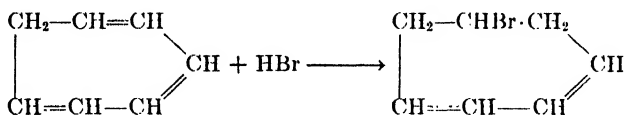
Willstätter [27] gives the following directions: To 20 g. of well cooled cycloheptatriene are rapidly added 45 g. of 40% hydrogen bromide in glacial acetic acid. At first, no reaction occurs and both layers stay separated even after being well shaken. After 10 minutes on the shaking machine the mixture warms to a little above room temperature and becomes homogeneous. When cooled below room temperature it separates into two layers. The homogeneous solution is allowed to stand at room temperature for 2 hours, after which it no longer separates into two layers on cooling. Ice is added and the mixture is extracted with ether. The ether extract is washed with ice water several times, then with ice-cold, dilute sodium carbonate solution, and again with water. After drying over calcium chloride, the ether is removed by distillation in a vacuum. The air admitted through the capillary tube has to be dried. The residual, light yellow oil is fractionated in a vacuum. Two fractions are thus obtained, the lower boiling (74° to 75°C. at 8 to 9 mm.) monohydrobromide of cycloheptadiene and the higher boiling (125° to 126°C. at 15 mm.) dihydrobromide. The yield of monohydrobromide, that is bromocycloheptadiene, amounts to about 25 g. (65%).

In the terpene series the addition of hydrogen halides to double bonds often proceeds with rearrangement of the ring system. As an example the reaction of camphene with hydrogen chloride will be described in detail. Meerwein and van Emster [28] investigated this reaction and found the conditions under which the addition of hydrogen chloride takes place without noticeable rearrangement.

[25] D. Vorländer et al., Ber., 37, 1644, 3364 (1904); Ann., 341, 1 (1905).
[26] R. Willstätter, Ann., 317, 267 (1901).
[27] R. Willstätter, Ann., 317, 263 (1901).
[28] H. Meerwein and K. van Emster, Ber., 53, 1815 (1920); 55, 2500 (1922).

As starting material for the preparation of camphene hydrochloride [29] camphene obtained from isoborneol by heating with 25% sulfuric acid is used. The melting point of the camphene is 48.5° to 50.5°C. Since impurities having catalytic action must be painstakingly avoided, a clean all-glass apparatus with ground joints is required. For filtration a funnel with a sintered plate is best. Moisture from the air has to be excluded carefully. The camphene [30] is dissolved in half its volume of dry ether and about 1 mole of hydrogen chloride is passed into the mixture with good cooling. After a short time snow-white, fern-like crystals separate, the amount of which is increased greatly by removing part of the ether in a current of dried air. After the material is filtered and dried over potassium hydroxide, about 70% of a chlorohydrate is obtained with a melting point of 126° to 127°C. It is never possible to obtain the camphene hydrochloride completely free from isobornyl chloride, as Meerwein and van Emster have found that even the best products contain 9 to 10% of it. Since the chlorine of the camphene hydrochloride bound to the tertiary carbon atom is much more reactive than the secondary chlorine in isobornyl chloride, the content of camphene hydrochloride can easily be determined by titration with alcoholic potassium hydroxide.

The preparation described above is not the only one which might be given. Meerwein and van Emster [31] have found that pinene treated in the cold with hydrogen chloride yields the true pinene hydrochloride containing a tertiary chlorine atom; however, only bornyl chloride is formed at higher temperatures. Below 0°C. pinene hydrochloride spontaneously changes to bornyl chloride.

2. Addition to Acetylenic Bonds

The addition of hydrogen halides to the acetylenic bond can proceed in two steps exactly as the addition of halogen. It was for a long time without special importance, as the reaction products of the first step, *e.g.* vinyl chloride and vinyl bromide, could be prepared much more conveniently by removing hydrogen halide from ethylene dichloride and ethylene dibromide respectively. The addition products of the second step, ethylidene chloride, bromide, and iodide, either have little importance or, like ethylidene chloride, may be obtained more conveniently by chlorination of ethyl chloride. Recently the reaction has become of the greatest industrial importance. The reaction of hydrogen chloride with vinyl acetylene to produce 2-chlorobutadiene is shown by the equation

$$CH_2{:}CH{\cdot}C{:}CH + HCl \xrightarrow{\mathrm{Cu_2Cl_2}} CH_2{:}CH{\cdot}CCl{:}CH_2$$
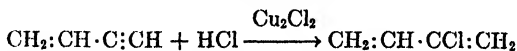
2-Chlorobutadiene, the so called chloroprene, polymerizes to give a synthetic rubber called "neoprene." Laboratory methods for the preparation of 2-chlorobutadiene have not been published. For further illustrations of new uses of this reaction in the chemistry of acetylene see Nicodemus.[32]

[29] H. Meerwein and K. van Emster, *Ber.*, **55**, 2525 (1922).
[30] H. Meerwein and K. van Emster, *Ber.*, **53**, 1821 (1920).
[31] H. Meerwein and K. van Emster, *Ber.*, **55**, 2521 (1922).
[32] O. Nicodemus, *Angew. Chem.*, **49**, 787 (1936).

C. Addition of Halogen to Radicals

Radicals of the triphenylmethyl type react instantaneously with halogen. Gomberg[33] has found that chlorine and bromine even at $-10°C$. effect both addition and substitution, making it impossible to prepare triphenylmethyl chloride and triphenylmethyl bromide by this method. However, the addition of iodine to triphenylmethyl in carbon disulfide solution at $0°C$. goes on readily and quantitatively. The amount of iodine used corresponds directly to the amount of hexaphenylethane or triphenylmethyl employed. In order to isolate the triphenylmethyl iodide the reaction must be carried out in dry carbon dioxide. By-products are filtered off and the product isolated by adding petroleum ether and cooling the mixture with ice. As soon as a few crystals have appeared, the solution is decanted into another flask, cooled again, and the crystallization allowed to become complete. The crystals are purified by dissolving in carbon disulfide and precipitating with petroleum ether. The melting point of the rather unstable triphenylmethyl iodide is $135°C$. (with decomposition).

Later, Gomberg[34] used the addition of iodine as the basis of an approximate method for titration of triarylmethyls.

D. Addition of Hydrogen Hypohalides to Ethylenic Bonds

Halohydrins are prepared by the addition of hypohalous acids to unsaturated substances, $R \cdot CH:CH \cdot R + HOX \rightarrow R \cdot CHOH \cdot CHX \cdot R$, or from polyhydroxy compounds by partial substitution of hydroxyl with halogen; see page 99.

They are important as starting materials for the preparation of reactive ethylene oxides or oxido compounds. Aqueous hypochlorous acid or chlorine monoxide is prepared according to one of the following methods.

1. According to Markovnikov,[35] freshly precipitated yellow mercuric oxide (160 g. from 200 g. of mercuric chloride) is suspended in 1500 cc. of water, and a fast stream of chlorine is admitted while the mixture is cooled with ice and stirred. After 60 g. of chlorine have been added, the reaction vessel is allowed to stand in the cold overnight, during which time the mercuric oxide is dissolved. The solution is distilled and the first 800 cc. are collected over mercuric oxide. The hypochlorous acid content is determined by titration.

2. According to Wohl,[36] 50 g. of sodium bicarbonate are covered with 600 cc. of ice water, and chlorine is added while the material is cooled with ice until a sample no longer gives a precipitate on being heated with a solution of barium chloride. The reac-

[33] Gomberg, *Ber.*, **33**, 3158 (1900).
[34] Gomberg, *Ber.*, **35**, 1826 (1902).
[35] Markovnikov, *Ann.*, **336**, 314 (1904).
[36] Wohl, *Ber.*, **40**, 94 (1907).

tion proceeds according to the equation, $NaHCO_3 + Cl_2 \rightarrow NaCl + HOCl + CO_2$, and the resulting solution contains only sodium chloride and hypochlorous acid. This may be used immediately for most purposes.

3. Bamberger [37] suggests a third method.

Addition to the ethylenic bond takes place when the material stands in the cold with a 2 to 3% solution of hypochlorous acid. When difficultly soluble unsaturated compounds are used, stirring or shaking is necessary. Gaseous reaction components are run into the reaction vessel.

In the addition of a hypohalous acid the halogen atom joins the carbon having the most hydrogen and the hydroxyl group joins the carbon atom with the least hydrogen: $CH_3 \cdot CH:CH_2 + HOCl \rightarrow CH_3 \cdot CHOH \cdot CH_2Cl$; thus the addition is reversed to the addition of hydrogen halides according to the rule of Markovnikov (see page 66).

Hypobromous and hypoiodous acids react in the same manner. Thus, Brunel [38] obtained cyclohexene iodohydrin as follows:

40 g. of cyclohexene dissolved in 150 cc. of ether are shaken in the cold with a paste made from 55 g. of mercuric oxide and 7 cc. of water, while 124 g. of iodine are added in small portions. As soon as the iodine color is almost gone, the filtered solution is shaken, first with potassium iodide solution, then with sodium bisulfite solution. The ether solution is dried with sodium sulfate, the ether evaporated, and the residue crystallized from petroleum ether.

Another example is the preparation of cyclohexene chlorohydrin, α-chlorocyclohexanol, which is found in *Organic Syntheses*.[39]

Erlenmeyer and Lipp [40] give the preparation of phenylchlorolactic acid as follows:

An excess of chlorine is passed, at 4°C., into a solution of 286 g. of sodium carbonate (hydrate) in 2 liters of water. As soon as chlorine is no longer absorbed, the solution of hypochlorous acid is slowly added with stirring to a cooled (4°C.) solution of 150 g. of cinnamic acid and 70 g. of potassium carbonate in 2 liters of water. Carbon dioxide is evolved and a little chlorostyrene always separates. After 30 minutes, the excess hypochlorous acid is decomposed with sulfur dioxide and 210 cc. of concentrated hydrochloric acid are added. The solution is allowed to stand 24 hours and the chlorostyrene and cinnamic acid are filtered off. The filtrate is concentrated until it turns cloudy and the phenylchlorolactic acid separates as an oil which solidifies on scratching. The crystals are removed by filtration and the filtrate again concentrated until sodium chloride starts to crystallize. The rest of the phenylchlorolactic acid is extracted with ether. The total yield amounts to about nine-tenths of the weight of the cinnamic acid used.

---

[37] Bamberger, *Ann.*, **288**, 81 (1895).
[38] Brunel, *Compt. rend.*, **135**, 1055 (1902).
[39] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 158.
[40] Erlenmeyer and Lipp, *Ann.*, **219**, 185 (1883).

II. BY SUBSTITUTION

A. Replacement of Hydrogen by Halogen

General Aspects

The direct reaction of halogen with organic compounds does not necessarily yield uniform products, especially if several hydrogen atoms have an equal or similar substitution potential. Because the reaction of halogen with hydrocarbons from petroleum, from coal and wood distillation, and from coal hydrogenation is the first step in making these compounds more reactive, the systematic study of halogen substitution is of especial importance.

Fundamental investigations of this question were made long ago. It might be expected that a very large excess of organic material would produce more uniform reaction products, but according to Michael [41] this is not the case. Hexane, even with only 50% of the amount of bromine necessary for monosubstitution, yields not only monobromohexane, but also a considerable amount of higher brominated compounds.

Another example is the chlorination of toluene. It is easy to influence the reaction so that substitution can be made to take place either in the nucleus or in the side chain. When substitution is made in the nucleus, a mixture of two isomeric chlorotoluenes is obtained which cannot be separated in a practical manner. If the substitution is directed to the side chain, the first chlorination product, benzyl chloride, can be easily isolated. On further chlorination, benzal chloride and trichlorotoluene are always formed simultaneously, though only the amount of chlorine theoretically necessary for the next step is used. Markwald [42] states that 25% of the chlorine used is taken up in the formation of the trichloro compound. Thus the molecular ratio of benzal chloride to benzotrichloride is about 2 : 1. There is a possibility of separating the mixture of benzal chloride and benzotrichloride by fractional distillation though this is not easy to perform because of their boiling points (205° and 214°C.). However, the products of hydrolysis, namely benzaldehyde and benzoic acid, are of so different a chemical nature that their separation can be effected very readily. The manufacture of benzaldehyde with benzoic acid as a by-product is quite feasible. It might well be advantageous to prepare small amounts of pure benzal chloride from benzaldehyde. To prepare large amounts, fractionation of the commercial chlorination mixture seems to be the more economical method.

Another method which is not practical in this particular case, but which is used in similar cases, leads first to production of the trichloride,

[41] A. Michael, *Ber.*, **34**, 4037 (1901).
[42] Markwald, German Patent, 142,939.

then back to the dichloride by replacing a halogen atom with hydrogen. Whether or not this is practical depends mainly on the following condition; namely, the threshold of the step from dichloride to monochloride must be much higher when hydrogen is substituted for halogen than the threshold of the step from di- to trichloride when halogen is initially substituted for hydrogen. It is indeed possible that a mixture is obtained in this way, but this mixture is free of trichloride, containing only mono- and dichloride. These two can always be separated by distillation better than di- and trichloride (benzyl chloride 179°C., benzal chloride 205°C., benzotrichloride 214°C.). The matter assumes a different aspect whenever the manufacture of the higher substituted products is cheaper and more convenient. Such a case exists with methylene chloride-chloroform and methylene bromide-bromoform. Here it is quite feasible to prepare the methylene bromide from bromoform and the methylene chloride from chloroform (see above).

Finally, the subsequent exchange of one halogen for another may be better than the direct substitution of hydrogen or of other groups.

In view of all these facts it is evident that direct halogenation is of preparational importance in the laboratory only if certain hydrogen atoms are very easily substituted. Thus the halides of aliphatic hydrocarbons may in general be prepared more conveniently by the addition to olefins or by the exchange of the hydroxyl or carbonyl groups in alcohols, aldehydes, and ketones. However, under certain conditions, tertiary hydrogen atoms, and in a few cases secondary ones, are so reactive that their direct substitution may serve the purpose. Older systematic investigations on the chlorination and bromination of normal aliphatic hydrocarbons and on the regularities observed therein were carried out by Herzfelder [43] and by Kronstein. [44]

The more recent investigations of Wertyporoch [45] on the direct chlorination of paraffins partly contradict the older observations. Wertyporoch found earlier [46] during the chlorination of toluene derivatives that antimony pentachloride in small amounts (0.01 mole) catalyzes the formation of mono-substituted products, while iodine causes the formation of products with more halogen substituents. Furthermore, he gives data on the differences encountered in dry and wet chlorination. Recently it has been shown that antimony pentachloride slows down the chlorination; the best results were obtained with wet chlorination.

More important for laboratory practice is the direct halogenation of aromatic hydrocarbons in the nucleus or in the side chain. Here

[43] Herzfelder, *Ber.*, 26, 2432 (1893); 27, 489 (1894).
[44] H. Kronstein, *Ber.*, 54, 1 (1921).
[45] P. Wertyporoch, *Ber.*, 66, 732 (1933).
[46] P. Wertyporoch, *Ann.*, 493, 153 (1932).

regularities are found about which more will be said below (page 206). Chlorine and bromine are generally introduced without difficulty, but occasionally it is necessary to employ carrier substances. Iodine effects substitution only under very special conditions; that is, if the hydrogen iodide formed during the reaction is constantly removed by oxidation or if it is bound in some other way. Fluorine in the elementary state generally causes destruction of organic substances; thus fluorine derivatives can with few exceptions be obtained only by indirect methods. Besides the halogens proper, under certain conditions compounds containing halogens are used; e.g., phosphorus pentachloride, antimony pentachloride, and sulfuryl chloride.

Furthermore, the reaction with halogens occurs with especial ease in the case of the hydrogen atoms which are adjacent to certain groups, above all the carbonyl and carboxyl groups. In such a case, as the halogenation progresses, both hydrogen atoms are substituted if 2 are available. Thus propionic acid yields 2,2-dibromopropionic acid and butyric acid yields 2,2-dibromobutyric acid, and only after this occurs does it sometimes happen that still more hydrogen atoms are attacked. Ketones are halogenated quite easily; an adjacent CH_2 group has the preference over a CH_3 group. Therefore, methylethyl ketone with elementary chlorine yields mainly 3-chlorobutanone, $CH_3 \cdot CO \cdot CHCl \cdot CH_3$. 1-Chlorobutanone, $CH_2Cl \cdot CO \cdot C_2H_5$, is obtained in a smaller amount. With a moderate reaction, e.g. by diluting chlorine with carbon dioxide and cooling, the former may be obtained almost exclusively (see Korschun [47]). The higher homologues react in a similar manner.

Aldehydes, like ketones, may be substituted, but they also are partially oxidized; aromatic aldehydes, such as benzaldehyde, very readily exchange the aldehyde hydrogen for halogen, forming acid chlorides.

Alcohols also are easily oxidized or dehydrogenated and then further substituted.

The peculiar differences observed by Herzfelder (see page 72) for the behavior of chlorine and bromine apply only to the halogenation of hydrocarbons. When monochlorides or monobromides are treated with chlorine or bromine, the next halogen atom is always added to an unsubstituted carbon atom and prefers the position neighboring to an existing one. The subsequent bromination proceeds in the same direction; each carbon atom which can be substituted and carries hydrogen takes up a bromine atom. Thus, from propane 1,2,3-tribromopropane is obtained. However, when more than 1 chlorine atom is already substituted, it can be noted quite frequently that subsequent chlorination proceeds at the carbon atoms which already have been substituted by

[47] Korschun, Ber., 38, 1128 (1905).

chlorine; thus 1,2-dichloropropane yields 1,1,2-trichloropropane. But these observations, while theoretically significant, are hardly of any preparative importance.

The ease with which the hydrogen atoms of carboxylic acids adjacent to the carboxyl group can be substituted is still greater than in the case of malonic acids. The synthesis of higher molecular carboxylic acids is accomplished frequently through the malonic acid step: $R \cdot CH_2 X +$ $CHNa(COOC_2H_5)_2 \rightarrow NaX + R \cdot CH_2 \cdot CH(COOC_2H_5)_2$; therefore, under certain conditions, it is practical, if α-halogenated acids are to be prepared, to brominate the substituted malonic acid and to split off carbon dioxide from the bromomalonic acid: $R \cdot CH_2 \cdot CBr(COOH)_2 \rightarrow$ $R \cdot CH_2 \cdot CHBr \cdot COOH + CO_2$.

Halogen Carriers

The question of the effectiveness of carrier substances for direct halogenation is apparently completely clarified. They are directly effective only if they find systems capable of substitution, as in the case of nuclear substitutions. The halogenation of side chains, on the other hand, is influenced by the carriers as little as is the halogenation of purely aliphatic chains.

Chlorine carriers are metal salts, like iron and antimony or iodine chlorides.

Different from this formulation of reaction is that which is presumed in the direct chlorination of carboxylic acids. If phosphorus, phosphorus trichloride, or pentachloride is added, carboxylic acid chlorides are formed first, though in small amounts, and can be substituted much more readily than the free carboxylic acids. The chlorinated carboxylic acid chlorides thus formed are not further halogenated but are changed with an excess of carboxylic acid to acid anhydrides. The anhydrides in turn are further chlorinated and finally hydrolyzed to the chlorinated carboxylic acids; or, with the same end effect, the carboxylic acid anhydride is chlorinated and the chlorinated anhydride is decomposed, because it can be hydrolyzed more readily. In any case the reaction does not involve the free carboxylic acid itself.

The typical bromine carriers are the same substances as those used for chlorination.

1. Iron and Iron Salts, Especially for Nuclear Substitutions in Aromatic Compounds— m-Bromonitrobenzene can be prepared free of chlorine, according to Scheufelen,[48] in a sealed tube at 100°C. from 10 g. of nitrobenzene, 2 g. of ferric chloride, and 4.3 cc. of bromine.

*2. Iodine—*Traces of iodine readily start the bromination of benzene by means of iron as a carrier; the bromination occasionally starts only after some time and then very violently.

[48] A. Scheufelen, *Ann.*, **231**, 164 (1885).

3. *Sulfur*—Sulfur is used for the preparation of monobromoacetic acid in boiling glacial acetic acid (5% sulfur) with a little more than the theoretical amount of bromine.

4. *Aluminum, Aluminum Chloride, Aluminum Bromide*—According to Blümlein [49] 1 g. of aluminum powder is added slowly to 150 g. of bromine, in which it dissolves with ignition; the mixture is then allowed to cool.

Temperature and Light

Temperature rise, as is true in any reaction, speeds up the substitution in the nucleus as well as in the side chains, but exposure to light seems to have an especially favorable effect on the substitution in the side chain. In the nucleus, light favors the addition.

Combination of Influences

1. Benzene. In the light, when cold as well as when hot, and in the presence of carriers, chlorine yields stereoisomeric 1,2,3,4,5,6-hexachloro-cyclohexanes in varying amounts; see Matthews.[50] In the presence of iodine, ferric chloride, and antimony chloride chlorobenzene, *p*-dichloro-benzene, and a little *o*-dichlorobenzene are formed, then 1,2,4-trichloro-benzene, 1,2,4,5-tetrachlorobenzene, penta-, and finally hexachloroben-zene; see for instance Jungfleisch,[51] Page,[52] and Willgerodt.[53]

2. Toluene. If carriers are absent, a pure addition leading to hexa-chloromethylcyclohexane does not occur. With an excess of chlorine, octachloromethylcyclohexane, $C_6H_5Cl_6 \cdot CHCl_2$, is formed.[54] When chlor-ine is passed into boiling toluene, benzyl chloride only is formed. This occurs even at room temperature and in sunlight. In the presence of carriers, *p*-chlorotoluene, *o*-chlorotoluene, 2,3- and 2,4-dichlorotoluene, 2,3,4- and 2,4,5-trichlorotoluene, and finally tetrachlorotoluenes and pentachlorotoluene are obtained simultaneously.

3. Naphthalene. The behavior of naphthalene when it is halogenated differs fundamentally from that of the benzene hydrocarbons. While the latter always add halogens up to the cyclohexane step, naphthalene with-out a carrier readily and simultaneously yields naphthalene dichloride, $C_{10}H_8Cl_2$, and 1,2,3,4-naphthalene tetrachloride (see Fischer [55]), and furthermore mono- and dichloronaphthalene tetrachloride (see Faust and Saame [56] and Schwarzer [57]). When carriers are used at elevated temper-

[49] Blümlein, *Ber.*, **17**, 2486 (1884).
[50] Matthews, *J. Chem. Soc.*, **59**, 166 (1891).
[51] Jungfleisch, *Ann. chim. phys.*, **15**, 264 (1868).
[52] Page, *Ann.*, **225**, 200 (1884).
[53] Willgerodt, *J. prakt. Chem.*, **34**, 264 (1886); **35**, 391 (1887).
[54] Pieper, *Ann.*, **142**, 304 (1867).
[55] E. Fischer, *Ber.*, **11**, 735, 1411 (1878).
[56] Faust and Saame, *Ann.*, **160**, 67 (1871).
[57] Schwarzer, *Ber.*, **10**, 379 (1877).

atures, α-chloronaphthalene and finally perchloronaphthalene, $C_{10}Cl_8$, are obtained; see Berthelot and Jungfleisch [58] and Ruoff.[59]

4. Anthracene. The behavior of anthracene is similar to that of naphthalene. According to Perkin [60] an unstable 9,10-dichloride is obtained which with more chlorine changes first to 9,10-dichloroanthracene (see Graebe and Liebermann [61]) and then to 9,10-dichloroanthracene 1,2,3,4-tetrachloride (see Schwarzer [62] and Hammerschlag [63]). The perchlorination cannot be effected; only octachloroanthracenes are described, the uniformity of which is not certain. According to Ruoff [64] hexachlorobenzene and tetrachloromethane are finally obtained.

5. Phenanthrene. Similar reactions are shown by phenanthrene, a dichloride of which is not known, but rather a dichlorophenanthrene tetrachloride; furthermore, an octachlorophenanthrene is formed, but finally in this case also decomposition occurs with the formation of perchlorobenzene.

Preparational Details of Chlorinations and Brominations

Chlorine may be prepared from potassium dichromate and concentrated hydrochloric acid, or from potassium permanganate crystals with hydrochloric acid ($D = 1.16$); see also Wedekind.[65] Finally, the action of hydrochloric acid on bleaching powder in the Kipp apparatus gives a steady stream of chlorine.

Bromine can be dried by shaking with sulfuric acid, calcium bromide, or phosphorus pentoxide, but completely dry bromine does not always work as well as the ordinary bromine.

In some simple cases the substance to be halogenated may be treated with chlorine or bromine without any diluting solvent.

As solvents for chlorinations the following liquids may be used.

1. Carbon tetrachloride, absolutely stable.
2. Chloroform changes to carbon tetrachloride, especially in the light.
3. Glacial acetic acid, at low temperature, quite stable.
4. In addition, phosphorus oxychloride, nitrobenzene, sulfuric acid, water, and other aliphatic halides, *e.g.* tetrachloroethane, have been used.

For brominations there is a wider choice of solvents. All of the solvents mentioned for chlorine may be used for bromine; furthermore, additional solvents are as follows:

[58] Berthelot and Jungfleisch, *Ann. chim. phys.*, **15**, 331 (1868).
[59] Ruoff, *Ber.*, **9**, 1486 (1876).
[60] Perkin, *Bull. soc. chim.*, **27**, 465 (1877).
[61] Graebe and Liebermann, *Ann., Supplement*, **7**, 282 (1870).
[62] Schwarzer, *Ber.*, **10**, 377 (1877).
[63] Hammerschlag, *Ber.*, **19**, 1108 (1886).
[64] Ruoff, *Ber.*, **9**, 1483 (1876).
[65] Wedekind, *Angew. Chem.*, **22**, 580 (1909).

1. Carbon bisulfide, absolutely stable.

2. Diethyl ether, sufficiently stable when ice-cold.

3. Alcohol, not very stable.

4. Pyridine. When bromine is dissolved in pyridine, quite a considerable heating effect occurs (see Krause [66]); the bromine is presumably present in the form of a loose molecular compound. Bromine-pyridine solutions offer means of halogenations at a lower energy level and the substitution is effected quite mildly. In spite of this fact, however, substitutions which occur with elementary bromine only in the presence of catalysts still take place. Cross and Cohen,[67] for instance, have shown that 60 g. of bromobenzene are obtained in a vigorous reaction from a mixture of 50 g. of benzene, 120 g. of bromine, and a few drops of pyridine. Naphthalene reacts in a similar way.

5. A method used on many occasions, that is the generation of bromine directly at the place of reaction, has been taken over from analytical techniques. 1 mole of bromate is mixed with 5 moles of bromide and the mixture acidified, $HBrO_3 + 5HBr \rightarrow 3Br_2 + 3H_2O$, or bromate is added slowly to a solution containing hydrobromic acid.

Chlorine diluted with air or carbon dioxide may serve the purpose better than pure chlorine under certain conditions. Chlorine in "*status nascens*" is used sometimes on account of its more energetic action, a fact that does not necessarily mean that by this procedure especially highly substituted products are obtained.

According to Leulier [68] chlorinations as well as brominations may be carried out very well by generating chlorine in the nascent state in the reaction mixture from hydrochloric acid and hydrogen peroxide. Zinke [69] chlorinated perylene in a similar manner.

Excess bromine is removed from the reaction mixture either by a current of air, carbon dioxide, or steam, or chemically with sulfur dioxide or a sodium bisulfite solution, or by shaking with mercury (mercuric bromide is soluble in ether).

The hydrogen halides formed during the substitution cause no trouble in most cases. If the reaction is performed at higher temperatures, they escape in gaseous form and may be collected or otherwise disposed of. Occasionally, however, they have to be removed immediately from the reaction mixture; this can be done with calcium carbonate or powdered limestone.

Because it is not practical to weigh in advance the amount of chlorine to be used, for almost all reactions carried out with elementary chlorine either a predetermined amount of chlorine has to be generated chemically or the progress of the reaction has to be watched. The following methods are suitable for this purpose.

[66] E. Krause, *Ber.*, **56**, 1801 (1923).

[67] Cross and Cohen, *Proc. Chem. Soc.*, **24**, 15 (1908).

[68] A. Leulier, *Bull. soc. chim.*, **35**, 1325 (1924).

[69] A. Zinke, *Ber.*, **58**, 330 (1925).

1. The amount of chlorine is determined from the increase in weight of the reaction vessel.

2. When larger batches are made, it is practical to determine the loss in weight of the chlorine cylinder; the cylinder can be mounted on scales.

3. A change in property of the reaction mixture is used as indicator; *e.g.*, increasing boiling point, specific gravity, and others.

1. Chlorination and Bromination of Aromatic Hydrocarbons

Benzene.   To prepare chlorobenzene in the laboratory is hardly worth while.   By employing different carriers it may be obtained by direct chlorination.   Jungfleisch [70] recommends the use of iodine; Mouneyrat and Poret [71] employ aluminum chloride.   The catalyst for industrial use is ferric chloride.

Naphthalene.   The direct halogenation of naphthalene yields α substitution products mainly, but with chlorine such a large amount of β-chloronaphthalene is obtained as by-product, which is hard to remove, that α-naphthylamine is better used as a starting material.   β-Chloronaphthalene cannot be prepared at all by direct chlorination.

α-Bromonaphthalene may be prepared readily by direct bromination according to directions in *Organic Syntheses.*[72]   The older method of Blicke [73] therefore seems to be out of date.

It is notable that α-bromonaphthalene can be partially rearranged to β-bromonaphthalene by heating with aluminum chloride in carbon bisulfide; see Roux.[74]

Toluene.   The direct halogenation of toluene yields benzyl halide or a mixture of *o*- and *p*-halogenotoluene, depending on the conditions, but only *p*-bromotoluene can be prepared in this way.   As starting material for the other *o*- and *p*-halogenotoluenes the corresponding toluidines (see page 114) are used; for the preparation of *m*-halogenotoluenes one has the choice of two methods: either one starts from *m*-nitrotoluene and proceeds by way of *m*-toluidine, as mentioned above, or one chooses as starting materials such halogenated acetotoluides as contain a methyl group and halogen in the *m* position to one another; the amino group is then replaced by halogen according to the method mentioned on page 56.

The preparation of *p*-bromotoluene by direct bromination of toluene may be carried out according to Henle [75] as follows:

[70] Jungfleisch, *Ann. chim. phys.*, **15**, 212 (1868).
[71] Mouneyrat and Poret, *Compt. rend.*, **127**, 1026 (1898).
[72] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 121.
[73] Blicke, *J. Am. Chem. Soc.*, **49**, 2845 (1927).
[74] Roux, *Ann. chim. phys.*, **12**, 343 (1887).
[75] F. W. Henle, *Anleitung für das organisch-chemische Praktikum.*   Akadem. Verlagsgesellschaft, Leipzig, 1927, p. 45.

2 g. of iron filings are freed from oil and added to 92 g. of toluene; then 50 cc. of bromine are added dropwise. The reaction which starts after a few minutes is regulated by heating or cooling in such a way that only minute amounts of bromine are entrained by the generated hydrogen bromide; the latter is absorbed in water. After the reaction is finished, the mixture is steam-distilled; the oil is dried and distilled and the portion boiling at about 180°C. is collected separately. The bulk of the p-bromotoluene crystallizes from this fraction when it is cooled in a freezing mixture. The product is collected on a Büchner funnel and freed from oily parts on a cooled porous plate. The yield is 60 g. of p-bromotoluene with a melting point of 28°C.

2. Chlorination and Bromination of Carboxylic Acids

Directions for the preparation of chloroacetic acid can be found in any textbook. The direct chlorination of normal homologues of acetic acid yields in every case mixtures of isomers. Therefore, either α-hydroxy acids are used as starting materials and the hydroxyl replaced by chlorine (see page 99), or alkyl-substituted malonic acids or esters are prepared, the tertiary hydrogen atom of which can readily be replaced by elementary chlorine according to the scheme $R \cdot CH(COOC_2H_5)_2 \rightarrow R \cdot CCl(COOC_2H_5)_2$. Then the malonic esters are saponified and carbon dioxide is split off from the chlorinated malonic acids. In another method which is applicable on some occasions cyanohydrins prepared from aldehydes with 1 carbon atom less are used. The aldehyde is transformed into the cyanohydrin, $C \cdot CHOH \cdot CN$, the hydroxyl is replaced by chlorine by means of phosphorus pentachloride, and finally the chlorinated compound hydrolyzed to the acid.

However, in acetic acid homologues with branched chains the hydrogen atom in the α position may easily be replaced by chlorine if it is a tertiary one. Thus, from isobutyric acid, $CH_3 \cdot CH(CH_3) \cdot COOH$, only α-chlorodimethylacetic acid is obtained, but from isovaleric acid, $(CH_3)_2:CH \cdot CH_2 \cdot COOH$, β-chloroisovaleric acid, $(CH_3)_2:CCl \cdot CH_2 \cdot COOH$, is the product.

It is noteworthy, however, that α-chlorobutyric acid may be prepared from butyryl chloride by way of α-chlorobutyryl chloride, as was shown by Markovnikov.[76] It is quite probable that other acid chlorides might show similar reactions but apparently no details are known. Cloves [77] described the preparation of α-chlorobutyric acid by way of ethyl malonate.

The α-chlorocarboxylic acids are of much less preparative importance than the α-bromocarboxylic acids. The direct substitution of carboxylic acids with elementary bromine yields, almost without exception, α-bromocarboxylic acids; phosphorus bromides are used as carriers. Elementary red phosphorus which should be freed of phosphoric acid by shaking with

[76] Markovnikov, *Ann.*, **153**, 241 (1870).
[77] Cloves, *Ann.*, **319**, 357 (1901).

water, as recommended by Volhard,[78] until the acid reaction disappears may be used. It is then dried carefully. Phosphorus trichloride may be used equally well. In every case, the Volhard method yields (either as by-product or as main product) brominated acid bromides which are hydrolyzed subsequently to the free carboxylic acids.

E. Fischer and Mouneyrat [79] give the following directions for the preparation of α-bromo-n-butyric acid.

250 g. of butyric acid, 35 g. of red phosphorus, and 880 g. of dried bromine are mixed and, as soon as the reaction subsides, the mixture is heated on a steam bath for some time; then the liquid is added dropwise to 1 liter of hot water. When cooled, the heavy oil is separated from the water and the latter extracted with three 500 cc. portions of ether. The mixture of the ether extracts with the oil is dried with calcium chloride and fractionated in a vacuum. α-Bromobutyric acid (365 g.) is obtained, boiling at 127° to 128°C. at 25 mm., corresponding to a yield of 80% of the theoretical.

Directions for preparing α-bromo-n-caproic acid can be found in *Organic Syntheses.*[80]

Fundamental changes in this method are not necessary even when one works with higher molecular weight acids. The tendency of bromine to substitute adjacent to the carboxyl group is so pronounced that isovaleric acid, $(CH_3)_2 : CH \cdot CH_2 \cdot COOH$, for instance, is brominated at the secondary α-carbon atom and not at the tertiary β-carbon atom when treated with bromine and phosphorus. The same can be said about isocaproic acid, $(CH_3)_2 : CH \cdot CH_2 \cdot CH_2 \cdot COOH$, which is important because of its relation to leucine; see E. Fischer.[81]

The carboxylic acid esters also show the same behavior when halogenated. Ethyl bromoacetate which is important for the Reformatski synthesis is prepared in one operation from glacial acetic acid according to Auwers and Bernhardi.[82] The following directions are taken from Vanino.[83]

In a round flask of 500 cc. capacity, equipped with a reflux condenser and a dropping funnel, 60 g. of pure glacial acetic acid are mixed with 10.2 g. of red phosphorus. To this mixture are added dropwise, with shaking, 330 g. (= 100 cc.) of bromine (2 moles). After 6 hours heating on a water bath, the reaction is finished and the excess bromine is removed by distillation. The reaction mixture is allowed to cool and then 130 g. (= 165 cc.) of absolute ethanol are added carefully. Thus, the bromoacetyl chloride formed is changed to bromoacetic acid ethyl ester and hydrogen bromide and ethyl bromide respectively. Finally the reaction mixture is poured onto a mixture of ice

[78] Volhard, *Ann.*, **242**, 145 (1887).
[79] E. Fischer and Mouneyrat, *Ber.*, **33**, 2387 (1900).
[80] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 115.
[81] E. Fischer, *Ber.*, **36**, 2988 (1903).
[82] K. v. Auwers and Bernhardi, *Ber.*, **24**, 2216 (1891).
[83] L. Vanino, *Handbuch der präparativen Chemie.* Vol. II, Enke, Stuttgart, 1937, p. 108.

and sodium carbonate solution, the separated oil is washed with sodium bisulfite and sodium carbonate solutions, dried with sodium sulfate, and distilled; 100 g. of ethyl bromoacetate boiling at 159°C. are obtained. This corresponds to a yield of 60% of the theoretical.

Malonic acid and ethyl malonate and the substituted ethyl malonates mentioned above can be halogenated with exceptional ease; the added halogen atom has no choice, of course, and in any case substitutes in the position neighboring to the carboxyls. Ethyl chloromalonate is formed by passing chlorine into ethyl malonate at 70°C.; the free acid is obtained by saponification according to Conrad and Reinbach.[84]

Bromomalonic acid is prepared by the same authors [85] from 10.4 g. of malonic acid suspended in 75 cc. of ether; after the slow addition of 16 g. (= 5.3 cc.) of bromine, with shaking, a clear solution is obtained. The ether is removed by distillation in a vacuum and the remaining oil soon crystallized. After recrystallization from ether it melts at 113°C. with decomposition. Ethyl bromomalonate is prepared simply by mixing molecular amounts of ethyl malonate and bromine; the reaction product is fractionated and boils at 150° to 152°C. at 25 mm. pressure.

The preparation of substituted α-bromomalonic acids proceeds quite similarly. According to E. Fischer,[86] for instance, 50 g. of benzylmalonic acid are dissolved in 250 g. of absolute ether and 55 g. (= 16.3 cc., 1.3 moles) of bromine are added slowly, whereupon hydrogen bromide escapes. After 30 minutes the mixture is washed with water and the reddish brown solution allowed to evaporate spontaneously. The residue is recrystallized from 250 cc. of toluene; the yield of bromobenzylmalonic acid, $C_6H_5 \cdot CH_2 \cdot CBr(COOH)_2$, amounts to as much as 95% of the theoretical.

Much more difficult to halogenate directly are succinic acid and the higher homologues. Therefore, chlorosuccinic acid is prepared from malic acid or from fumaric acid (see page 66). Bromosuccinic acid can also be obtained by way of dibromosuccinic acid as in the case of α-bromobutyric acid. Volhard [87] gives directions for several methods.

It is very likely that dicarboxylic acids could be brominated in such a manner that the acid bromide step is used only as an intermediate, that is with less phosphorus and correspondingly less bromine, but higher temperatures and sealed systems would be necessary. The higher dicarboxylic acids, e.g. glutaric and adipic acids, may well be halogenated under certain conditions, in the form of their anhydrides; they also yield α,α'-dibromo-substituted products readily.

Polyhalogenated Carboxylic Acids

According to the foregoing discussions, different products have to be expected during the continued substitution of α-halogenocarboxylic acids,

[84] Conrad and Reinbach, *Ber.*, **35**, 1814 (1902).
[85] Conrad and Reinbach, *Ber.*, **35**, 1816 (1902).
[86] E. Fischer, *Ber.*, **37**, 3063 (1904).
[87] Volhard, *Ann.*, **242**, 141 (1887).

depending on whether chlorine or bromine is made to react.   In the case of acetic acid the method of direct chlorination is suitable only for the preparation of monochloroacetic acid (see benzal chloride, page 157). Trichloroacetic acid is obtained from chloral by oxidation, and dichloroacetic acid from trichloroacetic acid by means of potassium ferrocyanide. It is remarkable that dibromoacetic acid can be obtained readily according to Genvresse [88] from glacial acetic acid and bromine with sulfur as carrier; but tribromoacetic acid, on the other hand, is best prepared from bromal. The continued chlorination of acetic acid homologues does not give uniform products, but the α,α-dibromo fatty acids are obtained readily from α-bromo fatty acids with elementary bromine at higher temperatures, the α,α-dichloro fatty acids from α-ketocarboxylic acids with phosphorus pentachloride.

Carboxylic acids with several chlorine or bromine atoms on different carbon atoms are not easy to prepare by direct substitution.   They may be obtained by addition from unsaturated acids or by substitution of hydroxyl from glyceric acids or from halohydrins.   Difficulties are encountered also when halogen is substituted for hydrogen in fatty aromatic carboxylic acids.   In this case side chain and nucleus compete for the halogen offered; therefore, the purpose is almost always achieved more conveniently by detours.   Thus, α-bromophenylpropionic acid is obtained quite readily by decarboxylation of the bromobenzylmalonic acid mentioned above: $C_6H_5 \cdot CH_2 \cdot CBr(COOH)_2 \rightarrow C_6H_5 \cdot CH_2 \cdot CHBr \cdot COOH$. Phenylchloroacetic acid, $C_6H_5 \cdot CHCl \cdot COOH$, is best prepared from mandelic acid or its nitrile.

Halogenation of Aromatic Carboxylic Acids

Benzoic acid is not readily substituted in the nucleus.   Only at 150°C. and under pressure is m-chlorobenzoic acid obtained; see Hübner and Weiss.[89] m-Bromobenzoic acid can also be prepared from benzoic acid and bromine in a sealed tube; directions for its preparation by means of iron bromide and bromine according to Wheeler and Farland [90] follow.

Benzoic acid (20 g.) is melted together with 6 g. of iron filings or fine iron wire and 48 g. of bromine are added dropwise with air cooling; the temperature is increased during 90 minutes from 170° to 260°C.   After cooling, the reaction product is dissolved in a solution of sodium hydroxide, and the solution is filtered and acidified with hydrochloric acid.   The precipitated acid is extracted with ether, the ether solution dried, and the acid distilled from a flask with a sabre-shaped condensing tube. m-Bromobenzoic acid (20 g.) distils between 280° and 300°C. and after recrystallization from alcohol melts at 152° to 153°C.

[88] Genvresse, *Bull. soc. chim.*, 7, 365 (1892).
[89] Hübner and Weiss, *Ber.*, 6, 175 (1873).
[90] Wheeler and Farland, *Am. Chem. J.*, 19, 364 (1897).

3. Chlorination and Bromination of Ketones and Aldehydes

Ketones are halogenated even more easily than carboxylic acids. The preparative significance of the reaction is much lessened by the fact that the formation of mixtures of isomers has to be taken into consideration. Thus, methyl ethyl ketone with chlorine simultaneously yields $CH_3 \cdot CO \cdot CHCl \cdot CH_3$ and $CH_3 \cdot CH_2 \cdot CO \cdot CH_2Cl$, the first in preponderant amount; corresponding products are formed with bromine. The boiling points of the isomers lie very close together, as can be expected. This complication does not exist, of course, with symmetrical ketones. Since the hydrogen halides formed during the substitution promote self-condensation of the ketones, they have to be removed during the reaction. Their removal is best effected by the addition of carbonates.

The halogen substitution products of acetone give a very instructive example for the possibilities of direct halogenation. They are prepared as follows:

1. Monochloroacetone, $CH_2Cl \cdot CO \cdot CH_3$, from acetone and chlorine.

2. 1,1-Dichloroacetone, $CHCl_2 \cdot CO \cdot CH_3$, from acetone and chlorine.

3. 1,3-Dichloroacetone, $CH_2Cl \cdot CO \cdot CH_2Cl$, only in small amounts with *2*; better prepared by dehydrogenation of 1,3-dichlorohydrin, $CH_2Cl \cdot CHOH \cdot CH_2Cl$.

4. 1,1,1-Trichloroacetone, $CCl_3 \cdot CO \cdot CH_3$, from chloral, $CCl_3 \cdot CHO$, with diazomethane.

5. 1,1,3-Trichloroacetone, $CHCl_2 \cdot CO \cdot CH_2Cl$, from $CHCl_2 \cdot CO \cdot CH_2Br$ with mercuric chloride.

6. 1,1,1,3-Tetrachloroacetone, $CCl_3 \cdot CO \cdot CH_2Cl$, from isopropanol, $CH_3 \cdot CHOH \cdot CH_3$, or from acetone and methanol with chlorine.

7. 1,1,3,3-Tetrachloroacetone, $CHCl_2 \cdot CO \cdot CHCl_2$, from 1,1-dichloro-3,3-dibromoacetone with mercuric chloride; from different ring ketones with chlorine and subsequent hydrolysis, *e.g.* from

$$
\begin{array}{c}
\diagup CCl_2 \diagdown \\
CO CO \\
|| \\
CCl_2 CCl_2 \\
\diagdown CO \diagup
\end{array}
\quad \text{hexachlorotriketohexamethylene.}
$$
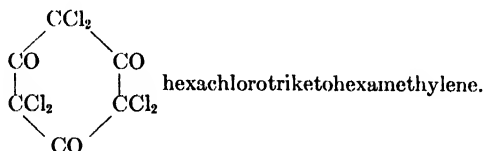
8. Pentachloroacetone and hexachloroacetone, from acetone and chlorine.

Thus, in this case chlorine also shows the tendency to accumulate at the same carbon atom which bromine shows already in the halogenation of carboxylic acids. Similar results are observed, as can be expected, but to an even greater degree during the bromination. While (*4*) apparently cannot be caught in the direct chlorination, the analogous 1,1,1-tribromoacetone, $CBr_3 \cdot CO \cdot CH_3$, has been prepared, not from acetone, to be sure, but from isopropanol, which amounts to the same thing.

When halogenation is carried out alternately with chlorine and bromine, a most remarkable reversal occurs in the reaction; the newly substi-

tuting bromine atoms are directed to the α-carbon which has not been attacked by chlorine. Thus, monochloroacetone with bromine yields $CH_2Cl \cdot CO \cdot CBr_3$; 1,1-dichloroacetone consecutively gives $CHCl_2 \cdot CO \cdot CH_2Br$ and $CHCl_2 \cdot CO \cdot CHBr_2$. These have been mentioned above as starting materials.

The bromine substitution products of acetone, not mentioned so far, are prepared in similar ways, but a difference exists in regard to the symmetrical tetrabromoacetone and the hexabromoacetone. Namely, when ring ketones which on treatment with chlorine and subsequent hydrolysis yield symmetrical tetrachloroacetone (7) are treated with bromine, hexabromoacetone is obtained: symmetrical tetrabromoacetone is made from acetonedicarboxylic acid by way of its tetrabromo derivative and by decarboxylation.

The iodine derivatives of acetone have not been studied so thoroughly. Although iodoacetone may be obtained by iodination with iodine and iodic acid, it is better prepared from chloroacetone and potassium iodide (see page 94). It is quite interesting that, according to Völker,[91] on treatment with iodine trichloride, ICl_3, acetone gives a good yield of 1,3-diiodoacetone, $CH_2I \cdot CO \cdot CH_2I$. This fact, in accordance with the regularities discussed above, allows us to draw the following conclusions about the course of the reaction. Apparently chlorine effects a substitution, forming monochloroacetone, but before reacting further it is changed to iodoacetone; this in turn is chlorinated again and the 1-iodo-3-chloroacetone finally is transformed into 1,3-diiodoacetone.

A few directions for the preparation of important halogenated acetones are given below.

Monochloroacetone is prepared according to Fritsch [92] as follows:

In a flask equipped with a reflux condenser, a dropping funnel, a gas delivery tube, and a thermometer which reaches the bottom, 125 g. of powdered calcium carbonate are covered with 500 g. of acetone and cooled with running water. A moderate stream of chlorine is admitted and at the same time 315 cc. of water are added dropwise. The temperature is kept between 10° and 30°C. As soon as the carbonate is almost used up, the temperature is increased to 40°C. and the mixture is allowed to stand for several hours to complete the evolution of carbon dioxide. During this time calcium carbonate should always be present; if necessary more may be added. Finally the layers formed are separated in a separatory funnel. The top layer is fractionated several times; pure monochloroacetone is obtained boiling at 118° to 120°C.; a higher boiling fraction contains dichloroacetone. From 4200 g. of acetone, 1100 g. of monochloroacetone are obtained.

This method employed deserves some further comments. The carbonate, of course, prevents the formation of mesityl oxide by hydrochloric acid; the addition of water serves to dissolve the calcium chloride formed, but the water is not added before the

[91] Völker, *Ann.*, 192, 90 (1878).
[92] Fritsch, *Ann.*, 279, 313 (1894).

reaction starts, because in that case the chlorine does not react promptly. If chlorine should accumulate, a violent reaction may take place later. The addition of water is stopped in the course of the chlorination whenever the color of chlorine becomes distinctly perceptible, until at 25°C. the color has disappeared again. Since at the end of the reaction the organic solution is on top of the highly concentrated calcium chloride solution, it is hardly necessary to dry it before the distillation. Yields could probably be increased by employing efficient stirring during the reaction.

Bromoacetone is prepared in a corresponding manner according to Scholl.[93]

To 4 parts of acetone and 1 part of calcium carbonate 2.5 parts of water are added gradually at 28° to 31°C. while a current of air saturated with bromine passes through the solution. On fractionation monobromoacetone is obtained, boiling at 31.4°C. at 8 mm. pressure (48° to 53°C. at 25 mm. pressure); a little dibromoacetone is also obtained.

Iodoacetone is obtained from chloro- or bromoacetone with potassium iodide; see page 94.

In the aromatic series the phenacyl halides are important from the point of view of their method of preparation, which is quite simple. Equimolecular amounts of bromine and ketone are combined in a suitable solvent (carbon bisulfide, chloroform, ether, etc.) and the solvent is allowed to evaporate or the mixture is shaken with water and sodium carbonate solution after the reaction is finished. Almost all the bromides crystallize well.

As an example directions for the preparation of p-bromophenacyl bromide, $Br \cdot C_6H_4 \cdot CO \cdot CH_2Br$, may be found in *Organic Syntheses*.[94]

. The nuclear halogenation of aliphatic aromatic ketones is not possible.

The action of halogen on aldehydes is more complicated. Theoretically the substitution on the carbon atom of the aldehyde as well as on the α-carbon may take place. Actually, this does occur and sometimes the conditions may be controlled so as to obtain either reaction. Thus acetaldehyde in aqueous solution yields dichloroacetaldehyde and chloral hydrate; in the absence of water, acetyl chloride is formed. The halogenated acetals of the aldehydes may ·be obtained more conveniently, since they are formed by the action of chlorine on alcohols. These reactions have been studied very little, and only with difficulty do they fit into a systematic discussion.

A certain importance, however, is attached to the halogenation of aromatic aldehydes to the corresponding acid halides, since this is one of the fundamental reactions in the history of organic chemistry; see Wöhler and Liebig.[95] Thus, a method for the preparation of o-chloro-

[93] Scholl, *Ber.*, 29, 1555 (1896).
[94] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 127.
[95] L. Wöhler and J. Liebig, *Ann.*, 3, 262 (1832).

benzoyl chloride by way of o-chlorobenzoic acid is available; the latter can readily be made to react with thionyl chloride according to good directions; see H. Meyer [96] and Frankland and collaborators.[97]   o-Chlorobenzoic acid, however, is industrially unimportant, while o-chlorobenzaldehyde is prepared commercially in large amounts and of high purity. Directions are given for the preparation of o-chlorobenzoyl chloride from o-chlorobenzaldehyde in *Organic Syntheses*.[98]

The bromination of aliphatic aldehydes has attracted attention recently as a means of preparing certain unsaturated aldehydes.   β-Methylcrotonaldehyde, $CH_3 \cdot C(CH_3):CH \cdot CHO$, cannot be prepared by means of an aldol condensation, since acetone and acetaldehyde yield only the isomeric ethylideneacetone (see page 426).   Because of its constitution, it is an important intermediate in the synthesis of natural polyene chains (see page 431).   Fischer and Löwenberg [99] therefore treated isovaleraldehyde with bromine in chloroform and then with ethanol to obtain α-bromoisovaleraldehyde acetal according to the equation, $(CH_3)_2:CH \cdot CH_2 \cdot CHO + Br_2 + 2C_2H_5OH \rightarrow (CH_3)_2CH \cdot CHBr \cdot CH(OC_2H_5)_2 + HBr + H_2O$.   For the removal of hydrogen bromide from it see page 318.

4. Chlorination and Bromination of Ethers

Halogens react very vigorously with ethers at room temperature, but diethyl ether, when ice-cold, is still somewhat stable towards bromine and thus can be used as a solvent for brominations.

The reaction of chlorine with diethyl ether was studied very carefully by Lieben [100] and Abeljanz.[101]   It is interesting to note that substitution occurs only in one ethyl group when the chlorination is carried out in the dark.   At low temperature 3 hydrogen atoms are replaced, the fourth and fifth at 90°C.   The remaining 5 hydrogen atoms can be substituted finally in direct sunlight.[102]

Phenol ethers are especially easily halogenated.   They are halogenated directly in the nucleus with phosphorus pentahalides; *e.g.*, anisole yields p-chloroanisole or p-bromoanisole.[103] ·

5. Chlorination and Bromination of Phenols and Amines

The halogenation of phenol offers one of the rare examples of radically changing the ratio of ortho to para isomers by changing the conditions of

[96] H. Meyer, *Monatsh.*, 22, 427 (1901).
[97] Frankland *et al.*, *J. Chem. Soc.*, 101, 2476 (1912).
[98] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 155.
[99] G. Fischer and K. Löwenberg, *Ann.*, 494, 272 (1932); *Ber.*, 64, 31 (1931).
[100] Lieben, *Ann.*, 111, 121 (1859); 146, 180 (1868).
[101] Abeljanz, *Ann.*, 164, 197 (1872).
[102] Malaguti, *Ann. chim. phys.*, 16, 4 (1846).
[103] W. Authenrieth and P. Mühlinghaus, *Ber.*, 39, 4098 (1906).

the reactions. At low temperatures, p-chloro- and p-bromophenols are obtained almost exclusively, but at 150° to 180°C. only o-halophenols are formed.

The best directions for the preparation of p-bromophenol are found in *Organic Syntheses.*[104]

p-Chlorophenol may be prepared by direct chlorination of phenol in a corresponding manner, but a more convenient method for the laboratory is given by Dubois.[105] Directions are given also by Vanino[106] and by Peratoner and Condorelli.[107]

Molecular amounts of phenol and sulfuryl chloride are mixed at room temperature. After the initial vigorous evolution of sulfur dioxide and hydrogen chloride has subsided somewhat, the mixture is heated on a steam bath until no more gases are evolved. The reaction product is washed with a solution of sodium carbonate, dried over calcium chloride, and fractionated. The yield of p-chlorophenol boiling at 216° to 218°C. (m.p. 37°C.) is almost quantitative.

o-Chloro- and o-bromophenol are recorded in the patent literature[108] but there is not a carefully worked out laboratory procedure available. The directions for the preparation of o-chlorophenol are as follows: an equimolecular amount of chlorine, that is 71 parts, is passed into 94 parts of phenol heated at 150° to 180°C.; the product is then fractionated. It is not readily freed from unchanged phenol because of the similarity of their boiling points (176° and 183°C.). Wohlleben[109] has shown that the less acid phenol may be extracted with ether from a solution of the mixture in aqueous potassium carbonate. In the industrial use of o-chlorophenol for the manufacture of pyrocatechol, the phenol content of the crude product is quite immaterial and a contamination of isomeric p-chlorophenol in small amounts is of no consequence. o-Bromophenol is prepared in a similar manner.

In order to prepare pure o-halogenophenols in the laboratory, it will probably prove necessary to start from o-chloro-, o-bromo-, or o-iodo-aniline and to proceed by way of the diazonium compounds (see page 111).

The specific details of the halogenation of the cresols and the general polyhalogenation of the phenols cannot be discussed here, but the course of the continued bromination of phenol may be treated briefly.

From o- and p-bromophenol with excess bromine (2 moles) 2,4,6-tribromophenol is obtained; see Körner.[110] Kastle and Loevenhart[111]

[104] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 128.
[105] Dubois, *Z. Chem.*, 1866, 705.
[106] L. Vanino, *Handbuch der präparativen Chemie.* Vol. II, Enke, Stuttgart, 1937, p. 430.
[107] Peratoner and Condorelli, *Gazz. chim. ital.*, 28, I, 210 (1898).
[108] E. Merck, German Patent, 76,597.
[109] J. Wohlleben, *Ber.*, 42, 4370 (1909).
[110] L. Körner, *Ann.*, 137, 209 (1866).
[111] Kastle and Loevenhart, *Am. Chem. J.*, 27, 32 (1902).

found that an additional molecule of bromine is added, thus yielding "tribromophenol bromide," that is, 2,4,6,6-tetrabromocyclohexadienone:

$$O=C \overset{CBr=CH}{\underset{CBr=CH}{\diagup\diagdown}} CBr_2$$
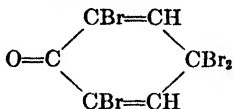
Phenol (4.7 g.) which has been liquefied with water is mixed with an aqueous solution of 13 cc. of bromine.   After several hours the precipitate is filtered off, dried on a porous plate, and recrystallized from carbon bisulfide.   The chlorination of polyphenols proceeds in a similar manner with the formation of hydroaromatic ketones; for instance, hexachlorotriketohexamethylene is formed from phloroglucinol (see page 83).

The direct halogenation of naphthols has been studied less thoroughly than that of the phenols, probably because they are of little practical importance.   It offers nothing new in the way of method.

The ease with which aromatic primary amines are halogenated often prohibits the isolation of monosubstitution products.   However, p-bromoacetanilide may be prepared in good yield by the careful addition of the calculated amount of bromine to a solution of acetanilide in glacial acetic acid.[111a]   If the halogenation is performed in strong sulfuric acid solution in which presumably acid aniline sulfate is the reacting substance, m derivatives are formed.   In some cases, it may be more advantageous to prepare the halogenated aromatic amines by reduction of the corresponding nitrohalide compounds.   It is possible to prepare p-chloroaniline by the reduction of nitrobenzene in strong hydrochloric acid solution.   In this reduction reaction steps occur which are, fundamentally, variations of direct halogenation.   Chlorophenylamine, C_6H_5NHCl, is assumed to be an intermediate as is the case in the reaction with elementary chlorine.

The ease with which aromatic amines are substituted as well as their basic nature makes it possible to prepare p-iodoaniline hydriodide from aniline and iodine (see page 89).

6. Chlorination with Hypochlorous Acid and Bromination with Hypobromous Acid

Straus [112] has pointed out that acetylene and diacetylene may be halogenated with sodium hypochlorite and hypobromite in aqueous solution to give dichloro- and dibromoacetylene, respectively, while the free hydrogen hypohalites add.   The positive hydrogens of other compounds which can be substituted by metals react in a similar way; e.g., in cyclopentadiene and indene, in propiolic acid, phenylacetylene, and acetylene alcohols.[113]

[111a] Remmeres, Ber., 7, 346 (1874); Adams and Johnson, Elementary Laboratory Experiments, Macmillan, New York, 1933, p. 237.
[112] F. Straus, Ber., 63, 1868 (1930).
[113] F. Straus, Ber., 63, 1886 (1930).

As an example the preparation of dichloroacetylene may serve.

To prepare the hypochlorite solution, chlorine is passed into a measured volume of ice-cold 12.5% potassium hydroxide until litmus is just bleached. The solution is then diluted with an equal volume of 25% potassium hydroxide. The apparatus used for further reaction consists of a large test-tube (about 150 cc. capacity) with a side outlet. Its top is closed by a rubber stopper through which pass a dropping funnel and a gas delivery tube with a fritted gas dispersion disk. The side outlet is connected through a charged calcium chloride tube to a receiver which is cooled in a dry ice-acetone bath. By means of a T-piece the gas delivery tube is connected to sources of nitrogen and acetylene. The solution of hypochlorite (about 30 cc.) is cooled in ice, the air replaced by nitrogen, and the acetylene passed in. The stream of nitrogen is reduced though never shut off completely. Dichloroacetylene separates as a colorless oil. After the reaction is finished, the nitrogen stream is increased in order to distil the chloride into the receiver. The product appears in long, felt-like needles. The melting point is −66° to −64.2°C.; the boiling point, as determined according to the method of Sivolobov,[114] is 32° to 33°C. at 748 mm. pressure.

Dibromoacetylene is prepared with a hypobromite solution which is obtained in a corresponding manner at 0°C. from bromine, potassium hydroxide, and water. The solution is 0.5 N with respect to hypobromite, and 0.2 N with respect to free potassium hydroxide.

The halogen acetylenes are extremely sensitive compounds; they ignite instantly in air, explode even when slightly heated, and their vapors form explosive mixtures with air. If acetylene is passed into a hypochlorite solution until an obvious turbidity exists and the mixture is then shaken with air, a strong crackling can be heard and sparks are visible in the dark.

7. Iodination

In general it is not possible to substitute elementary iodine for organic bound hydrogen unless care is taken to remove the hydriodic acid formed. This may be accomplished either by oxidation or binding. The molecule may contain a group which can bind hydriodic acid (see above), or a basic substance may be added. Aniline yields mainly p-iodoaniline hydriodide with solid iodine.[115]

For the removal of excess iodine from the reaction mixture either potassium iodide, sodium thiosulfate, alkalies, or mercury is used. Iodine can be liberated from excess hydrogen iodide by means of hydrogen peroxide, and the free iodine can be removed by steam distillation.[116]

In most cases solutions of iodine are used. Numerous organic liquids may be considered as well as aqueous potassium iodide solution. To remove the hydrogen iodide formed during the iodination the following oxidation media may be used.

1. **Iodic Acid.** When this is used, iodine and water only are formed; thus the method is very simple. Iodine and iodic acid, for instance, transform benzene in a sealed tube

---

[114] Sivolobov, *Ber.*, **19**, 795 (1886).
[115] A. W. v. Hoffmann, *Ann.*, **67**, 65 (1848).
[116] Hantzsch and Wild, *Ann.*, **289**, 301 (1896).

at 200° to 240°C. mainly into monoiodobenzene, although some di- and triiodobenzene are formed; see Kekulé.[117]   Similarly, mesitylene is iodinated in glacial acetic acid at atmospheric pressure, forming monoiodomesitylene (Klages and Storp [118]).

2. Fuming Sulfuric Acid.   According to Juvalta,[119] sulfuric acid with 50% sulfur trioxide may be used.   It oxidizes the hydrogen iodide to iodine with formation of sulfur dioxide.   To a solution, for instance, of 10 g. of phthalic anhydride in 60 g. of fuming sulfuric acid 40 g. of iodine are added very slowly at 90° to 100°C.   Then the temperature is increased to 180°C. and the tetraiodophthalic anhydride collects at the bottom.

The following substances remove excess hydriodic acid by reacting with it to form salts.

1. Mercuric Oxide.   Strangely, mercuric oxide is often still listed with the above oxidizing substances, although it is changed to mercuric iodide in the course of the reactions involved, thus not changing its valence at all.   Iodine and mercuric oxide are added in small portions to an alcoholic phenol solution.   It is necessary to wait for the disappearance of the iodine color before subsequent additions are made, and to moderate the heat of reaction by cooling.[120]

2. Other Alkaline Media.   Iodonicotyrine can be prepared by shaking 1 part of nicotyrine with a solution of 4 parts of iodine in a dilute solution of sodium hydroxide and slowly acidifying the solution with acetic acid after it has become clear.[121]   The red periodide, which can be changed to crystalline iodonicotyrine by rendering the solution alkaline, separates.

Sometimes the alkali salts of weak acids may be used in place of the alkalies; Classen,[122] for instance, used borax for the preparation of tetraiodophenolphthalein.

Vaughn and Nieuwland [123] recommend liquid ammonia.

For the preparation of diiodoacetylene 100 g. of iodine are placed in a 1500 cc. beaker and the bottom of the beaker cooled by immersion in a shallow dish of liquid ammonia. After a short time 750 cc. of liquid ammonia are added as rapidly as possible.   A violent reaction takes place and a small amount of iodine vapor is lost; however, even in larger batches not a single explosion was experienced.   The acetylene, washed with water and dried with sulfuric acid, was bubbled into the solution at a rate of 200 to 500 cc. per minute with mechanical stirring.   In $2\frac{1}{2}$ to 3 hours the solution becomes perfectly clear, indicating the end of the reaction.   The beaker is covered with a watch-glass and the ammonia evaporated on a hot water bath.   When the volume has been reduced to about 150 cc., 500 cc. of water are slowly added and the precipitated diiodoacetylene filtered by suction.   It is pressed as dry as possible with a rubber dam.   The moist product, weighing 60 to 65 g., is dissolved in 300 cc. of petroleum ether and treated with 35 g. of calcium chloride.   After the mixture has stood overnight, the solution is decanted from the calcium chloride into a large beaker cooled in liquid ammonia.   The crystals of diiodoacetylene are filtered on a funnel cooled with liquid ammonia.   A small funnel is inserted into a larger one, the annular opening closed by rubber tubing, and the space

[117] A. Kekulé, *Ann.*, **137**, 162 (1866).
[118] Klages and Storp, *J. prakt. Chem.*, **65**, 564 (1902).
[119] Juvalta, German Patent, 50,177.
[120] Hlasiwetz and Weselsky, *Chem. Zentr.*, **1870**, 63.
[121] Pictet and Crépieux, *Ber.*, **31**, 2019 (1898).
[122] Classen, *Ber.*, **28**, 1605 (1895).
[123] Th. Vaughn and A. Nieuwland, *J. Am. Chem. Soc.*, **54**, 787 (1932).

between the two funnels filled with liquid ammonia. A yield of 30 to 35 g. (corresponding to 54 to 63% of the theoretical) of material melting at 78.5° to 78.9°C. is obtained. From the mother liquor a further 3 to 5 g. of diiodoacetylene may be obtained. When treated in a similar manner, acetone yields iodoform; benzene, olefins, pentane, and triphenylmethane do not react.

The following preparation of 2-iodothiophene is an example of the direct iodination with iodine and mercuric oxide.

Meyer and Kreis [124] described the first preparation of this compound which they obtained from crude thiophene. The yield from 50 g. of starting material was 32 g. of iodothiophene. Later Thyssen [125] obtained 40 g. of iodothiophene from 25 g. of pure thiophene with 40 g. of yellow mercuric oxide, corresponding to a yield of 64% of the theoretical. Even though the yield obtained by Meyer and Kreis from crude thiophene does not allow an exact comparison, it is noteworthy that they first added the iodine to the thiophene and then the mercuric oxide. Despite the fact that, before they added mercuric oxide, once a quantity of thiophene turned into tar by a spontaneous reaction between the crude thiophene and the iodine with the formation of hydrogen sulfide, they came to the conclusion that it is "necessary after the addition of iodine, to treat the thiophene immediately with mercuric oxide." Thyssen proceeded in the reverse manner. He treated the mercuric oxide-thiophene mixture with iodine, thus always having an excess of binding agent, but he states that it is not necessary to dilute the thiophene as recommended by Meyer. Recently,[126] however, it has been found that dilution of the thiophene effects a slight increase in yield.

A mixture of 35 g. of thiophene and 50 cc. of benzene or ligroin (b.p. 100° to 120°C.) is cooled with ice, and during 12 to 20 minutes 75 g. of yellow mercuric oxide and 109 g. of iodine are added alternately in small portions. The solution is well shaken manually and, if necessary, cooled in ice. The precipitate is filtered off and washed three times with 50 cc. portions of ether. Any iodine present is removed by shaking with a sodium thiosulfate solution, and the product dried with calcium chloride and distilled. A yield of 63 to 66 g. of iodothiophene is obtained, boiling at 73°C. under 15 mm. pressure, corresponding to 72 to 75% of the theoretical. Traces of iodine which might possibly still be present may be removed by shaking with mercury oxide.

In most cases some diiodothiophene is obtained as a residue in the distilling flask. Some unchanged thiophene can be recovered from the forerun by means of mercury oxide and acetic acid by the method of Dimroth.[127]

As an example of the iodination with oxidizing agents directions for the preparation of iodobenzene can be found in *Organic Syntheses*.[128]

A general method for the direct iodination was described by Birkenbach and Goubeau.[129] It consists of treating the organic compound to be

[124] V. Meyer and H. Kreis, *Ber.*, **17**, 1558 (1884).
[125] Thyssen, *J. prakt. Chem.*, **65**, 5 (1902).
[126] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 357.
[127] Dimroth, *Ber.*, **32**, 759 (1899).
[128] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 323.
[129] L. Birkenbach and G. Goubeau, *Ber.*, **65**, 395 (1932).

iodinated in a solution of ether or benzene with a suspension of silver perchlorate and elementary iodine. The method has the advantage of being applicable at very low temperatures and also in a very mild manner. With fatty aromatic hydrocarbons like toluene nuclear substitution apparently takes place in the dark and in the cold, but in light substitution of the side chain occurs. This can be surmised from the fact that tarry by-products are formed. In order to bind the perchloric acid set free, magnesium oxide or calcium oxide or their carbonates are added. This has the added advantage that the perchlorates formed have a strong drying effect, thus preventing many side reactions.

For the preparation of iodobenzene, for instance, 22 g. of silver perchlorate and 10 g. of calcium carbonate are suspended in 100 cc. of benzene and 25 g. of iodine are added with cooling during 15 minutes. The mixture is filtered, washed three times with water, dried with calcium chloride, and distilled. The yield amounts to 16 g. of iodobenzene, boiling at 184°C., corresponding to 80% of the theoretical. The iodination of naph-. thalene in concentrated ethereal solution (50%) gives α-iodonaphthalene in a yield of 85%. The ether solution of iodine is not permanently stable towards perchlorate but it is not dangerous during the short time of reaction. Bromination may also be carried out in the same way.

Iodine carriers in a strict sense are not known; the use of iodine mono- or trichlorides might possibly be considered here. For instance, Michael and Norton [130] report a yield up to 90% of the theoretical of p-iodo-acetanilide from acetanilide in glacial acetic acid with iodine chloride. Sulfur monoiodide has a similar effect,[131] substituting iodine for hydrogen in benzene and xylene.

Solutions of iodine chloride are obtained by mixing an equimolecular solution of dichloramine-T, $C_7H_7O_2NCl_2S$ (N,N-dichloro-p-toluenesul-fonamide), in glacial acetic acid with hydriodic acid or with finely powdered sodium iodide.[132]

Iodine monochloride, ICl, apparently first chlorinates the organic compounds and then changes them subsequently to iodine compounds. These reactions proceed one after the other according to the general equation, $C_xH_y + ICl \rightarrow C_xH_{y-1}I + HCl$. However, the reaction succeeds only in cases in which the substitution of hydrogen atoms takes place readily. Such is the case, for instance, with phenols and amines.

Michael [133] succeeded in iodinating p-nitroaniline in this way. Directions for this procedure are given in *Organic Syntheses*.[134]

[130] Michael and Norton, *Ber.*, 11, 108 (1878).
[131] German Patent, 123,746.
[132] A. Bradfield, *J. Chem. Soc.*, 1928, 782.
[133] Michael, *Ber.*, 11, 113 (1878).
[134] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 196.

Diiodosalicylic acid, 2-hydroxy-3,5-diiodobenzoic acid, is obtained in a similar manner; see *Organic Syntheses*.[135]

I OH

—COOH
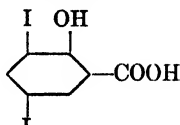
Diiodosalicylic acid

8. Fluorination

Mention was made above of the fact that elementary fluorine cannot be used for direct fluorination not only because it is very difficult to handle but also because of its extreme chemical reactivity. The organic fluorine compounds are prepared, with very few exceptions, by roundabout procedures the details of which may be found in the corresponding sections.

Of the different experiments to force direct fluorination, the following may be mentioned:

Ruff and Keim [136] studied the reaction of iodine pentafluoride with benzene. It is noteworthy that iodobenzenes were formed among the reaction products but no (or only small amounts of) fluoro- or iodofluorobenzenes. Conditions were worked out by Fredenhagen and Cadenbach [137] under which the reaction of organic substances with free fluorine takes place without complete decomposition. The apparatus is quite elaborate and the reaction products obtained are not uniform. Hence the method is not worthy of consideration for preparative purposes. Similar results were obtained by Bigelow and collaborators.[138]

The preparation of fluoro compounds, then, is generally by indirect procedures. The method of Swarts is used with success in the aliphatic series. In this method iodine compounds are made to react with mercury or silver fluorides (see page 94). Schiemann recently perfected a new method for the aromatic series, which proceeds by way of the complex borofluorides of diazonium salts (see page 115). Both methods are based on old directions. Dumas and Peligot,[139] for instance, prepared methyl fluoride from dimethyl sulfate and potassium fluoride in 1835 and Holleman [140] obtained fluorobenzene by heating a hydrofluoric acid solution of benzene diazonium fluoride in 1837.

[135] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 343.
[136] O. Ruff and R. Keim, *Z. anorg. allgem. Chem.*, 201, 245 (1931).
[137] K. Fredenhagen and G. Cadenbach, *Ber.*, 67, 928 (1934).
[138] A. Bigelow *et al.*, *J. Am. Chem. Soc.*, 55, 4614 (1933).
[139] Dumas and Peligot, *Ann.*, 15, 59 (1835).
[140] M. Holleman, *Ann.*, 24, 28 (1837).

B. Interchange of Halogen Atoms

1. Action of Elementary Halogen on Halides

Aliphatic iodides are frequently changed by elementary chlorine or bromine to the corresponding chloride or bromide. It is easily seen that this reaction, though interesting, has very little practical importance. Aliphatic bromides are stable towards elementary chlorine in that the bromine is not replaced by chlorine, but more hydrogen atoms are at times substituted by chlorine.

In general, aromatic bound iodine is not replaced. With chlorine, addition compounds are formed first, $R \cdot ICl_2$; then further substitution takes place in the nucleus. Bromine substitutes in the nucleus without forming addition compounds. Exchange takes place in the aromatic series only when there is no available hydrogen atom.

2. Action of Halogen Ions on Organic Halides

Exchange according to the scheme, $RX + I^- \rightarrow RI + X^- (X = Cl, Br)$, offers an important method for the preparation of organic iodides. A prerequisite is a certain mobility of the halogen to be exchanged, a condition which exists for chlorine and bromine attached to saturated carbon atoms. With olefinic or aromatic bound halogen this exchange takes place only under certain conditions.

Hydriodic acid is very effective but is sometimes accompanied by side reactions; that is, at the end of the reaction the halogen is replaced by hydrogen. The addition of phosphorus iodides makes these reactions proceed more readily.

Alkali iodides are better reagents to use, as they do not possess this disadvantage. The solvent is an important factor; water, methanol, ethanol, acetone, and glacial acetic acid may be used. Sodium iodide is more soluble in alcohols than potassium iodide; acetone will form a 15% solution. The use of acetone as solvent is advantageous whenever esterification might occur with alcohols or glacial acetic acid. Also, better yields are obtained in acetone.

Bromine may be replaced more readily than chlorine. Furthermore, primary halogen reacts better than secondary halogen, and this in turn better than tertiary. Aromatic halogen can be replaced only if it is in a chemically loosened state under the influence of other substituents.

A recent, important variation of the exchange method involves the organomercuric halides of aromatic compounds in which the group Ar—HgCl can be made to react readily with elementary iodine. Thus, o-iodophenol is obtained from o-chloromercuriphenol according to the equation $2C_6H_4(OH)HgCl + 2I_2 \rightarrow 2C_6H_4(OH)I + HgCl_2 + HgI_2$.

Since the chloromercuric compounds are often easily accessible, the method frequently competes with the Sandmeyer reaction; see page 117.

Iodoacetic acid [141] is obtained as follows:

Chloroacetic acid is heated in concentrated aqueous solution with an equimolecular amount of potassium iodide for 2 hours at 50°C. After the reaction mixture has been decolorized with sulfur dioxide, it is extracted with ether and the ethereal solution dried over calcium chloride. The ether is evaporated immediately and the residue recrystallized from a little water or from petroleum ether.

Isoamyl iodide [142] is prepared by boiling a saturated (15%) solution of sodium iodide in acetone (100 cc.) with 15 g. of isoamyl bromide. After the mixture has boiled for 1 hour under a reflux, 60 cc. are removed by distillation and the residue poured into water; the oil is separated, dried, and shaken with mercury to remove iodine. On distillation *in vacuo* 16.5 g. of isoamyl iodide are obtained, corresponding to a yield of 85% of the theoretical. But the preparation of isoamyl iodide in this way is hardly worth while, since it can be prepared directly from isoamyl alcohol.

The formation of allyl iodide may serve as an example of Spindler's method.[143]

Allyl chloride (2.1 g.), boiling at 46°C., is sealed into a small glass tube so that the latter is almost completely filled. This tube is put into a larger tube together with the calculated amount of calcium iodide (4.1 g.). The tube is then evacuated and sealed. All traces of moisture are excluded from the large and small tubes as well as from the calcium iodide, because moisture even in small amounts spoils the reaction. After the small tube with the allyl chloride is broken by shaking, the large tube is heated in an oven for 120 hours at 70° to 75°C. During the heating some carbon and iodine separate because of decomposition of allyl iodide. The liquid from the opened tube is freed from iodine by shaking with mercury until colorless. The boiling point of the product is 98°C., and a yield of 96% of theory is obtained.

For the preparation of acid bromides and iodides from acid chlorides see page 106.

Equally simple in principle is the replacement of iodine or bromine by fluorine with silver fluoride, used chiefly as the fluorine carrier.

Swarts [144] gives the following brief directions for the preparation of fluoroacetic acid.

Methyl iodoacetate and mercury or silver fluoride are heated in a platinum apparatus under a reflux to 170°C. The methyl iodoacetate boils at 104.5°C. In order to saponify the ester 5 moles of water are added, then the theoretical amount of barium hydroxide in portions of 1 g., time being allowed after each addition until the alkaline reaction has disappeared. The product is precipitated by the addition of 10 volumes of ethanol and the precipitate recrystallized from water. The mercury or silver salt thus obtained is distilled with sulfuric acid; fluoroacetic acid boiling at 165°C. is thereby obtained. Its melting point is 33°C.

[141] Abderhalden and Guggenheim, *Ber.*, **41**, 2853 (1908).
[142] H. Finkelstein, *Ber.*, **43**, 1531 (1910).
[143] Spindler, *Ann.*, **231**, 257 (1885).
[144] F. Swarts, *Bull. soc. chim.*, **15**, 1134 (1896).

The fact that the substituents in polysubstituted benzene derivatives are inclined to change their positions in reactions has been known for a long time. Asinger [145] found that by the action of chlorine on hot o-, m-, and p-bromotoluene, that is under conditions favoring the halogenation of side chains, no bromobenzyl chlorides are formed; but on the contrary, the bromine in the nucleus is replaced by chlorine and the former partly effects substitution in the side chain. The reaction always leads to mixtures of compounds which can be separated only with difficulty. Therefore, it offers no preparative possibilities.

C. Replacement of Hydroxyl Group and of Carbonyl Oxygen by Halogen

1. Alcoholic Hydroxyl Groups

The replacement of alcoholic hydroxyl by halogen can be accomplished generally according to the simple scheme, $R \cdot OH + HX \rightarrow R \cdot X + H_2O$.

The reaction takes place with increasing ease in the order hydrogen chloride, hydrogen bromide, hydrogen iodide. From a purely preparative point of view the bromides are the most important, since they are the most suitable for subsequent reactions. If at all possible, hydrogen bromide is not used alone but in the presence of water-binding substances. In the case of hydrogen iodide this is not necessary, but the side reactions caused by the reducing effect of hydrogen iodide have to be considered.

Schlubach and collaborators [146] stated that, strangely, the splitting off of water from aliphatic hydroxyl by dry hydrogen chloride at room temperature and moderate pressure progresses the more slowly the purer is the alcohol used for the reaction. A commercial product of n-butanol designated "very pure" yielded with hydrogen chloride during 20 hours at 32 to 39 atmospheres pressure about 30% n-butyl chloride. After the butanol was distilled twice from sodium, butyl chloride could not be isolated in a substantial amount. Only from the amount of hydrochloric acid used could it be calculated that about 4% butyl chloride must have been formed.

The halides formed are by no means always very stable substances. The more readily they are formed, the more easily is hydrogen halide in turn split off. The tertiary halides give up hydrogen halides most easily, the primary ones, with greatest difficulty. Among the latter, the ones with normal chains are most stable. Primary halides with branched chains are very sensitive at times. In a very special case, 2,2,2-trimethylethyl bromide, $(CH_3)_3C \cdot CH_2Br$, the tendency for rearrangement is so pronounced that the substance cannot be isolated; see page 489.

[145] F. Asinger, *Monatsh.*, **64**, 153 (1934).
[146] H. Schlubach *et al.*, *Angew. Chem.*, **47**, 130 (1934).

Since the reaction is seldom quantitative, at least under the conditions for preparational work, almost always a mixture of alcohol and halide is obtained, which cannot be separated completely by fractionation because the alcohols form azeotropic mixtures with the corresponding halides. When the alcohol is removed by chemical means, that is by shaking with concentrated sulfuric acid, great care must be exercised.

In particular, secondary alcohols of the aliphatic series react fairly uniformly with hydrogen halides only under very mild conditions. Thus, for instance, the preparation in a pure state of the three normal monobromopentanes from the corresponding amyl alcohols is quite a difficult task.

When aliphatic hydroxyl groups are replaced by chlorine by means of hydrogen chloride, the following has to be considered. Since the alcohols dissolve only a limited amount of hydrogen chloride, the quantity absorbed is not sufficient, in many cases, for a complete reaction. Therefore, rather large amounts of water have to be added occasionally, a procedure which at first appears to be quite inconsistent. For instance, when a mixture of 1 part of ethanol and 2 parts of water is saturated with hydrogen chloride and slowly heated, an excellent yield of ethyl chloride is obtained. If fused zinc chloride is added to the alcohol (about one-half of the weight of alcohol), more hydrogen chloride dissolves and the reaction becomes more complete. Sodium sulfate may also be used to bind the water.

In general, it is not necessary to employ the stronger reagents, such as phosphorus trichloride, phosphorus pentachloride, and thionyl chloride. Phosphorus oxychloride is a valuable reagent, since in special cases it reacts with alcoholic hydroxyl but not with the hydroxyl of the carboxyl group. Thus, diphenylchloroacetic acid may be obtained readily by heating equal amounts of benzilic acid and phosphorus oxychloride.

Usually, it is quite easy to replace aliphatic hydroxyl groups by iodine. Either concentrated hydriodic acid may be used or hydrogen iodide may be generated in the reaction mixture itself. For this purpose the hydroxyl compound is mixed with moist red phosphorus, and elementary iodine is added, with heating if necessary.

Since hydriodic acid is one of the most powerful reducing agents, side reactions must be expected often. Thus, glycerol does not yield 1,2,3-triiodopropane but only isopropyl iodide; in general, only óne of several alcoholic hydroxyl groups in a molecule can be replaced by iodine. However, frequently the iodides may be prepared more conveniently from the chlorides or bromides by subsequent exchange of iodine for chlorine or bromine; see page 106.

(a) Monohydric Alcohols

Very careful investigations of Kamm and Marvel [147] show that the usual method for the preparation of ethyl bromide, that is distillation of an alcohol with potassium bromide and sulfuric acid, always gives low yields when higher alcohols are used. This method, however, is still worth while for *n*-butyl alcohol. The directions may be found in *Organic Syntheses.* [148]

Organic Syntheses [149] also lists directions for the preparation of isoamyl bromide.

Higher alcohols and alcohols with branched chains can be made into bromides better by means of a mixture of hydrobromic acid and sulfuric acid.

Constant boiling hydrobromic acid (b.p. 125° to 126°C., 48% of hydrogen bromide) may be obtained commercially, but in the laboratory it is advantageous to collect in water the hydrogen bromide generated during brominations and to fractionate the accumulated quantities as needed.

Kamm and Marvel [150] give excellent directions for conveniently preparing hydrobromic acid by the reaction between bromine and sulfur dioxide. The mixture of aqueous hydrobromic acid and sulfuric acid thus obtained may be used directly on many occasions. Addition of a further quantity of sulfuric acid may be necessary if the traces of sulfur dioxide do no harm. The mixture contains 1 mole of hydrogen bromide for 0.5 mole of sulfuric acid. To prepare pure hydrobromic acid, the mixture is distilled from the reaction flask up to 130°C. and the distillate is rectified. 48% hydrobromic acid, boiling at 125° to 126°C., is obtained in an amount of about twice the weight of the bromine used. The first distillate contains traces of sulfuric acid and may be used without further purification after the specific gravity has been checked.

When bromides of high molecular weight are prepared, the bromide layer is separated in a separatory funnel after the reaction is finished and the mixture is diluted with water. *n*-Octyl alcohol gives 91% of the theoretical amount of *n*-octyl bromide; *n*-dodecyl alcohol, an equal yield of *n*-dodecyl bromide.

[147] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 32.
[148] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 29.
[149] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 28.
[150] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 26.

Aqueous hydrogen halides react almost instantly with tertiary alcohols, substituting halogen for the hydroxyl group. Therefore, in most cases it suffices to mix the alcohol with the acid at room temperature. According to Norris [151] tertiary butyl chloride, $(CH_3)_3C \cdot Cl$, separates immediately after trimethylcarbinol is mixed with 8 times its weight of concentrated hydrochloric acid ($D = 1.19$); the layers are separated and distilled. When hydrogen chloride or hydrogen bromide is passed into the ice-cold alcohols, in some cases after addition of a little water, the reaction is more complete. Rearrangements cause little trouble, because the formation of tertiary bromides from secondary bromides is the preferred reaction. At higher temperatures, however, equilibrium exists; thus, Faworski [152] states that tertiary butyl bromide at 210° to 220°C. changes in large part into isobutyl bromide, while, on the other hand, isobutyl bromide under the same conditions yields tertiary isomers.

All tertiary halides are extremely sensitive. Some, such as tertiary butyl iodide, are decomposed completely or partially when distilled at atmospheric pressure and are hydrolyzed even by cold water.

Secondary halides are usually fairly stable towards cold water, but they are decomposed by solutions of alkali carbonates, while primary halides are stable except when branched at a point close to the halogen. Therefore it is possible to determine roughly the content of primary, secondary, and tertiary halides in an unknown reaction mixture by alternate shaking with water and sodium carbonate solution and by titrating the hydrogen halide which is split off.

Methyl phenyl chloroacetate may be prepared from methyl mandelate [153] as follows:

A mixture of 12.5 g. of methyl mandelate and 12 g. of pyridine is well cooled in a freezing mixture and 11.5 g. of cooled phosphorus oxychloride are added in portions. Crystals start to separate. After the mass has been allowed to remain for 1 hour in the freezing mixture, it is kept for 12 hours at room temperature with occasional stirring. Ice water is then added and the oil extracted with chloroform. The extract is washed with water and with a solution of sodium bicarbonate, dried over sodium sulfate, and distilled *in vacuo*. Thus, 6.8 g. of methyl phenyl chloroacetate are obtained, boiling at 129° to 130°C. (corrected) at 13 to 15 mm.

(b) Polyhydric Alcohols

For the preparation of propylene chlorohydrin, $CH_2Cl \cdot CH_2 \cdot CH_2OH$, from propylene glycol, Derick and Bissell [154] give the following directions based on those of Carius.[155] A mixture of 250 g. of trimethylene glycol, 1,3-dihydroxypropane, and 450 g. of sulfur monochloride (S_2Cl_2) is shaken. It becomes warm and sulfur dioxide is evolved copiously

[151] Norris, *Am. Chem. J.*, **38**, 642 (1907).
[152] Faworski, *Ann.*, **354**, 344 (1907).
[153] Th. Wagner-Jauregg, *Helv. Chim. Acta*, **12**, 63 (1929).
[154] Derick and Bissell, *J. Am. Chem. Soc.*, **38**, 2481 (1916).
[155] Carius, *Ann.*, **124**, 257 (1862).

and elementary sulfur separates. The reaction proceeds for 1 hour without external heating and the mixture is then refluxed on a steam bath for 6 hours; finally the flask is heated for 30 minutes over a free flame. The evolution of sulfur dioxide subsides. The cooled reaction mixture is extracted with ether, the sulfur washed with more ether, and the sulfur dioxide removed from the ethereal solution by washing with a solution of sodium carbonate. Finally the ether solution is dried with sodium sulfate. A yield of 160 g. of trimethylchlorohydrin is obtained from the ether extract, corresponding to 60% of the theoretical. The boiling point is 160° to 164°C.

For larger batches the method given by Marvel and Calvery in *Organic Syntheses* [156] is preferable.

Although it is difficult, on the one hand, to replace a hydroxyl group of trimethylene glycol by chlorine, on the other hand, it is easy to perform the same operation with glycerol. Glacial acetic acid is used as catalyst, a procedure used also in industry.[157] Details for the preparation can be found in *Organic Syntheses*.[158]

Directions for the preparation of 1,3-dichlorohydrin [159] and trimethylene bromide [160] are given in *Organic Syntheses* also.

2. Phenolic Hydroxyl Group

Phenolic hydroxyl closely resembles the hydroxyl of the carboxyl group in chemical behavior. In general, it is not possible, as in alcohols, to replace the hydroxyl group by treatment with hydrogen halides. Rather, the reaction must be carried out with phosphorus halides or similar reagents. The reaction has no particular preparational importance, because the products formed are obtained more conveniently in nearly all cases by other methods. The conditions of the reaction are in all respects the same as for the preparation of acid halides. Details, therefore, are discussed below in order to avoid repetitions.

3. Hydroxyl in Carboxyl Group

The reaction takes place in general by treating the free carboxylic acids with inorganic acid halides. For preparing carboxylic acid chlorides, the following are used:

1. Phosphorus trichloride.
2. Phosphorus oxychloride.
3. Phosphorus pentachloride.
4. Thionyl chloride.
5. Sulfuryl chloride.

[156] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 533.
[157] Boehringer, German Patents, 197,308 and 197,309.
[158] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 294.
[159] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 292.
[160] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 30.

The choice of reagent depends on various circumstances. It must be taken into consideration which inorganic by-product is formed and how it can be separated from the desired acid chloride. From phosphorus trichloride is formed phosphoric acid; from phosphorus pentachloride, phosphorus oxychloride; from thionyl chloride, sulfur dioxide; from sulfuryl chloride, sulfuric acid. Phosphorus pentachloride produces the most intensive effect; its use is restricted to certain cases because of violent action. Thionyl chloride is of almost universal usefulness. Its advantage over phosphorus pentachloride lies in the fact that besides hydrogen chloride the reaction produces as by-product only sulfur dioxide. The commercial product is quite pure. Impurities found are stannous chloride (removed by distillation from 10% of its weight of quinoline), sulfur trioxide (removed by distillation from dimethylaniline), and phosphorus oxychloride, when the thionyl chloride was prepared from. phosphorus pentachloride and sulfur dioxide.

Auwers and Risse [161] observed explosion-like decompositions during the preparation of cinnamic and phenylpropiolic acid chlorides by means of technical thionyl chloride; after the thionyl chloride was redistilled once and freed from high boiling substances, no more difficulties were experienced.

The principle of the method is very simple, consisting substantially of mixing the components, sometimes with heating, and separating the reaction products. This may be done by fractionation or recrystallization. Since water is formed during the reaction, according to the general scheme,

$$2R \cdot COOH + PCl_5 \longrightarrow 2R \cdot COCl + POCl_3 + H_2O$$
$$2R \cdot COOH + SOCl_2 \longrightarrow 2R \cdot COCl + SO_2 + H_2O$$
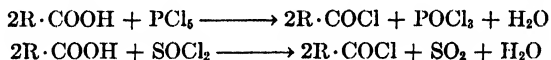
a part of the inorganic acid halide must be hydrolyzed. Therefore, it is almost always advantageous to work with an excess of the inorganic acid halide. The reaction with thionyl chloride, for instance, proceeds according to the scheme,

$$R \cdot COOH + SOCl_2 \longrightarrow R \cdot COCl + SO_2 + HCl$$
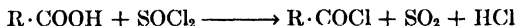
It is obvious that the inorganic halides will attack simultaneously or even preferably any hydroxyl or carbonyl group present in the molecule. Hydroxyl groups in particular may be blocked by acylation but they cannot be opened again without saponification of the acid chlorides. The chlorides of hydroxycarboxylic acids, therefore, cannot be prepared in this way.

When carboxylic acid anhydrides are used in place of the free acids, the carboxylic acid chlorides may be obtained without the formation of

[161] K. v. Auwers and E. Risse, *Ber.*, **64**, 2220 (1931).

water during the reaction; for instance

$$\begin{array}{c} R\cdot C{=}O \\ \diagdown \\ O + SOCl_2 \longrightarrow 2R\cdot COCl + SO_2 \\ \diagup \\ R\cdot C{=}O \end{array}$$
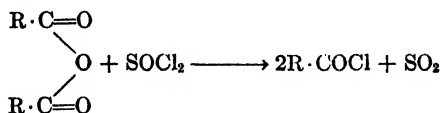
However, the usefulness of this variation is limited since most anhydrides are obtained by way of the acid chloride. Furthermore, the anhydrides appear as troublesome by-products during the treatment of some aromatic carboxylic acids with phosphorus pentachloride and can be transformed into the acid chlorides only with a large excess of pentachloride. Thus, no notable success is achieved by this variation. Only when the anhydrides are readily accessible does it prove more practical to start from them. · Such is the case with aromatic o-dicarboxylic acids, such as phthalic acid.

Several examples for the use of the reagents discussed above follow.

It is assumed that the preparation of acetyl chloride from glacial acetic acid and phosphorus trichloride is well known. Helferich and Schaefer [162] give directions for the preparation of butyryl chloride, which serve as pattern for many others.

As an example for the preparation of a complicated acid chloride Thayer's directions in *Organic Syntheses* [163] for acetylmandelyl chloride may be mentioned.

The experiences with thionyl chloride have in general been most satisfactory. However, for many preparations phosphorus pentachloride is still recommended, either because exact observations with thionyl chloride are not available, or because the low boiling point of thionyl chloride (78.8°C.) is a disadvantage. This boiling point determines the starting temperature of the reaction in open vessels and it cannot be exceeded much on account of the excess thionyl chloride that must be used.

The disadvantage of the low boiling point of thionyl chloride, therefore, excludes its use in some cases in which the reaction begins to a marked degree only at higher temperatures. Thus, H. Meyer [164] did not observe any reaction between phthalic anhydride and thionyl chloride. According to Kyrides,[165] however, an excellent yield of phthalyl chloride is obtained from thionyl chloride and phthalic anhydride when zinc chloride is used as catalyst.

·   [162] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 147.
    [163] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 12.
    [164] H. Meyer, *Monatsh.*, 22, 437 (1901).
    [165] P. Kyrides, *J. Am. Chem. Soc.*, 59, 206 (1937).

Phthalic anhydride (300 g.) and 1.5 g. of anhydrous zinc chloride are heated with stirring in a 3-necked flask with a reflux condenser to 220°C. Then 241 g. of thionyl chloride are dropped in over a period of 10 hours at such a rate that the temperature can be maintained at 220°C. The reaction mixture was distilled immediately *in vacuo*. Thus, 380 g. of distillate are obtained, boiling at 119° to 122°C., at 4.5 mm. Upon cooling, 22 g. of phthalic anhydride separate. Analysis indicates that the phthalyl chloride is 94% pure. It is quite suitable for many purposes.

The high price of thionyl chloride still prevents its general use. Phosphorus trichloride, besides being cheap, has the advantage in cases in which the carboxylic acid chloride is not used itself but for a subsequent reaction; *e.g.*, for a Friedel-Crafts synthesis. In this case the acid chloride may be extracted from the reaction mixture either with an indifferent solvent (petroleum ether, carbon bisulfide) or with the aromatic hydrocarbon which is used as a component in the subsequent condensation; isolation of the acid chloride is not then necessary. Allen and Barker's direction for the preparation of phenylacetyl chloride used for the preparation of desoxybenzoin can be found in *Organic Syntheses*.[166]

Thionyl chloride may be employed in the same manner. In this case a special separation is not necessary, because the excess thionyl chloride may be removed by distillation without difficulty. Several descriptions of this method have been given in recent times; see the preparation of 1,4-dibenzoylbutane from adipic acid [167] and of α-tetralone from γ-phenylbutyric acid.[168]

The quality of the phosphorus pentachloride used is of considerable importance both for good yields and for obtaining a pure product. o-Nitrobenzoyl chloride can be well purified by distillation at less than 1 mm. pressure only if it is prepared from very pure starting materials; otherwise, sudden decomposition and blackening frequently occur. Adams gives directions for the preparation of o-nitrobenzoyl chloride.[169] As a precautionary measure he recommends preparing the phosphorus pentachloride from phosphorus trichloride and chlorine in the laboratory. Chlorine is passed into phosphorus trichloride with occasional shaking until the weight has increased by 50%; the mass becomes solid at the end and may be used at once.

p-Nitrobenzoyl chloride may also be prepared by means of thionyl chloride.

[166] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 156.
[167] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 169.
[168] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 569.
[169] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 394.

E. Fischer [170] recommends acetyl chloride as a solvent in the preparation of amino acid chlorides. Because the acid chloride-hydrochlorides obtained are very sensitive towards moisture, a closed apparatus has to be used. The preparation of α-amino-n-butyryl chloride will serve as an example of this reaction.

The reaction is carried out in a wide mouth bottle containing an inverted fritted glass filter which is connected to a suction flask. Through a second opening of the rubber stopper a T-tube allows wash liquid to be syphoned in and dry air to be admitted.

In the sealed bottle 1 g. of anhydrous α-aminobutyric acid is shaken mechanically with 20 g. of acetyl chloride and 2.5 g. of powdered phosphorus pentachloride for 3 hours. The mother liquor is sucked off through the funnel and enough acetyl chloride admitted to cover the precipitate completely. The solvent is removed again by suction and the residue washed twice in the same manner with petroleum ether dried over phosphorus pentoxide. During this procedure the reaction bottle is cooled with ice to reduce the vapor tension. Finally the cooling bath is removed, dry air sucked through the filter to remove the petroleum ether, and the product dried in a vacuum desiccator. 1 g. of aminobutyric acid chloride-hydrochloride is obtained.

Other diluents in such reactions are chloroform, benzene, petroleum ether, or even phosphorus oxychloride. Phosphorus pentachloride is soluble in carbon tetrachloride and may therefore be used for washing if the acid chloride is only slightly soluble in it.

In many cases carboxylic acid chlorides are prepared more conveniently by double decomposition of the corresponding carboxylic acids and an organic halogen compound than with inorganic acid chlorides. Phthalyl chloride and benzotrichloride are best suited for this purpose. Whenever the products formed during the replacement of chlorine, that is phthalic acid or phthalic anhydride and benzoyl chloride respectively, are less volatile than the newly formed acid chlorides, the latter may be removed by distillation from the equilibrium and the reaction often proceeds practically quantitatively. Thus, butyryl chloride is obtained according to Kyrides [171] as follows:

A flask connected to a fractionating column is charged with 340 g. of phthalyl chloride, heated at about 140°C., and treated slowly with 132 g. of n-butyric acid. Hydrogen chloride is evolved and some butyryl chloride is distilled over by the hydrogen chloride that is evolved. The remainder is distilled in vacuo. Refractionation gives 146.5 g. of butyryl chloride (b.p. 100° to 102°C.) which represents a 91.5% yield of the theoretical.

Fumaryl chloride is obtained in nearly quantitative yield from 98 g. of maleic anhydride and 231 g. of 94% phthalyl chloride with 0.5 g. of zinc chloride as a catalyst (see page 102). The mixture is heated overnight at 140°C., and then distilled in a vacuum until phthalic anhydride begins to appear in the condenser. The distillate of 146 g. consists of 129 g. of fumaryl chloride and 15 g. of unchanged maleic anhydride.

[170] E. Fischer, *Ber.*, **38**, 606 (1905).
[171] P. Kyrides, *J. Am. Chem. Soc.*, **59**, 208 (1937).

Benzotrichloride is well suited for the preparation of phthalyl chloride from phthalic anhydride.[172]

A mixture of 225 g. of phthalic anhydride, 290 g. of benzotrichloride, and 20 g. of zinc chloride is heated for 20 hours at 110° to 120°C. and the reaction mixture fractionated at 23 mm. The fractions consist of 201 g. of benzoyl chloride, boiling at 90° to 95°C., a small second fraction, and 287 g. of phthalyl chloride boiling mostly at 150° to 152°C. The last fraction upon standing deposits a small amount of phthalic anhydride and contains 95% phthalyl chloride. The separation of phthalic anhydride from the phthalyl chloride when it is prepared in the usual manner with phosphorus pentachloride is not complete; see Ott.[173]

The preparation of ethyl chloroglyoxalate which is important for the synthesis of aldehydes according to Bouveault [174] may be effected in different ways. Either oxalic monoethyl ester is treated with thionyl chloride according to Adickes,[175] a procedure which gives only fair yields, or, by another method, cheap diethyl oxalate is used as starting material. It is transformed first into ethyl dichloroethoxyacetate with phosphorus pentachloride which splits off ethyl chloride, when distilled at atmospheric pressure, with the formation of ethyl oxalyl chloride. Sometimes this decomposition occurs spontaneously; otherwise it is necessary to catalyze it with a small amount of potassium.
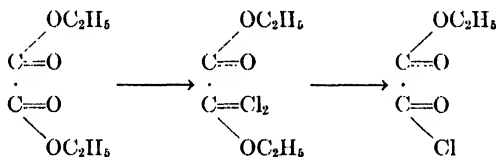
This was first observed by Scholl and Egerer [176] and explains many earlier failures. A good method is as follows:

A mixture of 200 g. of phosphorus pentachloride and 142 g. of diethyl oxalate (1 mole) is gently refluxed for 10 hours on an oil bath (maximum temperature 130°C.). The reaction mixture is carefully fractionated at reduced pressure through a column, giving phosphorus oxychloride, ethyl dichloroethoxyacetate (b.p. 96°C. at 40 mm.), a little unchanged oxalic ester, and phosphorus pentachloride. The ethyl dichloroethoxy-acetate is then repeatedly distilled at ordinary pressure with the addition of a little platinum metal until it boils at a constant temperature. The data of the boiling point of ethyl chloroglyoxalate differ somewhat; in some papers it is stated that a fraction boiling at 132° to 136°C. is obtained. Weygand found the boiling point to be lower. The quantities used in this run give a yield of 94 g. boiling at 130.5° to 132°C., corresponding to 72% of the theoretical. The preparation through oxalic acid monoethyl ester gives at best a yield of 36% of the theoretical. Since the monoester is difficult to prepare and

[172] P. Kyrides, *J. Am. Chem. Soc.*, **59**, 207 (1937).
[173] Ott, *Ann.*, **392**, 273 (1912).
[174] L. Bouveault, *Bull. soc. chim.*, **17**, 363 (1897); **15**, 1017 (1896).
[175] F. Adickes, *J. prakt. Chem.*, **130**, 163 (1931).
[176] Scholl and Egerer, *Ann.*, **397**, 326 (1913).

since the prices for phosphorus pentachloride and thionyl chloride are about equal, the method described should be first choice.

The preparation of acid bromides may be carried out in an analogous manner by means of phosphorus tribromide. It is worth noting that phosphorus pentabromide cannot be used. Instead of the tribromide, red phosphorus and bromine may be used, with equal success. The acid bromides have no general preparational importance, but acetyl bromide is used in carbohydrate chemistry.

To prepare acetyl bromide, 10 g. of red phosphorus are added to 150 g. of glacial acetic acid, and 400 g. of bromine are dropped in slowly. After the mixture has been refluxed for 1 hour, the acetyl bromide formed is distilled off; it boils at 76°C.

The preparation of oxalyl bromide illustrates the convenience of preparing certain bromides by replacing chlorine with bromine. Oxalic acid and phosphorus pentabromide react with decomposition of oxalic acid to carbon dioxide and carbon monoxide, with the liberation of hydrogen bromide.

Therefore, Staudinger and Anthes [177] pass four times the calculated amount of hydrogen bromide through 100 g. of pure oxalyl chloride during 12 hours and allow the mixture to stand 6 hours. The reaction product upon fractionation yields 146 g. of oxalyl bromide, boiling between 100° and 106°C. It is cooled slightly by bromine which can be removed by shaking with mercury. The pure oxalyl bromide has a boiling point of 102° to 103°C. at 720 mm., and a melting point of −19.5°C. It undergoes decomposition on standing, especially in light.

Acid iodides may be prepared in a corresponding manner by means of phosphorus triiodide or phosphorus and iodine. In many cases, however, the preparation from acid chlorides by reaction with calcium iodide is more convenient; see Spindler.[178]

The method of preparing aldehyde and ketone dichlorides is not different from the one of preparing acid chlorides. However, it is usually easier to isolate the reaction products because they are more stable.

D. Replacement of Amino Nitrogen by Halogen

Diazonium Compounds—The reaction known as "diazotization" is performed in different ways, depending on the conditions. If solutions of diazonium compounds are desired for coupling, for the Sandmeyer reaction, or for another subsequent reaction, the principle of the method is as follows:

If the base to be diazotized is soluble in strong acids, its mineral acid solution is treated, generally at low temperatures, with nitrous acid
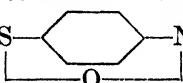
[177] Staudinger and Anthes, *Ber.*, **46**, 1431 (1913).
[178] Spindler, *Ann.*, **231**, 272 (1885).

mostly in the form of sodium nitrite. The solution of the diazonium salt is formed according to the following equation: $R \cdot NH_2 \cdot HX + NaONO + HX \rightarrow R \cdot N_2X + NaX + 2H_2O$.

If the acid salt of the amine is only slightly soluble in acids, the aryl-ammonium salt is divided as finely as possible by rapid crystallization of the warm solution. It is then stirred into a sodium nitrite solution, often yielding a solution of the diazonium compound.

If the amine is soluble in alkali, as is the case with aminosulfonic acids, the alkaline solution of the aminosulfonic acid is mixed with sodium nitrite and added to the mineral acid. A crystalline compound separates which was formerly designated as "inner diazonium salt," e.g.,

O_2S—⟨ ⟩—N_2, diazobenzenesulfonic acid from sulfanilic acid. Now
$\quad$└———O———┘

it is believed to be a zwitterion, $^-O_3S \cdot C_6H_4N_2{}^+$, a formula agreeing very well with the low solubility and high melting point of the substance.

Nearly all diazonium compounds are extremely unstable and are fairly safe only when damp or in solution. Large amounts of diazonium compounds have to be handled carefully because the decomposition according to the scheme, $R \cdot N_2X + H_2O \rightarrow ROH + N_2 + HX$, when once started, may increase to explosive violence if the heat of reaction is not removed. The diazonium salts of nitro compounds are relatively stable.

The proper method of diazotization is most important for the subsequent reactions with the diazonium compounds. The beauty of the tone of azo dyes in particular depends greatly on the care with which a large excess of nitrous acid is avoided. However, a definite excess of acid is necessary in order to avoid the formation of diazoamino compounds which might otherwise be formed by the side reaction, $R \cdot NH_2X + H_2N \cdot R \rightarrow R \cdot N:N \cdot NHR + HX$. An average of 2.5 equivalents of acid is necessary for each amino group. For some amines which couple easily in acid solution, such as α-naphthylamine, 3 to 4 equivalents are necessary. Because the ambiguous designation "concentrated hydrochloric acid" may mean acids of densities of 1.19, 1.18, 1.15, or 1.12, care has to be exercised when old methods are followed. It is advisable to recalculate the molecular proportions.

The diazotization reaction does not proceed instantly as does an ionic reaction. Although in most cases it is very fast, at least as long as the concentration of the amine is still fairly high, instances exist in which the reaction takes a longer time. The end-point of the reaction may be recognized easily by either of two tests.

1. Determination of the presence of nitrous acid; potassium iodide-starch paper shows a blue coloration.

2. Determination of the absence of a precipitate or of a yellow coloration after the excess mineral acid has been neutralized; if free amine is still present, diazoamino compounds are formed.

The commercial kinds of sodium and potassium nitrites always contain impurities. The nitrite content of the product can be determined by titration and taken into account when it is used. Sometimes it is practical to store a solution of 40% nitrite and measure the amount needed. In this case the test for free nitrous acid serves only for checking the progress of the diazotization. Otherwise, the commercial product may be assumed to be 90 to 95% sodium nitrite. The solution is added in smaller portions towards the end so that a considerable excess of nitrous acid may be avoided. When the reaction with potassium iodide-starch paper is tested, some time should elapse between tests. The reaction should occur instantly when the solution is tested after 10 minutes. In dubious cases the reaction of the solution may be tested further with Congo paper. During the reaction hydrogen ions disappear from the reaction mixture, first because of the formation of neutral salts, then because the diazonium compounds, contrary to the salts of the free amine, are not hydrolyzed. If the color of the indicator is not changed to a distinct blue, it may be well to increase the acid concentration towards the end of the reaction lest the diazotization should not proceed further.

Subsequent reactions of preparative importance which may be performed with diazonium salt solutions are as follows:

1. Reduction to arylhydrazines.
2. Reductive cleavage to hydrocarbons.
3. Changing to phenols by boiling.
4. Sandmeyer reaction, yielding halides or cyanides.
5. Coupling.

Directions for the preparation of certain diazonium salt solutions are described together with the subsequent reactions. The description is limited at this point to a few examples for the purpose of a general survey.

1. Benzenediazonium Chloride Solution. To a mixture of 20 cc. of hydrochloric acid ($D = 1.18$) with an equal amount of water (0.25 mole of HCl) are added 9.3 g. of aniline (0.1 mole), and the solution is cooled by the addition of pieces of ice until the latter does not melt any more. Then a solution of 7.2 g. of sodium nitrite (0.1 mole, calculated for 90% nitrite) in 200 cc. of water is slowly added with stirring. The solution should always contain pieces of ice; in all 70 g. of ice are used. The diazonium chloride solution is then 10%. If stronger solutions are desired, the reaction flask is cooled externally by means of a freezing mixture and less or no ice is added or a more concentrated solution of sodium nitrite may be used.

The diazotization is completed when a sample instantly gives a blue coloration with potassium iodide-starch paper shortly after the addition of sodium nitrate, or when the solution shows no yellow coloration on standing after the addition of sodium acetate.

It is advisable before larger batches are run with amino compounds of unknown origin (of dubious purity) to determine the "diazotization value" of a sample in the above manner; namely, to determine the amount of a nitrite solution of known content (or else of known concentration with unknown purity of the nitrite) which is just enough for complete diazotization. Thus, the time-consuming tests for completion during the main run may be avoided.

2. Diazobenzenesulfonic Acid. Anhydrous sulfanilic acid (17.3 g. = 0.1 mole) is dissolved with heating in a solution of 4 g. of sodium hydroxide in 50 cc. of water, and 8 g. of sodium nitrite are added. The mixture is cooled to 50°C. and slowly run, with stirring, into a mixture of 100 cc. of 20% sulfuric acid and 100 g. of ice. After 1 hour the precipitate is filtered with suction, washed free from acid with as little ice-cold water as possible, and then with alcohol and ether. The yield amounts to 16 to 18 g. The compound is stable when kept away from light, but occasionally it explodes violently at the slightest touch.

In this case it is impractical to test for completion of the reaction; hence the degree of purity of the sodium nitrite used has to be established first. A content of 96% has been assumed.

The preparation of solid diazonium salts should be avoided whenever possible. Small amounts of solid benzenediazonium chloride may be obtained as follows:

Aniline hydrochloride (6.5 g.) is dissolved in 50 cc. of absolute ethanol, 2 to 3 drops of concentrated hydrochloric acid ($D = 1.18$) are added, and, after the mixture is cooled to 5°C., 8 g. of isoamyl nitrite are added. After no more free aniline is present, as determined by testing a small sample with sodium acetate (see above), ether is added to precipitate the benzenediazonium chloride and the solid compound is filtered off by suction. It is kept moist with ether. When dry it is a dangerous explosive which detonates violently at the slightest provocation. Any unused diazonium chloride should be made harmless by the addition of water.

The aqueous solutions of the diazonium salts are in equilibrium with the diazonium hydroxides or the diazotates, depending on the acid concentration.

$$R \cdot N_2^+ + Cl^- + HOH \rightleftharpoons R \cdot N{:}N \cdot OH + HCl \rightleftharpoons R \cdot N{:}N \cdot Cl + H_2O$$

In a strongly alkaline medium, solutions of syn-diazotates are formed first; these change to anti-diazotates on being heated.

$$\text{Syn-diazotate} \quad \begin{matrix} R \cdot N \\ \parallel \\ NaO \cdot N \end{matrix} \qquad \text{Anti-diazotate} \quad \begin{matrix} R \cdot N \\ \parallel \\ N \cdot ONa \end{matrix}$$

For the preparation of benzene syn-diazotate and benzene anti-diazotate 30 g. of potassium hydroxide are melted with 10 cc. of water in a silver or copper crucible. After the mixture is cooled to room temperature, 25 cc. of a 15% solution of benzenediazonium chloride are mixed with the slurry. The benzenediazonium chloride solution is prepared as above with 30 g. of ice instead of 70 g. The solution clears up and contains the syn-diazotate which couples immediately with R-salt (sodium salt of 2-naphthol-3,6-disulfonic

acid). To effect rearrangement into the anti-diazotate, the syn compound is heated carefully (goggles) to 130°; after several minutes the boiling mass suddenly solidifies. The temperature is raised to 140°C. and then lowered to 100°C. and the mixture diluted with 30 cc. of water to effect solution. After the material is cooled to room temperature, the potassium anti-diazotate is filtered off, dissolved in the least possible amount of alcohol at 50°C., and the solution filtered. Several times its volume of ether are added to the cooled solution and silvery leaflets of anti-diazotate are precipitated. The yield is 2 g.

p-Nitrobenzene anti-diazotate [179] is obtained as follows:

A hot solution of 13.8 g. of p-nitraniline in 50 cc. of hydrochloric acid ($D = 1.18$) and 50 cc. of water is poured onto 100 g. of ice and diazotized with 8 g. of sodium nitrite in 25 cc. of water. The diazonium solution is rapidly stirred at 50° to 60°C. into 400 cc. of an 18% solution of sodium hydroxide. When cooled, the golden yellow sodium salt of p-nitrophenylnitramine ($NO_2 \cdot C_6H_4 \cdot N:NONa$ or $NO_2 \cdot C_6H_4 \cdot N:NNa$) crystallizes and
$$\overset{..}{O}$$
is recovered by filtration. A yield of 96% of the theoretical is obtained. For purification, it is dissolved in 90% alcohol at 60°C., filtered, and the solvent partially evaporated.

The diazotization of weak bases presents mounting difficulties; for instance, trihalogenoanilines and 2,4-dinitroaniline can be diazotized only at very high acid concentrations. The reason for this is that the concentration of the ammonium salt necessary for the reaction is too low in weakly acid solutions of such amines. Schoutissen [180] has shown that, when the high acid concentration is established by using concentrated sulfuric acid, diazotization is not successful, because the nitrous acid is bound by sulfuric acid as nitrosylsulfuric acid. This theory is confirmed by the behavior of such compounds as p-aminobenzaldehyde which cannot be diazotized with sodium nitrite in concentrated sulfuric acid. It is possible to hinder the formation of nitrosylsulfuric acid by the addition of a weak acid, such as phosphoric acid. Phosphoric acid is better than acetic acid which under certain conditions promotes side reactions; see Schoutissen [181] and Misslin. [182]

3 g. of 2,4-dinitraniline are dissolved in 15 cc. of concentrated sulfuric acid. To this solution, cooled to 0°C., is added nitrosylsulfuric acid prepared from a little more than the theoretical quantity of sodium nitrite in 15 cc. of concentrated sulfuric acid. While being stirred vigorously, 60 cc. of phosphoric acid ($D = 1.7$) are added. After the mixture has been allowed to stand for 30 minutes at 0°C., 2 g. of urea are added to decompose excess nitrous acid, and the solution is poured on ice. The very faintly yellow colored diazonium salt solution is completely clear and it yields the theoretical amount of azo dye when coupled with β-naphthol.

Picramide is diazotized as follows: To a solution of 3.3 g. of picramide in 15 cc. of nitrobenzene is added 1 g. of sodium nitrite in 10 cc. of concentrated sulfuric acid and the

[179] Schraube and Schmidt, *Ber.*, 27, 518 (1894).
[180] J. Schoutissen, *J. Am. Chem. Soc.*, 55, 4531, 4535 (1933).
[181] J. Schoutissen, *Rec. trav. chim.*, 40, 753 (1921).
[182] Misslin, *Helv. Chim. Acta*, 3, 626 (1920).

mixture is cooled to −10°C. The temperature is kept below 0°C. as 20 cc. of phosphoric acid ($D = 1.7$) are added with vigorous stirring. After 30 minutes, 2 g. of powdered urea are added and then a little more than the theoretical amount of β-naphthol. The pale yellow colored solution turns to reddish brown. After 30 minutes the reaction mixture is poured on ice. The azo dye remains dissolved in the nitrobenzene layer. By addition of alcohol to the nitrobenzene solution 80 to 90% of the theoretical amount crystallizes. The diazonium solution can be coupled with phenol, anisole, and phenetol by a similar procedure.

The same conditions that prevail during the diazotization of weak bases are present during the tetrazotization of phenylenediamines. The diazotization of the first amino group proceeds normally, but the aminobenzenediazonium salt is about as weak a base as is 2,4-dinitraniline, and the diazotization of the second amino group can be accomplished only under special conditions. In such cases the phosphorus acid method as recommended by Schoutissen (see above) is also suitable, but the tetrazotization of o-phenylenediamine, which had been attempted unsuccessfully many times before, was·not completely successful. That it was at least partially successful was proved by the formation of o-diiodobenzene.

For the diazotization of weak bases, *e.g.* dinitronaphthylamines, Hodgson and Walker [183] suggest dissolving the nitroamine in 12 times its weight of hot glacial acetic acid, quickly cooling the solution to room temperature, and stirring it into a solution of sodium nitrite in sulfuric acid. The latter solution is prepared by adding finely powdered sodium nitrite to cold, concentrated sulfuric acid; the mixture is then heated to 70°C., to dissolve the nitrite, cooled, and, if necessary, filtered from deposited sodium bisulfate. The diazotization is carried out below 20°C., and 10% excess of nitrite is used. The 100% excess of sodium nitrite recommended for diazotization in concentrated sulfuric acid is not necessary when the method described above is used. It is absolutely necessary to add the glacial acetic acid solution to the sulfuric acid solution of the amine. With the reverse procedure the sulfate of the base is precipitated and the velocity of the reaction decreases considerably.

If diazonium solutions prepared in this way are to be used for the Sandmeyer reactions, dilution has to be avoided; otherwise tarry byproducts and sometimes biaryls are formed.

Preparation of Halides from Diazonium Compounds

The Sandmeyer reaction is of prime importance for preparational work. It proceeds according to the scheme, $R \cdot N_2 X \rightarrow RX + N_2$. In principle, it is possible in the aliphatic as well as in the aromatic series, but actually it is important in the aromatic series only. Here the course $R \cdot H \rightarrow R \cdot NO_2 \rightarrow R \cdot NH_2 \rightarrow R \cdot X$ is often the only means of intro-

[183] H. Hodgson and J. Walker, *J. Chem. Soc.*, 1933, 1620.

ducing halogen and other substituents in definite positions in relation to one another. Thus, *m*-dihalogenobenzenes are obtained in the following manner:
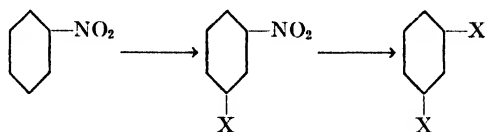
or
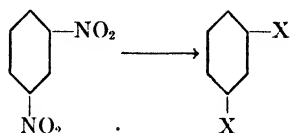
Nitrobenzene is used as an intermediate, because the nitro group directs towards the *m* position. Furthermore, many aromatic iodo compounds can be satisfactorily prepared in this way only because of the difficulty of introducing iodine directly into the nucleus. The cyano group may be introduced by the Sandmeyer reaction also. Because of the similarity of methods this variation is dealt with in this chapter, in spite of the fact that, from the point of view of classification, it belongs in the chapter on the formation of carbon-carbon bonds (see page 366), where more details can be found.

The procedure depends on the halogen or pseudohalogen to be introduced and on other circumstances.

Simplest is the introduction of iodine, because the diazonium hydriodides are decomposed readily in hot aqueous solutions; phenols which might be expected to appear according to the scheme $R \cdot N_2X + H_2O \rightarrow R \cdot OH + HX + N_2$, are not formed as by-products. Under similar conditions diazonium chlorides and bromides, however, in the main yield phenols. The reaction may be directed in the desired course by means of copper powder or cuprous halides. It is possible to prepare aromatic bromides from a solution of the corresponding diazonium chloride or sulfate. The reason for this change lies in the fact that cuprous halides first form molecular compounds. ·   .

Cyanides are prepared in most cases with alkaline cuprous cyanide solutions.

Examples of Preparation of Iodides

1. Iodobenzene. This is obtained according to Neumann [184] as follows: A diazonium chloride solution is prepared (see page 108) from a solution of 48 g. of aniline in a mixture of 1 liter of water and 100 g. of hydrochloric acid ($D = 1.18$) with 35 g. of sodium nitrite. Then a concentrated aqueous solution of 83 g. of potassium iodide is added. The evolution of nitrogen which starts immediately is allowed to subside and finally the mixture

[184] Neumann, *Ann.*, 241, 35 (1887).

is heated on a steam bath until the reaction is finished.   Sodium hydroxide is added to render the solution alkaline and the lower layer of iodobenzene is separated.   The yield is almost quantitative.   For the preparation of iodobenzene by direct iodination see page 90.

2. Pentaiodobenzene.   10 g. of 2,3,4,5-tetraiodoaniline [185] are added to 50 cc. of ice-cold concentrated hydrochloric acid, followed by 1.5 g. of finely powdered sodium nitrite, and the mixture is stirred well for 2 hours.   Then an ice-cold solution of 4 g. of potassium iodide in 10 cc. of water is added slowly, the solution heated to 40°C., and after the addition of 2 liters of ice water the precipitated pentaiodobenzene is filtered off.

3. β-Iodoanthraquinone.   According to Kaufler,[186] a suspension of 20 g. of β-amino-anthraquinone in 150 cc. of glacial acetic acid is heated to boiling, 15 cc. of concentrated hydrochloric acid are added, the solution is brought to a boil again, and, after rapid cooling, 20 g. of isoamyl nitrite are added.   The mixture is allowed to stand for 2 hours at room temperature with occasional stirring.   The anthraquinonediazonium chloride which contains a little hydrogen chloride is filtered off and washed with ether.   The filtrate deposits some more diazonium chloride.   Therefore it is advantageous to saturate the reaction mixture with ether before the filtration.   The filtered diazonium salt is shaken with portions of water of 30°C. until the extracts are not colored any more by coupling when treated with alkaline phenol solution; the total amount of water extract should be about 3 liters.   About 3 g. of aminoanthraquinone which is formed by hydrolysis remain as a residue.   To the combined extracts a solution of 25 g. of potassium iodide is added.   Evolution of nitrogen and separation of a little iodine take place. After standing for several hours the solution is boiled, filtered hot, and washed with sodium hydroxide in order to remove hydroxyanthraquinone which is formed as a by-product.   Vacuum distillation of the crude product (22 g.) gives 17 g. of pure β-iodo-anthraquinone, corresponding to a yield of 67% of the theoretical.   Occasionally yields up to 75% are obtained.

4.   In a similar manner aminobenzenecarboxylic acids give the analogous iodine compounds.   Thus, Gabriel and Herzberger [187] prepared o-iodocinnamic acid and Kloeppel [188] obtained iodotoluic acids; see Abbes.[189]

5. o-Nitroiodobenzene.   This can be prepared [190] as follows: 100 g. of o-nitraniline are added to 1 liter of water.   After addition of 600 g. of concentrated sulfuric acid the clear solution is cooled to 50°C. and diazotized with the corresponding amount of sodium nitrite while the temperature is not allowed to exceed 10°C.   The diazonium sulfate solution is added in portions to a solution of 200 g. each of potassium iodide and iodine in 200 cc. of water.   After the nitrogen evolution has subsided, the mixture is heated on the steam bath for some time, the iodine removed by shaking the warm solution with sulfite solution, and the o-iodonitrobenzene allowed to crystallize in the cold.   The yield is quantitative, and the product melts at 54°C.   For the addition of iodine see Baeyer.[191]

Examples of Preparation of Bromides

Bigelow's methods for the preparation of o-bromotoluene and p-bromo-toluene can be found in *Organic Syntheses.*[192]

[185] Willgerodt and Arnold, *Ber.*, **34**, 3353 (1901).
[186] Kaufler, *Ber.*, **37**, 60 (1904).
[187] Gabriel and Herzberger, *Ber.*, **16**, 2037 (1883).
[188] Kloeppel, *Ber.*, **26**, 1733 (1893).
[189] Abbes, *Ber.*, **26**, 2955 (1893).
[190] Baeyer, *Ber.*, **38**, 2760 (1905).
[191] Baeyer, *Ber.*, **38**, 589 (1905).
[192] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. I, 2nd ed., Wiley, New York, 1941, pp. 135, 136.

A variation of the Sandmeyer reaction proceeds by way of diazonium perbromides, $R \cdot N_2Br_3$, which are formed from monobromides and bromine in aqueous solution. They are obtained by diazotization in a mixture of hydrobromic acid and bromine. When boiled with alcohol the perbromides are changed to bromides according to the scheme, $R \cdot N_2Br_3 \xrightarrow{2H} R \cdot Br + N_2 + 2HBr$. The alcohol acts as a reducing agent. For more about this reaction see Saunders [193] and Richter.[194]

Examples of Preparation of Chlorides

Cuprous chloride, which is necessary for the reactions below, may be prepared according to one of the following methods when it is not commercially available.

(a) In a 12 liter flask a solution of 1250 g. of copper sulfate and 325 g. of sodium chloride in 4 liters of hot water is prepared. A solution of 265 g. of sodium bisulfite and 175 g. of sodium hydroxide in 2 liters of water is then added during 5 to 10 minutes with vigorous stirring. When the mixture is cooled, colorless cuprous chloride crystallizes. It is washed by decantation.

(b) A solution of 250 parts of copper sulfate and 120 parts of sodium chloride in 500 parts of water is boiled with 1000 parts of concentrated hydrochloric acid and 130 parts of copper metal (thin sheet or chips) until the mixture becomes colorless. After the solution has been made up to 2036 parts (by weight) with concentrated hydrochloric acid, it contains about 10% of cuprous chloride and can, after decantation from sediment, be stored if air is excluded.

If crystalline cuprous chloride is desired, the filtered solution is diluted with water and allowed to cool.

(c) Cuprous chloride, partly oxidized during storage, is dissolved in warm hydrochloric acid, preferably with the addition of ammonium chloride, and boiled with copper or sodium sulfite until a colorless solution is obtained. After the addition of water and cooling, the precipitate is filtered off.

o-Chlorotoluene and *p*-chlorotoluene can be prepared by the procedure of Marvel and McElvain; see *Organic Syntheses*.[195]

m-Chlorobenzaldehyde cannot be prepared by direct substitution; Erdmann gives the following directions.[196]

m-Nitrobenzaldehyde (50 g.) is reduced with 225 g. of stannous chloride and 300 cc. of concentrated hydrochloric acid. The usual removal of tin by means of zinc is not mentioned, although it is better to treat the solution with excess zinc dust and to filter the solution. The *m*-aminobenzaldehyde solution is diazotized with 23 g. of sodium nitrite and added to a boiling solution of cuprous chloride acidified with hydrochloric acid. The *m*-chlorobenzaldehyde is steam-distilled.

[193] Saunders, *Chem. Zentr.*, 1892, I, 169.
[194] Richter, *Ber.*, 8, 1428 (1875).
[195] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 170.
[196] Erdmann, German Patent, 31,842.

Preparation of Nitriles from Diazonium Compounds

The necessary solution of cuprous cyanide can be prepared by several methods:

(*a*) To a warm solution of 50 parts of copper sulfate in 200 parts of water a solution of 55 parts of potassium cyanide in 100 parts of water is added with heating. The cupric cyanide formed is decomposed to cuprous cyanide while cyanogen escapes. The procedure requires an efficient hood.

(*b*) Cuprous chloride, prepared from 1250 g. (5 moles) of copper sulfate according to the directions given above, is suspended in 2 liters of water contained in a 15 liter flask. A solution of 650 g. of potassium cyanide (about 13 moles for 98% cyanide) in 1 liter of water is added. Cuprous cyanide is formed in solution as much heat is liberated. Finally the solution is cooled.

1. Methods for the preparation of *o*- and *p*-tolunitrile are given in *Organic Syntheses*.[197]

2. A laboratory method for the preparation of small amounts of *p*-tolunitrile is described below. This method is less elaborate than the one in *Organic Syntheses*. It is carried out in acid or much less alkaline solution. Hydrocyanic acid, however, is generated, which in small amounts is readily removed through the hood, but for larger batches the hydrogen cyanide formed would be a source of grave danger practically impossible to control.

A cuprous cyanide solution is prepared from 50 g. of copper sulfate in a 2 liter flask according to the method given above (*b*). At the same time, a diazonium solution is prepared in the usual manner from 20 g. of *p*-toluidine and 50 g. of hydrochloric acid (*D* = 1.18) in 150 cc. of water and 16 g. of sodium nitrite in 80 cc. of water. The diazonium solution is added with vigorous stirring to the cuprous cyanide solution heated to 50° to 60°C. The mixture is finally heated for 15 minutes on a steam bath and steam-distilled. The distillate is extracted with ether, and the cresol which contaminates the product is removed by shaking with a solution of sodium hydroxide. On distillation about 15 g. of *p*-tolunitrile boiling at 218°C. are obtained.

Preparation of Fluorides from Diazonium Compounds

The introduction of fluoride into the aromatic nucleus can readily be accomplished in many cases [198] by way of borofluoride complexes which are easily accessible from diazonium chlorides. These are quite easily decomposed by heat according to the equation, $ArN_2BF_4 \rightarrow ArF + N_2 + BF_3$. The borofluoride complexes are difficultly soluble, and hence easy to isolate. They can be well dried, are not explosive, and, therefore, may be used easily in larger quantities without danger.

They are prepared by diazotization as usual in concentrated hydrochloric acid solution and by treating the diazonium solution with excess

[197] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 514.
[198] G. Schiemann, *J. prakt. Chem.*, 140, 97 (1934).

concentrated fluoboric acid (about 40%).   The commercial fluoboric acid contains fluosilicic acid but in general this is immaterial.   The yields are dependent on the one hand upon the solubility of the diazonium fluoborate complexes, which is as usual greatest with o-substituted benzene derivatives.   The yields are usually in the neighborhood of or in excess of 70% of the theoretical.   On the other hand, it is evident that the yields from the thermal decomposition of the complexes are better the lower the decomposition temperature.   Yields of 40% are obtained even when the decomposition temperature lies around 200°C., as is the case with phenylenediamines.   The boron fluoride generated during the decomposition is best considered lost.   If an attempt is made to absorb it in sodium hydroxide or sodium carbonate solutions, clogging of the absorption tubes may occur.   The decomposition is best carried out in a glass distilling flask filled to nine-tenths of the bulb capacity.   The top edge of the charge is heated at one point with a free flame until the reaction starts. It usually continues by itself and should be so regulated by heating and cooling that the bubbles of gas which rise in one or more connected gas washing bottles filled with water can still be counted.   In the water of the washing bottles, which should be cooled with ice, boric or silicic acids may separate in large quantities; therefore care must be exercised to prevent clogging, and, if necessary, the rubber connections should be cut in order to avoid high pressure in the reaction flask.   Some diazonium borofluorates, especially from nitranilines, must be mixed with sand or soda ash since otherwise they might decompose too violently.

Fluorophenols and fluorocarboxylic acids cannot be prepared in this way because their diazonium borofluorides do not separate from aqueous solutions.   To prepare fluorophenols, phenol ethers are best used as starting materials and the fluorophenol ethers decomposed with hydriodic acid (see p. 117).   For the preparation of fluorocarboxylic acids, aminocarboxylic esters are used as the starting material.   This method is more convenient and gives better yields than the oxidation of fluorotoluenes. In the paper of Schiemann mentioned above, directions are given for the preparation of more than 50 different mono- and difluorobenzene derivatives.   In addition it contains 78 literature references.

1. Fluorobenzene.   Flood gives directions for a modified method of Balz and Schiemann in *Organic Syntheses.*[199]

2. In the same book [200] Schiemann and Winkelmüller describe the preparation of p-fluorobenzoic acid.

[199] A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. II, Wiley, New York, 1943, p. 295; Balz and Schiemann, *Ber.*, 60, 1188 (1927).
[200] A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. II, Wiley, New York, 1943, p. 299.

3. Directions for a method of preparing a fluorophenol by way of its methyl ether are as follows:

o-Methoxybenzenediazonium borofluoride is obtained, as greenish white needles melting at 97°C., from pure o-anisidine in the manner described above. The yield is 52% of the theoretical. 100 g. of the complex are decomposed at 125°C. The decomposition has to be sustained by heating. The distillate is dissolved in ether and the residue in the flask is steam-distilled. A total yield of 36 g. of o-fluoroanisole, boiling at 59.2°C. at 12 mm., is obtained, corresponding to 67% of the theoretical. A mixture of 41 g. of o-fluoroanisole, 50 cc. of acetic anhydride, and 90 cc. of hydriodic acid ($D = 1.96$) is refluxed for 6 hours. The reaction mixture is poured into 600 cc. of water, the acid almost neutralized with potassium hydroxide, and the still slightly acid solution extracted with ether. The ether extract is shaken with bisulfite solution until colorless and then three times with 15% sodium hydroxide solution. The alkaline solution is acidified with hydrochloric acid, extracted with ether, and the ethereal solution dried with calcium chloride. o-Fluorophenol (30 g.), boiling at 46°C. at 10 mm., is obtained, a yield of 82% of the theoretical.

E. Replacement by Mercury of Halogen

Of the organometallic compounds proper which serve as important intermediates in organic reactions, some mercury derivatives should be mentioned, by means of which hydrogen may be replaced by halogen. They possess the general formula $R \cdot HgX$ and correspond, therefore, to the Grignard compounds. They are, however, prepared by different procedures.

Of prime importance for preparative work is the mercuration which proceeds according to the scheme

$$R \cdot H + (CH_3 \cdot COO)_2Hg \longrightarrow R \cdot Hg \cdot OOC \cdot CH_3 + CH_3 \cdot COOH$$
$$R \cdot Hg \cdot OOC \cdot CH_3 + NaX \longrightarrow R \cdot HgX + CH_3 \cdot COOH$$
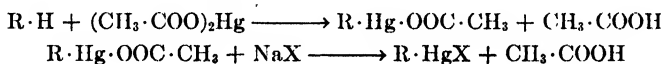
It can generally be used successfully with aromatic hydrocarbons, but in this case it offers no advantages because the halides formed in the subsequent reactions are in most cases more conveniently prepared by other means.

$$2R \cdot HgX + 2X'_2 \longrightarrow 2R \cdot X' + HgX_2 + HgX'_2$$
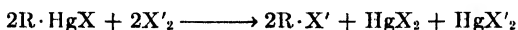
The substituted aromatics, however, which easily react with mercury compounds, may yield valuable products. Thus, the preparation of o-iodophenol, for instance, by way of o-chloromercuriphenol (see below) is preferable to other methods. Furthermore, the chloromercury compounds are so stable that they may undergo considerable transformations before the —HgCl group is replaced by halogen. Thus, p-tolylmercuric chloride, $CH_3 \cdot C_6H_4 \cdot HgCl$, is obtained from toluene either by direct mercuration according to Dimroth [201] (see also Steinkopf [202]) or by way

[201] Dimroth, *Ber.*, **32**, 761 (1899).
[202] W. Steinkopf, *Ann.*, **413**, 329 (1917).

of sodium *p*-toluenesulfonate or *p*-toluenesulfinic acid according to Peters.[203]   *p*-Tolylmercuric chloride may also be transformed to *p*-chloromercuribenzoic acid by means of an alkaline permanganate solution.[204] When *p*-chloromercuribenzoic acid is treated with iodine, it is transformed into *p*-iodobenzoic acid.[205]

As examples for the preparation and subsequent transformation of mercury compounds, the preparation of *o*-chloromercuriphenol by the method of Whitmore, Hanson, and Middleton [206] and a method for its transformation to *o*-iodophenol by Whitmore and Hanson [207] may be mentioned.

[203] Peters, *Ber.*, **38**, 2569 (1905).
[204] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 159; *J. Am. Chem. Soc.*, **48**, 534 (1926).
[205] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 325.
[206] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 161; *J. Am. Chem. Soc.*, **43**, 622 (1921).
[207] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 326.

Formation of Carbon-Oxygen Bonds

The oxygen compounds of organic chemistry exhibit greater variety than the halogen compounds, owing to the larger number of valences of the oxygen atom.

In this section the bivalent oxygen only will be treated; the "tetravalent" is not really tetravalent but has a coordination valency of 3.

The peculiarity of the oxygen compounds makes it seem advantageous to treat the splitting of the C—O—C bonds in a separate section of the book. Otherwise, the subdivisions of this section are as much as possible the same as in the preceding sections.

I. BY ADDITION

A. Addition of Oxygen to Ethylene Bond

Molecular oxygen, O_2, like the halogen molecule, in the primary stage certainly adds to the double bond; that is, to the carbon-carbon bond as well as to the carbon-oxygen bond. In most cases, however, no structurally saturated products are formed the formulas of which should be

$$R_2:C—C:R_2 \qquad \text{or} \qquad R:C—O$$
$$\overset{|}{O}—\overset{|}{O} \qquad\qquad\qquad \overset{|}{O}—\overset{|}{O}$$
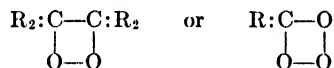
Common aliphatic ethylene bonds are relatively stable towards molecular oxygen, at least oxygen is not readily absorbed in large amounts by unsaturated hydrocarbons. Greater addition tendency is shown by the double bonds in compounds such as asymmetrical diphenylethylene and in unsaturated hydroaromatic compounds; this is also true in the case of aldehydes.

It is difficult to decide what reaction mechanism should be considered for all these cases. It is certain that more frequently than was believed formerly molecular oxygen does not attack the double bond in unsaturated compounds at all, but rather it attacks saturated carbon atoms, even though the latter are directly adjacent to the double bonds and may be considered activated by them. A good example of this is offered by cyclohexene which, as was known for a long time, can react quite readily with atmospheric oxygen even at room temperature. Formerly it was

supposed that a cyclohexene peroxide was formed having the formula:

$$
\begin{array}{ccccc}
CH_2 & —CH_2 & —CH & —O \\
| & & | & | \\
CH_2 & —CH_2 & —CH & —O
\end{array}
$$
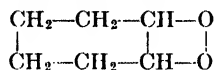
Recently, however, Criegee [1] showed that the reaction product possesses the constitution of a cyclohexenyl hydroperoxide of the formula:

$$
\begin{array}{ccc}
H_2C & —CH_2 & —CH \\
| & & \| \\
H_2C & —CH & —CH \\
& | & \\
& OOH &
\end{array}
$$
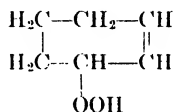
The reaction of cyclohexene and oxygen, therefore, does not represent an addition of the oxygen molecule to the double bond, but rather a reaction type peculiar to the oxygen molecules and hardly known otherwise. It is the insertion of an oxygen molecule between a carbon and hydrogen atom, or, to state it more plainly, it is an addition of a compound $R \cdot H$ to the oxygen molecule according to the scheme $O:O + R \cdot H \rightarrow R \cdot OO \cdot H$. This type of reaction seems to play a much larger part than might have been supposed formerly; it will be discussed in detail in the section beginning on page 128.

The addition of active oxygen, ozone, proceeds more readily. As far as is known ozone always attacks the unsaturated points in the molecule and probably first forms real addition compounds which, however, have not been isolated thus far. Staudinger [2] was the first to realize that the so called ozonides, that is the first products between ozone and unsaturated compounds which can be isolated and defined, are not addition compounds. They no longer contain the original carbon structure of the unsaturated compound, but rather this structure has been ruptured according to the scheme:

$$
R_2{:}C{:}C{:}R_2 + O_3 \longrightarrow R_2\underset{\underset{\text{O}}{\underline{\qquad}}}{C{-}OO{-}C}{:}R_2
$$
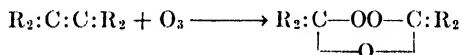
It has never been possible to recover the original carbon structure from ozonides by any reducing agent. Rieche,[3] however, was able to prepare ozonides by removing water from peroxidic compounds without ozone. The ozonides and their cleavage, therefore, will be discussed on pages 456 to 458.

The addition of molecular oxygen is of little preparational importance for laboratory use.

[1] R. Criegee, *Ann.*, **522**, 84 (1936).
[2] H. Staudinger, *Ber.*, **58**, 1088 (1925).
[3] A. Rieche, *Angew. Chem.*, **45**, 441 (1932).

More important is a reaction which proceeds according to the scheme:

$$R_2:C:C:R_2 + O \longrightarrow R_2:C\underset{O}{\overset{}{\diagdown\diagup}}C:R_2$$
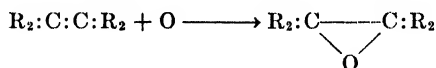
Atomic oxygen appears to add to the $C:C$ bond. This reaction will be dealt with in the section of this chapter on "oxido compounds" (see page 122).

1. Molecular Oxygen

As already mentioned above, the addition of oxygen to double bonds according to the scheme

$$>C=C< \longrightarrow \underset{O-O}{\overset{}{>C-C<}}$$
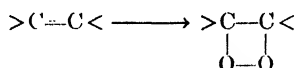
is not realized very often. The ethylene bond must be quite strongly activated if the oxygen is taken up at all and, furthermore, the primary reactions are frequently concealed by polymerizations caused by the influence of oxygen. One of the best elucidated examples is the autoxidation of 1,1-diphenylethylene. Staudinger [4] gives directions for the preparation of diphenylethylene peroxide.

In a small test-tube equipped with a cold finger, 10 g. of 1,1-diphenylethylene are illuminated with a 500 watt incandescent lamp while oxygen is passed through. After 3 days, 0.5 to 1 g. of colorless, amorphous diphenylethylene peroxide is isolated by means of petroleum ether. The substance does not show any hydroperoxide reactions proper: no iodine is liberated from potassium iodide; indigotin is not decolorized; when heated it explodes. The molecular structure of the substance is not certain. Corresponding peroxides could also be prepared from ketenes.

While these addition products are apparently not at all well defined, Windaus and Brunken [5] succeeded in preparing a very well characterized ergosterol peroxide.

A solution of 4 g. of ergosterol in 1200 cc. of 95% ethanol is heated to 60°C. and after addition of 6 mg. of eosin submitted to radiation in a large beaker as follows: A smaller beaker is inserted into the large one which contains the alcoholic solution. Inside the smaller beaker a 200 watt bulb is immersed in water which can be changed continually. The diameter of the inner beaker is 12 cm.; of the outer, 15.5 cm. In order to make better use of the light the apparatus is placed inside a box lined with mirrors. A slow stream of oxygen is passed through the ergosterol solution until, after about 3 hours, a precipitate is no longer formed with an alcoholic solution of digitonin; all the ergosterol is then used up. The larger part of the alcohol is now removed by distillation, and the crystals separating from the residue are isolated and recrystallized from alcohol or

[4] H. Staudinger, *Ber.*, **58**, 1075 (1925).
[5] H. Windaus and J. Brunken, *Ann.*, **460**, 227 (1928).

acetone until they show a constant melting point of 178°C.   The yield amounts to 70% of the theoretical.

The peroxide is obtained still more conveniently by direct irradiation with sunlight of alcoholic solutions of ergosterol colored with eosin.   The exposures are made for several hours in flat, loosely covered dishes filled with layers 2 to 3 cm. high.   For the reconversion of ergosterol peroxide to ergosterol see the paper of Windaus and Brunken.

Many papers by Moureu and Dufraisse are available on the addition of oxygen to the highly unsaturated systems of fulvene and of the related rubrene; see the review of Dufraisse.[6]   It is remarkable that in this case the autoxidation is readily reversed again and is accompanied by radiation of light.

2. Ozone

As explained above, the reaction between ethylene bonds and ozone effects a fundamental cleavage of the carbon bonds.   Therefore, the ozonides are treated in Chapter Twelve (page 456), even such cases as those in which the cleavage does not cause a breaking up of the chain into smaller pieces (oleic acid) and those in which only a ring is opened as with cyclohexene.

3. Oxido Compounds, Ethylene Oxides from Ethylene Derivatives

The direct addition (considered formally) of oxygen to the ethylene bond is performed with organic per acids of the general formula

$$R \cdot C \overset{\displaystyle O}{\underset{\displaystyle OOH}{\diagup}}$$
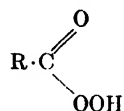
J. d'Ans and Frey [7] give a method for the preparation of peracetic acid; its reaction mechanism was more thoroughly studied later on by d'Ans and Kneip.[8]

1 mole of acetic anhydride is mixed slowly and carefully with 1 mole of hydrogen peroxide and efficient cooling with ice water is provided during the mixing.   After the addition of about 1% of sulfuric acid (calculated to $CH_3 \cdot CO \cdot O \cdot OC \cdot CH_3 + 2H_2O_2$), a second mole of hydrogen peroxide is added.   The acetic anhydride reacts violently with the hydrogen peroxide.   The mixture is allowed to stand for 12 hours at room temperature; then it is distilled between 20° and 30°C. at 10 to 20 mm. pressure.   Thus, distillates are obtained containing an average of 78% peracetic acid.   With higher concentrations of sulfuric acid the yields may be increased.   For instance, from 100 g. of acetic anhydride, 68.15 g. of hydrogen peroxide (98.45% pure) and 22.35 g. of sulfuric acid (147.56 g. of a peracetic acid of 88%) are obtained.

[6] Ch. Dufraisse, *Bull. soc. chim.*, **53**, 789 (1933).
[7] J. d'Ans and W. Frey, *Ber.*, **45**, 1848 (1912).
[8] J. d'Ans and A. Kneip, *Ber.*, **48**, 1141 (1915).

Arbuzov [9] gives somewhat different directions.

By concentrating 29% hydrogen peroxide *in vacuo* at 18 mm. until the temperature measured at the top of the column is 55°C., hydrogen peroxide of 90% H_2O_2 is obtained as residue in the flask. From a mixture of 64 g. of 90% hydrogen peroxide, 88 g. of acetic anhydride, and 18 g. of concentrated sulfuric acid, the following fractions were obtained: first fraction, 15 g. of 89% peracetic acid, boiling point up to 25°C. at 12 mm.; second fraction, 107 g. of 90.2% peracetic acid, boiling point 25°C. at 12 mm.; third fraction, 10 g. of 69% peracetic acid, boiling point 22°C. at 10 mm.

More convenient to handle is perbenzoic acid, benzoyl hydroperoxide; directions for the preparation of it are given in *Organic Syntheses*.[10]

An example of the addition reaction is the preparation of styrene oxide from styrene according to *Organic Syntheses*.[11] As an improvement of the directions found there, a vacuum distillation for the isolation of the final product might be recommended.

Cyclohexene oxide may be prepared from cyclohexene and peracetic acid according to Arbuzov and Michailov [12] as follows:

To a solution of 20.8 g. of cyclohexene in 400 cc. of anhydrous ether are added 28.5 g. of 70% peracetic acid, prepared according to the directions given above; the mixture becomes warm. After standing for 68 hours the solution is neutralized with alkali, dried over potassium carbonate, and fractionated. A yield of 13.2 g. of cyclohexene oxide is obtained, boiling at 129.5° to 130.5°C.; this corresponds to 67% of the theoretical.

Godchot and Bédos [13] recommend a different procedure without giving details. They add a solution of the calculated amount of perbenzoic acid in chloroform to a chloroform solution of cyclohexene at 0°C. and claim a theoretical yield of cyclohexene oxide, boiling at 131° to 132°C.

Contrary to earlier beliefs (see Boeseken and Schneider [14]) peracetic acid and perbenzoic acid have the same effect whenever the same indifferent solvent is used. However, solutions of peracetic acid in glacial acetic acid react differently: they give acetyl compounds of 1,2-diols which are formed by hydrolysis of the oxides.

B. Addition of Water to C—C Multiple Bonds

1. Addition of Water to Ethylene Bonds

The reaction, $R \cdot CH : CH \cdot R + HOH \rightarrow R \cdot CH_2 \cdot CHOH \cdot R$, which is simple in principle, is important as a method only in special cases. It occurs under the influence of acids and alkalies. For preparative work

[9] A. Arbuzov, *J. prakt. Chem.*, **131**, 365 (1931).
[10] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 431.
[11] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 494.
[12] B. A. Arbuzov and B. Michailov, *J. prakt. Chem.*, **127**, 97 (1930).
[13] M. Godchot and P. Bédos, *Compt. rend.*, **174**, 461 (1922).
[14] J. Boeseken and G. Schneider, *J. prakt. Chem.*, **131**, 285 (1931).

the method generally can be used only if the molecule does not contain other easily attacked groups. It is used chiefly, therefore, in work with unsaturated hydrocarbons.

During the addition of sulfuric acid at first esters, which in the presence of excess water are sometimes spontaneously saponified, are formed.

As a general rule it may be assumed that the hydroxyl group adds to that carbon atom of the two forming the ethylene bond which has less hydrogen; but this regularity is not especially pronounced.

One of the simplest cases of this kind is the formation of tertiary amyl alcohol, amylene hydrate, from amylene of fusel oil. Trimethylethylene, $CH_3 \cdot CH : C : (CH_3)_2$, so called β-isoamylene, for the most part is formed by removal of water from the main constituent, isobutylcarbinol, as well as from the active secondary butylcarbinol; the trimethylethylene adds sulfuric acid when shaken with 50% sulfuric acid in the cold. After dilution with water and boiling, tertiary amyl alcohol is formed by hydrolysis of the sulfuric acid amyl ester:

$$CH_3 \cdot CH_2 \cdot \underset{OSO_3H}{C} : (CH_3)_2 \longrightarrow C_2H_5 \cdot COH : (CH_3)_2$$
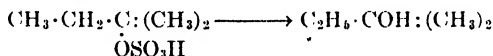
Details for this procedure are given by Adams.[15]

A mixture of 500 g. of ice and 500 g. of concentrated sulfuric acid is cooled to 0°C. and 500 cc. of amylene are added with vigorous stirring and the stirring continued after the addition is completed. The aqueous layer is separated in a separatory funnel from unchanged amylene and mixed with 2000 g. of ice. The mixture is then neutralized cautiously with a concentrated solution of 720 g. of sodium hydroxide. Following this the solution is distilled until amyl alcohol no longer separates when the distillate is salted out with potassium carbonate. The distillate is saturated with potassium carbonate to separate the amyl alcohol and the alcohol dried with the same salt. Depending on the composition of the starting material, a yield of 90% or more of the theoretical is obtained as a fraction boiling between 101° and 103°C. The boiling point of pure tertiary amyl alcohol lies at 102.5°C.

The conditions for the formation of a uniform hydration product are not always as favorable as in the above example.

2. Addition of Water to Acetylene Bond

The reaction proceeding according to the general scheme

$$R \cdot C : C \cdot R + H_2O \longrightarrow R \cdot CH : C(OH) \cdot R \longrightarrow R \cdot CH_2 \cdot CO \cdot R$$
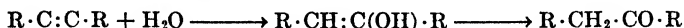
is of importance for industry as well as for the laboratory. The fundamental reaction consists of the addition of water to acetylene with the

[15] R. Adams, *J. Am. Chem. Soc.*, **40**, 1955 (1918).

formation of acetaldehyde. Gattermann-Wieland [16] gives the following directions for laboratory conditions.

Mercuric oxide (5 g.) is dissolved for the most part in a warm solution of 50 cc. of concentrated sulfuric acid and 110 cc. of water. The mixture is poured into a flask, and the air replaced and shaken for 8 to 10 hours in an atmosphere of acetylene. The acetylene, as free as possible from air, is generated as usual and washed with acidified dichromate and with cupric nitrate solutions.

After the absorption of about 10 liters of acetylene which is best stored in a gas holder over saturated sodium chloride solution, the reaction mixture with the separated molecular compound of mercuric sulfate and acetylene is heated in a round flask on a conical air bath. The mixture is then steam-distilled, liberating acetaldehyde from the addition complex. The water vapors are condensed as much as possible in a condenser fed with water of 25° to 30°C. The acetaldehyde is extracted with ether and the extracts are dried with calcium chloride. The product is isolated as usual as the acetaldehyde-ammonia compound. It has proved to be a good practice occasionally to flush the shaking flask with acetylene during the reaction, since obviously gas residues, like air, easily accumulate in it, thus decreasing the acetylene concentration; see also Neumann and Schmidt.[17]

This method of preparation of carbonyl compounds for use in the laboratory is not practical in the simplest case; in more complicated cases it is less so, because the starting material is expensive and difficult to obtain.

The addition of water proceeds more easily in the aromatic than in the aliphatic series; phenylacetylene changes the acetophenone with sulfuric acid even when cold; benzoylphenylacetylene, under the same conditions, yields dibenzoylmethane-enol according to the equation

$$R \cdot CO \cdot C : C \cdot R + H_2O \xrightarrow{\;H_2SO_4\;} R \cdot CO \cdot CH : C(OH) \cdot R, \qquad R = C_6H_5$$
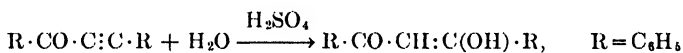
In this case the addition of water actually takes place in the manner that must be assumed according to the general scheme given above, but the first step cannot be caught in most cases. If benzoylphenylacetylene is dissolved with cooling in 10 times its weight of sulfuric acid, and the solution allowed to stand in air, dibenzoylmethane crystallizes at the same rate at which the sulfuric acid is diluted by absorption of water. Usually the appearance of metastable forms can be noticed; see Weygand and Bauer.[18]

The reaction has recently become of considerable technical importance. Vinyl methyl ketone, $CH_2 : CH \cdot CO \cdot CH_3$, a starting material for synthetic polymers, is obtained from vinylacetylene, $CH_2 : CH \cdot C : CH$, but laboratory methods for the preparation of these compounds which polymerize very readily are not available.

[16] Gattermann-Wieland, *Die Praxis des organischen Chemikers*. de Gruyter, Berlin, 1936, p. 210.

[17] Neumann and Schmidt, *Angew. Chem.*, **33**, 189 (1920).

[18] C. Weygand and E. Bauer, *Ber.*, **62**, 572 (1929).

C. Addition of Hydroxyl Groups to Ethylene Bond

Potassium permanganate reacts in sodium carbonate solution with almost all ethylene compounds, according to the generally applicable scheme, $R \cdot CH : CH \cdot R + O + H_2O \longrightarrow R \cdot CHOH \cdot CHOH \cdot R$. This amounts formally to an addition of hydrogen peroxide. Hydrogen peroxide itself, however, leads primarily to oxido compounds, $R \cdot CH : CH \cdot R + H_2O_2 \rightarrow R \cdot CH \cdot CH \cdot R + H_2O$, from which glycols are

$$\underset{O}{R \cdot CH \diagdown \diagup CH \cdot R}$$

obtained by subsequent saponification.

As an example of the use of this procedure which is very simple in principle, the method of Fittig [19] for the preparation of phenylglyceric acid from cinnamic acid is given. He was the first to generalize the earlier accidental observations.

1 mole of cinammic acid is dissolved in the calculated amount of sodium carbonate, so that a 1 to 2% solution of the acid is obtained, and, with stirring and cooling with ice, 1 mole of 2% potassium permanganate solution is added slowly. After filtration of the manganese oxides the mother liquor is concentrated and the phenylglyceric acid isolated as usual.

This method can be used almost universally. It is applicable to heterocyclic carboxylic acids. Einhorn and Sherman [20] have shown that from α-quinolylacrylic acid
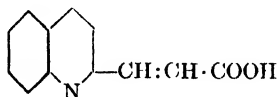
the corresponding glyceric acid is obtained as follows:

To a solution of 5 g. of quinolylacrylic acid in the calculated amount of sodium carbonate (total volume, 500 cc.), 800 cc. of a 0.5% solution of potassium permanganate are added during 2 hours. The mixture is filtered, acidified with hydrochloric acid, and evaporated to dryness. The residue is dissolved in as little water as possible and the solution is rendered very weakly acid by careful addition of sodium carbonate. The hydrochloride of quinolylglyceric acid crystallizes.

The reaction has been of primary importance for the hydroxylation of ethylene hydrocarbons in the terpene series. If several isolated double bonds are present in the molecule, tetrahydric alcohols or diglycols are usually obtained. On the other hand, conjugated double bonds cannot both be hydroxylated simultaneously. While one takes up hydroxyl, the other one is easily split. In certain cases, however, erythrol derivatives are obtained with four adjacent hydroxyl groups.

[19] R. Fittig, *Ber.*, **21**, 919 (1888).
[20] Einhorn and Sherman, *Ann.*, **287**, 35 (1895).

Unsaturated alcohols with a hydroxyl group next to the double bond give glycerols.   Ketones, such as mesityl oxide, may be treated in acetone, but methylcyclohexenone reacts better in aqueous solution.

Aldehyde groups are protected by acetalization.   Glyceraldehyde is thus obtained from acrolein acetal according to Wohl.[21]   Directions for this procedure are given in *Organic Syntheses.*[22]

D. Addition of Oxygen-Containing Compounds to Olefin and Acetylene Bonds

The preparational importance of the reaction which leads to ethers, esters, and acid anhydrides may be illustrated by a few examples.

In principle the carbon double bond adds organic carboxylic acids in the same way that it adds water, the more readily, the more the ethylene bond involved is activated by neighboring substituents.   The ester thus formed can frequently be obtained more conveniently by other means, but occasionally alcohols may be obtained in this way from naturally occurring, unsaturated substances.   Bertrand and Walbaum [23] suggest the use of glacial acetic acid and 50% sulfuric acid.   They give the following directions for preparing isobornyl acetate from camphene.

A mixture of 100 g. of camphene, 250 g. of glacial acetic acid, and 10 g. of 50% sulfuric acid is heated for several hours at 50° to 60°C.   The volume of the top layer decreases slowly and a clear, reddish homogeneous solution is formed from which isobornyl acetate is precipitated with water after the substance is cooled.   After the solution has been washed and dried, a fraction boiling at 107°C. at 13 mm. is obtained.

The crude product may be transformed into isoborneol.

Technically important is the transformation of pinene to borneol, which proceeds in a corresponding manner.   It may be effected by way of bornyl benzoate according to Bouchardat and Lafont [24] or through bornyl oxalate.[25]   Kondakov [26] made a special study of the effect of zinc chloride as an accelerator and prepared addition compounds of zinc chloride with ethylenic hydrocarbons.   The esters of tertiary alcohols are formed with exceptional ease, as might be expected; see the paper of Kondakov.

While the addition of carboxylic acids, which leads to esters, takes place in an acid medium, alcohols on the other hand are added in alkaline solution.   Purdie [27] obtained from maleic and fumaric esters with sodium

[21] Wohl, *Ber.,* **31,** 1799 (1898).

[22] A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. II, Wiley, New York, 1943, p. 307.

[23] Bertrand and Walbaum, *J. prakt. Chem.,* **49,** 1 (1894).

[24] Bouchardat and Lafont, *Compt. rend.,* **125,** 111 (1897).

[25] German Patent, 134,553 (1902).

[26] J. Kondakov, *J. prakt. Chem.,* **48,** 467 (1893).

[27] Purdie, *Ber.,* **14,** 2238 (1881); **18,** 536 (Ref.) (1885).

alcoholates alkoxysuccinic esters. The alkylidenemalonic esters of the general formula, $R_2:C:C(COOR)_2$, react more readily. Liebermann [28] obtained from benzalmalonic ester in the first step a sodium compound of the formula, $C_6H_5 \cdot CH(OC_2H_5) \cdot CNa(COOR)_2$.

Especially noteworthy is the addition of alcohols to halogen-containing double bonds of unsaturated ketones. This reaction was studied by Dufraisse and Gerald.[29] According to the equation

$$C_6H_5 \cdot CO \cdot CBr:CH \cdot C_6H_5 + R \cdot OH \xrightarrow{\qquad} \overset{OH}{C_6H_5 \cdot CO \cdot CHBr \cdot CH(OR) \cdot C_6H_5}$$
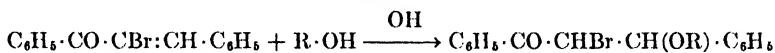
α-bromobenzalacetophenone in absolute alcoholic solution adds methanol, ethanol, normal and branched propanols, and butanols in the cold in the presence of a little alcoholate. At higher temperature the addition products formed split off hydrogen bromide in an alkaline medium and change to enol ethers with the formula, $C_6H_5 \cdot CO \cdot CH:C(OR) \cdot R$.

The addition of carboxylic acids to ketenes leads to acid anhydrides. From ketene and glacial acetic acid, acetic anhydride is formed according to the equation, $CH_2:C:O + CH_3:COOH \rightarrow CH_3 \cdot CO \cdot O \cdot OC \cdot CH_3$. The reaction may even be of practical importance, but no details have been released with the exception of numerous patents. The addition of oxygen-containing compounds to the acetylenic bond gives vinyl esters and enol ethers.

The preparation of vinyl esters in this way has considerable practical importance; it succeeds at higher temperature without any special additions.

The addition of alcohols to acetylene ketones readily takes place in an alkaline medium. It offers a very easy method for the preparation of isomeric enol ethers, $R' \cdot CO \cdot CH:C(OR) \cdot R''$ and $R' \cdot C(OR):CH \cdot CO \cdot R''$, of the 1,3-diketone, $R' \cdot CO \cdot CH_2 \cdot CO \cdot R''$.

According to Dufraisse and Gerald [30] for instance, 10 g. of benzoyl-phenylacetylene are dissolved with heating in 25 cc. of an ethylate solution containing 0.11 g. of sodium. The solution is then neutralized immediately with the calculated amount of acetic acid. After the solution has been concentrated, β-ethoxychalcone, $C_6H_5 \cdot CO \cdot CH:C(OC_2H_5) \cdot C_6H_5$, is obtained in a yield of 70% of the theoretical; see Weygand and Bauer.[31]

E. Addition of Organic Compounds to Oxygen Molecule

The basis for all the reactions to be discussed in the following paragraphs is the scheme, $R \cdot R' + O_2 \rightarrow R \cdot OO \cdot R'$ and $R \cdot H + O_2 \rightarrow R \cdot OOH$.

[28] Liebermann, *Ber.*, **26**, 1876 (1893).
[29] Ch. Dufraisse and P. Gerald, *Compt. rend.*, **173**, 985 (1921); **174**, 1631 (1922); *Bull. soc. chim.*, **31**, 1292 (1922).
[30] Ch. Dufraisse and P. Gerald, *Bull. soc. chim.*, **31**, 1301 (1922).
[31] C. Weygand and E. Bauer, *Ber.*, **62**, 572 (1929).

One of the best known examples is the formation of tetralin peroxide by the method of Hock and Susemihl.[32]

If a well dispersed air current is passed through 1 liter of commercial tetralin for 50 to 60 hours at 75°C., the tetralin soon turns yellow.   Losses by evaporation can be reduced by passing the escaping air through a reflux condenser; thus 80% of the amount of the starting material can be obtained as a highly autoxidized solution.   The yellow color is not caused by peroxides but by decomposition products formed simultaneously; therefore it is not advisable to continue the treatment with air too long.   It is true that more highly autoxidized solutions are obtained but the peroxide can be isolated from them with difficulty only or not at all.   The reaction mixture is distilled from an all-glass apparatus at 1 to 2 mm., a water bath heated to about 75°C. being used.   After four-fifths of the total volume has been removed (this being unchanged tetralin), the distillation residue partially crystallizes after standing for some time.   It crystallizes faster when cooled to 0°C.   The peroxide is collected by filtration and dried on a porous plate; the yield of crude product amounts to 15 to 17% of the weight of the autoxidized mixture. To purify it, the crude product is recrystallized several times from a large volume of petroleum ether.   The peroxide is obtained colorless and almost odorless with a melting point at 56°C.   The constitution of the tetralin peroxide is assumed to be
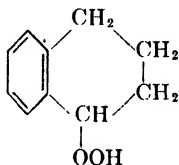
because when reduced it yields α-tetralol.

It is significant that unsaturated cyclic hydrocarbons, such as cyclohexene, also react with molecular oxygen in an analogous manner by inserting the oxygen molecule at the saturated carbon atom adjacent to the double bond and not at the double bond as was assumed formerly without further consideration.   Zelinskii and Borissov [33] thought a product which they obtained by treating cyclohexene with molecular oxygen at room temperature to be cyclohexene peroxide of the formula,
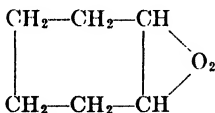
Criegee, however, recently [34] obtained the product involved by treating cyclohexene with oxygen in sunlight; he was able to distil the monomeric oil in a high vacuum and suggests, in accordance with its properties, the

[32] H. Hock and W. Susemihl, *Ber.*, **66**, 64 (1933).
[33] N. Zelinskii and P. Borissov, *Ber.*, **63**, 2362 (1930).
[34] R. Criegee, *Ann.*, **522**, 84 (1936).

formula,

$$\begin{array}{c} CH_2\!-\!CH_2\!-\!CH \\ \mid \qquad \quad \parallel \\ CH_2\!-\!CH\!-\!CH \\ \mid \\ OOH \end{array}$$
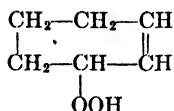
In agreement with this are the facts that the "cyclohexenyl peroxide" forms salts and is readily reduced to cyclohexenol by alkali sulfite. However, no specific details for the preparation are given in the paper cited above.

A corresponding mechanism supposedly must be assumed for the autoxidation of turpentine. While it was known for a long time that occasionally very unstable residues remained after the distillation of autoxidized turpentine, this phenomenon in the case of cyclohexene was overlooked until recently. Rieche and Meister [35] have pointed out that the autoxidation of ether is also a completely analogous reaction. They assume that in the first step diethyl ether hydroperoxide is formed from diethyl ether, possibly through an unstable moloxide, according to the equation,

$$CH_3 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_3 + O_2 \longrightarrow CH_3 \cdot \underset{\underset{OOH}{\mid}}{CH} \cdot O \cdot CH_2 \cdot CH_3$$
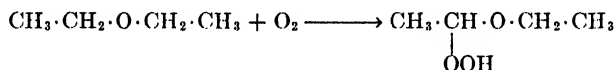
Diethyl ether peroxide, the "ether peroxide" proper, could be synthesized from ethanol and the addition product of acetaldehyde and hydrogen peroxide according to the equation,

$$CH_3 \cdot \underset{\underset{OOH}{\mid}}{CHOH} + HO \cdot CH_2 \cdot CH_3 \longrightarrow H_2O + CH_3 \cdot \underset{\underset{OOH}{\mid}}{CH} \cdot O \cdot CH_2 \cdot CH_3$$
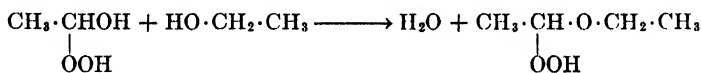
It is decomposed by hydrolysis to give acetaldehyde, ethanol, and hydrogen peroxide. When it is heated, the highly explosive ethylidene peroxide is formed especially when autoxidized ether is distilled off and the distillation residue is overheated at the end of the distillation. Diethyl ether hydroperoxide explodes mildly when heated.

The reactions mentioned here have hardly gained any preparative importance for the laboratory; but their importance in industry and in physiological chemistry is greater. Peroxides, as is known, are not only assumed to be polymerization accelerators for the drying of oils, and for the preparation of high polymeric synthetic materials, but they are sometimes actually used for these purposes. Rieche's monograph gives information concerning this subject.[36]

[35] A. Rieche and R. Meister, *Angew. Chem.*, **49**, 101 (1936).
[36] A. Rieche, *Die Bedeutung der organischen Peroxyde für die chemische Wissenschaft und Technik.* Enke, Stuttgart, 1936.

Heavy metals very likely play the rôle of catalysts during the autoxidation of ethers, as they do in other cases. This is proved by the fact that diethyl ether which is inclined to form peroxides quickly autoxidizes again even if it is freed from peroxidic constituents, whereas other kinds of ether are much more stable. For the preparation of pure ether Rieche and Meister [37] first treat the quantity to be purified with ferrous sulfate solution. Dismutation of the peroxides occurs on shaking with ferrous sulfate solution; then the ether is allowed to stand over solid sodium hydroxide (it is best to use pellets) in order to bind acid constituents, to resinify the acetaldehyde present, and to precipitate iron as hydroxide. Then the ether is shaken with an aqueous chromic acid solution to remove the last traces of acetaldehyde and distilled from anhydrous sodium carbonate. The distillate is not dried as usual with calcium chloride but treated when still wet with sodium metal. Finally the ether is distilled from sodium and stored in the dark.

Addition of Oxygen to Free Radicals

The addition of oxygen to carbon radicals takes place very readily. Even at room temperature, for instance, solutions of triphenylmethyl add oxygen from air with the formation of triphenyl peroxide, according to the equation,

$$2(C_6H_5)_3C + O_2 \longrightarrow (C_6H_5)_3C \cdot OO \cdot C(C_6H_5)_3$$
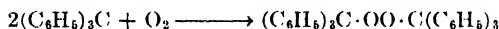
II. BY EXCHANGE, WITH FORMATION OF HYDROXYL AND CARBONYL GROUPS

A. Replacement of Hydrogen by Oxygen

1. Replacement of Hydrogen by Hydroxyl Group

The direct oxidation of hydrocarbons to primary alcohols is of practical importance for the laboratory only in special cases. There are numerous recent patents on the oxidation of methane or mixtures containing methane (natural gas) by catalytic means with oxygen, air, or nitrogen oxides, but these methods have so far been useless in small scale operations. Some oxidation methods yield from toluene and its derivatives the corresponding benzyl alcohols; manganese dioxide, lead dioxide, lead tetraacetate, and Caro's acid serve as oxidizing agents.

· *Preparation of Lead Tetraacetate*—Pure red lead oxide (minimum, 200 g.) is added in very small portions with vigorous stirring to 1000 cc. of glacial acetic acid while the temperature is maintained at 80°C. From the solution (filtered, if necessary) colorless needles of lead tetraacetate crystallize on cooling. They are filtered off, washed with a small amount of glacial acetic acid, and dried in a desiccator; see Dimroth and Schweizer.[38] For the preparation of larger amounts see Dimroth and Schweizer.[39]

[37] A. Rieche and R. Meister, *Ber.*, **68**, 1468 (1935).
[38] O. Dimroth and R. Schweizer, *Ber.*, **53**, 485 (1920).
[39] O. Dimroth and R. Schweizer, *Ber.*, **56**, 1377 (1923).

The directions of Dimroth and Schweizer [40] for the preparation of benzyl acetate from toluene are given as an example of this type of reaction:

A mixture of 120 g. of lead tetraacetate and 40 g. of toluene in 200 cc. of glacial acetic acid which has been distilled from permanganate is boiled for 4 hours; then most of the glacial acetic acid is removed by distillation and the residue added to water. The mixture is extracted with ether and the extract shaken with sodium bicarbonate solution and dried. On distillation in a vacuum 7.5 g. of crude benzyl acetate are obtained.

The advantage of the tetraacetate-glacial acetic acid mixture over other oxidizing agents is due mainly to the fact that the alcohols formed are protected from further oxidation by esterification.

In the aliphatic series methyl groups next to carbon atoms which already carry oxygen are frequently oxidized readily by lead tetraacetate to CH_2OH groups. From acetone, monohydroxy- and dihydroxyacetone were obtained in the form of their acetates; acetic anhydride yields the diacetate of glycolic anhydride; acetophenone gives benzoylcarbinol acetate; see Dimroth and Schweizer.[41]

The formation of secondary alcohols is effected with the same oxidizing agents. Diphenylmethane yields diphenylcarbinol acetate with lead tetraacetate; the oxidation takes place a little more easily than with toluene. Malonic ester yields acetoxymalonic ester, while acetoacetic ester gives α-acetoxyacetoacetic ester, compounds which are very difficult to obtain in other ways.

The methylene group next to the carbonyl in ketones is left intact by Caro's acid, but a hydroxyl group is added to the β-carbon atom. Methyl propyl ketone, for instance, yields $CH_3 \cdot CO \cdot CH_2 \cdot CHOH \cdot CH_3$. This is a reaction analogous to the biological oxidation of fatty acids in the organism which cannot be represented in model form in the test-tube. An exception is diethyl ketone which yields the keto alcohol, $C_2H_5 \cdot CO \cdot CHOH \cdot CH_3$. As a modern example we may mention the transformation of acenaphthene to acenaphthenol with lead dioxide and glacial acetic acid, according to Marquis.[42]

Francis and Gauntlett [43] treated solid paraffin at 100°C. for 1200 hours with air in the presence of 5% turpentine and found secondary alcohols in the non-acid reaction products.

Of primary importance is the preparation of tertiary alcohols in this way.

1. Aliphatic Compounds with Tertiary Carbon Atom. Since an oxidation of tertiary alcohols takes place only with a scission of the carbon

[40] O. Dimroth and R. Schweizer, *Ber.*, 56, 1384 (1923).
[41] O. Dimroth and R. Schweizer, *Ber.*, 56, 1375 (1923).
[42] R. Marquis, *Compt. rend.*, 182, 1227 (1926).
[43] F. Francis and H. Gauntlett, *J. Chem. Soc.*, 1926, 2377.

structure and since there is considerable resistance to this scission, stronger means of oxidation may be employed for this reaction.

It is apparently not certain whether aliphatic hydrocarbons with tertiary carbon atoms may be oxidized directly to carbinols; 3-methylpentane decolorizes a cold solution of permanganate, according to Zelinskii and Zelikov,[44] but Tafel[45] found the hydrocarbon to be stable. Fatty acids with branched chains, however, are oxidized quite readily by alkaline permanganate solution to hydroxy acids or their lactones, respectively. R. Meyer[46] thus obtained α-hydroxybutyric acid from isobutyric acid; hydroxycumic acid is obtained similarly. From isocaproic acid, isocaprolactone is formed.

2. Triphenylmethane Derivatives. The oxidation of triphenylmethane derivatives to triphenylcarbinols takes place easily by means of various oxidizing agents. Triphenylmethane proper is transformed to triphenylcarbinol with nitric acid or with chromic acid in glacial acetic acid; into triphenylcarbinol acetate by means of lead tetraacetate. The primary importance of the reaction is for the industrial manufacture of triphenylmethane dyes from the leuco bases. To accomplish this, a variety of oxidizing agents are used, such as arsenic acid, nitrobenzene, nitrous acid, or nitrosylsulfuric acid. The leuco bases formed during the industrial processes by condensation are not isolated.

Leuco compounds isolated as such are best oxidized to the dye salts in hydrochloric acid solution with manganese dioxide or lead dioxide, from which the carbinols are liberated as follows:

Leucomalachite green (3.3 g.) is dissolved in 40 cc. of hot normal hydrochloric acid, the solution is diluted with water and cooled, and a suspension of 2.4 g. of lead dioxide in 20 cc. of water is added slowly with thorough shaking during 5 minutes. The mixture is shaken for an additional 5 minutes on a steam bath and a clear solution of 4 g. of zinc chloride is added. Then the dye is salted out with sodium chloride, filtered with suction, again dissolved in hot water, and again salted out. The yield is about 3 g. of the zinc chloride addition complex of the dye salt.

By the procedure of Villiger and Kopetschni[47] a very dilute solution of sodium hydroxide or sodium carbonate is added dropwise with stirring to the dilute aqueous solution of the dye salt and the precipitated carbinol base is filtered off. After recrystallization from ligroin, the base is obtained in crystalline crusts, melting at 120° to 122°C., whereas, when crystallized from ether, it forms cubes melting at 109° to 110°C. This is obviously due to dimorphism which exists, according to E. and O. Fischer,[48] in the case of the leuco base also.

[44] N. Zelinskii and J. Zelikov, *Ber.*, **34**, 2866 (1901).
[45] G. Tafel, *Ber.*, **45**, 452 (1912).
[46] R. Meyer, *Ann.*, **219**, 240 (1883).
[47] V. Villiger and E. Kopetschni, *Ber.*, **45**, 2916 (1912).
[48] E. and O. Fischer, *Ber.*, **12**, 798 (1879).

3. Phenols. The classic example for the direct introduction of a phenolic hydroxyl group by oxidation is the transformation of β-hydroxyanthraquinone into alizarin. There are other cases which also have preparational value. Quinoline changes to 2-quinolinol, carbostyril, when melted with alkalies; see Tchichibabin.[49]

2. Replacement of Hydrogen by Carbonyl Oxygen

The direct transformation of hydrocarbons into carbonyl compounds by means of oxygen in air is quite practical for industry but of no importance as a laboratory method. In the case of tetralin, α-tetralone may be obtained even at low temperatures by admitting oxygen in the presence of oxidation catalysts like lead, cobalt, or manganese oleates; see Schroeter.[50]

In other cases the methyl or methylene groups may be oxidized to the carbonyl group with many different reagents. This oxidation depends very definitely on the constituents next to these groups. In the aliphatic series, the direct method of treating hydrocarbons is seldom successful, but it is possible to oxidize an aliphatic methylene group adjacent to a keto group. Here a suitable method is available, especially in the aliphatic series, by way of the isonitroso ketones; see pages 159 and 267.

The direct oxidation of an aromatic or heterocyclic bound methylene group at the end to an aldehyde group may be accomplished according to Étard's method with chromyl chloride as well as with certain inorganic oxides like manganese dioxide and lead dioxide.

A general method for Étard's reaction has been perfected by Bornemann.[51] The toluyl aldehydes described in his paper are no longer prepared in this manner, but to date moderate amounts of substituted aromatic aldehydes cannot be prepared better in any other way. Slightly less than 2 moles of chromyl chloride is always used for 1 mole of the compound to be oxidized, i.e., for one methylene group. The components are dissolved separately in carbon disulfide; Bornemann used 15% solutions, while Wörner[52] recommended 25 to 30% solutions when o- and p-bromobenzaldehydes are being prepared. When the solutions are mixed, considerable heat is sometimes evolved, in which case it is necessary to cool in order to prevent the carbon disulfide from boiling. After the addition of each portion of chromyl chloride one has to wait until the chocolate-brown double compound has separated. After some time the mixture is filtered, the carbon disulfide is removed from the filter cake *in vacuo* with gentle heating, and the molecular compound is decom-

[49] Tchichibabin, *Ber.*, **56**, 1883 (1923).
[50] G. Schroeter, *Chem. Abstracts*, **27**, 1890 (1933); German Patent, 568,338.
[51] E. Bornemann, *Ber.*, **17**, 1462 (1884).
[52] C. Wörner, *Ber.*, **29**, 153 (1896).

posed by cold water; aldehyde, chromic chloride, and chromic acid are obtained. Depending on the circumstances, it might be best to distil the aldehyde immediately with steam or to decompose the chromic acid by passing in sulfur dioxide. When large quantities are used, the oxidation with chromyl chloride is not entirely without danger, because the addition compounds sometimes unexpectedly explode.

Patents are about the only literature available which deals with the oxidation with manganese dioxide and sulfuric acid, or with manganic salts. Law and Perkins [53] obtained only poor results when they used these reagents for laboratory experiments.

Recently selenium dioxide was added to the list of oxidation reagents. It is frequently able to oxidize activated methylene groups to carbonyl groups in excellent yields, while the selenium dioxide is in turn changed to elementary selenium. Since selenium separates readily from organic solvents, no disturbing additions are present in the liquid reaction mixture except the water formed by the oxidation. The subsequent work with the reaction mixtures is very easy. Since the selenium may be recovered in most cases almost quantitatively, the method is not much more expensive than the transformation of methylene groups into carbonyl groups through the isonitroso ketones, a method which accomplishes the same purpose.

Thus, phenylglyoxal, for instance, which otherwise has been obtained by inconvenient and partly dubious methods, can be prepared in excellent yield from acetophenone with selenium dioxide. Riley gives directions for this in *Organic Syntheses* [54] as an example of the method proposed by him and Morley and Friend.[55]

Phenylglyoxal polymerizes on storage but may be reconverted to the monomeric form by vacuum distillation without substantial loss. The monohydrate is stable; it can be obtained as colorless crystals by dissolving it in 3.5 to 4 volumes of hot water and cooling. The monomeric, anhydrous phenylglyoxal can be recovered also from the hydrate by vacuum distillation.

Occasionally the selenium conglomerates to form solid clumps which may break the reaction flask. This can be avoided by stirring the top section of the reaction mixture only. Consequently the selenium clump lies harmless at the bottom of the flask.

Riley [56] gives the warning not to be careless when recovering selenium. During the selenium oxidations, glassy selenium is occasionally formed

[53] O. Law and M. Perkins, *J. Chem. Soc.*, **91**, 258 (1907).
[54] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 509.
[55] Riley, Morley, and Friend, *J. Chem. Soc.*, **1932**, 1875.
[56] L. Riley, *J. Chem. Soc.*, **1933**, 394.

which reacts more violently with nitric acid than the common form. Such glassy selenium which probably still contained traces of organic compounds exploded like gun-powder during the attempt to burn it to selenium dioxide with oxygen. Therefore, it seems better to recover selenium in the laboratory with nitric acid.

Müller [57] oxidized reactive methylene groups with selenium dioxide. He succeeded, at low temperature in the presence of indifferent diluting solvents, in obtaining diethyl mesoxalate from ethyl malonate, and ethyl diketobutyrate from ethyl acetoacetate. The yields were not very high but were satisfactory. As an example of this, directions are given for the preparation of mesoxalic ester, which, compared with the following method in which nitrous gases are used for the oxidation, is less prolific but much more convenient as far as the apparatus is concerned.

Ethyl malonate (32 g., 1 mole) and 22.5 g. of selenium dioxide (1 mole) are refluxed at 130°C. with 30 g. of xylene for 16 hours. A constant evolution of carbon dioxide and carbon monoxide can be noticed. Only black, metallic selenium remains in the liquid which is filtered off and washed with ether. It weighs 15 g.; that is, 95% calculated to the amount of selenium dioxide used. The filtrate is diluted with ether, dried over sodium sulfate, and, after the removal of the ether, distilled *in vacuo.* After the xylene is distilled, the following fractions are collected: Fraction A between 64° and 94°C. at 9 mm.; Fraction B between 94° and 112°C., at 9 mm. The latter (2 g.) is a bad smelling, yellow liquid which still contains selenium. Fraction A on redistillation yields Distillate 1 (7.7 g.) from 64° to 90°C. at 10 mm. Distillate 2 (7.7 g.) boiling at 94°, at 10 mm., is a greenish yellow oil which when exposed to air absorbs water and solidifies to colorless crystals of ethyl mesoxalate hydrate. After re-crystallization from acetone, it has a melting point of 57°C.; the yield is 7.7 g., corresponding to 23% of the theoretical when calculated on the basis of the ethyl malonate used. See the original paper for the nature of the by-products formed.

The oxidation of ethyl malonate to mesoxalic ester by means of nitrous gases was first described by Bouveault and Wahl [58]; details for the preparation may be found in *Organic Syntheses.*[59] The apparatus used there may well be replaced by the all-glass apparatus as illustrated in Fig. 3.

On comparison of the two modern methods for the preparation of mesoxalic ester, it is difficult to decide which is to be preferred. Ethyl malonate is a relatively cheap starting material; the selenium used for the

[57] R. Müller, *Ber.*, **66**, 1668 (1933).
[58] Bouveault and Wahl, *Compt. rend.*, **137**, 196 (1903).
[59] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 266.

oxidation may be recovered by treatment with nitric acid.   The double
yield obtained with the nitrogen oxide method must be rather dearly paid
for by considerable inconvenience, by a long reaction time, and by the
large expenses for arsenic trioxide which is practically lost as arsenic acid.
For the preparation of larger quantities the second method, however, is
preferable.
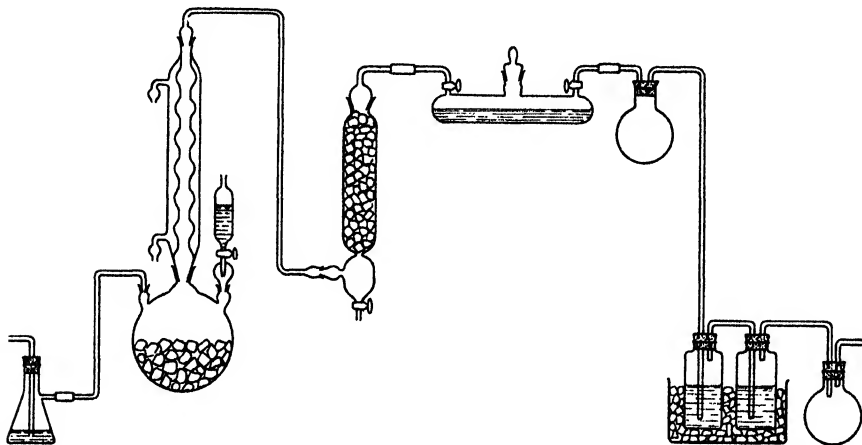
Fig. 3.—Apparatus for the preparation of mesoxalic esters.

Anthraquinone may be advantageously prepared in the laboratory
from anthracene by means of sodium chlorate and vanadium pentoxide
as catalyst.   *Organic Syntheses* gives short directions.[60]

Compared with this method, the usual preparation of anthraquinone
from anthracene by means of glacial acetic acid-chromic acid according
to Graebe and Liebermann [61] is without a doubt inferior.   The yield is
not much smaller, to be sure; about 4 g. are obtained by boiling a mixture
of 5 g. of pure anthracene dissolved in 225 g. of glacial acetic acid and
75 g. of chromic acid (anhydride) dissolved in a mixture of 25 g. each of
water and glacial acetic acid.   The product is isolated by diluting with
water.   This method, however, is not as convenient as the one in *Organic
Syntheses*, and the amount of glacial acetic acid used is much larger.

3. Replacement of Hydrogen by Carboxyl Oxygen

Methyl groups of aromatic or heterocyclic rings may be oxidized to
carboxyl groups according to the general scheme, $R \cdot CH_3 \rightarrow R \cdot COOH$.
The reaction is important not only because in this manner a certain

[60] A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. II, Wiley, New York, 1943,
p. 554.

[61] Graebe and Liebermann, *Ann., Supplement*, **7**, 284 (1870).

number of carboxylic acids may be obtained from natural or synthetic materials, but also because it is a step on the way for the reconversion to the mother nucleus; see Chapter Twelve, page 452. The oxidation agents involved are usually permanganate and chromic acid. If several methyl groups are present in the molecule, one of them can usually be oxidized with nitric acid while the others remain intact.

The preparation of benzoic acid from toluene cannot be described here, but essential aspects may be found in the patent literature. The three isomeric xylenes are transformed into the toluic acids each with a different degree of ease: o- and p-xylene are attacked even by dilute nitric acid, but their oxidation to the corresponding toluic acids has no practical importance. They may be obtained more easily from their nitriles; see page 161. m-Toluic acid can be prepared from pure m-xylene according to Reuter [62] as follows:

Equal volumes of m-xylene and nitric acid (2 volumes of 1.4 N nitric acid and 3 volumes of water) are boiled several hours; then the unchanged xylene is removed by steam distillation until the residue is heavier than water. The xylene in the distillate is separated from the water and treated again with nitric acid of the same concentration until after several operations all the m-xylene is used up. The oily portion not distilling with steam solidifies on cooling. It is extracted with sodium carbonate solution; this extract gives crude m-toluic acid when acidified. The acid may be purified through the calcium salt.

Van Scherpenzeel [63] gives a more efficient purification method which had been tried before by Ador and Rilliet.[64] The ethyl ester of the crude acid is prepared; this is fractionated and yields a main portion boiling at 103° to 105°C. at 10 mm. and a residue of ethyl nitrotoluate. Saponification of the ethyl m-toluate gives m-toluic acid melting at 110°C.

The oxidation of xylenes to phthalic acids also proceeds differently with each isomer. Chromic acid decomposes o-xylene, while potassium permanganate oxidizes it to o-phthalic acid. o-Toluic acid cannot be isolated in this reaction; see Klaus and collaborators.[65] The oxidation of m- and p-xylenes, on the other hand, may be accomplished with chromic acid as well as with potassium permanganate.

The oxidation of substituted toluenes takes place more easily at times, and at times with greater difficulty than in unsubstituted ones. Toluenes substituted with chlorine and bromine as well as aromatic nitro hydrocarbons may generally be readily oxidized. Cresols can be transformed with difficulty into hydroxybenzoic acids by means of the oxidation agents mentioned. Jacobsen [66] studied the effect of fused potassium hydroxide

[62] A. Reuter, Ber., 17, 2028 (1884).
[63] L. van Scherpenzeel, Rec. trav. chim., 20, 161 (1901).
[64] Ador and Rilliet, Ber., 12, 2300 (1879).
[65] A. Klaus et al., Ber., 19, 3083 (1886).
[66] Jacobsen, Ber., 11, 2052 (1878); German Patent, 170,230.

on cresols. Cresol ethers, however, may easily be oxidized to alkoxy-benzoic acids by means of permanganate.

Some naphthalene homologues are very stable towards the usual oxidation reagents; thus, Weissgerber and Kruber [67] did not succeed in transforming 1,6-dimethylnaphthalene into 1,6-naphthalenedicarboxylic acid either by means of chromic acid or with permanganate. They proceeded as follows:

Dimethylnaphthalene (4 g.) in a solution of 250 g. of potassium ferricyanide and 43 g. of potassium hydroxide in 1 liter of water are heated with stirring for 24 hours at 60°C.; then 80 g. of potassium ferricyanide and 14 g. of potassium hydroxide are added, and the heating is continued at 60°C. for an additional 24 hours. Finally the unchanged dimethylnaphthalene is distilled with steam, and the residual liquor filtered, acidified, and extracted with ether. From the ether solution was isolated 0.5 g. of the desired dicarboxylic acid.

It is a striking fact that one of the methyl groups in 1,6-dimethyl-naphthalene may be oxidized with relative ease by means of dilute nitric acid; see also Mayer and Schnecko.[68]

The homologues of pyridine, of quinoline, of thiophene, and of different other heterocyclic compounds may be oxidized to carboxylic acids in the same manner as the benzene homologues, with the ring kept intact, but in the pyrrole series this cannot be accomplished directly but through intermediates; see H. Fischer and collaborators.[69] In the quinoline series also, detours sometimes prove to be advantageous. Thus, Rabe and coworkers [70] prepared the corresponding carboxylic acid from 4-methyl-6-methoxyquinoline,
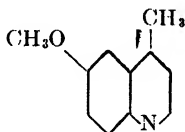
not by direct oxidation, but through the condensation product with benzaldehyde; the carboxylic acid was needed for the total synthesis of hydroquinine.

The preparation of o-chlorobenzoic acid was described by Emmerling.[71] He had available a mixture of o- and p-chlorotoluenes which was practically free from m-chlorotoluene. Therefore he obtained a mixture of o- and p-chlorobenzoic acids which he separated by recrystallization from water. All the details for this procedure can be found in *Organic Syntheses*.[72]

[67] R. Weissgerber and O. Kruber, *Ber.*, **52**, 352 (1919).
[68] Mayer and Schnecko, *Ber.*, **56**, 1408 (1923).
[69] H. Fischer *et al.*, *Ann.*, **461**, 270 (1928).
[70] P. Rabe *et al.*, *Ber.*, **64**, 2487 (1931).
[71] O. Emmerling, *Ber.*, **8**, 880 (1875).
[72] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 135.

As examples of the chromic acid and of the permanganate oxidation the preparation of o-chlorobenzoic acid and p-nitrobenzoic acid is cited.

p-Nitrobenzoic acid was obtained by Beilstein and Geitner [73] by oxidation with potassium dichromate and sulfuric acid. Kamm and Matthews found that the duration of the oxidation may be shortened very much by the use of a large excess of sulfuric acid and a concentration of sulfuric acid higher than usual. Special care has to be taken that the reaction does not get out of control. Details for their improved method are given in *Organic Syntheses*.[74]

If several side chains are present, the reaction may be stopped, as mentioned above, at the monocarboxylic acids by the choice of suitable, milder oxidation agents. If the side chains are different, it is sometimes possible to degrade the longer one first by using one oxidation agent, or the shorter one first by using another oxidation agent. Thus, p-cymene when treated with dilute nitric acid yields p-toluic acid by way of tolyl methyl ketone:

$$(CH_3)_2 \cdot CH \cdot C_6H_4 \cdot CH_3 \longrightarrow CH_3 \cdot CO \cdot C_6H_4 \cdot CH_3 \longrightarrow HOOC \cdot C_6H_4 \cdot CH_3$$

On the other hand, oxidation with alkaline permanganate solution yields α-hydroxyisopropylbenzoic acid, $(CH_3)_2C(OH) \cdot C_6H_4 \cdot COOH$. Regularities of general validity, which would permit determination of the course of such oxidations in advance, have not been established.

The oxidation of side chains containing halogen by means of nitric acid is difficult, but it is made possible by the addition of silver nitrate in order to bind the halogen. Halogen attached to the nucleus frequently makes the oxidation difficult, or protects adjacent chains from attack. Halogenoxylenes give only halogenotoluenemonocarboxylic acids with chromic acid. These change with permanganate to halogenoterephthalic acids; see Schultz.[75]
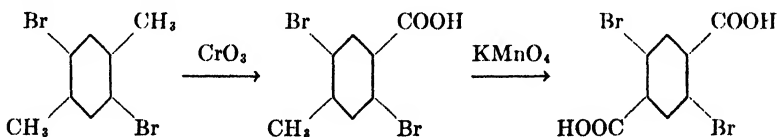
The application of these indefinite regularities to higher condensed carbocyclic ring systems and to heterocyclic compounds is not possible because of a lack of extensive experience. In general it may be stated that pyridine homologues may be treated exactly like benzene homologues because of the stability of the pyridine ring; the same may be said about

[73] Beilstein and Geitner, *Ann.*, **139**, 335 (1866).
[74] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 392.
[75] Schultz, *Ber.*, **18**, 1762 (1885).

quinoline derivatives.   Methylthiophenes also can be oxidized to thio-phenecarboxylic acids with permanganate.

Nitro groups in the nucleus also make the degradation of side chains difficult.   Therefore, the nitrobenzoic acids have to be prepared from nitrotoluenes with permanganate or chromic acid-sulfuric acid mixture. For these reactions the dichromate-sulfuric acid mixture is still superior to the pure chromic trioxide in glacial acetic acid.   Trinitrotoluene, for instance, is changed to trinitrobenzoic acid by the former agent, while it is not attacked by chromic acid in glacial acetic acid.   The sulfonic acids show similar reactions.   o-Toluenesulfuric acid amide, which can be obtained from o-toluenesulfonic acid chloride with ammonia, is transformed to saccharin by means of an alkaline permanganate solution at 60°C.
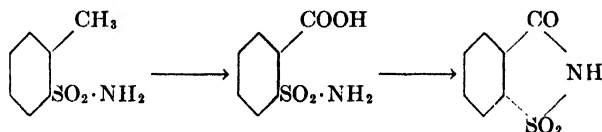
If nitro and sulfo groups are present in the nucleus simultaneously, information gleaned from patents [76] seems to recommend that the oxidation of the side chains be performed with persulfate.

The oxidation of side chains in the presence of autoxidizable substances like amino groups obviously is not successful without special precautions.   The amino group may be acetylated; thus, from p-acetotoluide, p-acetylaminobenzoic acid may be prepared with permanganate.[77] In a corresponding manner, anthranilic acid is made from o-acetotoluide. The reaction mixture is kept neutral by the addition of magnesium sulfate.[78]

Industrially benzoic acid is prepared from toluene in a different way in order to save oxidizing agents.   Toluene is chlorinated hot to benzyl, benzal, or benzotrichloride and oxidized during the saponification.   Toluene also can be oxidized to benzoic acid with a mixture of permanganate and hypochlorite, which amounts to the same thing.

The oxidation of the methyl group at the end in fatty aromatic methyl ketones to the carboxyl group with permanganate is relatively easy.   It is true that the esters of the arylglyoxylic acids formed by these reactions may be prepared also by nuclear synthesis (see page 396), but the oxidation method is illustrated by one example.   Claus and Neukranz [79] studied in detail the conditions for the reaction; they give the following directions for the preparation of phenylglyoxylic acid.

[76] German Patent, 80,165.
[77] Meisenheimer et al., Ann., 423, 86 (1921).
[78] German Patent, 94,629.
[79] A. Claus and W. Neukranz, J. prakt. Chem., 44, 77 (1891).

12 g. of acetophenone in 200 cc. of water are thoroughly stirred and a warm (70°C.) solution of 32 g. of potassium permanganate and 12 g. of potassium hydroxide in 200 cc. of water is added in five to six portions, time for the decolorization of the liquid being allowed between subsequent additions. The total time required for the reaction is less than 30 minutes. When the material is worked up by filtering, acidifying, extraction with ether, etc., more than 7 g. of phenylglyoxylic acid are obtained. p-Tolylmethyl ketone gives a 70% yield of the theoretical p-tolylglyoxylic acid.

4. Dehydrogenation of Alcohols to Carbonyl Compounds

(a) Aldehydes

Because of the ease with which aliphatic primary alcohols can be obtained, their dehydrogenation to the corresponding aldehydes plays a particularly important rôle in preparative work. It is remarkable that a mixture of dichromate and sulfuric acid, a very active oxidizing agent, gives good results, although usually aldehydes are not very stable towards strong oxidizing agents.

The two lowest homologues, formaldehyde and acetaldehyde, are prepared by a different method, but it is not advantageous to prepare these compounds in the laboratory. Formaldehyde manufactured from methanol by oxidation of the vapor with air over metal catalysts (copper, or, in industry, silver) is stored either as an aqueous solution, formalin, or as solid paraformaldehyde. The monomeric aldehyde is fairly stable only at very low temperatures. Hexamethylenetetramine may also serve as a starting material. Gaseous formaldehyde is sometimes used for Grignard syntheses, but in most cases the solid paraformaldehyde is employed. This consists of a mixture of polymerization products of different molecular weights and gives the monomeric aldehyde at a slightly elevated temperature.

Acetaldehyde is made commercially from acetylene (see above) and stored as paraldehyde. If the monomeric aldehyde is required, paraldehyde is distilled from a little sulfuric acid, and the vapor dried over calcium chloride. Its low boiling point of 21°C. necessitates its storage in sealed ampules, but it always polymerizes somewhat after a time.

The preparation of the next higher homologues is carried out by the use of the following general method. The oxidation mixture is prepared either from 60 parts of potassium dichromate, 80 parts of concentrated sulfuric acid, and 270 parts of water (the so called Beckmann mixture) or from 60 parts of sodium dichromate and equal parts of sulfuric acid and water (according to Kiliani). These solutions contain 10% of chromic acid.

The preparation of isobutyraldehyde by Lipp's [80] method (see also Pfeiffer [81]) follows:

[80] Lipp, *Ann.*, **205**, 2 (1880).
[81] Pfeiffer, *Ber.*, **5**, 699 (1872).

A mixture of 100 g. of isobutyl alcohol and 750 cc. of water in a flask with a dropping funnel and a condenser is heated to 70° to 80°C., and a solution of 135 g. of potassium dichromate in 675 cc. of water and 50 g. of concentrated sulfuric acid is added dropwise. Carbon dioxide is passed through the flask so that the product is removed rapidly from the oxidizing mixture. The aldehyde is recovered from the distillate as the bisulfite compound. It is regenerated by excess sodium carbonate and distilled. The pure aldehyde boils at 61°C.

The same method may be used for aldehydes of higher molecular weight. Numerous patents indicate that it is used industrially, but the method has to be changed somewhat on account of the lower volatility of the aldehydes involved.

A number of quite similar directions for the preparation of isovaleraldehyde from fermentation amyl alcohol are given by Bouveault and Rousset,[82] Kohn,[83] and van Marle and Tollens.[84] It is interesting to follow the development of the method with this example. Bouveault and Rousset state that it is more advantageous to add the oxidizing agent to the alcohol than to follow the reverse procedure, as suggested by Fossek [85] for the preparation of isobutyraldehyde. Kohn, omitting reference to the French authors, but referring to Fossek, gives a method quite similar to that of Bouveault and Rousset, which follows.

200 g. of isoamyl alcohol, boiling at 130° to 132°C., are heated to the boiling point in a flask equipped with a condenser set for distillation, and a cooled mixture of 114 g. of sodium dichromate, 148 g. of sulfuric acid, and 350 cc. of water is added dropwise at a rapid rate (about 30 minutes). The mixture is boiled 15 minutes longer. During the whole operation a mixture of water, unchanged alcohol, and isovaleraldehyde distils. Separation and rectification of the oily part of the distillate produces an aldehyde fraction boiling at 90° to 94°C. Some isoamyl alcohol distils because the amount of dichromate is insufficient for its complete conversion to the aldehyde. Kohn emphasizes that the purification of the isovaleraldehyde through the bisulfite compound proved to be impractical.

Van Marle and Tollens did not know of Kohn's paper or else disregarded it. They refer only to Bouveault and Rousset, and give the following directions.

To 100 parts of hot amyl alcohol in a large tubulated retort the neck of which is inclined upward a mixture of 110 parts of sodium dichromate, 225 parts of water, and 90 parts of concentrated sulfuric acid is added dropwise. The retort is set in a bath heated to 110° to 120°C. The retort is connected to a T-tube one arm of which is connected to a condenser set for distillation. The other arm holds a thermometer. The temperature of the vapors passing over should not exceed 92.5°C. The oily layer is separated, dried, and rectified. As is evident from the ratio of the quantities used, van Marle and Tollens use considerably more dichromate for the oxidation.

[82] L. Bouveault and L. Rousset, *Bull. soc. chim.*, **11**, 300 (1894).
[83] L. Kohn, *Monatsh.*, **17**, 126 (1896).
[84] C. M. van Marle and B. Tollens, *Ber.*, **36**, 1342 (1903).
[85] Fossek, *Monatsh.*, **4**, 660 (1883).

In recent years the method of chromic acid oxidation seems to have been abandoned. In the manufacture of perfumes, in which the higher aliphatic aldehydes are important, these compounds are prepared from the corresponding alcohols almost exclusively by the catalytic method of Bouveault described below. Apparently, the reason for this is that the higher aliphatic primary alcohols are now made conveniently and cheaply by catalytic reduction of fatty acids and fats, a method which makes Piria's distillation of the calcium salts of the corresponding acids (see page 438) of historical significance.

Copper or brass is used in most cases for catalytic dehydrogenation of alcohols. Bouveault [86] gives details for carrying out the reaction. The apparatus (see Fig. 4) consists of a boiler from which the alcohol vapors pass into a heated catalyst chamber which is a vertical glass or copper tube. Above this is a fractionation apparatus which separates the aldehyde from the unchanged alcohol. The alcohol is returned to the boiler, and the aldehyde passes through the condenser into the receiver while the hydrogen escapes. The dimensions must be adjusted according to the space available. A catalyst chamber 1 m. long has a diameter of 25 to 30 mm. It is packed with rolls of copper screening impregnated with washed, moist, copper oxide, and is heated by a resistance wire wound around the tube and insulated with asbestos. After the apparatus has been dried by careful heating in a hydrogen atmosphere, the copper oxide is reduced at 300°C. (this takes about 8 to 10 hours). The temperature is measured by a thermometer inserted into the chamber. When aldehydes boiling below 200°C. are being prepared, the reaction can be carried out at atmospheric pressure, but in other cases reduced pressure is necessary. The temperature of the catalyst chamber has to be slightly above the boiling point of the aldehyde involved.

FIG. 4.—Apparatus for the catalytic dehydrogenation.

[86] L. Bouveault, *Bull. soc. chim.*, **3**, 118 (1908).

Geraniol is transformed into α- and β-citral at atmospheric pressure, and phenylethyl alcohol yields phenylacetaldehyde.   Allyl alcohol gives a little acrolein, but the chief product is propionaldehyde, formed by the reduction of the acrolein by the hydrogen formed in the reaction.

Apparently this method is not used extensively in the laboratory. Dispersal of the catalyst on a carrier of larger surface presents difficulties, because the usual carriers, such as pumice and clay, effect dehydration, thus favoring side reactions.   Instead of copper and brass, metallic platinum catalysts have been used.   In conclusion, it should be mentioned that the removal of hydrogen from alcohols may proceed pyrochemically in the absence of catalysts, a reaction which probably involves the wall of the flask.

Frequently, by means of suitable catalysts, the dehydrogenation may be carried out in liquids or melts instead of in the vapor phase, but this method is better suited for the dehydrogenation of secondary alcohols. Therefore, it will be discussed further in the following section.   An all-glass apparatus for the dehydrogenation has been described by Ruzicka and Stoll.[87]   Originally it was not intended for the preparation of aldehydes, but it may very well be used for this purpose.

Few detailed directions can be found in recent scientific publications for dehydrogenation reactions by the method of Bouveault.   Therefore, the preparation of n-nonyl aldehyde from n-nonyl alcohol according to the procedure of Lewinsohn,[88] which appears to be a well tested one, is given.

The success of the method shows considerable dependence on the careful preparation of the dehydrogenation catalyst.   An aqueous solution of pure copper nitrate is treated with the calculated amount of pure sodium hydroxide and the precipitated copper hydroxide is washed by decantation with lukewarm water until the washings are neutral. The excess water is removed on a Büchner funnel, without allowing the hydroxide to become too dry.   This material may be stored as a paste in closed bottles.   The copper hydroxide paste is spread thinly on pieces of copper screening measuring 10×5 cm. The pieces of copper screen are rolled into cylinders 10 cm. long and put into a copper pipe 80 cm. long and of sufficient diameter to hold thirty of these rolls.   The screen should not be of too fine mesh, as this causes a reduction in the activity of the catalyst. The apparatus is built exactly as was Bouveault's.   The copper hydroxide is reduced to mossy metallic copper by filling the whole apparatus with hydrogen which has been washed with permanganate and dried with sulfuric acid, and heating the copper pipe to 300°C. electrically.   At this point the original paper speaks of "oxidized copper spirals" which are reduced together with the copper hydroxide, indicating that the copper screen may have been oxidized superficially before being coated with copper hydroxide. The reduction takes 8 hours.   The apparatus is cooled in a current of hydrogen if it is not to be used immediately, and if it stands overnight a slow current of hydrogen is allowed to pass through the apparatus continually.   Before the reaction is started, the

[87] L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, **7**, 89 (1924).
[88] A. Lewinsohn, *Perfumery Essent. Oil Record*, **15**, 13 (1924).

apparatus is heated again to 300°C. for 30 minutes and flushed thoroughly with hydrogen. *n*-Nonyl alcohol is then put into the boiler, the hydrogen stream is reduced, and the apparatus is evacuated to a pressure of 3 to 5 mm. The temperature in the contact tube is maintained at 240°C., and the nonyl alcohol is brought to a boil. The vacuum receiver is equipped to collect several fractions, so that if undecomposed nonyl alcohol should pass over because of a too rapid speed of distillation (indicated by a temperature increase at the top of the distilling column) these portions may be collected separately to prevent contamination of the aldehyde. The apparatus obviously requires careful supervision, and it takes some time before the speed of distillation becomes normal. The apparatus may be run continuously, or aldehyde-alcohol mixtures which were not completely dehydrogenated may be recirculated.

After the operation has been finished, the apparatus is filled with hydrogen and allowed to cool without admission of any air in order to prevent deactivation of the catalyst. The yield of nonyl aldehyde boiling at 78°C. at 3 mm. is 90%.

(b) Ketones

Nothing essentially new can be said about the dehydrogenation of secondary alcohols to ketones. The same oxidizing agents and methods are used, but, in general, the reactions take place more readily because ketones are considerably more resistant to an excess of the oxidizing agent than are aldehydes. An example of this method, the preparation of menthone from menthol, is described in *Organic Syntheses*.[89] It is based on the work of Beckmann.[90]

If natural *l*-menthol is used as a starting material, *l*-menthone is obtained by this process because of the small amount of sulfuric acid present. When glacial acetic acid is used, *d*-menthone is the principal product.

Sometimes dichromate may be replaced by potassium permanganate, but a comparison of the following sets of directions for the preparation of tropinone shows that this is rarely advantageous.

Permanganate Oxidation (*Willstätter* [91])—To 25 g. of tropine dissolved in 10 times its weight of 20% sulfuric acid are added 18.7 g. of a 4% solution of potassium permanganate in six to eight portions over a period of 45 minutes, the temperature being kept between 10° and 12°C. Each portion of permanganate which causes heating and the precipitation of manganese dioxide is decolorized after a few minutes. The reaction is complete in 1 hour. A large excess of sodium hydroxide is added and the mixture is steam-distilled until 1 liter of distillate has been collected. The tropinone is isolated as the dibenzal compound by mixing the distillate with a solution of 40 g. of benzaldehyde in 500 cc. of alcohol and 40 g. of 10% sodium hydroxide solution. After several days the dibenzaltropinone separates as yellow needles. The yield is 15.5 g. (27.8%). After recrystallization from alcohol the product melts at 150°C.

Chromic Acid Oxidation (*Willstätter* [92])—A solution of 12 g. of chromic acid in the same amount of water (the theory requires 2 moles of chromic acid for 3 moles of tropine)

[89] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 340.
[90] Beckmann, *Ann.*, **250**, 325 (1889).
[91] R. Willstätter, *Ber.*, **33**, 1169 (1900).
[92] R. Willstätter, *Ber.*, **29**, 396 (1896).

and 60 g. of glacial acetic acid is added dropwise and with constant stirring over a period of 4 hours to a warm (60° to 70°C.) solution of 25 g. of tropine in 500 cc. of glacial acetic acid. After the mixture has been heated for a short time on the steam bath until all the chromic acid has disappeared, it is cooled and made strongly alkaline with sodium hydroxide. Extraction with six 500 cc. portions of ether and removal of the ether give an oil which crystallizes readily. It may be purified by fractional distillation or through the picrate. The yield of material boiling at 224° to 225°C. (corrected, 714 mm.) is 80%. The picrate melts at 220°C., with decomposition.

A comparison of various oxidative methods for use with more sensitive compounds may be made in the case of the oxidation of cholesterol to the unsaturated ketone, cholestenone.

Diels and Abderhalden [93] melted 5 g. of cholesterol in a wide test-tube and heated the tube in a metal bath to 280° to 300°C. On the addition of 1 g. of copper oxide powder in three or four portions, a vigorous reaction which is finished in 20 to 25 minutes occurs, accompanied by the evolution of hydrogen and water. The hot reaction mixture is poured into a round bottomed flask and coated over the inner wall while it cools. Two extractions with 25 cc. portions of anhydrous methanol dissolve the cake almost completely. The solution is treated with charcoal and filtered from the insoluble residue. Evaporation *in vacuo* over sulfuric acid effects the separation of cholestenone in a yield of 25 to 30%. After recrystallization from warm methanol (40°C.) it melts at 78°C.

Windaus [94] first transformed cholesterol into dibromocholesterol (see page 63) in order to protect the sensitive position in the molecule. The dibromide may be oxidized either with chromic acid in glacial acetic acid at 70°C. or with potassium permanganate in the cold. The latter method is as follows:

30 g. of dibromocholesterol dissolved in 300 cc. of benzene are shaken mechanically for 5 hours with a solution of 500 cc. of 4% potassium permanganate and 100 cc. of 20% sulfuric acid. The manganese oxides which precipitate are dissolved by bubbling sulfur dioxide (an excess should be avoided) through the mixture. The benzene layer is separated, 150 cc. of glacial acetic acid and 10 g. of zinc dust are added, and the benzene is removed by distillation on a steam bath. To the residue are added 10 cc. of water and the mixture is refluxed for 1 hour. The oil precipitated by addition of more water to the cooled mixture is taken up in ether, and the ethereal solution is shaken with potassium hydroxide to remove all acidic compounds. The ether is evaporated, and the residue is extracted with ethanol until most of it has dissolved. Water is added carefully to the filtered solution from which the cholestenone crystallizes. After several recrystallizations from methanol it melts at 81° to 82°C.

Diels and Abderhalden later [95] improved their method described above. Their new directions are as follows:

[93] O. Diels and E. Abderhalden, *Ber.*, **37**, 3099 (1904).
[94] A. Windaus, *Ber.*, **39**, 518 (1906).
[95] O. Diels and E. Abderhalden, *Ann.*, **459**, 21 (1927).

100 g. of cholesterol are heated to 300°C. and 20 g. of copper oxide, not too finely powdered, are added in portions after the addition of which the temperature of the bath is kept at 300° to 310°C. for 15 minutes. The reaction mixture is dissolved while still warm in 1 liter of methanol and the filtered solution is stirred at 0°C. and seeded with crystallized cholestenone. When formation of crystal is complete, the methanol is evaporated over sulfuric acid *in vacuo*. A total yield of 60 g. of cholestenone is obtained.

Sexton [96] uses a different method.

The apparatus consists of a distilling flask of Jena glass with a cooling jacket slipped over the side arm, a second distilling flask used as a receiver, and a U-tube filled with glass-wool to serve as a trap between the receiver and an oil pump. A mixture of 20 g. of pure cholesterol and 15 g. of copper powder is heated carefully in the first flask at a pressure of 2 to 3 mm. When the cholesterol starts to melt, a violent reaction takes place and a thick white mist distils. This condenses in the receiver as a colorless powder. After several minutes the reaction subsides and the catalyst conglomerates. The temperature is raised slowly and 17 g. of a golden yellow, very viscous oil distil at 280° to 290°C. at 3 to 4 mm. pressure. Crystallization of the oil from methanol and cooling in ice yield 6 g. of crystallized cholestenone. Evaporation of the mother liquor over calcium chloride *in vacuo* affords an additional 10 g. of a crude product, making a total yield of 80%. Only 0.2 g. of cholesterol appears as a sublimate in the receiver. The melting point of the cholestenone was raised to 80°C. by repeated crystallizations.

Ruzicka and coworkers [97] relied on the above method of Windaus, and gave the following directions.

A solution of 30 g. of dibromocholesterol in 300 cc. of benzene is shaken with a mixture of 10 g. of chromic acid (excess) in 100 cc. of water and 200 cc. of glacial acetic acid for 6 hours. The layers are separated and the benzene solution is washed thoroughly with water. After the addition of 150 cc. of glacial acetic acid and 10 g. of zinc wool three-fourths of the benzene is removed by distillation and the residue is refluxed for 1 hour. The cooled solution is dissolved in ether and washed with dilute alkali and with water. Evaporation of the ether affords a residue which is dissolved in 200 cc. of hot ethanol. The solution is decanted from a small amount of rosin which precipitates, and is concentrated to 50 cc. Cooling in ice gives 15.5 g. of cholestenone melting at 76° to 80°C. (corrected).

For the removal of the bromine from cholestenone dibromide, Schoenheimer [98] suggests refluxing the dried benzene solution, obtained by the above method, with sodium iodide instead of with zinc.

The benzene solution is boiled for 2 hours with an alcoholic solution of sodium iodide. After being shaken with sodium thiosulfate solution to remove the iodine, it is washed with water and concentrated. This affords cholestenone melting at 79.5° to 80°C. in an 89% yield.

According to Ach and Knorr [99] poor yields of codeinone are obtained from codeine.

[96] W. Sexton, *J. Chem. Soc.*, **1928**, 2825.
[97] L. Ruzicka *et al.*, *Helv. Chim. Acta*, **17**, 1413 (1934).
[98] R. Schoenheimer, *J. Biol. Chem.*, **110**, 461 (1935); *Chem. Abstracts*, **29**, 5454 (1935).
[99] F. Ach and L. Knorr, *Ber.*, **36**, 3070 (1903).

Codeine (32 g.) is dissolved with cooling in 200 cc. of water and 40 g. of concentrated sulfuric acid. The addition of 20 g. of potassium dichromate in one portion precipitates codeine chromate which dissolves as the temperature rises spontaneously to about 50°C. The clear solution is cooled with ice, is made slightly alkaline with soda ash, and sodium hydroxide is added to redissolve the chromium oxide which precipitates. The mixture is extracted with 1500 cc. of ether, the ether is distilled; and the residue is recrystallized repeatedly from ethyl acetate to remove unchanged codeine. The yield is very poor.

Another method suggested in a patent (Merck [100]) is as follows:

Chromic acid is added to a solution of codeine in aqueous acetic acid. An oily precipitate forms which dissolves when the solution is stirred and heated to 50°C. The cooled solution deposits brown crystals of codeine chromate which are filtered and decomposed with ammonia. The codeine is extracted by ether from the reaction mixture, and the mother liquor is again extracted with ether after being made alkaline with ammonia. The combined ether extracts are concentrated, and the residue is crystallized from ethanol. A 40% yield of codeinone melting at 186°C. is obtained.

(c) *Oxidation of Polyhydric Alcohols to Aldehydo Alcohols and Keto Alcohols*

The transformation of polyhydric alcohols to aldehydo and keto alcohols by methods similar to those discussed above has less importance, because the desired compounds may often be prepared more conveniently in other ways.

Fenton and Jackson [101] originated a general method in which hydrogen peroxide and ferrous sulfate are used as the oxidant. Primary as well as secondary monohydric alcohols are perfectly stable towards this reagent. The preparation of glycolaldehyde is a good example of this method. A solution of 6.2 g. of ethylene glycol in 70 cc. of water is mixed with an aqueous solution of 5.2 g. of crystallized ferrous sulfate, and this mixture is added to 65.6 cc. of hydrogen peroxide solution containing 0.0559 g. of peroxide per cubic centimeter. The temperature rises considerably after several minutes. After standing for 90 minutes, the mixture is treated with sodium acetate to reduce the acidity, and a solution of 21.5 g. of phenylhydrazine in 50% acetic acid is added. The solution is allowed to stand for 5 hours at 38°C., and 12 hours at room temperature, during which time 2.8 g. of glyoxalosazone which must have been formed from glycolaldehyde are deposited.

Mannose is prepared from mannitol by adding 150 cc. of hydrogen peroxide (same concentration as above) to a mixture of a solution of 50 g. of mannitol in a little water and an aqueous solution of 12.5 g. of crystalline ferrous sulfate. After the reaction has subsided, the mixture is treated with an excess of freshly precipitated barium carbonate

[100] C. Merck, German Patent, 408,870.
[101] H. Fenton and H. Jackson, *J. Chem. Soc.*, **75**, 1 (1899).

and filtered. The filtrate is concentrated at 50°C. at a pressure of 30 mm., and the residue is evaporated *in vacuo* to a syrup which is mixed with 10 times its weight of absolute alcohol. Excess ether is added to the filtered solution and a light yellow syrup which becomes somewhat crystalline when mixed with a little alcohol and ether precipitates. The yield of mannose identified by its conversion to the phenylhydrazone is not given.

Still earlier Fischer and Hirschberger [102] had prepared large quantities of mannose by treatment of mannitol with nitric acid.

A solution of 3 kilos of mannitol in 20 liters of water and 10 liters of nitric acid ($D = 1.41$) is shaken and heated to 45°C. Not until 4 or 5 hours later do a noticeable reaction and evolution of a gas begin. Every 20 minutes a sample is neutralized with sodium carbonate and treated with phenylhydrazine in acetic acid. If the sample shows the formation of a thick yellow precipitate after several minutes (this usually takes place 5 to 6 hours after the reaction is started), the solution is cooled to 25°C. by the addition of pieces of ice, made slightly alkaline by adding crystalline sodium carbonate, and reacidified by acetic acid. To the colorless solution is added a solution of 1 kilo of phenylhydrazine in dilute acetic acid, and the mixture is allowed to stand for 1 hour. The mannose phenylhydrazone, which should be pale yellow in color, is collected in a Büchner funnel, washed with cold water, and pressed dry. For purification the product is recrystallized from water in the following manner. After one-fourth of the precipitate is boiled with 5 liters of water for 15 minutes, the mixture is filtered. The filtrate is decolorized by treatment with zinc dust and ammonia and filtered again while hot. Mannose phenylhydrazone crystallizes from the cooled filtrate in the form of pale yellow leaflets. The mother liquor is used for the recrystallization of further amounts to avoid losses due to the great solubility of the phenylhydrazone in cold water. It cannot be recovered pure by concentration of the mother liquor. A 10% yield of mannose phenylhydrazone is obtained.

The phenylhydrazone is converted into the free sugar by dissolving 100 g. portions in 400 g. of hydrochloric acid ($D = 1.19$) and allowing the solution to stand for 30 minutes at room temperature. After the mixture has been cooled in a freezing mixture, the phenylhydrazine hydrochloride is removed by filtration through glass-wool or through a fritted glass filter. The dark red filtrate is diluted with twice its volume of water, neutralized with lead carbonate, filtered, and the filtrate is made alkaline with barium hydroxide. Extraction with ether removes the residual phenylhydrazine and the colored substances. The aqueous layer (2 to 3 liters) is saturated with carbon dioxide, decolorized with charcoal, filtered, and concentrated to 300 cc. *in vacuo* on a steam bath. Barium

[102] E. Fischer and J. Hirschberger, *Ber.*, 22, 365 (1889).

chloride is removed from this solution by adding sulfuric acid, neutralizing the excess acid by lead carbonate, and concentrating the filtered solution *in vacuo*.   The lead chloride which separates is removed by filtration and the mother liquor is evaporated to a syrup.   The residue is dissolved as completely as possible in 5 times its volume of absolute alcohol, and the solution is treated with hydrogen sulfide.   Mannose is precipitated from the filtered solution as a colorless syrup by the addition of ether.   From 100 g. of phenylhydrazone are obtained 60 g. of mannose (about 90% pure), a yield of 80%.   Crystallized mannose was first obtained by van Ekenstein [103] by the decomposition of mannose phenylhydrazone by benzaldehyde.

The chemical oxidation of polyhydric alcohols containing a primary hydroxyl group at the end of the chain produces aldehydes in every case. The preferential oxidation of secondary alcoholic hydroxyl groups is successful only in biological processes, of which the preparation of sorbose from sorbitol is the best known example.   Sorbitol, now available commercially, may be used as the starting material instead of the fruit juices which Bertrand [104] suggested.   Recently Schlubach and Vorwerk [105] made some suggestions for improving the method, the details of which may be found in the original paper.

Quinone may be prepared most conveniently and economically in the laboratory not from aniline but from hydroquinone.   The procedure in which sodium or potassium dichromate is used as the oxidizing agent is much more simple and is little more expensive.   The stability of quinone depends very much on the care exercised during its preparation.   The details of a method based on that of Vliet [106] are given.

The dehydrogenation of hydroquinone with sodium chlorate and vanadium pentoxide as a catalyst [107] offers no material advantages in comparison with the method of Vliet.

The dehydrogenation of pyrocatechol with silver oxide leads to *o*-quinone which may be prepared by the directions of Willstätter and Pfannenstiel.[108]

As the successful preparation of the quinone depends on the quality of the silver oxide, Willstätter and Müller [109] give the following directions for its preparation.   Silver oxide which has been prepared in the usual manner from silver nitrate and sodium

[103] A. van Ekenstein, *Rec. trav. chim.*, **15**, 221 (1896).
[104] M. G. Bertrand, *Bull. soc. chim.*, **15**, 627 (1896).
[105] H. Schlubach and J. Vorwerk, *Ber.*, **66**, 1251 (1933).
[106] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 482.
[107] A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. II, Wiley, New York, 1943, p. 553.
[108] R. Willstätter and A. Pfannenstiel, *Ber.*, **37**, 4744 (1904).
[109] R. Willstätter and F. Müller, *Ber.*, **41**, 2581 (1908).

hydroxide is washed by decantation twelve times with water, six times with acetone, and six times with absolute ether.

To a solution of 2.5 g. of pyrocatechol in 150 cc. of absolute ether are added 10.5 g. of silver oxide (twice the calculated amount) and 8 g. of ignited sodium sulfate, and the mixture is shaken mechanically for 1 hour. It is filtered, the filtrate is concentrated on a steam bath, and the residue is crystallized. The o-quinone separates as bright red leaflets having no definite melting point. Between 60° and 70°C. it decolorizes and decomposes.

Willstätter and Pfannenstiel found that a colorless as well as a colored form of o-quinone exists, but it is obtained only during the preparation of relatively small amounts.

A suspension of 1.5 g. of silver oxide and an equal amount of sodium sulfate in 7 cc. of ether is shaken for 15 seconds with a solution of 0.08 g. of pyrocatechol in 3 cc. of ether. The mixture is filtered immediately through a filter containing some sodium sulfate, and the light green filtrate is mixed without shaking with an equal volume of petroleum ether. After a short time a voluminous crystalline mass of colorless prisms appears. Rearrangement of colorless to colored form takes place within a short time.

5. Oxidation of Alcohols and Aldehydes to Carboxylic Acids

The methods for the preparation of aldehydes by dehydrogenation of alcohols by means of strong oxidizing agents show that aldehydes are not as unstable towards oxidizing agents as is occasionally stated. It is also very likely that absolutely pure aldehydes, their structure notwithstanding, are stable towards the oxygen of air, and that their autoxidation is very likely caused by catalysis by heavy metals. In the laboratory the conversion of aldehydes to carboxylic acids by means of atmospheric oxygen is quite out of the question from a practical consideration, but in industry the method apparently plays some part. At any rate, it is one of the more rarely used methods in the chemical laboratory, because the compounds desired are usually obtained more easily in other ways. There is little to recommend one oxidizing agent or another, but in the aliphatic as well as in the aromatic series hydrogen peroxide is sufficiently reactive for use in most cases (Stoermer [110]). Frequently, and especially for experiments with small amounts, potassium permanganate in acetone is a suitable oxidizing mixture.

The preparation of enanthic (n-heptanoic) acid from enenthaldehyde, as given in *Organic Syntheses*,[111] is an example of the oxidation of an aldehyde with acid permanganate.

Special methods for the oxidation of aldehyde groups are used in sugar chemistry. Here one must distinguish between oxidation for analytical purposes and oxidation for preparative purposes. At the present time,

[110] R. Stoermer, *Ber.*, 44, 655 (1911).
[111] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 315.

the conversion of aldoses into aldonic acids is carried out almost exclusively by a method first described by Isbell and Frush,[112] and improved later by Kiliani.[113] It is very well suited for the oxidation not only of hexoses but also for pentoses (Bernhauer and Stein [114]). The directions of Kiliani for the preparation of *d*-mannonic acid from *d*-mannose are an excellent example of the method.

To a solution of 100 g. of *d*-mannose in 2 liters of water are added 17.7 g. of calcium bromide and 55 g. of calcium carbonate. The stirred mixture is electrolyzed in a cylindrical vessel equipped with carbon electrodes 12 cm. in diameter and about 8 cm. apart. The current should be 0.5 to 0.7 ampere. After 50 to 55 hours, when the solution shows only slight reducing properties, it is filtered, concentrated as much as possible, and allowed to solidify. The jelly-like mass is cut into small pieces and dried. The preparation of crystallized calcium mannonate is described in the original paper. For the conversion of *d*-mannonic acid to its lactone, 1 part of the calcium salt is dissolved on the steam bath in 3 parts of water, the solution is mixed slowly with excess oxalic acid, and the precipitated calcium oxalate is removed by filtration. The filtrate is concentrated until its weight is equal to that of the calcium salt used and the concentrate is allowed to crystallize.

Goldschmidt [115] stated that small amounts of carboxylic acids are formed along with hydrogen when a mixture of the corresponding aldehyde and water vapor is passed over chromium oxide catalysts, but the reaction is of no practical importance.

ҕ. Preparation of Alcohols and Carboxylic Acids by Cannizzarro Reaction

The reaction of aldehydes with alkalies,

$$2R \cdot CHO + H_2O \xrightarrow{\quad OH^- \quad} R \cdot COOH + R \cdot CH_2OH$$
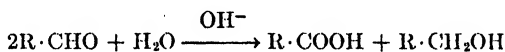
is called the Cannizzarro reaction after its inventor. It is probably related in principle to the reaction of Tishchenko which yields esters from aldehydes (see page 185).

Cannizzarro's reaction is discussed at this point because it is of value only for the preparation of carboxylic acids, for alcohols can be obtained more conveniently from aldehydes by their reduction. The importance of the Cannizzarro reaction in physiological chemistry can only be mentioned in passing.

Its value is illustrated by the preparation of pyromucic acid (2-furancarboxylic acid) and furfuryl alcohol from furfural, because in this case it was found that the direct oxidation of furfural by any other method does not give a satisfactory yield. The Cannizzarro reaction gives a

[112] Isbell and Frush, *Bur. Standards J. Research*, **6**, 1145 (1931); *Chem. Abstracts*, **25**, 4850 (1931).

[113] H. Kiliani, *Ber.*, **66**, 117 (1933).

[114] K. Bernhauer and W. Stein, *Biochem. Z.*, **249**, 216 (1932).

[115] M. Goldschmidt, *Ber.*, **67**, 202 (1934).

limited yield but the convenience of the method and the production of a valuable by-product compensates for this (*Organic Syntheses* [116]).

The use of purer starting materials than those specified in the directions is apparently unnecessary, because resinification occurs during the reaction. Runs made with pure materials did not give higher yields, but the end-products were apparently more stable. It is preferable to purify small amounts of 2-furancarboxylic acid by sublimation at 2 mm. pressure.

B. Replacement of Halogen by Oxygen

The replacement of halogen by oxygen yields alcohols, aldehydes or ketones, carboxylic acids, or phenols. An aliphatic halogen atom can be replaced more or less readily, depending on whether it is attached to a primary, a secondary, or a tertiary carbon atom (see page 96).

1. Replacement of Halogen by Hydroxyl Group

The reaction may be carried out directly by boiling the halide with aqueous alkalies or with a suspension of lead oxide; or indirectly by treating the halide with alkali acetate and saponifying the esters produced thereby. Every elementary textbook discusses the advantages and disadvantages of these methods in connection with the preparation of ethylene glycol from ethylene dibromide. A useful method for some cases is that of Bouveault [117] who treated the Grignard compound of the halide with oxygen in ethereal solution and subsequently decomposed the reaction mixture with water. This method may also be used, in principle at least, in the aromatic series, but the necessity of replacing an aromatic halogen atom by a hydroxyl group should arise only in rare cases.

The method is illustrated by the preparation of benzyl alcohol by Lauth and Grimaux [118] who boiled benzyl chloride for 2 hours with 3 times its weight of freshly precipitated lead oxide and 10 times its weight of water. As the iodides react more easily than the chlorides in the aliphatic series, Flawitzkii [119] prepared isopropanol from isopropyl iodide by treating the iodide with 10 parts of water and an excess of lead oxide and removing the last traces of it with moist silver oxide. Meunier [120] boiled molecular amounts of benzyl chloride and potassium carbonate with 8 to 10 parts of water until an oil rose to the surface after several hours. The yield is not mentioned.

Good directions for the preparation of glycolic acid in the laboratory are given by Witzemann [121] who used barium carbonate for the saponifica-

· [116] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 276.
[117] L. Bouveault, *Bull. soc. chim.*, 29, 1053 (1903).
[118] C. Lauth and E. Grimaux, *Ann.*, 143, 81 (1867).
[119] F. Flawitzkii, *Ann.*, 175, 380 (1875).
[120] J. Meunier, *Bull. soc. chim.*, 38, 159 (1882).
[121] E. Witzemann, *J. Am. Chem. Soc.*, 39, 109 (1917).

tion in place of calcium carbonate which was employed in the old method of Hölzer.[122] This reaction is more important for the preparation of α-hydroxycarboxylic acids than for simple alcohols.

To a filtered solution of 50 g. of monochloroacetic acid in 500 cc. of water are added slowly 170 g. of barium carbonate. The mixture is refluxed until carbon dioxide is no longer evolved (about 30 hours) and, as the reaction nears completion, the flask is shaken frequently. With mechanical stirring the reaction time might be shortened. The excess barium carbonate is removed by filtration and 52.1 g. of 95% sulfuric acid are added to the hot filtrate. This amount of acid is equivalent to 95% of the soluble barium salts formed during the reaction. The mixture is stirred for a short time, filtered, and the filter cake is washed with water several times. The filtrate and washings are combined and mixed with small amounts of sulfuric acid until the solution contains only a trace of barium ion. The filtrate is concentrated *in vacuo*, and the small amount of barium sulfate which separates is filtered. The syrupy residue has a strong odor of hydrochloric acid the greater part of which is removed by heating on a steam bath for 2 hours. When the residue, which weighs 40 g., is scratched with a glass rod or seeded with crystalline glycolic acid, 16.5 g. (41%) of glycolic acid crystallize. The aqueous solution should not be concentrated too much, as the yield of crystallized glycolic acid depends largely on concentrating it carefully. If the glycolic acid will not crystallize, it may be reconverted to the barium salt and the above procedure repeated. The total yield of glycolic acid is 88.7%, of which half is obtained as the calcium salt.

This method is not suitable for the preparation of α-hydroxybutyric acid, and Bischoff and Walden [123] recommend the following procedure.

100 g. of α-bromobutyric acid are refluxed with an equivalent amount of potassium carbonate (83 g.) and 500 cc. of water for 5 to 6 hours. The mixture is evaporated, the residue is treated with the calculated amount of hydrochloric acid, and the thick slurry is filtered from the potassium chloride-potassium bromide mixture. The filtrate is extracted with ether in a continuous extraction apparatus, the ethereal solution is dried with sodium sulfate, and the ether is distilled. Repeated fractionation of the residue affords α-hydroxybutyric acid boiling at 140°C. at 12 mm., and melting at 42°C. in an unspecified yield.

The predominant side reaction which is a complicating factor in the saponification of aliphatic halides is the removal of hydrogen halide. It is recommended that freshly prepared silver oxide be used in dubious cases, because it reacts in the cold; but even then the formation of unsaturated compounds cannot always be prevented. In such cases the preparation of the hydroxylic compound via the acetate is more advantageous.

An aromatically bound halogen atom is replaced by the hydroxyl group only with difficulty. Meyer and Bergius[124] carried out experiments on the behavior of chlorobenzene towards sodium hydroxide at elevated temperatures in an autoclave. The mobility of the halogen atom in the

[122] Hölzer, *Ber.*, **16**, 2955 (1883).
[123] C. Bischoff and P. Walden, *Ann.*, **279**, 102 (1894).
[124] K. H. Meyer and Bergius, *Ber.*, **47**, 3155 (1914).

nucleus increases with the number of substituents present, details of which are given in a paper by Borsche and collaborators.[125]

2. Replacement of Halogen by Carbonyl Oxygen

The conversion of halides to aldehydes is more important than their conversion to alcohols. It is not necessary to prepare dihalides, which are hydrolyzed easily to carbonyl compounds, as monohalides can be saponified and oxidized simultaneously. Many aromatic aldehydes can be obtained in good yield according to the equation $R \cdot CH_2Cl + O \rightarrow R \cdot CHO + HCl$.

The preparation of benzaldehyde by boiling benzyl chloride with aqueous copper nitrate solution was a standard method for a long time, but that of Sommelet [126] is usually more useful.

Hexamethylenetetramine reacts with benzyl chloride, benzyl bromide, and substituted benzyl halides with the formation of a compound which can be isolated and which has a sharp melting point. When boiled with water the addition product is decomposed in a manner as yet not clearly understood, and often the corresponding aldehyde is obtained in excellent yield. Experimental details have been given for certain aldehydes [127] but, since the method is apparently used extensively in industry, most of the literature available consists of patents.[128] The addition products need not be isolated, and it generally suffices to boil the corresponding chlorides or bromides in aqueous alcoholic solution for some time. The aldehydes which are volatile with steam, such as *m*-tolualdehyde, may be steam-distilled directly from the reaction mixture. The preparation of *o*-tolualdehyde is a little more difficult, as the following directions show:

60 g. of ω-bromo-*o*-xylene are mixed with 250 cc. of ethanol, and 48 g. of hexamethyl-enetetramine (small excess) and 50 cc. of water are added. The mixture becomes warm as the urotropine dissolves. After the smell of bromo-*o*-xylene has disappeared (5 minutes), an additional 200 cc. of water are added and the mixture is refluxed for 2 hours. The product is distilled with steam until the condensate no longer smells of aldehyde (after about 1.5 liters have been collected). The distillate is extracted with ether; the ether solution is washed with water, dried, and fractionated. A yield of 27 g. (70%) of *o*-tolualdehyde is obtained which boils from 86° to 88°C. at 19 mm. Whether this or a similar method or whether a reaction involving the dihalide is used depends largely on the compound desired and its properties. It is not possible to obtain pure benzal chloride for the conversion of toluene into benzaldehyde by direct chlorination, since benzyl chloride and benzotrichloride are obtained as by-products. The usual method [129] which consists of the saponification of a mixture of benzal chloride and benzotrichloride yields

[125] W. Borsche *et al.*, *Ber.*, **49**, 2222 (1916).
[126] M. Sommelet, *Compt. rend.*, **157**, 852 (1913).
[127] Mayer and Sieglitz, *Ber.*, **55**, 1846 (1922); Hewett, *J. Chem. Soc.*, **1940**, 297; see also foot-note 126.
[128] German Patent, 268,786.
[129] Gattermann-Wieland, *Die Praxis des organischen Chemikers*. de Gruyter, Berlin, 1936, p. 210.

a mixture of benzaldehyde and benzoic acid easily separable by steam distillation.   Industrial plants find no disadvantage in this procedure, since both benzaldehyde and benzoic acid are useful products.

To overcome the difficulties involved in preparing pure benzaldehyde from toluene and chlorine, a more recent industrial method has been developed by Makarov-Zemlianskii and Prokin.[130]

Chlorine is passed into boiling toluene until the boiling point has risen to 195°C. The mixture is cooled, washed with water, dried with calcium chloride, and fractionated. Portions of 161 g. each of the fraction distilling between 96.5° and 102°C. at 5 mm. are heated with 74 g. of boric acid in a flask fitted with an air condenser 70 cm. long.   As the metal bath surrounding the flask is heated to 130°C., the reaction mixture expands and hydrogen chloride is evolved.   The heating is continued for a total of 4 hours, towards the end of which time the bath temperature is increased to 160°C.   The cooled liquid is extracted four times with ether, and the ethereal extract is shaken with a solution of bisulfite.   From the bisulfite extract 60 g. (89%) of pure benzaldehyde can be isolated in the usual manner.   After the ether solution has been washed with a 20% sodium carbonate solution, 30 g. of benzyl chloride may be recovered from it by distillation. The hydrogen chloride formed is recovered as hydrochloric acid, the boric acid quantitatively as such, and a little benzoic acid is obtained as a by-product.

This method may possibly be used advantageously in other cases, but as yet no observations on this matter are available.   In simpler cases in which the pure dichlorides are available, the saponification can be effected more readily with marble, barium carbonate, or some other alkaline reagent.

3. Replacement of Halogen by Carboxyl Oxygen

The saponification of the trihalides proceeds readily by any of the methods discussed above; therefore this subject needs no further comment.

C. Replacement of Nitrogen by Oxygen

1. Replacement of Primary Amino Group by Hydroxyl Group

In the aliphatic series the replacement of the amino group by a hydroxyl group can be brought about without difficulty by the use of nitrous acid according to the general scheme, $R \cdot NH_2 + ONOH \rightarrow N_2 + H_2O + R \cdot OH$.   Its preparative importance is not particularly significant, because the aliphatic amines are almost always more difficult to obtain than the corresponding hydroxyl compounds, and often rearrangements are encountered which lead to unexpected products.   According to Walden's [131] procedure, l-malic acid is prepared from l-asparagine as follows:

[130] J. Makarov-Zemlianskii and S. Prokin, *J. prakt. Chem.*, **147**, 319 (1936).
[131] P. Walden, *Ber.*, **28**, 2771 (1895).

Nitrogen oxides are passed into a solution of 25 g. of asparagine in 50 cc. of dilute nitric acid for 7 hours, while the solution is heated on the steam bath. After the evolution of nitrogen has ceased, the solution is neutralized with potassium hydroxide and lead acetate is added. The precipitate is collected, washed with warm water, suspended in water, and decomposed with hydrogen sulfide. The filtrate from the lead sulfide is concentrated to a syrup on a steam bath and the residue is dissolved in hot acetone. The solution is filtered and the acetone is removed by distillation *in vacuo*. Crystallization of the residue affords 10 g. of dry *l*-malic acid.

This reaction is of greater importance in the aromatic series, in which the intermediate diazonium compounds, the preparation of which is described on page 106, are more stable. Because of the nature of the subsequent reactions, these diazotizations cannot be carried out in the presence of 'nitric or hydrohalide acids. Sulfuric acid has to be used, although the slight solubility of the aromatic amine sulfates complicates the reaction somewhat. The preparation of *m*-nitrophenol from *m*-nitroaniline was first described by Fittig [132]; Holleman and Wilhelmy [133] used a very large quantity of very dilute sulfuric acid for the hydrolysis, and Adams and Wilson [134] also used relatively large amounts of liquids. A much more convenient method is that of Manske, which is given in *Organic Syntheses*.[135]

The hydrolysis of the diazonium salt by means of boiling sulfuric acid may also be used for other, more stable nitrodiazonium compounds. Whenever the diazonium compounds are unstable, their isolation in a solid form should be avoided. For the preparation of *m*-chlorophenol, Holleman and Rinkes [136] give the following directions.

The diazonium sulfate solution prepared from *m*-chloroaniline in the usual way is added dropwise to a solution of 2 parts of concentrated sulfuric acid and 1 part of water, maintained at a temperature of 140°C. The mixture is steam-distilled, the distillate is extracted with ether, and the extract is dried over sodium sulfate. Vacuum distillation of the ethereal solution yields 27 g. (67%) of *m*-chlorophenol (from 40 g. of *m*-chloroaniline). *m*-Chlorophenol boils at 214°C. at atmospheric pressure, but no boiling point is given at the reduced pressure. The crude yellow product melts at 30°C. and may be purified by crystallization from warm ligroin (30°C.). By cooling the solution in an ice bath and seeding it, a colorless product is obtained which solidifies at 32°C.

On comparison of the procedures for the preparation of *m*-nitrophenol and of *m*-chlorophenol it is surprising to find that Holleman has already perfected the method for making chlorophenols which Manske (see above) used later for the preparation of *m*-nitrophenol; *i.e.*, decomposition of the

[132] R. Fittig, *Ber.*, **7**, 179 (1874).
[133] Holleman and Wilhelmy, *Rec. trav. chim.*, **21**, 435 (1902).
[134] R. Adams and W. Wilson in *Organic Syntheses*, **3**, 87 (1923).
[135] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 404.
[136] A. Holleman and J. Rinkes, *Rec. trav. chim.*, **30**, 81 (1911).

solution of the diazonium salt with rather concentrated sulfuric acid.   In preparing nitrophenols, however, he used a mixture of 2 liters of water and 125 cc. of sulfuric acid.

The replacement of the amino group in amides usually does not present any difficulties.   The procedure with strong alkalies and acids is the same as that involved in the saponification of esters (see page 197), and the carboxylic acids are isolated by an appropriate method.   Occasionally however, certain amides, usually those which have been prepared from nitriles, which are difficult to saponify, resist this treatment.   According to Bouveault [137] such amides may be converted into carboxylic acids by treatment with nitrous acid, a method which Heyl and Meyer [138] used for the conversion of triphenylacetamide into triphenylacetic acid.

The finely powdered amide (0.2 g.) is dissolved in 2 g. of warm concentrated sulfuric acid.   The solution is cooled in an ice bath and an ice-cold solution of 0.2 g. of sodium nitrite in 1 cc. of water is added very slowly.   The mixture is heated cautiously on a water bath, and at 60° to 70°C. a violent evolution of nitrogen takes place, which ceases when the temperature reaches 80° to 90°C. The reaction mixture is heated for a few minutes longer on a steam bath and is cooled.   The triphenylacetic acid is precipitated by the addition of ice water, and is crystallized from glacial acetic acid.   It melts at 225°C. (with decomposition).   For further examples of this method see Sudborough [139] and Gattermann.[140]

2. Replacement of Nitrogen by Carbonyl Oxygen

The necessity of preparing carbonyl compounds from oximes, semi-carbazones, phenylhydrazones, and other derivatives will seldom arise but, since these derivatives are often used for the purification and isolation of aldehydes and ketones, their reconversion from these derivatives is of considerable importance.

Details of the method involving their hydrolysis with acids or alkalies are given below.   Sensitive aldehydes, especially those in the sugar series, may require the use of another method: $R \cdot CH{:}N \cdot R' + R'' \cdot CHO \leftrightarrows R'' \cdot CH{:}N \cdot R' + R \cdot CHO$, in which the desired carbonyl compound is displaced from its derivative by another carbonyl compound.

The hydrolysis of oximes and other derivatives of simple structure presents no difficulties, and a useful method for this which is quite general has been described by Tiemann.[141]   Steam distillation of a mixture of phthalic anhydride and semicarbazones of volatile aldehydes affords nearly quantitative yields of the aldehydes.

Difficulties are frequently encountered during the hydrolysis of iso-nitroso ketones.   Several authors, following the procedure of Pech-

[137] L. Bouveault, *Bull. soc. chim.*, 9, 370 (1893).
[138] G. Heyl and V. Meyer, *Ber.*, 28, 2783 (1895).
[139] Sudborough, *Ber.*, 28, 917 (Ref.) (1895).
[140] Gattermann, *Ber.*, 30, 1279 (1897).
[141] F. Tiemann, *Ber.*, 33, 3721 (1900).

mann [142] in which the bisulfite compound of the keto aldehyde is obtained as an intermediate, have been unable to repeat successfully the preparation of phenylglyoxal from isonitrosoacetophenone (see page 135). The reason for this is not known.

As an example of a decomposition with benzaldehyde, directions by E. Fischer [143] based on an observation of Herzfeld [144] are given.

Galaheptose phenylhydrazone (10 g.) obtained from the reduction products of heptanoic acid lactone is dissolved in 400 cc. of hot water, and the solution is shaken with 5 cc. of pure benzaldehyde. When the oily reaction product has separated almost completely and the liquid has become clear, an additional 6 g. of the phenylhydrazone are dissolved in the reaction liquid by heating and decomposed by shaking the solution with 2.5 cc. of benzaldehyde. After the same operation has been repeated, the mixture is boiled for 15 minutes and cooled. The benzaldehyde phenylhydrazone is filtered off. The filtrate is shaken with ether to remove excess benzaldehyde and benzoic acid, decolorized with activated carbon, filtered, and evaporated to dryness *in vacuo*. The galaheptose remains as a colorless syrup.

Osazones may also be decomposed in this manner (E. Fischer [145]). A solution of 20 g. of phenylmaltosazone in 1600 cc. of boiling water is mixed thoroughly with 16 g. of pure benzaldehyde. If the benzaldehyde is well dispersed, the reaction takes 20 minutes. The cooled mixture is filtered with suction to remove the benzaldehyde phenylhydrazone which forms in an almost theoretical amount, and the filtrate is processed in the manner described above.

Ruff and Ollendorff [146] substituted formaldehyde for benzaldehyde in the decomposition of pentose benzylphenylhydrazones.

A mixture of 1 g. of benzylphenylhydrazone and 2 to 3 cc. of freshly distilled formalin is heated on a steam bath. The solution becomes cloudy after several minutes and the separation of the formaldehyde hydrazone is complete in 1 hour. The oil is extracted with ether and the aqueous layer is evaporated to dryness. The residue is redissolved in water and the liquid is evaporated several times to volatilize the polymerization products of formaldehyde. The sugar is isolated in the usual manner. Other hydrazones may also be processed by this method.

The decomposition of succinaldehyde dioxime, which can be prepared by treating pyrrole with hydroxylamine (see page 277), is difficult because of the instability of the dialdehyde. According to Harries [147] the treatment of 20 g. of the dioxime with nitrous gases affords only 7 g. of the polymeric aldehyde. The following directions given by Mannich and Budde [148] are apparently more advantageous.

[142] H. v. Pechmann, *Ber.*, 22, 2557 (1889).
[143] E. Fischer, *Ann.*, 288, 145 (1895).
[144] Herzfeld, *Ber.*, 28, 442 (1895).
[145] E. Fischer, *Ber.*, 35, 3142 (1902).
[146] O. Ruff and G. Ollendorff, *Ber.*, 32, 3234 (1899).
[147] Harries, *Ber.*, 41, 255, foot-note 4 (1908).
[148] Mannich and Budde, *Arch. Pharm.*, 270, 283 (1932).

30 g. of succinaldehyde dioxime are suspended in 40 cc. of dioxane and the mixture cooled in ice. Over a period of about 40 minutes 45 to 50 cc. of ethyl nitrite are added at such a rate that the temperature remains between 5° and 15°C. The reaction is completed when further addition of nitrite causes no rise in temperature. After standing overnight the reaction mixture is fractionated in an atmosphere of carbon dioxide. After the forerun of dioxane has distilled, 13 to 14 g. (60%) of monomeric aldehyde pass over at 67°C. at 13 mm. The monomeric aldehyde is stable for a longer period of time if moisture is excluded, but it changes gradually to a glassy polymer from which the monomer may be recovered by distillation.

3. Replacement of Nitrogen by Carboxyl Oxygen; Hydrolysis of Nitriles to Carboxylic Acids

The reaction, $R \cdot C \vdots N \rightleftharpoons R \cdot COOH$, is important in aliphatic as well as in aromatic and heterocyclic chemistry, and is apparently quite simple in principle, although numerous difficulties may be encountered. The last traces of nitriles or of the acid amides, which are formed as intermediates, are not always removed easily. Steric hindrance, similar to that encountered during the saponification of esters of carboxylic acids, complicates the hydrolysis of aromatic nitriles. Küster and Stallberg [149] as well as Jacobsen [150] have carried out elaborate experiments in a study of this factor. Even nitriles, which can be saponified only with the greatest difficulty, can be hydrolyzed to the corresponding acid amides whose conversion to carboxylic acids can be effected by nitrous acid (see page 159).

The nature of the individual compound determines whether the saponification should be carried out in acid or alkaline media. The product is isolated most easily when fuming hydrochloric acid (as in the preparation of mandelic acid from mandelonitrile) or sulfuric acid is used. The extent of dilution is important; purely aromatic nitriles, such as o-tolunitrile, are saponified with 75% sulfuric acid (Cahn [151]). Directions for this procedure and for the saponification of phenylacetonitrile (benzyl cyanide) to phenylacetic acid are in *Organic Syntheses*.[152]

The older method of Mann,[153] recommending the use of alkali instead of sulfuric acid for the saponification, apparently has some advantages if an odorless product is desired.

Benzyl cyanide is heated with potassium hydroxide in aqueous alcoholic solution until ammonia is no longer evolved, the alcohol is removed by distillation, and phenylacetamide and unchanged benzyl cyanide are extracted from the cooled aqueous residue with ether. After acidification of the solution, the phenylacetic acid is isolated in the usual way.

[149] W. Küster and Stallberg, *Ann.*, 278, 207 (1894).
[150] Jacobsen, *Ber.*, 22, 1222 (1889).
[151] E. Cahn, *Ann.*, 240, 279 (1887).
[152] A. H. Blatt, ed., *Organic Syntheses*, Collective Vol. II, Wiley, New York, 1943, p. 588. H. Gilman and A. H. Blatt, ed., *Organic Syntheses*, Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 436.
[153] W. Mann, *Ber.*, 14, 1645 (1881).

Phenylacetic acid is purified most easily by distilling it *in vacuo* before attempting to crystallize it. It melts at 76.5°C. and boils at about 180°C. at 50 mm.

It is best to use alkali for the hydrolysis of aliphatic nitriles. Good results are obtained with the method of Shriner and coworkers [154] for the preparation of margaric acid from margaronitrile (cetyl cyanide). Their product melted at 61.2°C. Reid [155] reported a melting point of 60.66°C. for the stable form.

The saponification of nitriles may sometimes be effected advantageously by indirect methods. Pfeiffer [156] was the first to observe that the saturation of a hot methanol solution of a stilbene derivative by hydrogen chloride caused the conversion of the cyano group into a carbomethoxy group. Spiegel,[157] using 10 moles of alcohol and 1 mole of sulfuric acid per mole of nitrile, found that heating on a steam bath does not always give satisfactory yields, and that it is best to carry out the heating in a sealed tube at 130° to 140°C. Nearly theoretical yields are obtained in this way (Pfeiffer [158]).

D. Replacement of Sulfonic Acid Group by Hydroxyl Group

The replacement of a sulfonic acid group by a hydroxyl group is one of the best methods for the preparation of phenols. This is usually accomplished by fusing the sulfonic acid with alkalies, $R \cdot SO_3K + KOH \rightarrow K_2SO_3 + R \cdot OH$, but this reaction does not always proceed as simply as is indicated by the equation. Oxidation reactions, illustrated by the conversion of anthraquinone-β-sulfonic acid to alizarin, occur simultaneously to the normal exchange reaction.

In spite of their apparent similarity, potassium and sodium hydroxide differ greatly in the effects they produce, but either one is preferable in every case. Potassium benzene sulfonate may be converted almost quantitatively to phenol by means of potassium hydroxide, while with sodium hydroxide the conversion is only partial. According to Barth,[159] the relationship is reversed if one tries to convert benzenetrisulfonic acid to phloroglucinol. Only two sulfonic groups can be replaced by means of potassium hydroxide, while with sodium hydroxide all three are replaced, but the yield is poor.

By choosing suitable reaction temperatures and concentrations, several sulfonic acid groups can be replaced successively with potassium or sodium hydroxide.

[154] R. L. Shriner *et al.*, *J. Am. Chem. Soc.*, **55**, 1496 (1933).
[155] E. Reid, *J. Am. Chem. Soc.*, **55**, 1577 (1933).
[156] P. Pfeiffer, *Ber.*, **44**, 1115 (1911).
[157] L. Spiegel, *Ber.*, **51**, 296 (1918).
[158] P. Pfeiffer, *Ber.*, **44**, 805 (1911).
[159] Barth, *Ber.*, **12**, 422 (1879).

Details for carrying out the reaction can be found in elementary text-books; therefore, only one example is described (Erdmann [160]).

A mixture of 60 g. of potassium hydroxide, 20 cc. of water, and 14 g. of 1,8-naphthalenesulfonic acid anhydride is melted in a silver crucible and heated with stirring for 15 to 20 minutes at 200° to 230°C. The crucible should be covered as tightly as possible to prevent oxidation of the melt. The dark colored reaction mass is allowed to cool and is decomposed with 300 cc. of 13% hydrochloric acid. Concentrated hydrochloric acid is added until there is no further effervescence. After the addition of 1 liter of water, the mixture is heated until everything except a small amount of resin has dissolved. From the cooled filtrate 6 g. of 1,8-dihydroxynaphthalene crystallize, and 2 g. can be obtained by ether extraction of the mother liquor. The compound may be recrystallized from hot water containing sulfur dioxide. Its melting point is 140°C.

III. BY REPLACEMENT OF HALOGEN WITH FORMATION OF ADDITIONAL C—O BONDS: ETHERS, ESTERS, AND ACETALS

A. Ether Linkage

1. Open Chain Ethers

There are three types of open chain ethers, in which the component parts may be derived from (1) aliphatic alcohols, (2) a phenol and an aliphatic alcohol, and (3) phenols. The removal of water under acidic conditions, $2ROH \rightarrow ROR + H_2O$, is a method of value only in the formation of compounds of the first type. For the preparation of compounds of the second type the following reactions are typical:

(1) $R'ONa + XR'' \rightarrow NaX + R'R''$ (phenolate and alkyl halide).

(2) $R'OH + R_2''SO_4 \xrightarrow{OH^-} R''HSO_4 + R'OR''$ (phenol and dialkyl sulfate in the presence of alkali).

(3) $ROH + CH_2N_2 \rightarrow N_2 + ROCH_3$ (phenol and diazomethane and its homologues).
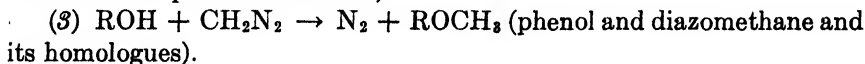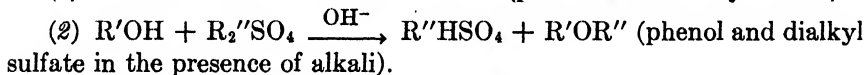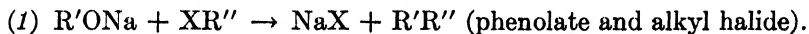
The ease of formation of ethers from aliphatic alcohols increases with increased branching on the carbinol carbon atom. It also increases with the load of aromatic residues, as evidenced by the formation of ethers of triphenylcarbinol and benzhydrol by crystallizing them from alcohols containing a trace of acid.

(a) Aliphatic Ethers

The method of synthesis of aliphatic ethers is illustrated by the preparation of diisoamyl ether according to the directions of Schorigin and Makarov-Zemlianskii.[161] The Grignard reagent used for the determination of active hydrogen in organic compounds is prepared in this ether.

[160] H. Erdmann, *Ann.*, 247, 356 (1888).
[161] P. Schorigin and J. Makarov-Zemlianskii, *Ber.*, 65, 1293 (1932).

A mixture of 1.5 kilos of isoamyl alcohol and 300 g. of *p*-toluenesulfonyl chloride is boiled in a large flask connected to a reflux condenser which is equipped with a water separator. Hydrogen chloride escapes while the vapors of water, isoamyl alcohol, and isoamyl ether are condensed and collected in the separator. The water is drained from the bottom, and the alcohol and ether mixture is returned to the reaction flask. The heating is continued until no more water collects (9 to 10 hours). The reaction proceeds as follows:

$$C_5H_{11} \cdot OH + Cl \cdot SO_2 \cdot C_7H_7 \longrightarrow HCl + C_5H_{11} \cdot O \cdot SO_2 \cdot C_7H_7$$

$$C_5H_{11} \cdot O \cdot SO_2 \cdot C_7H_7 + C_5H_{11} \cdot OH \longrightarrow (C_5H_{11})_2O + C_7H_7 \cdot SO_3H$$

$$C_5H_{11} \cdot OH + C_7H_7 \cdot SO_3H \rightleftharpoons C_5H_{11}O \cdot SO_2 \cdot C_7H_7 + H_2O$$
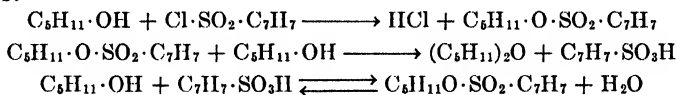
The reaction product is dried over potassium carbonate and distilled. After a forerun of 240 g., boiling between 75° and 132°C., has distilled, 1036 g. of crude ether containing about 7% of isoamyl alcohol are collected. An amount of boric acid, calculated on the basis of the isoamyl alcohol contained in the distillate, and 200 g. of benzene are added to the crude ether. The mixture is distilled, the benzene-water distillate is separated, and the benzene is returned to the distilling flask. After all the water has been removed, the benzene is distilled, the flask is cooled, and the mixture of isoamyl borate and ether is fractionated *in vacuo*. After the removal of a little benzene, pure isoamyl ether distils at 60° to 61°C. at 10 mm., leaving a residue of triisoamyl borate. Rectification of the product over sodium yields 950 g. (70 to 75%) of pure isoamyl ether. Using isoamyl alcohol purified with ferrocyanic acid, Schorigin and Makarov-Zemlianskii obtained a yield of only 65 to 70% by use of the sulfuric acid method of Schröter and Sondag.[162]

(b) *Phenol Ethers*

According to Ullmann, one or both of the alkyl groups in a dialkyl sulfate may take part in the alkylation of phenols. Alkylation by means of the first alkyl group, $R \cdot OH + SO_4(CH_3)_2 \rightarrow R \cdot O \cdot CH_3 + SO_4HCH_3$, takes place easily at moderate temperatures. When small amounts are to be prepared, the second alkyl group need not be used. The price of the alkyl sulfate is negligible compared to that of the compound which is alkylated. However, it is often desirable to use the second alkyl group for alkylation of another mole of the phenol, as illustrated by the preparation of anisole according to the directions of Hiers and Hager (*Organic Syntheses* [163]). It is hardly worth while to prepare either anisole or nerolin (β-naphthyl ether) by this method. (The yield reported is 65 to 73%.) The method is of value, however, for the preparation of some rare phenol ethers which are not available commercially.

Noller and Dutton [164] compared the alkylating effect of trialkyl phosphates to other inorganic esters such as halides, sulfates, etc. The meager data that are available show that the yields in the alkylation of the phenols are generally so poor that the method is of no importance.

[162] Schröter and Sondag, *Ber.*, **41**, 1924 (1908).
[163] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 58.
[164] R. Noller and R. Dutton, *J. Am. Chem. Soc.*, **55**, 424 (1933).

The higher ethers of the phenols are prepared best by heating potassium phenolates and alkyl halides under pressure. Spiegel and Sabbath [165] used an autoclave in preparing nitrophenol ethers, a device which frequently gives poor results. Good yields are achieved by carrying out the reaction in a sealed tube as illustrated by the following. 20 g. of potassium p-nitrophenolate, 20 g. of n-bromopropane, and 10 cc. of alcohol are heated to 180°C. for 3 hours in a sealed tube. The cooled tube which shows no pressure is opened and the clear, reddish brown liquid covering the potassium bromide formed, is dissolved in ether. The solution is washed with water, dried, and fractionated. There are obtained 20 g. (97%) of p-nitrophenyl-n-propyl ether boiling at 124° to 125°C. at 5 mm.

(c) Aromatic Ethers

For the laboratory preparation of aromatic ethers of the type of diphenyl ether, the method of Ullmann and Sponagel [166] is the most convenient.

A mixture of 15.7 g. of bromobenzene, 11.8 g. of phenol, 6.2 g. of potassium hydroxide, and 0.1 g. of copper powder is refluxed for 2 to 2½ hours on an oil bath maintained at a temperature of 210° to 230°C. Distillation of the reaction mixture with steam gives at first unchanged bromobenzene and then the phenyl ether. The yield of product melting at 28°C. and boiling at 257°C. is 12.7 g. (90%).

Numerous patents have been issued for the manufacture of diphenyl ether and its derivatives, because they are used commercially for many different purposes. A paper by Briner, Bron, and Paillard [167] deals with the conditions under which the catalytic removal of water from phenol takes place. Industrially, a 64% yield of diphenyl ether can be obtained from phenol, but commercial methods are hardly suitable for use in the laboratory.

(d) Ethers of Sugars

The sugar molecule contains not only true alcoholic hydroxyl groups but also a glycosidic hydroxyl group. From the point of view of classification it would appear that ethers formed from these two types of groups should be considered separately, but the similarity of the methods used for their preparation makes it more practical to discuss these compounds in the same section.

The total methylation of monosaccharides may be carried out according to the directions of Haworth and Leitch.[168]

[165] Spiegel and Sabbath, *Ber.*, **34**, 1937 (1901).
[166] Ullmann and Sponagel, *Ber.*, **38**, 2211 (1905).
[167] E. Briner, J. Bron, and H. Paillard, *Helv. Chim. Acta*, **15**, 619 (1932).
[168] W. Haworth and G. Leitch, *J. Chem. Soc.*, **113**, 194 (1918).

To a solution of 27 g. of α-d-glucose in 10 cc. of water are added 30 g. (22 cc.) of dimethyl sulfate. The mixture is heated to 35°C. on a water bath. Then 38 cc. of a solution of 109 g. of sodium hydroxide in 190 cc. of water are slowly added with vigorous stirring. The temperature is slowly increased to 40°C. Then over an interval of 3 hours the temperature is raised gradually to 60°C. At this temperature the rest of the sodium hydroxide solution and 143 g. (109 cc.) of dimethyl sulfate are added slowly in about equimolecular amounts from two dropping funnels while the stirring is continued. Finally the temperature is raised to 100°C. and the reaction mixture is stirred for 30 minutes longer. The cooled solution is extracted with chloroform, and the extract is dried and fractionated. After the removal of the chloroform, the main fraction distils at 108° to 110°C. at 0.23 mm. It solidifies instantly when seeded with β-pentamethyl-glucose, and melts at 39° to 41°C. $[\alpha]_D = -13.3°$.

In a similar way Schlubach and Moog [169] obtained pentamethyl-galactose from galactose in almost theoretical yield. In these cases derivatives of β-methyl glucoside and β-methyl galactoside are formed. Their systematic names are 2,3,4,6-tetramethyl-β-methyl glucoside, and 2,3,4,6-tetramethyl-β-methyl galactoside.

In order to prepare the isomeric α compounds the α-glucosides must be used as starting material. Which stereoisomer is formed during the direct methylation of the sugars cannot be predicted in every case. Glucose, when treated with methanol and hydrochloric acid, yields α-methyl glucoside almost exclusively, but in other cases the β isomeric compound forms predominantly. Directions for the preparation of α-methyl-d-glucoside may be found in *Organic Syntheses* [170] (see also E. Fischer [171]).

A simpler method is as follows:

Dry hydrogen chloride is dissolved in 150 cc. of methanol until the increase in weight is 12 g. The solution is diluted with methanol to 500 cc., and is boiled under a reflux with 200 g. of glucose for 18 hours. The cooled solution deposits 95 g. of α-methyl glucoside, and a second crop of 20 g. may be obtained from the mother liquor by distilling in 240 cc. of alcohol.

β-Methyl glucoside is found only in small amounts in the mother liquors of these preparations. The best method for its preparation is that of Koenigs and Knorr.[172]

1 part of acetobromoglucose is dissolved in 15 times its weight of absolute methanol, and the solution is allowed to stand for 2 or 3 days. After being diluted with several volumes of water, the mixture is shaken with barium carbonate. The excess of the latter is filtered, and the neutral solution is treated with an excess of freshly precipitated silver

[169] H. Schlubach and K. Moog, *Ber.*, **56**, 1962 (1923).
[170] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 364.
[171] E. Fischer, *Anleitung zur Darstellung organischer Präparate.* Vieweg, Braunschweig, 1930, p. 93.
[172] W. Koenigs and E. Knorr, *Ber.*, **34**, 965 (1901).

chloride in order to convert the barium bromide into barium chloride which is insoluble in methanol. The filtered solution is evaporated to dryness on a steam bath; the residue is dissolved in alcohol, decolorized by charcoal, and crystallized. After several recrystallizations from ethyl acetate, it melts at 108° to 110°C., $[\alpha]_D^{20} = -34.2°$.

The preparation of β-methyl glucoside along with α-methyl glucoside has been carried out by Patterson and Robertson.[173]

Micheel and Littmann [174] gave the following directions for the preparation of α-methyl galactoside. Their method is somewhat different from the above, and it is supposed to be of general use for the preparation of other sugars.

A solution of 25.8 g. of α-d-galactose in 8 times its weight of methanol is boiled under a reflux for some time. The warm solution is cooled slowly to 15°C. while dry hydrogen chloride is passed into it until the hydrogen chloride concentration is 13.6%. The solution becomes darker, and, after standing overnight, no longer shows any reducing properties. Part of the hydrochloric acid distilled and the rest is removed by lead carbonate. The filtrate is evaporated to dryness *in vacuo*, and the residue crystallizes completely. The yield is 20.4 g. (73.9%). For purification the product may be recrystallized from ethyl acetate, water, or 50% aqueous acetone.

2,3,4,6-Tetramethyl-α-methyl glucoside has been prepared by Haworth [175] in a manner quite similar to that above (see page 166) for the preparation of its stereoisomer. α-Methyl glucoside is used as a starting material instead of α-d-glucose.

A detailed procedure for the preparation of 2,3,4,6-tetramethyl-α-methyl galactoside by this method is given by Micheel and Littmann.[176]

A solution of 9.9 g. of 2,3,4,6-tetraacetyl-1-α-methyl galactoside in 20 cc. of water is saponified with 15 cc. of 50% aqueous sodium hydroxide. Over a period of 1 hour during which time the reaction mixture is stirred vigorously and the temperature is maintained at 40°C., 22 cc. of dimethyl sulfate and 16.3 cc. of aqueous sodium hydroxide are added. The temperature is raised to 50° to 60°C., and the addition of dimethyl sulfate and sodium hydroxide is repeated. Finally, at 60°C., 11 cc. of dimethyl sulfate and 8.2 cc. of sodium hydroxide solution are added. The mixture is concentrated *in vacuo*, the sodium sulfate which separates is removed by filtration, and the filtrate is heated again with 20.8 cc. of dimethyl sulfate and 14.7 cc. of sodium hydroxide at 60°C. for 1 hour. The reaction mixture is extracted with chloroform, and the extract is dried and distilled in a high vacuum. Since the product showed a methoxyl content of 56.36% instead of 62.0%, it was treated again with a total of 69 cc. of dimethyl sulfate and 104 cc. of sodium hydroxide solution in the manner described above at 60°C. for 3 hours. Finally, 4.4 g. of pure tetramethyl-α-methyl galactoside boiling at 80° to 84°C. at 0.05 mm. are obtained.

By hydrolysis of the pentamethyl sugar with acids, the 2,3,4,6-tetramethyl sugar, having a free glucosidic hydroxyl group, is obtained.

[173] J. Patterson and J. Robertson, *J. Chem. Soc.*, **1929**, 300.
[174] F. Micheel and O. Littmann, *Ann.*, **466**, 124 (1928).
[175] Haworth, *J. Chem. Soc.*, **107**, 13 (1915).
[176] F. Micheel and O. Littmann, *Ann.*, **466**, 126 (1928).

The reaction is carried out with boiling aqueous alcoholic hydrochloric acid (Irvine and Oldham [177]).

A specific reaction for the formation of sugar ethers was discovered by Helferich and collaborators.[178] Usually, only primary hydroxyl groups react with triphenylchloromethane with the formation of trityl ethers. Since the trityl group can be removed subsequently, this method offers a way of preparing sugar derivatives which contain a free hydroxyl group in the 6 position. Such derivatives are of prime importance for the synthesis of certain disaccharides. The preparation of 6-triphenylmethyl-α-d-glucose by the method of Helferich, Moog, and Jünger [179] is a good example of this method.

Trityl ethers are also important in the synthesis of mixed glycerides, since either or both of the primary hydroxyl groups of glycerol may react with triphenylchloromethane (Helferich, Speidel, and Toeldte [180]).

A solution of 8 g. of glycerol and 12 g. of triphenylchloromethane in 30 cc. of pyridine is allowed to stand for 16 hours at room temperature. The reaction mixture, which may contain a few crystals of pyridine hydrochloride, is poured into water, and the oil which separates is extracted with ether. The extract is washed successively with hydrochloric acid, water, and aqueous bicarbonate, and the ether is removed by distillation. Cooling in ice for some time causes the oily residue to crystallize. After recrystallization from alcohol, benzene, and ethyl acetate, 3 g. of analytically pure glycerol-α-triphenylmethyl ether, m.p. 92° to 94°C., are obtained.

For the preparation of glycerol ditriphenylmethyl ether (presumably α, α') 1 g. of glycerol is heated with 20 cc. of pyridine and 7 g. of triphenylchloromethane for 30 minutes on the steam bath. Only a ditrityl ether, m.p. 170° to 171°C., can be isolated, despite the fact that a large excess of triphenylchloromethane is used.

2. Cyclic Ethers

Removal of Hydrogen Chloride from Chlorohydrins

The best laboratory method for preparing ethylene oxide is that of Roithner.[181]

Acetylmonochlorohydrin (chloroacetin, $CH_3 \cdot CO \cdot O \cdot CH_2 \cdot CH_2Cl$) is added dropwise to a mixture of coarsely ground potassium hydroxide and sand. The ethylene oxide generated is dried by passing it over freshly ignited soda-lime, and it is condensed in a freezing mixture. It boils at 12.5°C.

[177] Irvine and Oldham, *J. Chem. Soc.*, 119, 1748 (1921).
[178] B. Helferich *et al.*, *Ann.*, 440, 1 (1924); *Angew. Chem.*, 41, 871 (1928).
[179] B. Helferich, L. Moog, and A. Jünger, *Ber.*, 58, 875 (1925); *Organic Syntheses*, 22, 56 (1942).
[180] B. Helferich, P. Speidel, and W. Toeldte, *Ber.*, 56, 769 (1923).
[181] E. Roithner, *Monatsh.*, 15, 665 (1894).

It is hardly worth while to prepare ethylene oxide in the laboratory, because it can be purchased cheaply stored in steel cylinders.

The preparation of epichlorohydrin from dichlorohydrin and sodium or potassium hydroxide gives poor yields when the reaction is carried out in aqueous solution. Better yields (76 to 81% according to *Organic Syntheses* [182]) are obtained with finely powdered sodium hydroxide. Epichlorohydrin is prepared commercially by the use of calcium hydroxide.[183] The yields are somewhat lower, but this is offset by the cheapness of calcium hydroxide and the convenience of the method. *Organic Syntheses* [184] gives directions for the preparation of both epichlorohydrin and epibromohydrin.

According to Derick and Bissell [185] trimethylene oxide may be prepared in 22% yield by the action of moist potassium hydroxide on γ-chloropropyl acetate.

According to Freudenberg [186] epoxypropionic acid (see Melikov [187]) can be prepared as follows:

A mixture of the two isomeric chlorohydroxypropionic acids is formed, acrylic acid and an aqueous solution of hypochlorous acid being allowed to react over a period of 24 hours in the dark and in the cold. The reaction mixture is evaporated to dryness on a steam bath, the residual syrup is extracted with ether, and the ethereal extract is dried. After removal of the ether by distillation, a syrupy mixture of 1-chloro-2-hydroxy- and 2-chloro-1-hydroxypropionic acid remains which is used without further purification. It is added in portions of 100 g. to a solution of 90 g. of potassium hydroxide in 450 cc. of absolute alcohol, the temperature being kept below 50°C. The reaction mixture is allowed to stand at room temperature for 1 hour and in a freezing mixture for 2 hours. The salts which separate are filtered with suction and extracted by boiling them for 5 minutes first with 300 cc. of alcohol and a second time with 100 to 200 cc. of alcohol. From the cooled filtrates 50 to 55 g. of potassium glycidate are obtained. The free glycidic acid can be prepared by decomposition of the potassium salt with an equivalent amount of sulfuric acid in a concentrated aqueous solution, and extraction with ether. After the ethereal solution has been dried, the ether is removed and the free acid remains as a syrup.

The formation of monomeric cyclic ethers from glycols is of little im-

[182] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 233.
[183] German Patent, 246,242.
[184] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 256.
[185] C. G. Derick and D. W. Bissell, *J. Am. Chem. Soc.,* **38**, 2483 (1916).
[186] Freudenberg, *Ber.,* **47**, 2034 (1914).
[187] Melikov, *J. Russ. Phys.-Chem. Soc.,* **13**, 212 (1880).

portance. Although it is possible to prepare tetrahydropyran by heating pentamethylene glycol with 60% sulfuric acid in a sealed tube at 100°C. (Demjanov [188]), this method, the details of which are not available, apparently gives poor yields. St. Allen and Hibbert [189] prepared tetrahydropyran by the action of zinc oxide on pentamethylene bromide in 96% yield.

Apparently the conditions for the formation of pentamethylene oxide are very favorable. Tetrahydrofuran (b.p. 64°C.) may be prepared (Strukov [190]) from tetramethylene glycol and thionyl chloride, but a preferable method might be the catalytic hydrogenation of furan (see page 29). The preparation of trimethylene oxide is similar to that of ethylene oxide (see page 168).

Recently such compounds as dioxane, which are cyclic double ethers of α-glycols, have become quite important. Many patents are available for the preparation of dioxane, but its preparation in the laboratory apparently has not been attempted very often. Faworski [191] states that ethylene glycol, when distilled with 4% sulfuric acid, yields dioxane primarily along with some acetaldehyde and a glycol acetal of the formula

$$CH_3 \cdot \overset{\displaystyle O—CH_2}{\underset{\displaystyle O—CH_2}{\overset{\diagup}{\underset{\diagdown}{CH}}}}$$
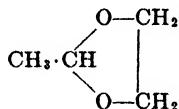
The best method of purification is that with solid potassium hydroxide, which eliminates the acetaldehyde as a resin. The by-product (glycol acetal, b.p. 82.5°C.) is removed from the dioxane (b.p. 101°C.) by fractionation. Wagner and Simons [192] describe a laboratory method.

B. Ester Linkage

The esterification reaction calls for a short discussion even though the reaction scheme, $R' \cdot COOH + HO \cdot R'' \rightarrow R' \cdot COOR'' + H_2O$, would indicate that it is quite simple. Not only the hydroxyl group in carboxylic acids but also many other types of hydroxyl groups react with alcohols in a very similar fashion when subjected to the conditions of esterification. Such hydroxyl groups are the glucosidic ones of sugars and those phenolic hydroxyl groups in which the hydrogen atom has been made sufficiently acidic by the influence of substituents. Esterification may be intermolecular as well as intramolecular, as in the case of lactone formation.

[188] Demjanov, *J. Russ. Phys.-Chem. Soc.*, **22**, 389 (1890).
[189] St. Allen and H. Hibbert, *J. Am. Chem. Soc.*, **56**, 1400 (1934).
[190] Strukov, *Chem. Abstracts*, **30**, 1769 (1936).
[191] A. Faworski, *Chem. Zentr.*, 1907, I, 15.
[192] E. Wagner and J. Simons, *J. Chem. Education*, **13**, 265 (1936).

Since the attention of the chemist usually is focused particularly on one of the component parts of the ester, it is justifiable to treat methods of esterification in which the acid is the important fragment (esterification of carboxylic acids and of compounds having an acidic hydroxyl group) separately from methods of acylation (acetylation, benzoylation, etc.) in which the alcohol, phenol, or enol is the important fragment.

In very special cases the esterification of carboxylic acids with methanol apparently can take place also under the influence of alkaline reagents. Chemiakine [193] reports a reaction between nitroöpianic acid and aqueous methanol in the presence of freshly precipitated silver oxide, in which the methyl ester is formed in an intermediate stage. A thorough investigation of this remarkable reaction has not yet been published.

1. Esterification of Carboxylic Acids

The following typical reactions are of preparative importance.

1. The spontaneous removal of water from carboxylic acids and alcohols.

2. The removal of water from carboxylic acids and alcohols by acid catalysis.

3. Metathetical reactions between the salts of carboxylic acids and alkyl halides or alkyl sulfates.

4. The action of diazomethane or higher homologues of diazomethane on carboxylic acids.

Less important generally, though quite important in special cases, are the following typical reactions.

5. The reactions between carboxylic acid chlorides or anhydrides and alcohols, or between carboxylic acid chlorides and alcoholates. These reactions are important for the acylation of alcohols.

(a) Spontaneous Removal of Water

Since a carboxylic acid catalyzes its own esterification at a rate proportional to its acidity, it is possible to prepare an ester merely by heating a carboxylic acid with an alcohol. This method is of particular importance for two types of preparation: (*1*) for the half esterification of dicarboxylic acids or the partial esterification of polycarboxylic acids, and (*2*) for the formation of esters of polyhydroxy compounds, such as glycol and especially glycerol.

The reaction becomes more and more complete as the water formed is removed from the reaction mixture. This removal is always easy when none of the reaction components boils at a lower temperature than

---

[193] M. Chemiakine, *Bull. soc. chim.*, **1**, 689 (1934).

water or is volatile with steam. Whether or not this method offers any advantages depends on many factors. A few simple examples may illustrate this point.

According to Simon [194] amyl pyruvate is obtained in a yield of 99% from equimolecular amounts of pyruvic acid and amyl alcohol when heated *in vacuo* (10 to 20 mm.). After equilibrium is established, the water is distilled slowly. Favorable conditions such as these rarely exist, but a similar situation is found in the analogous preparation of triglycerides from glycerol and fatty acids.

When the formation of esters proceeds at a rate sufficiently rapid for preparative work, without the addition of catalysts (as is generally the case with polycarboxylic acids), the water formed during the reaction may be removed advantageously by a chemical reaction or by adding a substance which causes an azeotropic mixture.

Examples of both of these methods as applied to the preparation of ethyl oxalate are described in detail in *Organic Syntheses*,[195] together with the apparatus suitable for use in these procedures.

An apparatus developed by Thielepape [196] (usually constructed of ground glass) is shown in Fig. 5.

Flask *1* contains the acid, the alcohol, and a suitable solvent. Carbon tetrachloride and many other solvents, such as trichloroethylene, perchloroethylene, other aliphatic halides, benzene, toluene, xylene, and anisole, may be used. When the stop-cock to *S* is closed, the vapors of the azeotropic mixture are forced into the condenser attached to tube *E* and condensed. The condensate is dried in the extraction thimble in tube *E* which is filled with calcium carbide. From time to time, as flask *2* is filled, tube *E* is shut off temporarily, and the contents of flask *2* are distilled into *S*. From there the condensate is drained back into flask *1*.
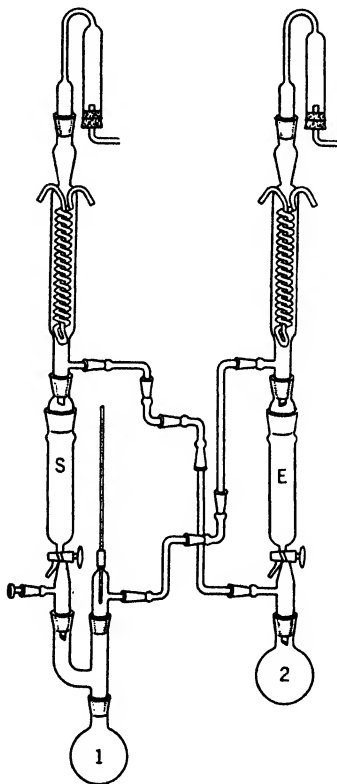
FIG. 5.—Thielepape apparatus for preparation of esters.

[194] Simon, *Ber.*, **26**, 769 (Ref.) (1893).
[195] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 261.
[196] E. Thielepape, *Ber.*, **66**, 1454 (1933).

The use of calcium carbide as the dehydrating agent has many advantages. It is cheap, and the reaction with water forms a solid (calcium hydroxide) rather than a liquid product. Thielepape recommends a double walled extraction thimble in *E*, because the finely divided calcium hydroxide might otherwise not be retained. In any case no solid material reaches the reaction flask *1*, because the liquid collected in flask *2* is *distilled* into flask *1*. With this apparatus, and with the use of toluene as a solvent, a yield of more than 89% of ethyl oxalate is obtained.

A simple extraction apparatus for use in these experiments is that described by Hagen [197] and improved by Thielepape.[198] In this case also the drying agent is put in the extraction thimble.

Guttmann [199] describes a laboratory apparatus for esterifications, in which neither a water separator nor a drying agent is used, which is practical and compact, but it does not afford any improved yields.

The methods and apparatus described above can also be used very advantageously for catalytic esterification.

The esterification of glycerol with higher fatty acids takes place very easily, even without a catalyst, although zinc dust has proved to be an effective promoter. An example of this method is the preparation of tritridecylin from glycerol and *n*-tridecanoic acid described by Verkade, Lee, and Meerburg.[200]

To 8 g. of tridecanoic acid dissolved in 1.1 g. of distilled anhydrous glycerol is added a trace of zinc dust, and the mixture is heated in a slow current of carbon dioxide at a pressure of 150 mm. The temperature is increased gradually from 130° to 200°C. (bath temperature), over a period of 7 hours, and during the next 3 hours the pressure is reduced to 120 mm. and the temperature is allowed to rise to 240°C. The residue in the flask, while still warm, is dissolved in ether, the zinc dust and zinc salts are removed by filtration, and the filtrate is neutralized with potassium hydroxide (phenolphthalein). After decolorization with activated charcoal the solution is mixed with twice its volume of alcohol and allowed to crystallize by cooling in ice. After standing overnight, the triglyceride is filtered with suction and washed carefully with ice-cold alcohol. The yield of product melting at 43.0°C. (thermometer immersed) was about 90%.

Although it is a simple matter to prepare triglycerides in this manner, it is extremely difficult to obtain the various isomeric mono- and diglycerides. Only a few of the more recent papers can be mentioned here. Bergmann and Carter [201] have prepared β-monoglycerides through the α,α'-benzylidene glycerol. Hilditch and Rigg [202] discovered that monoglycerides can be obtained in good yields by heating molecular proportions

[197] Hagen, *Chem.-Ztg.*, **47**, 598 (1923).
[198] E. Thielepape, *Chem. Fabrik*, **4**, 293, 302 (1931).
[199] E. Guttmann, *Chem.-Ztg.*, **57**, 1001 (1933).
[200] Verkade, Lee, and Meerburg, *Rec. trav. chim.*, **51**, 851 (1932).
[201] Bergmann and Carter, *Z. physiol. Chem.*, **191**, 214 (1930).
[202] Hilditch and Rigg, *J. Chem. Soc.*, **1935**, 1774.

of fatty acid and glycerol dissolved in phenol, although in the absence of phenol no monoglyceride can be isolated even when a huge excess of glycerol is added. Special methods, which cannot be discussed further here, have been developed for the synthesis of mixed glycerides.

(b) Catalytic Esterification with Strong Mineral Acids

Little needs to be said about the original, crude laboratory method. The best catalysts are hydrochloric and sulfuric acids, both of which possess a strong water-binding tendency. They not only act as catalysts, but they also shift the reaction equilibrium so as to favor formation of the ester.

When sulfuric acid is used, the reaction components are heated under a reflux until equilibrium is established. Hydrogen chloride is passed into alcoholic solutions of the acid until the solution is saturated. Whether the mixture is warmed, refluxed, or allowed to stand at room temperature depends on the individual reaction under consideration. The method of isolation varies somewhat according to the ester prepared and its stability.

Whenever sulfuric acid is used as a catalyst, the removal of the water formed in the reaction presents difficulties, because the acid retains it. Nothing is gained by distilling the alcohol, which is usually used in an excessive amount. On the other hand, if hydrogen chloride is used, the yield can be improved by concentrating the reaction mixture, since both hydrochloric acid and water distil with the excess alcohol, leaving the ester and unchanged acid behind. Pure alcohol is added, the mixture is saturated with hydrogen chloride, and the whole operation is repeated. The method is of value only in those cases in which the ester and the carboxylic acid or the ester and the alcohol are volatile to such an extent that appreciable losses do not occur.

Although the method is very crude, it has the advantage of not requiring any special apparatus, and although it requires more time than other methods it at least should give comparable results.

When the apparatus described in *Organic Syntheses* [203] is used, it is better to use the sulfuric acid method. Lower concentrations of sulfuric acid can be used successfully either with or without the addition of a solvent. In these cases higher temperatures are desirable and are often necessary, so that it is practical sometimes to carry out the reaction with alcohol vapor. Corson, Adams, and Scott describe an apparatus (*Organic Syntheses* [204]) with which they prepared a number of esters in good yield. Low boiling esters may be prepared in this or in a similar way by the

[203] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 261.
[204] *Organic Syntheses*, 10, 48 (1930).

use of ether as a solvent (see Thielepape, page 172), but these are not practical.

Difficulties are encountered in the esterification reaction involving tertiary or other sensitive alcohols, because the catalysts used for esterification easily cause the dehydration of the alcohols.

By the use of a reaction between fatty acids and the corresponding olefins in the presence of zinc chloride, Kondakov [205] succeeded in preparing esters of tertiary alcohols. A more reliable method is the following, in which there is essentially no acid reaction. The tertiary alcohol is allowed to react with a simple Grignard reagent, and the resulting alkyl magnesium ethylate is treated with the chloride or anhydride of the acid to be esterified: $R' \cdot OH + C_2H_5MgX \rightarrow R' \cdot OMgX + C_2H_6$; $R' \cdot OMgX + ClOC \cdot R'' \rightarrow R' \cdot OOC \cdot R'' + MgXCl$; or $R' \cdot OMgX + R'' \cdot CO \cdot O \cdot CO \cdot R'' \rightarrow R' \cdot OOC \cdot R'' + MgX \cdot OOC \cdot R''$.

According to Houben's directions [206] the Grignard reagent is prepared from 8.2 g. of magnesium and 37 g. of ethyl bromide in 200 cc. of ether. To the cooled solution 25 g. of isobutanol are added dropwise and the mixture is gently boiled for 30 minutes. The reaction mixture is cooled in ice and 35 g. of acetic anhydride dissolved in ether are added. After being heated for a short period, the mixture is allowed to stand for 12 hours, and the end-product is isolated in the usual way.

Acid Esters of Polycarboxylic Acids

The preparation of acid esters of polycarboxylic acids cannot be represented by one general reaction. Their successful synthesis by direct methods depends on the difference between and on the magnitude of the single dissociation constants of the acidic groups involved.

According to Guérin [207] tartaric acid yields the acid ester very readily by being distilled with absolute alcohol. The addition of water causes the ester to crystallize.

The acid esters of phthalic acid can be obtained easily and conveniently by boiling phthalic anhydride with ethanol. They crystallize well, are not volatilized easily, and as half esters they form salts with organic bases. They are used for the isolation of alcohols from mixtures with other compounds and for the resolution of racemic mixtures of asymmetric alcohols. The latter is accomplished by forming the acid phthalate of the alcohol to be resolved, and then allowing that product to react with an optically active base.

A general method for the preparation of the mono esters of dicarboxylic

[205] Kondakov, *J. prakt. Chem.*, **48**, 477 (1893).
[206] J. Houben, *Ber.*, **39**, 1738 (1906).
[207] Guérin, *Ann.*, **22**, 252 (1837).

acids which form anhydrides is as follows:

$$(CH_2)_n \diagdown \begin{array}{c} CO \\ \diagup \\ O \\ \diagup \\ CO \end{array} + C_2H_5ONa \longrightarrow (CH_2)_n \diagup \begin{array}{c} CH_2COONa \\ \diagdown \\ COOC_2H_5 \end{array}$$
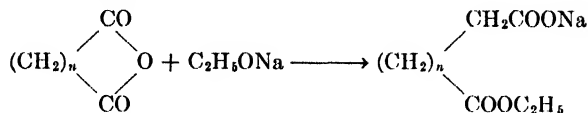
Auwers [208] prepared ethyl hydrogen tetramethyl succinate by dissolving equivalent amounts of sodium and the acid anhydride in ethanol, and removing the alcohol by distillation. The product was isolated by dissolving the residue in water and acidifying the solution.

Anschütz [209] gives the following directions for the preparation of ethyl hydrogen oxalate.

A mixture of 1 part of anhydrous oxalic acid and 1 part of absolute ethanol is heated slowly to 135°C. The excess oxalic acid is removed from the cooled mass by filtration, and the filtrate is concentrated *in vacuo* in an oil bath, the temperature being maintained below 140°C. A good vacuum is difficult to maintain while the dissolved oxalic acid decomposes, but the pressure diminishes slowly as the end of the decomposition is reached. Distillation and rectification of the residue *in vacuo* afford pure ethyl hydrogen oxalate (b.p. 117°C. at 15 mm.).

According to Freund [210] ethyl hydrogen malonate is obtained as the potassium salt by the partial saponification of diethyl malonate. A solution of 8.8 g. of potassium hydroxide in 100 cc. of alcohol is added dropwise and with stirring to a solution of 25 g. of the diethyl ester in 100 cc. of absolute ethanol, during which time no ester salt should separate. If the reaction mixture after standing for some time is no longer alkaline, it is heated to the boiling point and filtered to remove any potassium malonate which has formed as a by-product. The filtrate and the concentrated mother liquors yield a total of 70 to 80% of the weight of ester used as potassium ethyl malonate, which can be recrystallized from alcohol. The free half ester can be obtained by neutralizing the potassium salt with the calculated amount of hydrochloric acid, evaporating the solution to dryness *in vacuo*, and extracting the residue with ether. A colorless syrup remains after evaporation of the solvent.

In many cases this method of partial saponification of the poly esters of polycarboxylic acids is probably the most convenient for the preparation of acid esters.

Special Methods for Preparation of Esters

The preparation of esters from the salts of carboxylic acids and alkyl halides by the reaction, $R' \cdot COOMe + XR'' \rightarrow R' \cdot COO \cdot R'' + MeX$, is

[208] K. v. Auwers, *Ann.*, **292**, 178 (1896).
[209] R. Anschütz, *Ber.*, **16**, 2413 (1883).
[210] M. Freund, *Ber.*, **17**, 780 (1884).

in some instances and especially in cases involving much steric hindrance, the only method which can be used with success. The salt of the carboxylic acid is heated with the halide, in some cases in a sealed tube or in an autoclave, and the ester is isolated by an appropriate procedure.

Several considerations determine the choice of the basic constituent. Silver salts react most vigorously, but lead or even alkali salts may be used. In the case of the halides, the iodides, as would be expected, react most readily. They are to be preferred in cases in which lower homologous halides are to be used on account of their higher boiling points. Diluents, such as xylene, whose boiling points are not too low are advantageous in some cases. Occasionally esters may also be prepared by treating a mixture of the acid and the halide with silver oxide in a solvent, according to Liebermann and Lindenbaum.[211]

When working with tautomeric compounds which are not simple carboxylic acids, one may sometimes obtain quite different derivatives, depending on whether alkali, lead, or silver salts are used; see page 359.

This method is of further importance either when several alcoholic hydroxyl groups or when different carboxylic groups may react. At best, mixtures which may or may not be separated readily are obtained by the general methods of esterification. Monoacylated compounds of ethylene glycol may be prepared easily from the monochlorohydrin by the reaction,

$$R \cdot COONa + Cl \cdot CH_2 \cdot CH_2 \cdot OH \rightarrow R \cdot COO \cdot CH_2 \cdot CH_2 \cdot OH + NaCl.$$

Brühl[212] observed that even freshly prepared sodium salts often do not react smoothly with alkyl halides. In such cases a small amount of methanol sometimes starts the reaction. Lassar-Cohn recommends washing precipitated lead and silver salts with water, alcohol, and ether only since these salts are especially reactive if they are not dried by heat. It is necessary to find out whether the salt is sufficiently dry in each case, since water of crystallization is not removed by this procedure, and traces of moisture may diminish the yield considerably.

Formation of Esters and Ethers with Diazomethane and Diazo Hydrocarbons

When other methods fail, especially when the failure is due to the sensitivity of the acid molecule, the reaction with diazo hydrocarbons finds an application. It is carried out in an indifferent medium (usually ether), produces no side reaction to speak of, and is very convenient.

Diazomethane may be prepared from the following starting materials.

1. Hydrazine and chloroform.
2. Nitrosomethylurethane.
3. Nitrosomethylurea.
4. Nitroso amino ketones.

[211] C. Liebermann and S. Lindenbaum, *Ber.*, **42**, 1397 (1909).
[212] Brühl, *Ber.*, **35**, 3627 (1902).

The most convenient method, also the most expensive, is the second in which commercial nitrosomethylurethane is used. The preparation from nitrosomethylurea is cheap and just as easy, but it is not as convenient, because this product is not available commercially.

The preparation of diazomethane from hydrazine and chloroform gives good but varying yields, so that the amount of diazomethane available cannot be predetermined in every case; see Staudinger and Kupfer.[213]

The adaptation of Pechmann's [214] and Schlotterbeck's [215] methods which give good yields is the following: In a 1 liter flask equipped with a condenser arranged for distillation, a mixture of 12 cc. of nitrosomethylurethane, 480 cc. of ether, and 14.4 cc. of 25% aqueous potassium hydroxide is boiled on a water bath until the distillate passes over colorless. The yellow ethereal solution contains almost exactly a 50% yield of diazomethane (2.2 to 2.4 g., since each cubic centimeter of nitrosomethylurethane yields 0.18 to 0.20 g. of diazomethane).

Diazomethane is obtained from nitrosomethylurea (see page 261) according to the directions of Arndt and coworkers.[216]

Adamson and Kenner [217] describe a method for the preparation of diazo hydrocarbons from nitroso amino ketones. The latter are obtained by the addition of primary amines to mesityl oxide, $(CH_3)_2:C:CH \cdot CO \cdot CH_3 + NH_2R \rightarrow (CH_3)_2:C \cdot NHR \cdot CH_2 \cdot CO \cdot CH_3$. The secondary amines thus formed are nitrosated.

From the nitroso amino ketones solutions of the diazo hydrocarbons are obtained in the following manner:

1. A solution of 2 g. of sodium in 66 cc. of hot cyclohexanol is cooled and the wax-like mass is cut into small pieces and added to 300 cc. of dry ether in a 2 liter flask. To this mixture cooled to 10°C. is added a solution of $\frac{1}{3}$ mole of the nitroso amino ketone in 600 cc. of ether. The reaction mixture is distilled slowly by heating the flask to 50°C. in a water bath. The distillate is collected until it comes over colorless.

2. Over a period of 15 to 20 minutes a mixture of 0.2 mole of nitroso amino ketone and 60 cc. of anisole is added dropwise to the product obtained from 0.6 g. of sodium and 20 cc. of cyclohexanol. As this reaction takes place the pressure is reduced to 300 to 400 mm. The mixture is distilled in a current of nitrogen, and the vapors are passed through a condenser cooled with ice, through a U-tube filled with solid potassium hydroxide, and finally collected in a suitable solvent.

[213] Staudinger and Kupfer, *Ber.*, **45**, 501 (1912).
[214] v. Pechmann, *Ber.*, **28**, 856 (1895); **31**, 2640 (1898).
[215] Schlotterbeck, *Ber.*, **40**, 480 (1907).
[216] Arndt *et al.*, *Angew. Chem.*, **43**, 444 (1930); **46**, 47 (1933). A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 165.
[217] D. Adamson and J. Kenner, *J. Chem. Soc.*, **1935**, 286; **1937**, 1554.

From a run made with 1 g. of sodium, 33 cc. of cyclohexanol, $\frac{1}{6}$ mole of nitrosomethylaminomesityl oxide, and 300 cc. of ether, a yield of 5.1 g. (73%) of diazomethane was obtained in 35 minutes. It was collected in 650 cc. of ether cooled in an ice-salt mixture.

This method apparently affords the best yield of all the methods thus far recommended. There is a particular advantage in the fact that the nitroso amino ketones are not as easily decomposed as is nitrosomethylurea.

The ether solutions of the diazo hydrocarbons prepared in this manner may be purified without serious losses by distillation through a column to remove traces of mesityl oxide.

If necessary, the content of diazomethane solutions in ether may be determined easily by titrating an aliquot portion by an ethereal iodine solution. According to the equation, $CH_2N_2 + I_2 \rightarrow CH_2I_2 + N_2$, 1 mole of diazomethane (42.03 g.) is equivalent to 2 atoms of iodine (254 g.), or 1 g. of iodine corresponds to 0.166 g. of diazomethane. Titration to the point at which the color of iodine persists is sufficiently exact for most purposes. A volumetric determination of the amount of nitrogen generated is more accurate but more tedious. Marshall and Acree [218] also recommend a method for determining the yield. Arndt [219] suggests treating an aliquot portion of the solution with a weighed amount of excess benzoic acid at 0°C. in ether. After the ethereal solution has become colorless, and the evolution of nitrogen has ceased, the free benzoic acid is determined by titration with alkali.

The ethereal solutions of diazomethane are not stable, and they gradually evolve nitrogen and become colorless. Diazomethane solutions may be dried over potassium hydroxide, but some decomposition results.

The esters of carboxylic acids or the ethers of phenols and keto-enols are formed with diazomethane or diazo hydrocarbons by mixing ether solutions of the components at room temperature. If the acids are only slightly soluble in ether, another solvent which is stable towards diazomethane may be used. The solutions are allowed to stand until the evolution of nitrogen ceases. The reaction mixture may be heated gently if necessary. If the yellow color of diazomethane or the color of the diazo compound persists after the evolution of nitrogen has stopped, one may assume that esterification is complete. Otherwise, the alkylation must be repeated with another portion of diazomethane. The method of isolation of the reaction product depends on the properties of the ester or the ether which has been formed.

The formation of the ether from the enol of dibenzoylmethane with diazomethane, as carried out by Weygand and Bauer,[220] is an example of

[218] Marshall and Acree, *Ber.*, **43**, 2324 (1910).
[219] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 165.
[220] C. Weygand and E. Bauer, *Ber.*, **62**, 571 (1929).

this method.   This reaction is remarkable inasmuch as it leads to a good yield of the high melting β-methoxychalcone, a compound which is difficult to obtain in other ways.   At the same time it illustrates the value of the method for the preparation of pure stereoisomers.

The ethereal solution of diazomethane prepared from 5 g. of nitrosomethylurethane is distilled into a solution of 2 g. of dibenzoylmethane in a little ether.   After standing overnight the mixture is boiled under a reflux until the refluxing ether is colorless.   The reaction with ferric chloride characteristic of enols has disappeared by that time.   The ether is removed by distillation, and the residue, which crystallizes on being cooled, is washed with petroleum ether.   Recrystallization of the product from ether-petroleum ether affords 1.6 g. of β-methoxychalcone, $C_6H_5 \cdot CO \cdot CH : C(CH_3O) \cdot C_6H_5$, m.p. 81°C.   A small amount of a nitrogen-free, colorless compound of very high molecular weight, a by-product formed by the polymerization of diazomethane, is also obtained.

2. Esterification of Alcohols and Phenols (Acylation)

The acylation reaction is of considerable importance in the characterization of alcohols and phenols and is widely applicable in the sugar series, both for identification and synthetic purposes.   The phenol esters, which are prepared by this method, are valuable as starting materials for the Fries rearrangement.

Reagents commonly used for the preparation of esters for purposes of identification are acetyl chloride, acetic anhydride, benzoyl chloride, benzoic anhydride, and m- and p-nitrobenzoyl chlorides.   The last two form characteristic derivatives, which crystallize well.   The halogen derivatives of benzoyl chloride are also useful as reagents for identification purposes.

The proportions of the reactants recommended by Panormov [221] for producing the best possible yield of benzoylated product are 20 parts of 20% sodium hydroxide to 6 parts of benzoyl chloride, although Skraup [222] used 7 moles of sodium hydroxide and 5 moles of the acyl chloride per hydroxyl group.

The most general method of esterification, that of Schotten and Baumann,[223] consists of shaking the compound to be acylated with a mixture of benzoyl chloride (or nitrobenzoyl chloride) and 10% aqueous sodium hydroxide until all the acid chloride is used.   In the acylation of compounds which are sensitive to alkali (polyphenols), more dilute sodium hydroxide or a solution of carbonate or bicarbonate is preferable.   The method of Schotten and Baumann can also be carried out with acetyl chloride, but because of its instability it is better to use other methods for acetylation.

[221] Panormov, *Ber.*, **24**, 971 (Ref.) (1891).
[222] Skraup, *Monatsh.*, **10**, 390 (1889).
[223] Schotten and Baumann, *Ber.*, **19**, 3218 (1886).

In many cases the method described by Denninger [224] and Ullmann and Nadai [225] is particularly valuable.   In it the sodium hydroxide solution is replaced by tertiary organic bases such as diethylaniline, pyridine, or quinoline.   The compound to be acetylated is dissolved in 5 to 10 times its weight of the amine, the solution is cooled, and the acid chloride is added slowly.   Sometimes commercial pyridine has to be purified before use through the zinc chloride addition compound.   After standing 6 to 10 hours, the solution is added dropwise to cold, dilute sulfuric acid. Acetylation reactions are very easily effected, but benzoylation reactions must be watched carefully, since benzoic anhydride is always formed as a by-product.

Frequently the reaction is much more easily carried out by the use of an acid anhydride instead of the chloride.   The components may be mixed and heated without dilution either in an open flask or in sealed tubes. Occasionally benzoic anhydride may be used even in aqueous solution and sodium benzoate may be added in some cases.   Liebermann and Giesel [226] obtained cocaine from ecgonine in this way.

Wohl and Oesterlin [227] prepared diacetyltartaric anhydride by treating 100 g. of finely powdered tartaric acid with a mixture of 220 cc. of acetic anhydride and 3 cc. of concentrated sulfuric acid.   The reaction mixture becomes quite warm and the tartaric acid passes into solution.   After being boiled for a short time, the solution is allowed to cool and the crystals of diacetyltartaric acid anhydride are filtered and washed with benzene.   The yield is almost quantitative.   The crude product may be used directly for the preparation of carbon suboxide (see page 451).   A purer product, melting at 135°C., may be obtained by crystallizing the crude material from benzene.

A preparation of γ-chloropropyl acetate which affords a product pure enough for the preparation of trimethylene oxide (see page 169) is given by Derick and Bissell.[228]

Special Conditions Necessary for Acylation of Polyhydroxy Compounds

The conditions for the acylation of glycols, especially symmetrical ones, are relatively simple.   Glycol diacetates are frequently obtained as intermediates in the preparation of glycols from dihalides (see page 154). The two hydroxyl groups in glycols react stepwise, so that it is possible to prepare mono as well as mixed glycol esters.

The migration of acyl residues in glycerol compounds is a disturbing

[224] A. Denninger, *Ber.*, **28**, 1322 (1895).
[225] Ullmann and Nadai, *Ber.*, **41**, 1870 (1908).
[226] Liebermann and Giesel, *Ber.*, **21**, 3196 (1888).
[227] Wohl and Oesterlin, *Ber.*, **34**, 1139 (1901).
[228] C. G. Derick and D. W. Bissell, *J. Am. Chem. Soc.*, **38**, 2483 (1916).

factor. In monoglycerides an equilibrium always exists between the α- and β-glycerides:

$$CH_2 \cdot OOC \cdot R \qquad\qquad CH_2 \cdot OH$$
$$CH \cdot OH \qquad \rightleftharpoons \qquad CH \cdot OOC \cdot R$$
$$CH_2 \cdot OH \qquad\qquad CH_2 \cdot OH$$
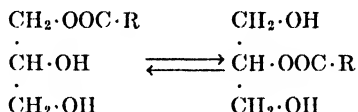
Both α-hydroxyl groups can be esterified selectively with triphenyl-methylchloromethane by Helferich's method (see page 168). The free β-hydroxyl may then be esterified, and the triphenylmethyl residues may be removed by the use of a glacial acetic acid solution of hydrogen bromide. In order for the process to be successful, the conditions of the last reaction must be sufficiently gentle, so that the β-acyl group retains its position.

Bergmann and Carter [229] protected the primary hydroxyl groups by preparing cyclic ethers from them with benzaldehyde, which shows a special preference for forming 1,3-benzalglycerol,

$$
\begin{array}{l}
CH_2 \cdot O \diagdown \\
CH \cdot OH \quad CH \cdot C_6H_5 \\
CH_2 \cdot O \diagup
\end{array}
$$
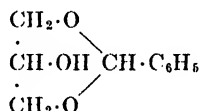
The free β-hydroxyl group is esterified and the benzal residue is removed by hydrogenolysis, the mildest method for clearing compounds of that type.

The conditions for the acylation of sugars and sugar alcohols are still much more complicated, but the desired compounds can be obtained by the use of the two methods which have been described. A few simple examples are given below, but a more detailed discussion may be found in Tollens-Elsner.[230]

The preparation of β-(p-nitrobenzoyl)-glycerol has been described by Helferich and Sieber.[231]

A mixture of 210 g. of triphenylchloromethane, 450 cc. of dry pyridine, and 35 g. of freshly distilled glycerol is heated on a steam bath for 1 hour with the exclusion of moisture. The cooled mixture is poured into 2 liters of water, while being stirred vigorously, and the syrup which separates is stirred with fresh portions of water until it solidifies. After being dried in air, the product crystallized from 7 parts by volume of acetone. The residue dissolved in the mother liquors is precipitated with water and recrystallized from acetone. A total of about 150 g. of α,α'-ditriphenylmethylglycerol melting at 174° to 176°C. (corrected) is obtained.

A solution of 37 g. of ditriphenylmethylglycerol in 150 cc. of dry pyridine is added dropwise to an ice-cold mixture of 17 g. of p-nitrobenzoyl chloride and 100 cc. of pyridine,

[229] Bergmann and Carter, Z. physiol. Chem., 191, 211 (1930).
[230] Tollens-Elsner, Kurzes Handbuch der Kohlenhydrate. Barth, Leipzig, 1935.
[231] B. Helferich and Sieber, Z. physiol. Chem., 170, 31 (1927); 175, 311 (1928).

which is shaken from time to time as the pyridine solution is added. The addition product of acid chloride-pyridine which separates is disregarded and the reaction mixture is allowed to stand for 2 days at room temperature. The excess acid chloride is decomposed by adding a little water to the ice-cold mixture. The product is extracted with 300 cc. of ether, and the ether solution is shaken with cold saturated aqueous potassium bisulfate and aqueous sodium bicarbonate, and is dried over sodium sulfate. The ether is removed by distillation *in vacuo* at room temperature, the residual syrup is dissolved in 1.5 parts of chloroform, and 7 parts by volume of petroleum ether are added. After recrystallization the crystals of β-(p-nitrobenzoyl)-ditriphenylmethylglycerol melt at 188°C. (corrected). The yield is 28 g.

A suspension of 50 g. of finely powdered β-nitrobenzoylditriphenylmethylglycerol in 150 cc. of glacial acetic acid is mixed with 25 cc. of glacial acetic acid saturated with hydrogen bromide at 0°C. After the mixture has been shaken mechanically in a closed bottle for half an hour, it is cooled in ice and filtered (the precipitate weighs 45 g.). The filtrate is mixed with 250 cc. of petroleum ether and the syrup which separates is dissolved in 250 cc. of ether. The ethereal solution is washed with 200 cc. of water and 200 cc. of aqueous sodium bicarbonate, and is dried over sodium sulfate. After the removal of the solvent *in vacuo* at room temperature, the residue is dried in a desiccator over soda-lime to remove traces of glacial acetic acid and ether. The dried product is dissolved in 5 parts of ethyl acetate and mixed carefully with about 10 parts of petroleum ether until the solution turns cloudy. After some time 3.4 g. of β-nitrobenzoylglycerol crystallize in star-like clusters of needles. Upon recrystallization from ethyl acetate-petroleum ether the melting point is 120° to 121°C. (corrected).

Hibbert and coworkers [232] have prepared β-palmitylglycerol from 1,3-benzalglycerol by allowing it to react with palmityl chloride in the presence of pyridine, and by removing the benzal residue by hydrogenolysis with use of a platinum catalyst. The preparation of 1,3-benzalglycerol has since been modified by Bergmann and Carter.[233]

Recently Stimmel and King [234] have published more data on the preparation and properties of β-monoglycerides. β-Glycerides of capric, lauric, myristic, and stearic acids were prepared by Hibbert's method.

Directions for the preparation of α,β-diglycerides are given by Fairbourne.[235]

Phenolic Esters of Carboxylic Acids

Usually carboxylic acids do not form esters as readily with a phenolic hydroxyl group as with an alcoholic hydroxyl group. One may prepare phenolic esters either by using acid chlorides or anhydrides, or by heating a mixture of the phenol and the carboxylic acid with phosphorus oxychloride. Presumably phenyl esters of phosphoric acid are formed as intermediates during the latter reaction, and they are converted into the esters of the carboxylic acids under the catalytic influence of hydrogen chloride.

The reason for the choice of a special method in these cases is the fact

[232] H. Hibbert *et al.*, *J. Am. Chem. Soc.*, **50**, 2239 (1928).
[233] Bergmann and Carter, *Z. physiol. Chem.*, **191**, 215 (1930).
[234] F. Stimmel and G. King, *J. Am. Chem. Soc.*, **56**, 1724 (1934).
[235] Fairbourne, *J. Chem. Soc.*, **1930**, 369.

that phenyl esters rearrange easily to acyl phenols: $C_6H_5 \cdot OOC \cdot R' \rightarrow$ $R \cdot CO \cdot C_6H_4 \cdot OH$; see Fries' rearrangement, page 484.

Much better results are obtained by replacing the free carboxylic acids by their sodium salts as some of the hydrogen chloride liberated in the reaction is fixed. Phosphorus oxychloride may be replaced by phosphorus pentachloride and phosphorus trichloride in certain cases.

The formation of phenol esters is effected easily by reactions between acid halides and salts of phenols. Diphenyl carbonate is formed in an almost quantitative yield by passing phosgene into a moderately concentrated solution of sodium phenolate. The product which crystallizes is remelted after being washed with aqueous sodium hydroxide and water, and the residual water is removed by pressing on a filter. After recrystallization from alcohol, it melts at 88°C. and boils at 306°C.

In a paper on the preparation of various esters Adickes and Brunnert [236] describe experiments on the preparation of phenyl formates in considerable detail. The preparation of phenol allyl ether by Claisen's directions [237] is exceptionally easy.

A mixture of 188 g. of phenol, 242 g. of allyl bromide, 280 g. of potassium carbonate, and 300 g. of acetone is refluxed on a steam bath for 8 hours during which time potassium bromide separates. Water is added to the slurry, the mixture is extracted by ether, and the ethereal extract is washed with dilute aqueous sodium hydroxide and dried over potassium carbonate. Upon distillation *in vacuo* 230 g. (86%) of phenol allyl ether boiling at 78°C. at 14 mm. are obtained.

For the preparation of diphenyl phthalate Blicke and Weinkauff [238] mixed equivalent amounts of phthalyl chloride and phenol. After several hours the reaction product which separated was filtered, washed with alcohol, and recrystallized from the same solvent. The yield of product melting at 74° to 76°C. is nearly quantitative. A similar method was used by Stoughton [239] for the preparation of the esters of α-naphthol.

The preparation of pyrocatechol monochloroacetate for the synthesis of adrenaline, according to the directions of Stolz (see page 486), is not so simple, because the Fries rearrangement can take place during the preparation of the ester if small amounts of impurities are present. Ott [240] stated that chloroacetyl chloride prepared with phosphorus trichloride gives poorer results in the reaction than that prepared with thionyl chloride. A good method which is used in these laboratories is as follows:

A solution of 55 g. of pyrocatechol, 60 g. of chloroacetyl, and 250 cc. of benzene is boiled for 45 hours. The benzene is distilled from the yellow reaction mixture *in vacuo*,

[236] F. Adickes and W. Brunnert, *J. prakt. Chem.*, **130**, 174 (1931).
[237] L. Claisen, *Ann.*, **418**, 78 (1919).
[238] F. Blicke and O. Weinkauff, *J. Am. Chem. Soc.*, **54**, 331 (1932).
[239] R. Stoughton, *J. Am. Chem. Soc.*, **57**, 203 (1935).
[240] E. Ott, *Ber.*, **59**, 1068 (1926).

and the residue is extracted with boiling carbon tetrachloride and filtered while hot to remove any chloroacetylpyrocatechol formed by rearrangement. At first the chloroacetate separates from the cooled filtrate as an oil; but after it has solidified, it is separated from the carbon tetrachloride and recrystallized from benzene. The recrystallized product is distilled at 3 mm. in a flask equipped with a cold finger to condense the pyrocatechol which sublimes at first. As soon as the main fraction begins to distil, the condenser is removed and the fraction distilling up to 160°C. is collected. It solidifies to a colorless mass, which is powdered, extracted several times with water to remove any pyrocatechol, and crystallized from benzene. The yield of pyrocatechol monochloroacetate melting at 79°C. is 30 g. (Ott reports a melting point of 81°C., b.p. 174°C., at 15 mm.). The dichloroacetate remains in the mother liquor and in the residue in the distilling flask.

Esterification of Alcohols with Ketenes

The fact that the preparation of ketene, $CH_2:C:O$, in the laboratory is relatively easy and that ketone reacts readily with most hydroxyl groups according to the equation, $CH_2:C:O + R \cdot OH \rightarrow CH_3 \cdot COO \cdot R$, affords a valuable special method for acetylating certain compounds; see page 452.

3. Formation of Esters from Aldehydes by Dimerization

A special method for the preparation of esters, the components of which have the same number of carbon atoms and a similar structure, involves the polymerization of aldehydes in a certain way in accordance with the general reaction, $2R \cdot CHO \rightarrow R \cdot COO \cdot CH_2R$. Esters of this type sometimes occur naturally (*e.g.*, whale oil is palmityl palmitate). Tishchenko [241] made the observation some time ago that in some cases aldehydes give good yields of esters in the presence of aluminum or magnesium ethylate. Tishchenko's reaction had been neglected for a long time until Child and Adkins [242] made a thorough investigation to discover the most favorable conditions for carrying out the reaction. The method presumably is not very practical for use in the laboratory, but in certain cases when the aldehyde is more readily available than the acid and the alcohol (for instance, furfural) it might be advantageous. Very pure starting materials are required, and the method is not a very convenient one.

Acetal Formation

The formation of acetals from carbonyl compounds and alcohols, $R_2C:O + 2R' \cdot OH \rightarrow H_2O + R_2C(OR')_2$, takes place smoothly under the catalytic influence of strong acids only in the case of reactions involving the simplest aliphatic alcohols.

Recently Adkins and his coworkers,[243] testing a number of compounds for catalytic activity, found calcium chloride and ferric chloride were the

[241] W. Tishchenko, *Chem. Zentr.*, **1906**, II, 1309, 1552.
[242] W. Child and H. Adkins, *J. Am. Chem. Soc.*, **47**, 798 (1925).

most efficient. Directions for the preparation of acetal and acetaldehyde diethyl acetal with calcium chloride may be found in *Organic Syntheses*.[244] The synthesis of methylal, $CH_3 \cdot CH_2 \cdot O \cdot CH_3$, a valuable solvent for Grignard reactions, has been described by E. Fischer and Giebe.[245]

A suspension of finely powdered paraformaldehyde in 2.5 times its weight of a solution of hydrogen chloride (1%) in methanol is heated at 100°C. until a clear solution forms and the odor of formaldehyde almost disappears (12 to 15 hours). The solution is neutralized with aqueous sodium hydroxide and fractionated through a good column (according to Fischer and Giebe through a dephlegmator). The yield of acetal, boiling at 41° to 42°C., is 80%. Methylal may also be prepared from commercial formalin (35 to 40% aqueous formaldehyde), by heating it with 1.5 times its weight of a 2% solution of hydrogen chloride in methanol. A weight of calcium chloride equal to that of the formalin used is added to combine with the water present in the solution. The mixture becomes warm and the oily methylal separates after 15 minutes. 15 hours later the solution is neutralized and the product is distilled. Rectification of the distillate affords a yield of 70% of pure methylal.

Besides these papers of a general nature by Adams and Adkins [246] mentioned above, there are several patents for the preparation of methylal from methylene chloride.

A general method for the preparation of acetals is found in the reaction of carbonyl compounds with orthoformic acid esters or other ortho esters (orthosilicic acid methyl and ethyl esters), which is catalyzed by small amounts of acids, $R_2C:O + HC(OR')_3 \rightarrow R_2C(OR')_2 + H \cdot COOR'$. The method is convenient because many ortho esters are available commercially. Not only free acids, but also inorganic salts such as ferric chloride and ammonium chloride, catalyze this reaction. Their catalytic effect depends on the slight acidity developed as the result of their hydrolysis in aqueous solutions. The reaction is effected in a simple manner. The carbonyl compound is dissolved in the alcohol and the ortho ester and the catalyst are added. When ferric chloride is used, the reaction is completed quickly and the solution is worked up at once, but when ammonium chloride is used the solution is allowed to stand for several hours. Since the acetals are saponified rather easily in the presence of the catalyst, it is especially important to stop the reaction at the right point. The acetals must be isolated from alkaline or neutral solutions because of being very sensitive to acids.

According to directions given by Claisen [247] 0.15 cc. of concentrated ethyl hydrochloric acid containing 0.06 g. of hydrogen chloride is added

[243] H. Adkins *et al.*, *J. Am. Chem. Soc.*, **44**, 2749 (1922); **47**, 1358 (1925); **50**, 178 (1928).

[244] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 1.

[245] E. Fischer and G. Giebe, *Ber.*, **30**, 3054 (1897).

[246] E. Adams and H. Adkins, *J. Am. Chem. Soc.*, **47**, 1358, 1368 (1925).

[247] L. Claisen, *Ber.*, **40**, 3906 (1907).

to a mixture of 37.5 g. of benzaldehyde, 57 g. of ethyl orthoformate, and 49 g. of ethanol. The temperature of the solution rises rapidly to 48°C. It is boiled for a very short time on a steam bath and is cooled quickly. After being made faintly alkaline by the addition of a few drops of alcoholic potassium hydroxide, the reaction mixture is fractionated without delay. The alcohol and ethyl formate distil first, and then benzaldehyde diethyl acetal distils at 217° to 223°C. The yield is 63 g. (99%). The hydrochloric acid may be replaced by 0.75 g. of finely powdered ammonium chloride. In this case the solution is boiled under a reflux for 10 minutes and fractionated immediately. The yield is almost quantitative. Very similar results were obtained by using 0.3 g. of potassium bisulfate or ferric chloride as the catalyst.

More recent directions for the preparation of acrolein diethyl acetal are those of H. O. L. Fischer and Baer.[248]

To a mixture of 22 g. of stabilized acrolein and 72 g. of ethyl orthoformate a warm solution of 1.5 g. of ammonium nitrate in 15 cc. of absolute alcohol is added. After being boiled under a reflux for 8 to 10 minutes, the solution is filtered, and the dark brown filtrate is diluted with twice its volume of ether. The ethereal solution is extracted two or three times with dilute ammonia, is washed with water as long as amorphous substances separate, and is dried over potassium carbonate. Fractionation yields 37.5 g. (73%) of acrolein diethyl acetal (b.p. 120° to 125°C.).

Ketone acetals are prepared in exactly the same way as are those of aldehydes. The yields are usually somewhat lower, but often are as high as 80%.

A number of experiments have been made with the aim of substituting other acetal-forming reagents for the esters of orthoformic acid.

Helferich and Hausen [249] prepared acetals by the use of esters of orthosilicic acid.

To a mixture of 1 g. mole of aldehyde or ketone, 2 to 3 moles of the anhydrous alcohol, and 1.1 moles of the ester of orthosilicic acid are added 10 drops of the alcohol saturated with hydrochloric acid at room temperature (instead of this a few bubbles of dry hydrogen chloride may be passed in). The mixture is stored for several days at room temperature or is boiled under a reflux for some time. Benzophenone dimethyl acetal crystallizes directly in a good yield, but in most cases the product has to be obtained by fractionation, often under reduced pressure.

The acetals obtained in this way are not entirely free of silicin compounds, and to destroy the latter it is necessary to add some alcoholic potassium hydroxide to the distillate and boil the mixture. An alternative method is to treat the crude reaction mixture before distillation as follows: The solution is poured into a solution of 30% potassium hydroxide (500 cc. per mole of ortho ester), which is cooled if necessary, and the

[248] H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 516 (1935).
[249] B. Helferich and J. Hausen, *Ber.*, **57**, 795 (1924).

mixture is shaken at room temperature for about 10 minutes (refluxing may be necessary when higher alcohols are used).   The alcoholic layer, which is free of silicin compounds, is separated, dried over potassium carbonate, and fractionated (extraction of the organic material with ether may be preferable).   The yield varies from 70 to 90%.

The ortho esters are prepared by adding 1 mole of silicon tetrachloride to 4.4 moles of the anhydrous alcohol with cooling and with the exclusion of moisture.   The mixture is brought to the boiling point very slowly (over a period of 1 hour).   (Mixtures with higher alcohols are heated in an oil bath to a temperature not greater than 150°C.)   After being refluxed for 45 minutes, at the end of which time no more hydrogen chloride is liberated, the solution is cooled in a freezing mixture and a solution of sodium alcoholate is added until the mixture shows a faintly acid reaction (Congo red paper).   Products free of hydrogen chloride are prepared in this way.   The alcohol is distilled and the residue is fractionated *in vacuo* without separation of the sodium chloride which precipitates.   The yield is 70 to 80%.

Recently Voss [250] suggested the use of dimethyl sulfite for the preparation of acetals.   Directions for the preparation of cyclohexanone dimethyl acetal are as follows:

A mixture of 49 g. of cyclohexanone, 60 g. of dimethyl sulfite, 60 cc. of methanol, and 1 cc. of an 11.2% solution of hydrogen chloride in methanol is refluxed on a water bath.   After several minutes a violent evolution of sulfur dioxide takes place.   The solution is heated for 3 hours, cooled, and made alkaline with a few drops of sodium methylate.   By shaking the mixture with 200 cc. of 40% aqueous potassium hydroxide any unchanged dimethyl sulfite is destroyed.   After being diluted with water, the solution is extracted with ether and the ether extract is dried over potassium carbonate. Fractionation of the ether solution yields 57 g. (79%) of the acetal boiling at 63° to 65°C. at 22.5 mm.

The homologues of dimethyl sulfite are equally useful, but it is interesting to note that acetals of higher aliphatic alcohols are formed when the higher alcohol is used as the solvent.   To a mixture of 10.5 g. of benzaldehyde, 12 g. of dimethyl sulfite, and 27 g. of *n*-butanol in a flask equipped with a distilling column are added a few drops of a 20% solution of hydrogen chloride in methanol.   When the mixture is refluxed in an oil bath, the evolution of sulfur dioxide takes place as described above. Over a period of 2 hours, while the bath temperature is increased to 150° to 160°C., 20 cc. of a mixture of methanol and a little butanol are distilled (65° to 70°C.).   The residue (probably after being made alkaline) is fractionated under reduced pressure and rectified.   18.5 g. (80%) of benzaldehyde di-*n*-butyl acetal, boiling at 145° to 150°C. at 14 mm., are obtained.

[250] W. Voss, *Ann.*, 485, 283 (1931).

Accordingly, the acetals of such alcohols of high molecular weight as acetyl alcohol may be synthesized, and apparently acetals of sugars also may be prepared advantageously in such a manner.

The formation of the simple glycosides has already been discussed. At this point, the acetal-like acetone and benzaldehyde derivatives of sugars should be discussed briefly (see α,α'-benzalglycerol, page 182).

d-Glucose reacts readily with acetone to form diacetone glucose,

$$\text{CH}_2\cdot\text{CH}\cdot\text{CH}\cdot\text{CHOH}\cdot\text{CH}\cdot\text{CH}$$

(structure with O bridges and two acetone ketal groups)

$$\text{O}\quad\text{O}\qquad\qquad\text{O}\quad\text{O}$$
$$\text{CH}_3\cdot\text{C}\cdot\text{CH}_3\qquad\text{CH}_3\cdot\text{C}\cdot\text{CH}_3$$
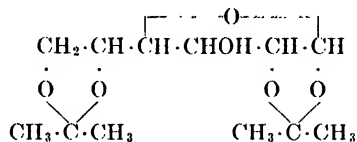
which has the glucofuranose or h-glucose (h = hetero) rather than the glucose-pyranose structure. Catalysts for the condensation are hydrochloric acid, sulfuric acid, and anhydrous copper sulfate. According to Freudenberg and coworkers [251] acetaldehyde is an accelerator and acetone which has been recovered from a condensation should be mixed with 1% of acetaldehyde if it is to be used again. Useful starting materials are β-glucose, α-glucose, and cane sugar. A method of Freudenberg and Smeykal [252] follows.

A suspension of 65 g. of finely powdered and screened α-d-glucose in 1.8 liters of pure commercial acetone and 55 cc. of concentrated sulfuric acid is shaken mechanically for 4 to 5 hours during which time almost all the glucose (except about 5 g.) passes into solution. The mixture is filtered and an excess of anhydrous sodium carbonate (150 to 200 g.) is added to the filtrate until the dark solution becomes light yellow. The mixture is filtered and evaporated to dryness, the final evaporation being done *in vacuo*. The residue is extracted with a little ether which does not dissolve the monoacetone glucose. The solution is allowed to stand overnight in a refrigerator to precipitate any monoacetone glucose which dissolves [253] and the mixture is filtered. Petroleum ether is added slowly to the filtrate; the thick mush of crystals is removed by filtration, washed with petroleum ether, and dried. A yield of 45 to 55 g. of diacetone glucose, melting at 102°C. (other sources give 110° to 111°C.), is obtained. $[\alpha]_D^{20} = -19°$.

Monoacetone glucose which is formed as a by-product in the above reaction was prepared by E. Fischer [254] from glucose and acetone containing hydrochloric acid by shortening the reaction time. Fischer had already observed that the quality of the acetone affected the success of the method and recommended using the commercial grade.

[251] K. Freudenberg *et al.*, *Ber.*, **61**, 1741 (1928).
[252] K. Freudenberg and K. Smeykal, *Ber.*, **59**, 107 (1926).
[253] K. Freudenberg *et al.*, *Ber.*, **61**, 1741 (1928).
[254] E. Fischer, *Ber.*, **28**, 2496 (1895).

The reaction between glucose and benzaldehyde differs in that a derivative of the normal glucopyranose is formed.

$$\begin{array}{c} \overset{\displaystyle \lceil\!\!-\!\!-\!\!-\!\!-\mathrm{O}\!\!-\!\!-\!\!-\!\!-\rceil}{\mathrm{CH_2 \cdot CH \cdot CH \cdot CHOH \cdot CHOH \cdot CHOH}} \\ \mathrm{O-CH-O} \\ \mathrm{C_6H_5} \end{array}$$
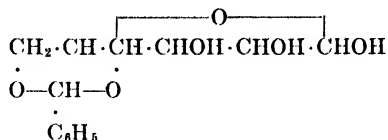
Zervas [255] gives the following directions for its preparation.

A mixture of 130 g. of dry *d*-glucose, 100 g. of finely powdered zinc chloride, and 300 cc. of freshly distilled benzaldehyde is shaken mechanically for 24 hours. Benzalglucose crystallizes instantly when 400 cc. of ice water are added to the viscous mass. The crystals are washed with cold water and with petroleum ether. The crude product weighs 60 to 70 g. and melts at 130°C. (not sharply). Upon repeated recrystallization from water containing ammonia, the melting point is raised to 188°C. The yield of pure benzalglucose, 4,6-benzylidene-*α*-*d*-glucose, is about 33%.

According to E. Fischer,[256] *d*-mannitol, $CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CH_2OH$, yields a triacetone compound if it is treated according to his directions. Acetone forms cyclic ethers with each pair of adjacent hydroxyl groups just as in the case of diacetone glucose.

1 part of finely ground mannitol is shaken with 10 parts of dry commercial acetone containing 1% of hydrogen chloride. After several hours a clear solution is formed but shaking is continued for 12 hours. The solution is neutralized with finely powdered lead carbonate, the mixture is filtered, and the filtrate is evaporated to dryness on a steam bath. The residual yellowish oil solidifies on cooling and is crystallized from alcohol-water. After being dried over sulfuric acid, the product melts at 68° to 70°C.; $[\alpha]_D = +12.5°$.

Irvine and Paterson hydrolyzed triacetone mannitol stepwise; see .

C. Preparation of Acid Anhydrides

Comparatively few direct methods are available for the preparation of anhydrides of carboxylic acid. The two most important ones are the removal of water either spontaneously or by means of catalysts, and the double decomposition reaction between acid chlorides and alkali salts of carboxylic acids.

Anhydrides of many carboxylic acids of high molecular weight are prepared by indirect methods, such as the reaction of acetic anhydride (a cheap dehydrating agent) with free carboxylic acids; see . Anhydrides often occur as undesirable by-products during the preparation of acid chlorides; see .

[255] L. Zervas, *Ber.*, **64**, 2293 (1931).
[256] E. Fischer, *Ber.*, **28**, 1168 (1895).

1. Preparation of Anhydrides by Dehydration of Acids

The dehydration of aromatic o-dicarboxylic acids is so easy that it is unnecessary to discuss the reaction further. The aliphatic dicarboxylic acids having 4, 5, or 6 carbon atoms are in a class by themselves. Glutaric acid is dehydrated spontaneously by being heated slowly to 230° to 280°C., and forms the anhydride melting at 56° to 57°C. Adipic acid yields the anhydride only upon being boiled for several hours with acetic anhydride. The distillation of adipic anhydride causes it to lose carbon dioxide and to be converted into cyclopentanone, but glutaric anhydride does not yield a cyclic ketone under the same conditions. This phenomenon is the basis for Blanc's rule [257] which states that 1,5-dicarboxylic acids give only acid anhydrides, while 1,6-dicarboxylic acids under the same conditions yield derivatives of cyclopentanone. The rigid application of this rule caused erroneous conclusions to be reached in the elucidation of the structure of cholesterol; see page 461. Succinic acid does not change spontaneously into the anhydride, but Volhard [258] was able to effect the conversion in the following way.

A mixture of 100 g. of dry succinic acid and 65 g. of phosphorus oxychloride is heated to 100° to 120°C. under a reflux until the evolution of hydrogen chloride ceases. Fractionation of the contents of the flask yields 80 g. (95%) of succinic anhydride boiling at 261°C. and melting at 116.5°C. Phosphorus pentachloride may be used in this reaction. The solution prepared by mixing thoroughly 57 g. of succinic acid and 100 g. of phosphorus pentachloride is added to 114 g. of succinic acid. The mixture is treated according to the above directions.

According to Mol,[259] glutaric anhydride is prepared by heating glutaric acid with twice its weight of acetyl chloride. At first the mixture is heated only to 40°C. and hydrogen chloride is liberated. The acetic acid which has formed is removed by distillation *in vacuo* while the temperature is raised gradually and either the residue of glutaric anhydride is fractionated *in vacuo* (b.p. 150°C. at 10 mm.) or it is crystallized from ether (m.p. 56° to 57°C.). According to McMaster and Ahmann,[260] a 78% yield of glutaric anhydride is obtained by heating glutaric acid with 2 to 3 times its weight of thionyl chloride for several hours.

Few experimental details can be found for the preparation of adipic anhydride, but according to Voerman [261] it is formed by refluxing adipic acid with 10 times its weight of acetyl chloride on a steam bath for 6 to 7 hours. The acetic acid and excess acetyl chloride are removed by distillation *in vacuo* on a steam bath, and the residue is dissolved in boiling

[257] Blanc, *Compt. rend.*, 144, 1356 (1907); *Bull. soc. chim.*, 3, 778 (1908).
[258] Volhard, *Ann.*, 242, 150 (1887).
[259] D. Mol, *Rec. trav. chim.*, 26, 381 (1907).
[260] McMaster and F. Ahmann, *J. Am. Chem. Soc.*, 50, 146 (1928).
[261] Voerman, *Rec. trav. chim.*, 23, 269 (1904).

benzene and precipitated with petroleum ether. After recrystallization from benzene the anhydride melts at 98°C. The yield is almost theoretical. In a similar manner the anhydrides of dicarboxylic acids up to sebacic acid may be prepared. Higher members of the series are frequently polymeric. Hill and Carothers [262] have experimented with large ring cyclic anhydrides.

Acetic anhydride is prepared industrially by the catalytic removal of water from acetic acid in a continuous process. Directions based on these methods have not been developed for use in the laboratory. Although the production of acetic anhydride itself in the laboratory is of little interest, experience gained with it should be of value in preparing homologous anhydrides by this process. Such anhydrides would be useful in Friedel-Crafts syntheses. In addition to the other methods, the homologues of acetic anhydride may be synthesized by the indirect method which will be discussed below.

2. Preparation of Anhydrides by Double Decomposition Reactions

Since the methods for the preparation of acid anhydrides from acid chlorides and the alkali salts of carboxylic acids are very simple, a detailed description need not be given here. Examples of the method, which is particularly important for the preparation of mixed anhydrides, may be found in any elementary textbook; see page 193.

The indirect method of preparing anhydrides by the reaction of acetic anhydride with free carboxylic acids is very valuable. Directions for the preparation of benzoic anhydride according to a method of Autenrieth and Thomae [263] are given in *Organic Syntheses*.[264]

By way of comparison a method of Kaufmann and Luterbacher,[265] which is suitable for small scale reactions, is described below.

A mixture of 48.8 g. of benzoic acid, 41 g. of acetic anhydride, and 200 g. of dry benzene is boiled under a reflux for 6 hours and then fractionated. There is collected a forerun of benzene and acetic acid and 9 to 10 g. of a by-product boiling at 330° to 347°C. The benzoic anhydride (36.8 g., 81%) distils at 347° to 348°C. It melts at 42°C.

In the paper mentioned above Autenrieth and Thomae give directions, some of which are detailed, of the preparation of anhydrides of other aliphatic and aromatic acids. They also give data for the preparation of mixed anhydrides, the existence of which was formerly questioned; see also Autenrieth.[266]

[262] W. Hill and W. H. Carothers, *J. Am. Chem. Soc.*, 55, 5023 (1933).
[263] Autenrieth and Thomae, *Ber.*, 57, 430 (1924).
[264] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 91.
[265] A. Kaufmann and A. Luterbacher, *Ber.*, 42, 3484 (1909).
[266] W. Autenrieth, *Ber.*, 34, 168 (1901).

The mixed anhydrides are seldom of any importance, but the mixed anhydride of formic and acetic acids is of interest, because the anhydride of formic acid alone is not stable. The mixed anhydride has been obtained by Béhal.[267]

An ice-cold mixture of 138 g. of anhydrous formic acid and 408 g. of acetic anhydride is allowed to stand for some time, after which it is heated to 50°C. on a water bath and cooled. The reaction mixture is distilled through a short column *in vacuo*. At 18 mm. three fractions are collected boiling at 29° to 31°C., from 31° to 32°C., and above 32°C. The middle fraction is treated with petroleum ether to dissolve the acetic acid and acetic anhydride. The residue contains about 70% of the mixed anhydride. It is refractionated, giving a middle fraction which contains 80.3% of the mixed anhydride. Repetition of the same operation increases the degree of purity of the product to 89%. This product is sufficiently pure for synthetic purposes. The pure compound boils at 29°C. at 17 mm.

Béhal, in the same paper, describes the preparation of many esters of formic acid by means of the mixed anhydride.

Zetzsche and coworkers [268] have suggested allowing the acid chlorides to react with acetic anhydride, thus forming acetyl chloride and the anhydride of higher molecular weight acids. There is a greater difference between the boiling points of the product and the starting materials in this case; see page 192.

Karrer and Gränacher [269] have synthesized anhydrides of amino acids.

[267] A. Béhal, *Ann. chim. phys.*, **20**, 417 (1900); *Compt. rend.*, **128**, 1460 (1899).
[268] F. Zetzsche *et al.*, *Helv. Chim. Acta*, **9**, 181 (1926).
[269] Karrer and Gränacher, *Helv. Chim. Acta*, **8**, 205, 211, 873 (1925).

Cleavage of Carbon-Oxygen Bonds

According to a very general rule, the cleavage of carbon-oxygen bonds becomes easier as 1 of the 2 carbon atoms of the group C—O—C becomes more heavily loaded with oxygen or nitrogen atoms.

The following types of compounds are arranged in the order of increasing stability.

Carboxylic acid anhydrides
Ortho esters, acetals, hemiacetals
Carboxylic acid esters
Ethers

These groups may be subdivided further and the members arranged according to the stability of their carbon-oxygen linkages. The ester linkage in lactones and lactides shows a greater tendency towards cleavage than that in normal esters. The oxygen-containing heterocyclic rings are less stable than the analogous open chain ethers and become more unstable the more oxygen atoms they contain. Thus, the heterocycles become more unstable in the order pyran, dioxane, and paraldehyde. In compounds containing only 1 heterocyclic oxygen atom such as pyran and furan, there are slight differences in stability due to the valency distribution and strain in such molecules.

The reactions leading to the rupture of the C—O—C linkages may be divided into the following types.

1. Hydrolysis: $\quad$ —C—O—C— + H$_2$O $\quad\longrightarrow\quad$ 2 $\,$C·OH

2. Acetolysis: $\quad$ —C—O—C— + HX $\quad\longrightarrow\quad$ —C·OH + XC—

$\qquad\qquad\quad$ —C—O—C— + R·COOH $\longrightarrow$ —C·OH + —C·OOC·R

3. Hydrogenolysis: —C—O—C— + H$_2$ $\quad\longrightarrow\quad$ —C·OH + HC—
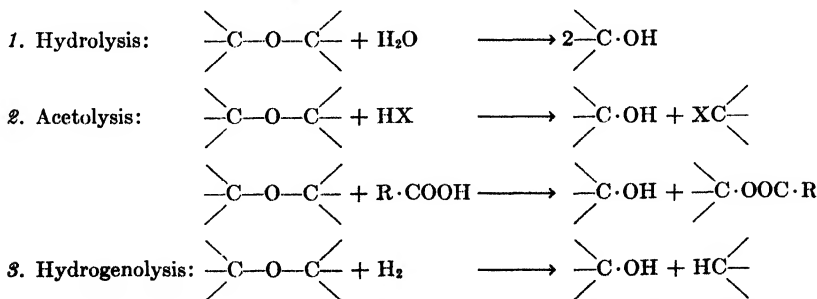
In the course of a study on organic catalysis Langenbeck and Baltes [1]

[1] W Langenbeck and J. Baltes, *Ber.*, **67**, 387 (1934).

investigated the influence of glycolanilide on the saponification of esters.

The hydrolysis of esters by enzymes will not be discussed here.

A. Cleavage of Ether Linkage

The methods for effecting the cleavage of ether linkages are most unsatisfactory and rarely afford good yields. The reagents which are commonly used for this purpose are hydrobromic and hydriodic acids, fuming sulfuric acid, aluminum chloride, and aluminum bromide which is best. Alkalies may be used at higher temperatures for the hydrolysis of phenol-alkyl ethers. The last method is of theoretical interest only.

The ease of cleavage of phenol ethers under alkaline conditions bears a direct relation to the ease with which they are formed. According to Stoermer and Kahlert[2] anisole affords only a little more than 11% of phenol when it is treated with 6 times its weight of 33% alcoholic potassium hydroxide for 15 hours at 180° to 200°C., and Bouveault[3] found that polyphenol ethers such as veratrole undergo partial saponification in the presence of alcoholic potassium hydroxide. On the other hand, the ethers of the more acid nitrophenols are saponified quite easily even at moderate temperatures, a behavior also shown by the ethers of hydroxyquinones (Nef[4]).

The ethers also vary in their behavior towards acidic reagents, the ones which are formed the most easily being hydrolyzed more readily.

Ethers of triphenylcarbinol are unstable even in the presence of dilute acids, and the ethers of tertiary aliphatic alcohols are converted into tertiary halides by the action of hydrochloric acid. Frequently unsaturated compounds are also obtained. Ziegler and Schnell[5] prepared diphenylethylene hydrocarbons by boiling diphenylalkylcarbinol ethers with alcohol and acetic acid.

Other reactive groups present in the molecule exert a decisive influence also. The vinyl ethers, the ethers of 1,3-diketones, and α-keto esters are as sensitive to acids as are the cyclic hemiacetals of the sugar series, the glycosides. The ethers of α-keto alcohols such as α-ketocyclohexanol are attacked with surprising ease, as was shown by Bergmann and Gierth.[6]

Most of the types of compounds discussed above are ethers only from the view-point of classification; true ether linkages, if not influenced by substituents, are always difficult to break.

[2] Stoermer and Kahlert, *Ber.*, **34**, 1812 (1901).
[3] L. Bouveault, *Bull. soc. chim.*, **19**, 75 (1898).
[4] U. Nef, *J. prakt. Chem.*, **42**, 168 (1890).
[5] K. Ziegler and Schnell, *Ann.*, **457**, 228 (1924).
[6] Bergmann and Gierth, *Ann.*, **448**, 65, 69 (1926).

Hydriodic acid is the only general reagent for the hydrolysis of ethers but its use is limited, since it is a most effective reducing agent, and is chemically active in other ways.   Presumably both constituent parts of aliphatic ethers are converted into iodides if excess hydriodic acid is used. Alkyl ethers of phenols always yield an alkyl iodide and free phenol when treated with hydriodic acid.   The direction of cleavage of unsymmetrical ethers under the influence of hydrogen iodide has been studied by Lippert.[7]

Hartmann and Gattermann [8] were the first to notice that phenol ethers are easily cleaved by aluminum chloride.   A crystalline addition compound is formed which decomposes on heating to an alkyl halide and aluminum chlorophenolate.   Phenol can be obtained from anisole by heating it with aluminum chloride for 3 hours at 120°C.   The methyl chloride escapes.   The residue is decomposed with water, the solution is acidified, and the phenol is isolated in the usual way.   Aluminum bromide is a much better reagent for the cleavage of ethers of phenol with the higher aliphatic alcohols.   According to Pfeiffer and Loewe [9] the reaction takes place as follows:

$$R-OCH_3 + AlBr_3 \longrightarrow R-O-CH_3 \cdot AlBr_3 \longrightarrow R-OAlBr_2 + CH_3Br$$
$$R-O-AlBr_2 + H_2O \longrightarrow R \cdot OH + AlBr_2(OH)$$
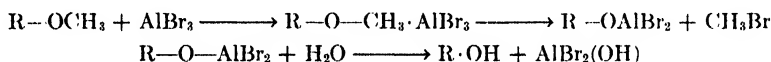
If the molecule contains a carbonyl group, a second molecule of aluminum bromide takes part in the reaction (Pfeiffer and Haack [10]).

The reaction has led to the development of a suitable method for the removal of alkyl groups from different aromatic alkoxy and methylenedioxy compounds.

Usually simple ethers can be cleaved by refluxing their solutions in thiophene-free benzene with the required amount of aluminum bromide, but in other cases a more complicated apparatus may be necessary.

The following reactions illustrate the method.

Preparation of o-Hydroxybenzophenone—A mixture of 0.82 g. of 2-methoxybenzophenone, 3.1 g. of aluminum bromide, and 27 cc. of benzene is boiled under a reflux for 4 hours.   The reaction mixture is cooled, excess hydrochloric acid is added, the layers are separated, and the aqueous layer is extracted with ether.   The phenol is extracted from the combined ether-benzene extracts with 2 *N* sodium hydroxide and the alkaline solution is added slowly to hydrochloric acid.   After extraction of the phenol with ether and evaporation of the ether, 0.74 g. (96%) of oily o-hydroxybenzophenone is obtained.

Preparation of p-Hydroxybenzoic Acid—A solution of 4.9 g. of aluminum bromide in 30 cc. of benzene is added to 0.79 g. of anisic acid (dried over phosphorus pentoxide) in 35 cc. of warm benzene and the mixture is boiled under a reflux for 4½ hours.   After it has cooled, concentrated hydrochloric acid is added, the solution is extracted with ether,

[7] Lippert, *Ann.*, **276**, 196 (1893).
[8] Hartmann and Gattermann, *Ber.*, **25**, 3531 (1892).
[9] P. Pfeiffer and W. Loewe, *J. prakt. Chem.*, **147**, 293 (1936).
[10] Pfeiffer and Haack, *Ann.*, **460**, 156 (1928).

and the ether extract is shaken with aqueous sodium hydroxide. The alkaline extract containing the sodium salt of the hydroxy acid is acidified and extracted with ether. After the removal of the ether by evaporation, 0.73 g. of *p*-hydroxybenzoic acid is obtained.

The removal of alkyl groups from compounds of a more complicated structure, such as papaverine and piperonal, has been effected by similar means.

The methods for the cleavage of ether linkages discussed thus far require reagents of a very active chemical nature.

A much less drastic method is the hydrogenolysis of benzyl ethers in the presence of platinum as outlined in a patent of Merck.[11] This was used by Freudenberg, Dürr, and Hochstetter [12] for the cleavage of the benzal compounds of sugars. The preparation of α-methyl glucoside [13] is an example of this method.

A solution of 0.3 g. of benzal (α-methyl) glucoside in 20 cc. of 50% ethanol is hydrogenated in the presence of 0.2 g. of platinum black. The solution is filtered and evaporated to dryness in a vacuum. The crystalline residue is dissolved in water, and the solution is filtered and allowed to crystallize. The residue consists of α-methyl glucoside.

This method is not important because of its possible general use, but because of its value in synthetic work. Hydroxyl groups can be protected by groups which are resistant to alkaline and acidic media while reactions involving other groups are carried out. The removal of the protecting group is effected by hydrogenolysis in neutral solution, a reaction which is least destructive to sensitive molecules.

B. Cleavage of Ester Linkage

The ester linkage may be cleaved by any of three fundamental methods, hydrolysis, alcoholysis, or acetolysis. These three basic reactions are represented by the following equations.

1. $\qquad$ $R \cdot COOR' + HOH \longrightarrow R \cdot COOH + R'OH$

2. $\qquad$ $R \cdot COOR' + R''OH \longrightarrow R \cdot COOR'' + R'OH$

3. $\qquad$ $R \cdot COOR' + R''COOH \longrightarrow R'' \cdot COOR' + R \cdot COOH$
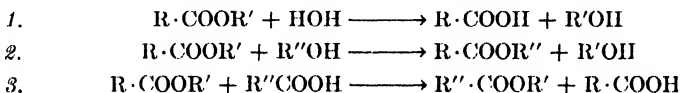
In the first case the C—O—C bond is hydrolyzed with the formation of two hydroxylic compounds, an alcohol and an acid. In the other two cases exchanges take place and only one hydroxylic compound, either an acid or an alcohol, takes part in the reaction. In these cases the same type of compound is formed as is used for the exchange.

The hydrogenolysis of esters has been described earlier in the section on hydrogenation methods on page 52.

[11] E. Merck, German Patent, 407,487.
[12] K. Freudenberg, W. Dürr, and H. v. Hochstetter, *Ber.*, **61**, 1739 (1928).
[13] K. Freudenberg, H. Toepffer, and C. Andersen, *Ber.*, **61**, 1759 (1928).

1. Saponification of Esters

The hydrolysis of esters of carboxylic acids may be carried out by alkali or acid, or by means of catalysts of which the hydrolytic enzymes are an example. The cleavage of esters in the laboratory is usually effected by saponification.

Very great differences in the velocity of saponification are shown by various esters. The rate is influenced by the structure of the alcoholic as well as the acidic components.

The esters of formic acid are in a class by themselves, as they are hydrolyzed easily by water in the absence of catalysts. The other extreme is represented by esters of carboxylic acids such as trimethylacetic acid or the vicinal dialkyl benzoic acids, the saponification of which is inhibited by steric hindrance.[14]

The ease of saponification of esters of aliphatic alcohols increases in the order, primary, secondary, tertiary. The phenolic esters, which undergo saponification very readily, belong to the last group.

Finer differences in the case of the saponification of esters of primary alcohols can be correlated with the molecular weight of the alcoholic fragment. An example of this is the greater ease of cleavage of amyl esters than of methyl or ethyl esters. According to Bischoff and Hausdörfer [15] the ethyl ester of phenylglycine can be saponified only by means of alcoholic potassium hydroxide, but the amyl ester is cleaved by boiling it with 32% aqueous sodium hydroxide.

Fine differences in the course of the reaction also depend on the solvent. Bouveault [16] found that the saponification of esters of α-keto acids with alcoholic potassium hydroxide results in extensive decomposition, while it proceeds without difficulty in aqueous solution.

The possibility that further reactions may take place is governed by the structure and configuration of the molecule and this must always be considered, since strongly alkaline media and high temperatures are often necessary.

Although the method for the alkaline hydrolysis of esters is simple, data on the relative concentrations of the reactants for the saponification of common fats according to the directions of Grün [17] may be valuable.

An excess of at least 3 times the theoretical amount of a solution of 30 g. of potassium hydroxide in 1 liter of pure alcohol is used for the saponification, and the mixture is boiled under a reflux for 30 to 60 minutes. The use of a caustic solution which contains water for the saponification slows the reaction to a considerable extent.

[14] V. Meyer, *Ber.*, **28**, 1262 (1895).
[15] C. Bischoff and A. Hausdörfer, *Ber.*, **25**, 2270 (1892); German Patent, 163,515.
[16] L. Bouveault, *Bull. soc. chim.*, **15**, 1017 (1896).
[17] A. Grün, *Analyse der Fette und Wachse.* Vol. I, Springer, Berlin, 1925, p. 144.

Fats and waxes which are difficult to saponify require the use of caustic solutions containing as little water as possible and the addition of an indifferent higher boiling solvent (such as benzene, toluene, butanol, xylene, amyl alcohol, and others) in an amount approximately equal to the volume of the reaction mixture. If mixtures of fats with unsaponifiable compounds slightly soluble in alcohol are to be treated, benzene is added. Often the potassium hydroxide is used in solution in higher boiling alcohols, such as amyl and benzyl alcohols, instead of ethanol. These modifications actually are taken from the directions for the determination of the saponification number of esters, but they may serve as a guide for carrying out saponifications of other esters on a preparative scale.

The saponification of common fats with aqueous alkalies is described in elementary textbooks, and the cleavage by enzymes cannot be discussed here. The acid hydrolysis of esters is used less frequently in the laboratory, although the method is employed commercially to a considerable extent for hydrolyzing fats. Certain catalysts are used which effect a very rapid reaction. All of these catalysts are developments based on and similar to the Twitchell reagent.[18] A very thorough study of the nature and the effect of these catalysts which are aromatic sulfonic acids has been made by Schlutius.[19]

This method is used primarily for the preparation of acids, and the fate of the alcoholic fragment of the ester is of little consequence; whether it appears as the halide or as the free alcohol when hydrogen halides are used for the hydrolysis of esters depends on several factors, among which the structure of the alcohol is particularly important.

2. Interchange of Components of Esters

The principle of the interchange of the components of esters is illustrated in elementary textbooks by the example of the conversion of ethylene glycol diacetate into ethylene glycol.

After the solution of the ester in methanol containing a suitable concentration of hydrogen chloride has been refluxed for some time, the catalyst is neutralized and the mixture is fractionated. The use of a large excess of alcohol shifts the equilibrium in the desired direction. By making a proper choice of the alcohol to be used in the ester interchange, it is possible to obtain reaction products the boiling points of which are far enough apart so that the isolation of the product is relatively easy.

This exchange reaction is used particularly in analytical chemistry for the quantitative determination of acetyl groups. It is being used to an ever increasing extent in industry, but directions suitable for its use in

[18] German Patent, 114,491.
[19] E. Schlutius, *J. prakt. Chem.*, **142**, 49 (1935).

the laboratory have never been published.   To give an idea of the possibilities that have not yet been exhausted, the most important points in connection with this method taken from a paper by Verley,[20] are given below.

He prepared the geraniol ester of anthranilic acid, which cannot be obtained in any other way, by the following method.

A mixture of 1 mole of methyl anthranilate, 1 mole of geraniol, and 0.05 mole of sodium, aluminum, or magnesium ethylate is heated to 100° to 120°C.   Methanol distils slowly.   The removal of the alcohol may be accelerated by evacuating the system. After all the methanol has been distilled, the residue is washed with 10% sulfuric acid to remove some unchanged methyl ester.   Acid of this strength does not attack the geraniol ester.   The product is a golden yellow oil, boiling at 188°C. at 4 mm.

In this way any primary alcohol can be replaced by another primary· or secondary alcohol having a higher boiling point, but this method is not suitable for the preparation of esters of tertiary alcohols.

Verley esterified tertiary alcohols by the following indirect method.

The tertiary alcohol, the ester of which is desired, is esterified with formic acid by allowing it to stand for several days with an excess of the mixed anhydride of formic and acetic acids (see page 193).   Under these conditions dehydration of the tertiary alcohol does not take place.   The ester of formic acid is isolated as usual, and is mixed with an equimolecular amount of the methyl ester of the carboxylic acid which is to furnish the acid component of the desired ester.   0.05 mole of the free tertiary alcohol and 0.05 mole of sodium are added and the mixture is heated to 100° to 120°C.   Methyl formate, which is the lowest boiling component of the equilibrium mixture, distils slowly.   The reaction is occasionally quite vigorous and is completed in 3 to 4 hours.   The processing of the residue from the distillation is not described in Verley's paper, as the method apparently is similar to that used for primary and secondary alcohols; see above.

The same method can be used for the preparation of esters of phenols.

C. Saponification of Acetals and Ortho Esters

The saponification of ortho esters has little importance for preparative purposes, because it leads to common carboxylic acids which are obtained conveniently, without exception, in other ways.   Ortho esters apparently do not occur naturally.

Occasionally the saponification of acetals is important, since unsaturated aldehydes are often synthesized by the use of their acetals as intermediates.   The Grignard synthesis of aldehydes also frequently produces the acetals of the corresponding aldehydes as intermediates.

[20] A. Verley, *Bull. soc. chim.*, **41**, 788 (1927).

Acetals as well as ortho esters can be hydrolyzed even by cold dilute acids. In most cases the treatment of the acetal with a little hydrochloric acid in aqueous alcoholic solution is sufficient to effect its hydrolysis.

G. Fischer, Ertel, and Löwenberg [21] have described a procedure for the hydrolysis of sensitive acetals of which β-methylcrotonaldehyde acetal is an example; see page 318.

A suspension of 53 g. of β-methylcrotonaldehyde acetal in 10 cc. of a cold saturated aqueous solution of tartaric acid is shaken until it becomes homogeneous. During this time the reaction mixture also becomes quite cool. The addition of 200 cc. of a saturated cold solution of calcium chloride causes the separation of the aldehyde as an oil.

The hydrolysis of larger quantities of the acetal may be effected by shaking a suspension of the acetal in an aqueous solution of tartaric acid until complete solution results. More acid is added from time to time until the mixture remains heterogeneous.[22] The aldehyde is extracted with ether, and the extract is shaken with concentrated calcium chloride solution and dried over calcium chloride. The ether is distilled and the residue is fractionated through a column 100 cm. in length. An isomer, α-methylacrolein which is formed from the corresponding isoamyl alcohol present in the starting material, distils at 75° to 85°C., and the β-methylcrotonaldehyde distils at 130° to 136°C. Rectification of the product produces 153 g. of the aldehyde (from 430 g. of acetal). It is very sensitive and is oxidized rapidly by oxygen to β-methylcrotonic acid. It should be handled and distilled in an atmosphere of nitrogen.

Irvine and Paterson [23] hydrolyzed triacetone *d*-mannitol stepwise in the following manner.

A stirred solution of 30 g. of triacetone mannitol (see page 190) in 450 cc. of ethanol which contains 32% water and 0.1% hydrogen chloride is maintained at a temperature of 4°C. by means of a thermostat for 150 minutes. The hydrogen chloride is removed by the addition of silver carbonate and the filtrate is decolorized with charcoal. The solution is concentrated under reduced pressure, and the triacetone mannitol which separates is removed by filtration. The filtrate is evaporated to dryness, and the residue is treated with cold acetone. The free mannitol remains undissolved. Mono- and diacetone mannitol pass into solution. When the acetone is evaporated *in vacuo*, 50% of the total amount of solid material is recovered as a mixture of the mono- and diacetone compounds. The mixture is separated by boiling it with a large excess of benzene, from which crystalline monoacetone mannitol separates on cooling. The benzene is removed from the filtrate; the residual syrup is distilled at 172°C. at 11 mm. After standing for several weeks in a refrigerator, the distillate crystallizes in a mass of needles which melt at 37° to 39°C. This product is 3,4,5,6-diacetone mannitol (α-diacetone mannitol). Its isomer, symmetrical 1,2,5,6-diacetone mannitol, can be obtained by partial acetonization of mannitol; see E. Fischer and Rund [24] and Vargha.[25]

By hydrolyzing α-diacetone mannitol, Irvine and Paterson obtained 3,4-monoacetone mannitol; see Müller.[26] The isomeric 1,2-monoacetone

[21] G. Fischer, L. Ertel, and K. Löwenberg, *Ber.*, **64**, 33 (1931): *Ann.*, **494**, 272 (1932).
[22] G. Fischer and K. Löwenberg, *Ann.*, **494**, 272 (1932).
[23] I. C. Irvine and B. M. Paterson, *J. Chem. Soc.*, **105**, 907 (1914).
[24] E. Fischer and Rund, *Ber.*, **49**, 91 (1916).
[25] L. v. Vargha, *Ber.*, **66**, 1397 (1933).
[26] A. Müller, *Ber.*, **65**, 1056 (1932).

mannitol was prepared by Vargha by means of a boric acid ester as an intermediate.

A remarkable example of the way in which old and tested methods of synthesis can be made obsolete by new ones is illustrated by the synthesis of dibenzoylmethane. The last step of the preparation which is now considered to be the best consists of the saponification of an enol ether (a compound of hemiacetal character).

According to Claisen [27] dibenzoylmethane may be obtained by the condensation of acetophenone and ethyl benzoate by means of sodium. The method is tedious, because the reaction mixture must be diluted with petroleum ether and extracted by shaking it with aqueous alkali to isolate the enol. This extraction is time-consuming and can be carried out only in small batches in the laboratory. An analytically pure product is produced, but it always has a pink color, and the yield is not always satisfactory.

· In another method benzalacetophenone which is easily prepared from acetophenone and benzaldehyde is used (see page 428) as a starting material. This process is carried out via the dibromide without alteration of the carbon skeleton. Wislicenus [28] was the first to prepare dibenzoylmethane in this way, but the course of the reaction was not elucidated until much later by Dufraisse and Gérald.[29] They established that the series of reactions which follow when benzalacetophenone dibromide is treated with alcoholic potassium hydroxide is

1. $C_6H_5 \cdot CHBr \cdot CHBr \cdot CO \cdot C_6H_5 + KOC_2H_5 \longrightarrow$
$$C_6H_5 \cdot CH:CBr \cdot CO \cdot C_6H_5 + KBr + C_2H_5OH$$

2. $C_6H_5 \cdot CH:CBr \cdot CO \cdot C_6H_5 + C_2H_5OH \longrightarrow$
$$C_6H_5 \cdot CH(OC_2H_5) \cdot CHBr \cdot CO \cdot C_6H_5$$

3. $C_6H_5 \cdot CH(OC_2H_5) \cdot CHBr \cdot CO \cdot C_6H_5 + KOC_2H_5 \longrightarrow$
$$C_6H_5 \cdot C(OC_2H_5):CH \cdot CO \cdot C_6H_5 + KBr + C_2H_5OH$$
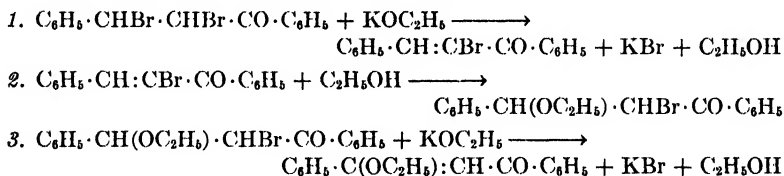
The O-ethyl ether of dibenzoylmethane undergoes acid hydrolysis easily with the production of the diketone (or its enol):

4. $C_6H_5 \cdot C(OC_2H_5):CH \cdot CO \cdot C_6H_5 + H_2O \longrightarrow$
$$C_6H_5 \cdot C(OH):CH \cdot CO \cdot C_6H_5 + C_2H_5OH$$
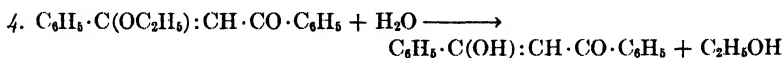
It is not necessary to isolate the intermediates in the preparation of dibenzoylmethane and benzalacetophenone prepared according to the directions on page 61. Directions for its preparation are given also in *Organic Syntheses*.[30]

[27] L. Claisen, *Ann.*, **291**, 52 (1896).
[28] J. Wislicenus, *Ann.*, **308**, 277 (1899).
[29] C. Dufraisse and P. Gérald, *Bull. soc. chim.*, **31**, 1920 (1922).
[30] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 205.

When recrystallizing dibenzoylmethane, one may employ an ingenious method for removing the color. Dibenzoylmethane crystallizes easily from methanol in a metastable form melting at 71°C., as was shown first by Dufraisse and Gérald.[31] This lower melting form does not trap colored impurities in the crystal lattice, while the stable form melting at 78°C. obstinately retains these impurities. The crude product is dissolved in boiling methanol and filtered. The neck of the Erlenmeyer flask is closed with a cotton plug and the solution is boiled until the vapors permeate the cotton plug. This procedure destroys traces of the stable form of which the crude product apparently consists after being stored for a short time. The flask is set in cold water to cool it moderately, but no separation of an oil must take place. If oil forms, the solution must be diluted.

In order to favor the formation of seeds the bottom of the flask is cooled for a short time by a freezing mixture. Usually, after 5 to 10 minutes (sometimes earlier) the glassy clear needles of the metastable form appear and if left undisturbed they grow several centimeters long. If filtration is delayed too long, conversion into the stable form may start, whereupon the needles disintegrate to a coarse powder, the mother liquor becomes lighter, and the powdery crystals turn pink. The mother liquor should be removed as quickly as possible during the filtration process, as exposure to air causes the conversion to the higher melting form to take place. This change almost always occurs in the funnel, and usually the higher melting form is obtained in preparative work.

This method was tested with a sample prepared according to Claisen's directions (see above). The dibenzoylmethane prepared from benzalacetophenone dibromide is more pure, but colorless dibenzoylmethane can be obtained only if the O-alkyl ethers are purified by vacuum distillation.

[31] C. Dufraisse and P. Gérald, *Ann. chim. phys.*, **4**, 306 (1926).

Formation of Organic Derivatives of Trivalent Nitrogen

Trivalent nitrogen bound to carbon is present in many types of compounds. In part, they are named as derivatives of ammonia, of hydrazine, and of hydroxylamine; in part they have acquired special designations when the simple inorganic basic substances are unstable; *e.g.*, diimide.

In accordance with the prevailing manner of presentation these compounds will be classified according to whether the three valencies of nitrogen are taken up by hydrogen, by carbon-containing radicals, or by nitrogen. Within these groups those in which no C—N multiple bonds occur will be described first. The next group will comprise the types of compounds in which oxygen is bound to nitrogen of the C—N linkage; then the ones with oxygen at carbon. A last group is formed by the derivatives of hydrazoic acid. More complicated types, which include the nitrogen-containing heterocyclic substances follow these simple ones, but they cannot be discussed systematically here.

I. AMINES

A. Primary Amines

1. By Addition of Ammonia to Ethylene Bond

The addition of ammonia to the ethylene bonds is not successful with simple hydrocarbons. This is not surprising, since ethylene compounds may be formed in the presence of ammonia; see below for the behavior of tertiary halides towards ammonia. Contrariwise, ammonia is added to unsaturated acids and ketones more or less easily if the double bond is adjacent to the carboxyl or carbonyl group; thus, from unsaturated acids of the type of acrylic acid, β-aminocarboxylic acids are formed. (See E. Fischer [1] and Engel.[2]) The addition takes place on heating with ammonia in a sealed tube at 100° to 105°C. Since the β-carboxylic acids are sometimes hard to obtain in other ways, this reaction has importance as a

[1] E. Fischer, *Ber.*, **34**, 3755 (1901).
[2] Engel, *Bull. soc. chim.*, **50**, 102 (1888).

preparative method. A similar behavior is exhibited by maleic and fumaric acids, but the yields of aspartic acid are very moderate. Hence other methods are usually preferable. Doubly unsaturated acids add 2 moles of ammonia; sorbic acid changes to diaminocaproic acid; see Fischer and Raske.[3]

α,β-Unsaturated ketones add ammonia very readily; mesityl oxide forms diacetonamine according to the equation, $CH_3 \cdot CO \cdot CH : C : (CH_3)_2 + H_3N \rightarrow CH_3 \cdot CO \cdot CH_2 \cdot C(NH_2)(CH_3)_2$, as described by Sokoloff and Latschinoff.[4] Experimental details can be found in *Organic Syntheses*.[5] The amino group adds to the carbon furthest from the carbonyl.

Even though the addition of ammonia to ethylene hydrocarbons does not succeed, as has been mentioned above, ethylene derivatives, such as vinyl chloride, which have a halogen atom at the double bond, react with ammonia, according to Engel,[6] by exchange of the halogen for the amino group, as well as by addition of a second molecule of ammonia; thus from vinyl chloride ethylenediamine is formed, though this is not a preparative method; see page 213.

2. By Exchange

(a) By Replacement of Hydrogen by Amino Group

The replacement of hydrogen by the amino group, with removal of water by hydroxylamine, succeeds only in a few cases with aromatics which contain especially reactive hydrogen atoms. According to Meisenheimer and Patzig,[7] at least two nitro groups must be present in the benzene nucleus in order that the reaction may take place. For naphthalene, however, one nitro group is sufficient, as was shown by Angeli.[8] α-Nitronaphthalene yields 1-nitro-4-naphthylamine, contrary to Holleman's substitution rules. In nitro derivatives of benzene, also, the amino group always adds in the o or p position to a nitro group. Thus, 2,4-dinitroaniline is obtained from m-dinitrobenzene, besides some 2,4-dinitro-1,5-phenylenediamine. Symmetrical trinitrobenzene yields picramide. As an example for this reaction directions from the above mentioned paper of Meisenheimer and Patzig follow for the preparation of 2-nitro-1-naphthylamine from β-nitronaphthalene.

2 g. of β-nitronaphthalene and 5 g. of hydroxylamine hydrochloride are dissolved in 110 cc. of alcohol and, after cooling to 30°C., 50 cc. of a solution of potassium hydroxide in methanol is added. After several minutes one-half its volume of water is added to

[3] E. Fischer and Raske, *Ber.*, **37**, 2357 (1904); **38**, 3607 (1905).
[4] Sokoloff and Latschinoff, *Ber.*, **7**, 1387 (1874).
[5] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 196.
[6] Engel, *Compt. rend.*, **104**, 1621 (1887).
[7] J. Meisenheimer and E. Patzig, *Ber.*, **39**, 2534 (1906).
[8] Angeli, *Gazz. chim. ital.*, **31**, I, 27 (1901).

the alcoholic solution and the mixture allowed to stand for 10 hours. At the end of this time, the addition of much water causes the precipitation of a red compound melting at 143°C.; after one recrystallization from alcohol red needles are obtained melting at 144°C.

Sachs [9] discovered a method of introducing amino groups into certain derivatives of naphthalene and anthraquinone by melting with sodium amide. Its success depends on the presence of at least one hydroxyl or amino group in the nucleus. It is surprising that the amino group takes its place in the unsubstituted naphthalene nucleus and as a matter of fact, always in 5 position, no matter whether α-naphthol, α-naphthylamine, β-naphthol, or β-naphtholamine is used as the starting material. Thus, 1,5-aminonaphthol, 1,5-naphthalenediamine, 2,5-aminonaphthol, and 2,5-naphthalenediamine are obtained. A certain parallel to the abnormal substitution [10] with hydroxylamine may be seen. The preparation of 1,5-naphthalenediamine from α-naphthylamine is given as an example of the procedure.

It is important to have the proper reaction temperature. The temperatures which can be used in glass vessels in the presence of sodium amide are not sufficient in all cases. Therefore, the reaction is carried out in copper pipes with braced bottom (for example, height 20 cm., diameter 6 cm., wall thickness 1 mm.). Vigorous stirring is necessary. The bottom of the container is covered with naphthalene; then a mixture of amine and sodium amide follows, in this case 10 g. of naphthylamine and 30 g. of sodium amide; the charge is finally covered with naphthalene. The melt is kept for 30 minutes at 230°C. while the evaporated naphthalene has to be replaced from time to time. Finally it is poured onto a lead plate. The naphthalene is mechanically removed from the cake, which is allowed to solidify as thoroughly as possible and is then added in small pieces to ice water. The further isolation is not described; 5.2 g. of almost pure 1,5-naphthalenediamine, corresponding to a yield of 47% of the theoretical, were obtained. For the numerous details and reactions in the use of sulfonic acid esters, naphthols, naphthylamines, and naphthalene hydrocarbons, the original paper must be consulted. In a peculiar reaction which is also reported in Sachs' paper, unsubstituted naphthalene may also be converted into α-naphthylamine and 1,5-naphthalenediamine by melting with sodium amide; phenol must be added ·to the reaction mixture, and is converted to benzene during the process.

[9] F. Sachs, Ber., **39**, 3006 (1906).
[10] These abnormal substitutions are all of the same nature; i.e., the nucleus is exhibiting cation instead of anion reactivity. For a fuller explanation and further examples see Bradley and Robinson, J. Chem. Soc., **1932**, 1254, and Bradley, J. Chem. Soc., **1937**, 1091.

(b) By Replacement of Halogen by Amino Group

The reaction, $R \cdot X + NH_3 \rightarrow R \cdot NH_2 \cdot HX$, is general in the aliphatic series. It is restricted to a few but important cases in the aromatic series. Many other reactions occur subsequently to the primary reaction given above. Excess ammonia liberates primary amine from the addition product, which reacts anew with the alkyl halide to form a secondary amine. In the same manner tertiary amine is formed from the secondary, and from the tertiary, finally, a certain amount of quaternary ammonium halide. The components of the reaction mixture which form under all conditions are more easily separated pure the larger the radical R is, because the boiling points of the free bases are then quite different from one another. The secondary amines are easiest to produce in a pure state according to methods described below. Other mineral acid esters, especially dialkyl sulfates, may advantageously take the place of the halides. Since numerous special methods for the preparation of the important primary amines are known, which give better yields, it will suffice at this point to mention briefly only one method. Ethylamine may be prepared according to the older directions of Erlenmeyer and Carl [11] from potassium ethyl sulfate with 5% alcoholic ammonia by heating in an autoclave. See also Tafel. [12]

With aryl halides which will react with ammonia, the primary amine is the main product; see the preparation of picramide from 2,4,6-trinitro-chlorobenzene (picryl chloride) by Turpin. [13] According to Ullmann, [14] aromatic bound halogen which does not react with ammonia alone may be made to react by activation with copper powder or copper salts; several patents are based on this observation [15] for the preparation of p-phenylene-diamine from p-chloroaniline or p-dichlorobenzene. Since temperatures up to 200°C. are necessary for these reactions and since they progress slowly under these conditions, the method has no advantage for the laboratory; the phenylenediamines are more easily accessible by reduction of nitroanilines; see page 205. The method is apparently used frequently in industry, as is shown by numerous patents. Wohl [16] adapted the method for the laboratory by the addition of alkali iodide to the reaction mixture; the accelerating effect of the addition is probably caused by a temporary exchange of chlorine or bromine, which is bound to carbon, for iodine.

[11] Erlenmeyer and Carl, *Jahresber.*, **1875**, 617.
[12] Tafel, *Ber.*, **19**, 1926 (1886).
[13] Turpin, *J. Chem. Soc.*, **59**, 714 (1891).
[14] F. Ullmann, *Ber.*, **38**, 2120 (1905).
[15] German Patent, 202,170.
[16] A. Wohl, *Ber.*, **39**, 1951 (1906).

p-Nitroaniline is prepared by heating molecular amounts of *p*-chloronitrobenzene and sodium iodide with 15 moles of alcoholic ammonia in a sealed tube for 10 hours at 100°C.; the yield of *p*-nitroaniline is 66% of the theoretical.

The method is worth considering, to be sure, but it is expensive and not very convenient.

The direct exchange of halogen for the amino group is of greater importance in more complicated cases than it is for the preparation of the simple primary amines. For example, it is important for the preparation of amino acids and amino aldehydes, details for which will be discussed below (page 209). The direct method also has significance in the preparation of the simplest aliphatic diamine. According to Kraut,[17] ethylenediamine is obtained by heating ethylene dichloride with an excess of ammonia at 115° to 120°C. Fargher [18] later gave details of his experiences with this method and stated that considerable amounts of diethylenetriamine and triethylenetetramine are formed, a fact which is not surprising. For more details, Fargher's paper must be read. According to Groggins and Shirton,[19] the ammonolysis proceeds quantitatively, but the authors give no preparative details. Ethylenediamine is best prepared in the laboratory according to Gabriel's method through ethylenediphthalimide; see below. Marvel, Bailey, and Sparberg [20] give a method for the preparation of taurine, aminoethanesulfuric acid, details for which may be found in *Organic Syntheses*.[21]

Similar in formula, though different as far as the chemical reaction is concerned, is a method for the preparation of primary amines given by Gabriel.[22] According to this method the readily available potassium phthalimide is allowed to react with organic halides and the substituted phthalimide is hydrolyzed with hydrochloric acid to give phthalic acid and the hydrochloride of the primary amine. Most of the complications of the direct method are avoided; particularly, the formation of secondary and tertiary amines is naturally rendered impossible.

The method is capable of countless variations: Mono- as well as dihalo compounds can be treated with 1 or 2 moles of potassium phthalimide; almost all aliphatic halides, even of a very complicated composition, react readily; reactive groups present in the substituted phthalimides may be further changed before saponification.

The substituted phthalimides may be split with 20% hydrochloric acid either directly by boiling or by heating in a sealed tube. In other cases

[17] K. Kraut, *Ann.*, **212**, 253 (1882).
[18] G. Fargher, *J. Chem. Soc.*, **117**, 1351 (1920).
[19] Groggins and Shirton, *Ind. Eng. Chem.*, **25**, 42 (1933).
[20] Marvel, Bailey, and Sparberg, *J. Am. Chem. Soc.*, **49**, 1836 (1927).
[21] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 563.
[22] S. Gabriel, *Ber.*, **20**, 2224 (1887).

potassium hydroxide is used for the saponification according to Posner [23]; thus, acids of phthalamide are formed, which in turn are completely hydrolyzed with hydrochloric acid.

Potassium phthalimide is prepared according to Hale and Britton [24] in the following manner.

To a solution of 200 g. of phthalimide in 4000 cc. of alcohol is added a solution of 76 g. of potassium hydroxide in 300 cc. of 75% alcohol. The solution is cooled quickly, the crystals of potassium phthalimide removed by filtration, and the filtrate heated again. 200 g. of phthalimide are added and then again a solution of 76 g. of potassium hydroxide in 300 cc. of 75% alcohol. The solution is cooled again and filtered. The potassium phthalimide is slurried with acetone, filtered, and dried with gentle heating in air. A yield of 450 g. is obtained, corresponding to 90% of the theoretical.

As an example for Gabriel's synthesis the preparation of racemic ornithine, α, δ-diamino-n-valeric acid, is discussed according to E. Fischer [25] and Gabriel.[26] It takes the following course.

Potassium phthalimide with 1 mole of ethylene bromide yields bromo-ethylphthalimide which reacts further with sodium malonic ester to give diethyl β-phthalimidoethyl malonate:
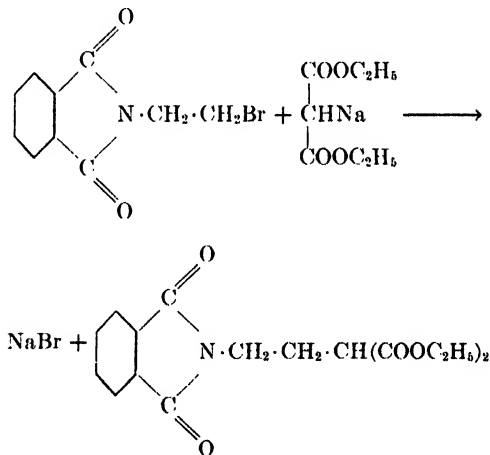
The hydrogen atom adjacent to the carboxyl groups in the substituted malonic acid, which can be obtained from the ester, may be replaced by bromine by the Volhard method, whereby α-bromo-δ-phthalimino-n-

[23] Posner, *Ber.*, **26**, 1858 (1893).
[24] W. Hale and E. Britton, *J. Am. Chem. Soc.*, **41**, 841 (1919).
[25] E. Fischer, *Ber.*, **34**, 2902 (1901).
[26] S. Gabriel, *Ber.*, **40**, 2647 (1907).

valeric acid is obtained while one carboxyl group is split off:

$$
\begin{array}{c}
\text{phthalyl ring structure} \\
\text{N} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CHBr} \cdot \text{COOH}
\end{array}
$$
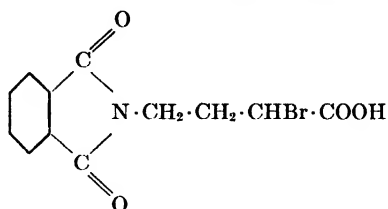
The value of the method lies in the possibility of introducing the bromine while, at the same time, the δ-amino group is protected by the phthalyl radical. This bromination is not possible when the amino group is free. The α,δ-diaminovaleric acid itself is then prepared in the usual manner, after the hydrolysis by the reaction with ammonia. According to Fischer, the bromination may also be carried out with the malonic ester. The bromine atom in the α position in the bromophthalimido acid may also be exchanged for an amino group.

The stability of the phthalimido derivatives permits many other subsequent reactions besides the ones mentioned above. For instance, if potassium phthalimide is treated with halogenated acid halides, it is not the chlorine at the carboxy group which reacts but the second chlorine atom. Thus, phthalimidocarboxylic acid chlorides are obtained, which may be changed by sodium malonic ester or by other alkali enolates to give β-keto acids or β-diketones, respectively, and finally, after hydrolysis, amino ketones. By use of carboxylic acid chlorides in the Friedel-Crafts reaction with aromatic compounds amino alkyl aryl ketones are obtained. Amino alcohols also can be prepared by Gabriel's synthesis; for instance, bromoethylphthalimide may be converted to ethanolamine with alcoholic potassium hydroxide. The yields obtained are good although the reaction is quite complicated. The bromine in bromoalkylphthalimides may, furthermore, be replaced by the mercapto group instead of the hydroxyl group. The mercapto group is introduced by treatment with potassium hydrogen sulfide and the compounds thus formed yield amino mercaptans upon saponification.

Sörensen [27] enlarged the scope of the synthesis still further, converting potassium phthalimide to phthalimidomalonic ester with bromomalonic ester:

$$
\text{phthalyl} \quad \text{NK} + \text{CHBr}(\text{COOC}_2\text{H}_5)_2 \longrightarrow \text{phthalyl} \quad \text{N} \cdot \text{CH}(\text{COOC}_2\text{H}_5)_2 + \text{KBr}
$$
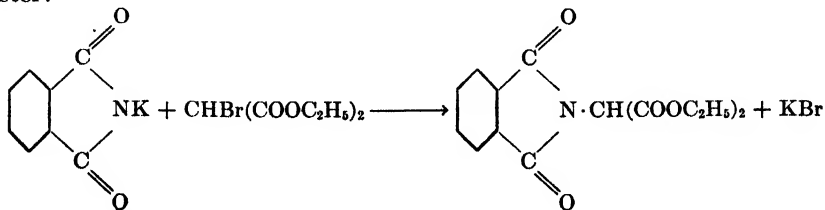
[27] Sörensen, *Chem. Zentr.*, 1903, **II**, 33.

This may be accomplished, for instance, by heating 210 g. of bromo-malonic ester with 165 g. of potassium phthalimide in an oil bath at 100° to 120°C. until the beginning of the reaction which then proceeds spontaneously to the end. After the material is cooled, the potassium bromide and unchanged potassium phthalimide are extracted with water. The residue is dried and crystallized first from benzene and then from absolute ethanol. 240 g. of phthalimidomalonic ester are obtained melting at 74°C. This corresponds to a yield of 80% of the theoretical; see also *Organic Syntheses*.[28]

The hydrogen atom in phthalimidomalonic ester can be substituted by sodium which in turn may be replaced by an aliphatic radical. Saponification leads through different intermediates to α-amino acids. Sörensen [29] calls attention to several facts which should be watched during the preparation of sodium phthalimidomalonic esters. The sodium compound must not segregate as a jelly nor in a coarsely crystalline state. Jelly-like products are difficult to separate from excess alcohol without decomposition and coarse, crystalline ones react with great difficulty. The sodium derivative is prepared as follows:

In a 500 cc. round flask equipped with a reflux condenser that has a calcium chloride tube at the top, 4.6 g. of sodium are dissolved in 80 to 100 cc. of alcohol freshly distilled from sodium. To this solution is added at a temperature of 60° to 70° C. a little more than the calculated amount (62 to 63 g.) of completely dry phthalimidomalonic ester which passes into solution when shaken, causing a yellow coloration. If the temperature is regulated exactly, the precipitation of the crystalline, yellow sodium compound starts soon. By continued shaking and suitable cooling crystals as fine as possible are obtained and the reaction is completed. The alcohol is removed by distillation in a vacuum with painstaking exclusion of moisture. At the end the temperature of the bath is increased to 140°C. The last traces of alcohol are removed by admitting dry, carbon dioxide-free air and by repeated evacuation.

Several detailed directions follow.

1. For the preparation of β-bromoethylamine according to Gabriel [30] a mixture of 100 g. of potassium phthalimide and 300 g. of ethylene bromide (3 moles) is boiled under a reflux with frequent shaking. After about 7 hours a syrup is obtained. Ethylene bromide is removed from the reaction mixture by distillation with steam. The viscous residue solidifies on cooling, the supernatant water is poured off, and the remaining compound is dissolved in 96% boiling alcohol. The filtered solution is allowed to cool; the crystals are filtered off and dried in air. The crude product, weighing 120 g., is extracted with 240 cc. of boiling carbon disulfide, leaving 8 g. of ethylenediphthalimide. Bromo-ethylphthalimide crystallizes from the filtered carbon disulfide solution and from the mother liquor after concentration. Thus, a total yield of 100 g. is obtained, corresponding to 73% of the theoretical.

[28] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 271.
[29] Sörensen, *Z. physiol. Chem.*, **44**, 454 (1905).
[30] S. Gabriel, *Ber.*, **22**, 1137 (1889).

According to Gabriel,[31] 20 g. of the bromoethylphthalimide are then heated in a sealed tube with 50 cc. of concentrated hydrobromic acid ($D = 1.49$) for 2 hours at 180° to 200°C. After the tube has been cooled, cold water is added, the solution is separated by filtration from undissolved phthalic acid, and the filtrate is evaporated to dryness on a steam bath. The dark colored residue solidifies on cooling and is recrystallized from 15 to 20 cc. of absolute ethanol. Thus, large crystals of bromoethylamine hydrobromide are formed together with a fine powder. The latter is decanted with the mother liquor and the crystals washed by decantation with cold absolute ethanol. The residue is then recrystallized from absolute ethanol. The free base is obtained from the hydrobromide by treatment with concentrated potassium hydroxide.

2. Preparation of cadaverine (pentamethylenediamine) according to Braun [32] is as follows:

For the preparation of cadaverine pure pentamethylene bromide (see page 277) may be used. But in this case it is not necessary to separate the benzonitrile present in the reaction mixture from the latter's preparation, and, therefore, benzoylpiperidine may be used as the starting material, as suggested by Braun.

Molecular amounts of benzoylpiperidine and phosphorus pentachloride are heated in a distilling flask, and the distillate shaken with ice water to destroy the phosphorus oxychloride. To this liquid, after it has been dried with calcium chloride, is added an excess of potassium phthalimide (2.5 moles), calculated on the basis of the benzoylpiperidine. The mixture is heated quickly, with stirring, in an open flask to 190° to 200°C., the mass melting to a brown viscous syrup which is heated for 1 to 2 hours at the given temperature. After the reaction mixture has been cooled, unchanged potassium phthalimide is extracted with boiling water, and the residue distilled with steam; benzonitrile and pentamethylene dichloride distil. The distillation residue is washed first with 50% alcohol, and then with absolute alcohol, which changes it slowly to a light powder. This is finally boiled with a generous amount of ethanol and the solution cooled and filtered. The residue is now dissolved in a large amount of chloroform and precipitated by alcohol. The crude product is recrystallized from a mixture of chloroform and ethanol and dried at 100°C. Pentamethylenediphthalimide, melting at 186°C., is obtained in a yield of 60 to 70% of the theoretical. This is heated in a sealed tube with 3 times its weight of concentrated hydrochloric acid for 2 hours at 200°C. Phthalic acid which separates on cooling is filtered off, and the filtrate evaporated to dryness on a steam bath. The residue is dissolved in water and again evaporated until all excess hydrochloric acid is removed. After the material is washed with alcohol and ether, an almost quantitative yield of pentamethylenediamine hydrochloride, melting at 255°C., is obtained.

3. Ing and Manske [33] suggest avoiding the preparation of potassium phthalimide by boiling phthalimide with the halide in the presence of potassium carbonate. They further suggest treating alkylphthalimides, which are hard to hydrolyze, with hydrazine hydrate. Thus phthalylhydrazide is formed and the organic base is set free. As an example directions follow for the preparation of benzylamine.

A mixture of 300 g. of phthalimide and 150 g. of dry potassium carbonate is heated under a reflux with 300 g. of benzyl chloride (20% excess) for 3 hours in an oil bath.

[31] S. Gabriel, *Ber.*, **21**, 567 (1888).
[32] J. v. Braun, *Ber.*, **37**, 3584 (1904).
[33] H. R. Ing and F. Manske, *J. Chem. Soc.*, **1926**, 2348.

Excess benzyl chloride is then removed by distillation with steam, and the residual benzylphthalimide filtered and washed with water. The yield amounts to 360 to 375 g.; the melting point, after recrystallization from glacial acetic acid, lies at 116°C. For the preparation of benzylamine, a suspension of finely powdered benzylphthalimide and an equimolecular amount of hydrazine hydrate in alcohol are heated. A gelatinous precipitate forms. This is decomposed by heating with excess hydrochloric acid and the phthalylhydrazide which separates is filtered and washed with water. The alcohol is removed by distillation from the filtrates. After cooling, the solution is filtered from a small amount of phenylhydrazide and the benzylamine is liberated with alkali and extracted with ether. The ethereal solution is dried with solid potassium hydroxide and fractionated; a yield of 90 to 95% of the theoretical is obtained. The boiling point of the benzylamine is 185° to 187°C.

4. Several other primary mono- and diamines can be prepared in exactly the same manner. As an example, directions for the preparation of ethylenediamine according to Putokhin [34] are given below.

Ethylenediphthalimide is prepared according to Gabriel [35] by heating 10 g. of potassium phthalimide with 12 g. of ethylene bromide for 2 hours at 200°C. The semiliquid mass which solidifies almost completely when cooled is extracted by boiling with a dilute solution of sodium hydroxide. The oily residue solidifies on cooling and is filtered off. It is dissolved in 50 cc. of boiling alcohol and the solution cooled, filtered from a small amount of contamination, and the filtrate evaporated to dryness. The residue consists of 8 g. of ethylenediphthalimide. Of this, 6.4 g. are saponified with a solution of 100 to 110 g. of potassium hydroxide in 300 cc. of water. The mixture is allowed to stand for 2 days with occasional shaking. The clear brownish solution thus obtained is distilled to dryness. The cooled residue is mixed with 100 cc. of water and distilled to dryness again. The combined distillates are neutralized with about 35 cc. of concentrated hydrochloric acid in 100 cc. of water, concentrated to 100 cc., and filtered. The volume is now reduced to 50 cc. and to the hot solution 30 cc. of alcohol are added. On cooling, filtering, and working up the mother liquor, a total yield of 25 g. of colorless crystals of the hydrochloride is obtained, corresponding to 95% of the theoretical. Ethylenediamine hydrate, boiling at 118°C., is obtained by decomposition of the hydrochloride with alkali, distillation, and drying with potassium hydroxide.

In a later paper Putokhin [36] changed his directions to adapt them to the method of Ing and Manske (see above). 250 g. of potassium phthalimide are ground together with 130 g. of potassium carbonate. This mixture is added to 190 g. of ethylene bromide and heated in a special apparatus to 185° to 195°C.

Anhydrous ethylenediamine can be obtained according to a method developed by Bailan.[37]

Finally, a paper by Putokhin [38] may be mentioned, in which he changes the synthesis of diamines according to Gabriel in that he splits the

[34] N. Putokhin, *Ber.*, **29**, 627 (1926).
[35] S. Gabriel, *Ber.*, **20**, 2225 (1887).
[36] N. Putokhin, *Chem. Abstracts*, **24**, 3756 (1930).
[37] Bailan, *J. Am. Chem. Soc.*, **56**, 955 (1934).
[38] N. Putokhin, *Chem. Abstracts*, **23**, 2938 (1929).

alkylenediphthalimides by distillation with alkali, instead of with hydrochloric acid under pressure.

Coleman and Hauser [39] showed that halogen may be replaced by the amino group in another way which, at first, appears to be quite cumbersome. According to the scheme, $R \cdot MgX + NH_2Cl \rightarrow R \cdot NH_2 + MgXCl$, Grignard compounds react with monochloroamine to form primary amines. The yields are consistently best if the Grignard compounds are prepared from chlorides. As both the Grignard compounds and the monochloroamine may be used as prepared, in ether solution, the method is greatly simplified. In order to give an idea of its possibilities, the method may be described here briefly.

Monochloroamine is prepared best, according to Coleman and Yager,[40] as follows:

200 cc. of 2 N sodium hydroxide solution are treated with the calculated amount of chlorine from a weighed quantity of dichromate and an excess of hydrochloric acid (see Marckwald and Wille [41]). The solution is cooled by adding pieces of ice. Then 200 cc. of a 1 N solution of ammonia, cooled to 0°C., are added. This mixture is immediately extracted with cold ether, one 100 cc. portion followed by three 50 cc. portions. The combined extracts are dried for a short time with calcium chloride. The concentration of monochloroamine in the solution may be determined in different ways: either 5 cc. are shaken for a short time in a closed bottle with 15 cc. of concentrated hydrochloric acid, the chlorine and ether are evaporated by gentle heating, and the remaining ammonium chloride is determined by the Kjeldahl method, or 5 cc. of the ethereal solution are shaken with an excess of sodium sulfite solution, the aqueous layer separated in a separatory funnel, and the excess sulfite titrated with permanganate after the solution has been acidified with nitric acid.

The Grignard solutions are prepared according to known methods. To make sure that an excess of Grignard reagent is present, the solutions are titrated according to Gilman (see page 374) before the calculated amount of monochloroamine solution is added. The addition is made with definite cooling. A precipitate is formed which changes to a gelatinous mass. When the reaction is completed, the flask is connected to a downward condenser with an adapter at its end dipping into dilute hydrochloric acid. The excess Grignard compound is destroyed by adding water dropwise, and the mixture is either directly treated with steam or is first acidified and then rendered alkaline again. The two layers of the distillate, the aqueous and the ethereal, are shaken well, and the

[39] G. Coleman and R. Hauser, *J. Am. Chem. Soc.*, **50**, 1193 (1928).
[40] G. Coleman and C. B. Yager, *J. Am. Chem. Soc.*, **51**, 567 (1929).
[41] W. Marckwald and M. Wille, *Ber.*, **56**, 1319 (1923).

solution of the amine hydrochloride is separated and evaporated to dryness. The further treatment of the distillation residue, which is always a mixture of ammonium chloride and of the desired amine hydrochloride, need not be described here. The yields given show great variations. Methylamine is not formed at all, because the usual side reaction, $R \cdot MgX + NH_2Cl \rightarrow R \cdot Cl + MgXNH_2$, becomes the main reaction in this case. The yields of different amines were as follows: n-butylamine 58.9%, benzylamine 85%, β-phenylethylamine 74%. Organo-magnesium chlorides were used as starting materials, as suggested above. Secondary and tertiary amines could also be obtained in yields of 60 to 70% of the theoretical. Experiments carried out with monobromoamide [42] gave poor results. For the preparation of secondary amines with alkyl chloramines see Coleman.[43]

(c) By Replacement of Hydroxyl by Amino Groups

In the aliphatic series, the replacement of the hydroxyl group by the amino group is of no practical importance. In the first place the reaction which is effected by heating the alcohol with zinc chloride-ammonia to high temperatures proceeds with such difficulty that the way through the halides is preferable under all conditions. Furthermore, in this method too, all the complications which were mentioned in the reaction of halides with ammonia arise. Merz and Gasiorovskii [44] obtained varying yields of amine mixtures by heating alcohols with zinc chloride-ammonia to 250° to 260°C.

Briner and Gandillon [45] by the use of a special apparatus systematically studied the removal of water from ammonia and methanol. They worked at atmospheric pressure and at elevated temperatures, that is 400°C. and over, and used catalysts such as clay, thorium oxide, silica gel, kaolin, and molybdenum blue. Aluminum oxide proved most effective. At 500°C. the methanol was converted almost quantitatively to a mixture of methylamines; 24% of the ammonia used was methylated. Monomethylamine 43%, dimethylamine 26%, and trimethylamine 31% were formed. By shortening the time of contact between the catalyst and the vapor mixture, less dimethyl- and more monomethylamine were formed. The exchange can be effected much more easily in the aromatic series.

1. In principle, almost all phenolic hydroxyl groups can be replaced by the amino group by heating phenols with zinc chloride-ammonia with the addition of a little ammonium chloride. Merz and Müller [46] in this

[42] G. Coleman, H. Sorcos, and C. B. Yager, *J. Am. Chem. Soc.*, **55**, 2075 (1933).
[43] G. Coleman, *J. Am. Chem. Soc.*, **55**, 3001 (1933).
[44] V. Merz and K. Gasiorovskii, *Ber.*, **17**, 623 (1884).
[45] E. Briner and J. Gandillon, *Helv. Chim. Acta*, **14**, 1283 (1931).
[46] V. Merz and P. Müller, *Ber.*, **19**, 2906 (1886).

manner converted phenol to aniline, naphthol to naphthylamine, and dihydroxynaphthalene to naphthalenediamine.

Pollak [47] described the preparation of *m*-aminophenol from resorcinol with ammonia and ammonium chloride alone; phloroglucinol changes to 5-aminoresorcinol even when treated with aqueous ammonia at room temperature. All these reactions, although they are interesting, have no importance from a preparative point of view. It will suffice to give an example, namely the preparation of *p*-nitrosoaniline from *p*-nitrosophenol according to Fischer and Hepp.[48]

1 part of *p*-nitrosophenol is mixed with 5 parts of ammonium chloride and 10 parts of dry ammonium acetate. A little ammonium acetate is then added and the mixture heated for 30 minutes on a steam bath. When added to cold water, *p*-nitrosoaniline separates from the dark green mixture in green crystals. A little more *p*-nitrosoaniline can be extracted with ether from the mother liquor. Upon recrystallization from benzene with the addition of charcoal, a yield of 50% of the theoretical is obtained. *p*-Nitroso-aniline forms steel-blue needles melting at 173° to 174°C.

The conversion of β-naphthol to β-naphthylamine in one of these ways was formerly used in industry. It takes place according to Graebe [49] even with gaseous ammonia under pressure. It is more successful with zinc chloride-ammonia or calcium chloride-ammonia with heating to 200° to 210°C. The yields are very good. They amount to 80% and only a little dinaphthylamine is formed, especially if calcium chloride-ammonia is used.

2. The naphthylamines may be obtained much more readily through the sulfurous acid esters of phenols; see Bucherer and collaborators.[50] The phenol sulfurous acid esters supposedly react in a tautomeric form, that is as ketone-bisulfite addition products, which explains the ease with which the reaction takes place. The method, when performed in the laboratory, calls for autoclaves equipped with stirrers, because the phenols do not dissolve in the ammonium hydroxide. For the preparation of β-naphthylamine from β-naphthol, Bucherer [51] gives the following directions.

100 g. of β-naphthol are well mixed with 150 cc. of a 40% solution of ammonium sulfite and 100 cc. of 20% aqueous ammonia. The mixture is put into an autoclave of 500 cc. capacity. The reaction proceeds best at temperatures between 100° and 150°C.; at higher temperatures increasing amounts of β-dinaphthylamine are formed. The end of the reaction may be recognized by the fact that the amount of β-naphthol no longer decreases (the reaction is not quantitative). The crude product is extracted with a dilute solution of sodium hydroxide in order to remove small amounts of β-naphthol, and the

[47] J. Pollak, *Monatsh.*, **14**, 401 (1893).
[48] O. Fischer and E. Hepp, *Ber.*, **21**, 684 (1888).
[49] C. Graebe, *Ber.*, **13**, 1850 (1880).
[50] Th. Bucherer *et al.*, *J. prakt. Chem.*, **80**, 201 (1909).
[51] Th. Bucherer, *J. prakt. Chem.*, **69**, 88 (1904).

residue is dissolved in dilute hydrochloric acid and filtered from any β-dinaphthylamine which may have formed.   The base is precipitated from the filtrate by sodium hydroxide.

(d) By Replacement of Other Groups by Amino Group

Besides halogen and hydroxyl, other groups also may be replaced under certain conditions by the amino group, above all the nitro and sulfo groups.   This holds true, of course, only if the substituents involved have been activated.   How important such reactions may become, under certain conditions, is shown by Kuhn's [52] synthesis of lactoflavin, vitamin B_2. As starting materials derivatives of 1,2-dimethyl-4-nitrobenzene were used; among others 1,2-dimethyl-4-nitro-5-bromobenzene and 1,2-dimethyl-4,5-dinitrobenzene:

$$
\begin{array}{ccc}
\text{CH}_3 & \quad & \text{Br} \\
& \bigcirc & \\
\text{CH}_3 & & \text{NO}_2
\end{array}
\quad \text{and} \quad
\begin{array}{ccc}
\text{CH}_3 & \quad & \text{NO}_2 \\
& \bigcirc & \\
\text{CH}_3 & & \text{NO}_2
\end{array}
$$
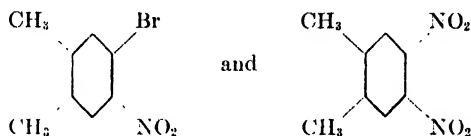
The bromine or one of the two nitro groups in these compounds reacts easily with ammonia or ammonia derivatives.   The retained nitro group may be reduced subsequently to an amino group; see Noelting.[53]

A complicated, although in some cases quite effective, introduction of the amino group into the aromatic nucleus by coupling with a diazonium compound, and reduction of the azo dye thus formed, occurs.   This reaction also played a rôle in the synthesis of lactoflavin, according to Karrer and Meerwein.[54]   The reaction is restricted to such cases in which the reductive cleavage does not cause any undesirable changes; see also page 229.

3. By Reduction of Nitrogen-Containing Compounds

In principle, almost all compounds (except the monosubstituted hydrazines) which contain nitrogen bound to 1 carbon atom only may be converted to primary amines; such compounds are nitro compounds, nitroso compounds, hydroxylamines, oximes, acid amides, nitriles, azo compounds, etc.   Any of the reduction methods may be employed for this purpose, more or less advantageously as the case may be.   By far the most important is the reduction of nitro compounds of the aromatic and heterocyclic series.

(a) Reduction of Nitro Group

The reduction of the nitro group to the amino group, one of the most important of all the typical reactions in organic chemistry, may be carried

[52] R. Kuhn, Angew. Chem., **49**, 6 (1936).
[53] Noelting, Ber., **35**, 628 (1902).
[54] P. Karrer and F. Meerwein, Helv. Chim. Acta, **19**, 264 (1936).

out almost without exception and with the best of yields.   Only the most important points about the course of the reaction may be reviewed here.

In the aromatic series monomolecular and dimolecular intermediates can be isolated; the former are nitroso and hydroxylamino compounds, the latter azoxy, azo, and hydrazo compounds.   The amino stage is always accessible from each of these intermediate steps by further hydrogenation.   From this fact it follows that primary aromatic amines are obtainable also if one of these intermediates can be prepared in any other way.   However, only azo compounds and azo dyes which can be obtained by coupling with diazonium compounds are of practical importance in this connection.

In the aliphatic series in which nitro compounds are generally more difficult to obtain than the corresponding primary amines, the reaction has importance only from the view-point of method.

Reducing Reagents and Methods

In principle, any known reducing reagent and method may be used. However, a more detailed description is necessary of all the methods which make possible reduction without attacking other sensitive groups, or the partial reduction of polynitro compounds.

1. Aliphatic Series.   Here complications arise most frequently.   Some reducing agents, such as stannous chloride, produce considerable amounts of hydroxylamines.   With zinc dust and glacial acetic acid, oximes or ketones may easily be formed; see Scholl.[55]

According to V. Meyer, iron filings with glacial acetic acid give the best results.   Catalytic reduction with nickel also proceeds readily; see Mignonac.[56]

2. Aromatic Series.   The reduction with tin or stannous chloride and hydrochloric acid may be considered the standard method for simple cases.   But even with nitrotoluenes the possibility of substitution with chlorine, in addition to the reduction, must be expected.   The course of the reaction has been studied little, but the complication presumably starts at the hydroxylamine step; see Bamberger.[57]   This side reaction becomes more pronounced if tin is replaced by cheap zinc; the latter, therefore, is not used.   Thus, according to the early investigations of Beilstein and Kuhlberg,[58] 2-amino-5-chlorotoluene is obtained from *o*-nitrotoluene.   Jannasch [59] prepared 1,4-dimethyl-2-amino-5-chlorobenzene from nitro-*p*-xylene.   Pinnow [60] suggested decreasing the over-

[55] R. Scholl, *Ber.*, **23**, 3492 (1890).
[56] G. Mignonac, *Bull. soc. chim.*, **7**, 154 (1910).
[57] E. Bamberger, *Ber.*, **35**, 3697 (1902).
[58] Beilstein and Kuhlberg, *Ann.*, **156**, 81 (1870).
[59] Jannasch, *Ann.*, **176**, 55 (1875).
[60] J. Pinnow, *J. prakt. Chem.*, **63**, 352 (1901).

voltage of hydrogen at the tin by addition of graphite; thus, the side reaction is supposedly depressed.

Iron is used in industry to a large extent to take the place of tin. Thus, only a fraction of the amount of hydrochloric acid otherwise used is sufficient for the preparation of aniline and of other compounds. Apparently the ferric chloride formed reacts with excess iron to produce ferrous chloride, which in turn effects further reduction, while ferric hydroxide separates. Since a mixture of a little aniline hydrochloride with much free base is obtained, less sodium hydroxide has to be used to set the amine free, and the process is therefore much cheaper. This method can also be used frequently in the laboratory. It has the further advantage of suppressing the formation of chlorine substitution products. West [61] gives the following directions.

1 mole of the nitro compound is brought to a boil with 500 cc. of methanol and 10 cc. of concentrated hydrochloric acid. Then 170 g. of iron filings are added in four parts at intervals of 5 minutes. The boiling and stirring must be vigorous in order to prevent the iron filings from caking together. The reaction is in most cases completed 2 hours after the last addition of iron. Steam distillation of the alkaline solution after the addition of 10 g. of sodium hydroxide gives first a clear methyl alcoholic, then a cloudy aqueous distillate, from which the free base is isolated. Alternatively, the hydrochloric acid is neutralized exactly with alcoholic sodium hydroxide, and the neutral solution is filtered while hot. The filter cake consisting of ferric hydroxide is washed with alcohol and the latter removed by distillation from the combined filtrates. The base is then isolated as the hydrochloride or in some other suitable manner.

This method offers advantages for the reduction of some halogen-containing nitro compounds as well as other compounds; thus, o-bromo-nitrobenzene when reduced with stannous chloride gives much aniline due to elimination of the bromine. However, according to the method of West, o-bromoaniline is obtained in a yield of 82% of the theoretical. p-Nitrobenzoic acid ester when reduced in strong hydrochloric acid solution yields much p-aminobenzoic acid, but by the above procedure an 80% yield of p-aminobenzoic acid ester is obtained.

Occasionally glacial acetic acid is used to advantage in place of hydrochloric acid, especially when the latter may have a hydrolytic effect as in the case of acetylated nitroamines; e.g., nitroacetanilide.

These acid reducing reagents are entirely sufficient for most cases. In addition, titanium chloride has been suggested; see Knecht, and Sachs and Sichel.[62]

The first reaction products obtained by reduction with tin are complex compounds which can sometimes be isolated easily and may thus be used advantageously for purification. Since nitro compounds are in most cases

[61] R. West, *J. Chem. Soc.*, **127**, 494 (1925).
[62] Knecht, *Ber.*, **36**, 166 (1903). Sachs and Sichel, *Ber.*, **37**, 1862 (1904).

but slightly soluble in aqueous reduction media, it is better under certain conditions to use organic solvents for the reaction. $SnCl_2 \cdot 2H_2O$ is especially suitable for such cases, because it is readily soluble in alcohol.

Among the alkaline reducing agents the following must be mentioned first: ammonium sulfide, sodium sulfide, and sodium hydrosulfide. Zinin [63] was the first to prepare aniline from nitrobenzene with ammonium sulfide. If hydrogen sulfide is passed into an alcoholic ammoniacal solution of nitro compounds, the reaction in many cases proceeds readily and smoothly even at room temperature. In other instances, however, the reaction has to be carried out in sealed vessels and at high temperatures. Willstätter [64] observed that during the reduction in the cold often only the hydroxylamine step is reached. Sodium sulfide, Na_2S, and sodium hydrosulfide, $NaHS$, may be substituted for ammonium sulfide, but ammonium hydrosulfide has no effect. Complications arise as soon as a nitro group or a halogen is present in an *o* position to a nitro group, for sulfur-containing compounds are formed by replacement of the *o* substituents. This method was almost completely neglected for a long time but in recent times has been used again to a larger extent. For special cases sodium disulfide, Na_2S_2, is suitable. It reacts according to the scheme, $R \cdot NO_2 + H_2O + Na_2S_2 \rightarrow R \cdot NH_2 + Na_2S_2O_3$. This method has the advantage that no sulfur is produced and that the amine formed is easily separated from the thiosulfate solution. However, no details are available except a patent [65] by Kunz. The solution of sodium disulfide is prepared as follows: 78 parts of anhydrous sodium sulfide are dissolved in 360 parts of water; the solution is brought to a boil and refluxed with 32 parts of sulfur. When crystallized sodium sulfide is used, a solution of 240 parts of it in 200 parts of water is treated in the same manner. After the addition of 123 parts of nitrobenzene to this solution and subsequent boiling, with stirring, for 12 hours, the reduction is complete.

As a further example the preparation of *p*-aminophenylacetic acid may be mentioned. It may be obtained from *p*-nitrophenylacetic acid by reduction with tin and hydrochloric acid, and with ferrous sulfate and ammonia, but neither of these methods is satisfactory. Robertson's directions, as given in *Organic Syntheses*,[66] show the superiority of the ammonium sulfide method.

Another alkaline reducing agent which is especially suitable for sensitive compounds, namely ferrous hydroxide, has been described by Claisen and coworkers.[67] Claisen's method was used chiefly with nitrocarboxylic

[63] Zinin, *J. prakt. Chem.*, **27**, 148 (1842); *Ann.*, **44**, 286 (1842).
[64] R. Willstätter, *Ber.*, **41**, 1936 (1908).
[65] Kunz, German Patent, 144,809.
[66] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 52.
[67] Claisen *et al.*, *Ber.*, **12**, 353, 1946 (1879).

acids of the aromatic series, for instance nitrobenzoylformic acid.   The acid is dissolved in the calculated amount of an· aqueous solution of barium hydroxide and, while warm, a solution of the calculated amount of ferrous sulfate is added.   More barium hydroxide solution is then added to precipitate all the iron and to render the solution alkaline.   As soon as the reaction is complete, the mixture of barium sulfate and ferric hydroxide is removed by filtration.   Excess barium is precipitated with carbon dioxide and the final filtrate now contains the barium salt of the desired amino acid.   In this case it is a matter of keeping the sensitive glyoxylic acid group intact, but in the reduction of other sensitive compounds, also, ferrous hydroxide has been found to have a similarly mild effect.   For example, m-amino-p-iodotoluene was obtained, even though not particularly smoothly, by the reduction of m-nitro-p-iodotoluene which, according to Willgerodt and Simonis,[68] reacts with the usual reducing reagents by splitting off iodine.

The reduction of nitrobenzaldehydes to the sensitive aminobenzaldehydes can also be successfully carried out with the same method.   The free nitrobenzaldehyde is less well suited for this reduction than the bisulfite compound.   On this subject only patents are available.[69]   The following procedure is that of Bamberger.[70]

To a suspension of 8 g. of o-nitrobenzaldehyde in a warm (90°C.) solution of 140 g. of ferrous sulfate in 244 cc. of water are added 3 cc. of 0.2 N hydrochloric acid.   An air condenser is attached to the flask and 25 cc. of concentrated ammonia are added while the flask is shaken in water at 90°C. for a few minutes until the green ferrous hydroxide has changed to yellow ferric hydroxide.   The same operation is repeated three times with portions of 10 cc. each of ammonia.   After each addition the change of ferrous to ferric hydroxide must be waited for.   Finally, the solution is rendered distinctly ammoniacal.   Isolation in the usual manner gives a yield of 75% of the theoretical.

Aluminum activated with mercuric chloride serves as a practically neutral reducing reagent; see Johnson and Guest.[71]

Sodium hydrosulfite, $Na_2S_2O_4$, according to Grandmougin,[72] is especially suitable for the preparation of the very sensitive aminophenols.

Of all the metal catalysts copper is best suited for the catalytic reduction of nitro compounds according to Sabatier.[73]   The copper catalyst is easy to prepare, since it is obtained from the oxide even below 180°C.   Furthermore, it is very resistant to catalyst poisoning and does not attack aromatic nuclei.   Therefore, hydrogenation according to this method has even been considered for industrial purposes.   According to a British pat-

[68] Willgerodt and Simonis, *Ber.*, **39**, 273 (1906).
[69] German Patents, 62,950 and 66,241.
[70] E. Bamberger, *Ber.*, **34**, 1330 (1901).
[71] Johnson and Guest, *Am. Chem. J.*, **43**, 310 (1910).
[72] Grandmougin, *J. prakt. Chem.*, **76**, 135 (1907).
[73] P. Sabatier, *Catalysis in Organic Chemistry*.   Van Nostrand, New York, 1923, p. 512.

ent [74] copper-coated pumice is preferable to copper. The former is prepared by reduction of copper oxide on pumice. The reduction temperatures lie a little higher than for nickel, mostly between 300° and 400°C. Aniline can be obtained from nitrobenzene with excess hydrogen in a yield of 98%. Correspondingly, toluidine can be prepared from nitrotoluene, and α-naphthylamine from α-nitronaphthalene at 330° to 350°C. Nitrochlorobenzenes also may be converted to chloroanilines at 360° to 380°C. Nitrophenols and nitroanilines can be reduced to aminophenols and phenylenediamine, respectively, according to Brown and Carrick.[75] The method, however, is not suitable for polynitro compounds and nitrobromobenzenes.

Recent investigations of Hein and Wagner [76] show that the preparation of polyamines from polynitro compounds by reduction with nascent hydrogen does not proceed satisfactorily. Thus, 2,4,6-triaminotoluene is best prepared by catalytic hydrogenation of trinitrotoluene with a palladium-barium sulfate catalyst.

20 g. of trinitrotoluene are dissolved in 500 cc. of 96% alcohol and this solution is added to 5 g. of previously reduced 1% palladium catalyst (see page 16), in a 1 liter shaking bottle. The calculated amount of hydrogen (about 19,500 cc.) is absorbed during 4 to 5 hours at a shaking frequency of 170 strokes per minute. The color of the solution turns to dark reddish brown and becomes olive-brown again towards the end of the reaction. After the addition of 1 g. of activated carbon suspended in 50 cc. of alcohol, the shaking with hydrogen is continued for an additional 30 minutes. After standing overnight under hydrogen, the solution is filtered in a stream of hydrogen and the clear yellow filtrate is evaporated at 20 to 30 mm. in a current of hydrogen in a water bath at 40°C. The yellowish brown, crystalline residue is dried for a short time over sulfuric acid in a desiccator and recrystallized from chloroform. The faintly yellow product is washed with a mixture of equal parts of alcohol and ether, then with pure ether, and dried in vacuo. A yield of 60% of the theoretical of triaminotoluene is obtained. Its melting point, determined in a bath preheated to 100°C., lies at 116.5° to 118°C.; in a bath preheated to 115°C., the product melts at 121°C.

The alcoholic solutions of the compound are very sensitive to air and turn dark brown rapidly. In the original paper details about the apparatus used can be found as well as reports on experiences with other polynitrobenzene derivatives, some of which could only be reduced to the diamino stage.

[74] British Patent, 5,692 (1915); *J. Soc. Chem. Ind.*, **35**, 920 (1916).
[75] Brown and Carrick, *J. Am. Chem. Soc.*, **41**, 436 (1919).
[76] F. Hein and F. Wagner, *Ber.*, **68**, 856 (1935).

Partial Reduction of Polynitro Compounds

Many reducing agents may be used for the partial reduction of poly-nitro compounds. Foremost among them are the alkali sulfides. *m*-Nitroaniline may be obtained as follows:

According to Brand,[77] 17 g. of dinitrobenzene are dissolved in 150 cc. of ethanol and the solution brought to a boil, the calculated amount of aqueous sodium hydrosulfide solution (1.5 moles = 8.5 g. of NaHS) is added slowly, and then the alcohol is removed by distillation and the nitroaniline isolated from the residue. The yield amounts to 13 g.

In industry, however, *m*-nitroaniline is prepared in a manner similar to that used for the reduction of aniline. *m*-Dinitrobenzene is reduced with the calculated quantity of iron for one nitro group and a small amount of hydrochloric acid. Only about 1% of phenylenediamine is formed, which is removed by boiling with water.[78] It is essential that the reduction be carried out in the presence of relatively little water to prevent the nitroaniline formed from passing into solution.

Occasionally, one or the other nitro group of several present in the benzene nucleus may be reduced to the amino group by suitable choice of the reducing agent. Anschütz and Heusler [79] observed, for instance, that ammonium sulfide converts 2,4-dinitrotoluene to 2-nitro-4-amino-toluene, while stannous chloride forms 2-amino-4-nitrotoluene.

Apparently ammonium sulfide generally attacks polynitro compounds in such a manner as to change only one nitro group. Zinc dust also may be used advantageously in some cases.

According to Schmidt,[80] 5 g. of 9-nitrophenanthrene are dissolved in 200 cc. of methanol. To this solution is added, in portions, a suspension of 10 to 12 g. of zinc dust in methanol. The mixture is boiled under a reflux while 100 cc. of a solution of ammonia in methanol are added in portions. After it has been boiled for 10 hours, the mixture is filtered. From the concentrated solution the 9-aminophenanthrene crystallizes.

(b) By Reduction of Nitroso Groups

The reduction of the nitroso group to the amino group is important, because (see page 259) the nitroso group can easily be introduced into the *p* position of tertiary amines, such as dimethylaniline. In this manner, from nitroso-*p*-dimethylaniline, for instance, the important asymmetrical dimethyl-*p*-phenylenediamine is obtained. True to expectation, the reduction proceeds under exactly the same conditions as does the reduction of the nitro group. As an example, one may compare, for instance, the preparation of aminodimethylaniline according to Gattermann-Wieland [81] and the preparation of aminothymol from nitroso-thymol as given in *Organic Syntheses*.[82]

[77] Brand, *J. prakt. Chem.*, **74**, 69 (1906).
[78] German Patent, 67,018.
[79] Anschütz and Heusler, *Ber.*, **19**, 2161 (1886).
[80] Schmidt, *Ber.*, **44**, 1498 (1911).
[81] Gattermann-Wieland, *Die Praxis des organischen Chemikers*. de Gruyter, Berlin, 1936, p. 313.
[82] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 512.

(c) By Reduction of Oximes

Almost all reducing agents which are used for nitro groups may be used for oximes also.   Whether or not the preparation through the oxime is advantageous can only be decided from case to case.   This method will frequently compete with the Hofmann degradation of acid amides whenever primary amines are to be prepared.   Thus, benzylamine may be prepared (other methods being discounted) on the one hand from benzaldoxime, on the other hand from phenylacetamide, the latter method, in this case, being preferable.   If, however, the aldehyde is more readily available than the next highest homologous acid, the oxime is the logical starting material.   Enanthaldoxime, for instance, may be reduced, according to Goldschmidt,[83] as follows:

4 g. of enanthaldoxime in 40 cc. of methanol are treated slowly at 40°C. with 150 g. of 2.5% sodium amalgam in small portions, glacial acetic acid being added to keep the solution acid.   After the reaction is completed, water is added and unchanged oxime (about 1 g.) is extracted with ether.   The solution, after extraction with ether, is rendered alkaline.   The n-heptylamine, which separates as an oil, is dissolved in hydrochloric acid and isolated as the hydrochloride.

In general oximes may be reduced to primary amines with nascent hydrogen also generated from sodium and alcohol.   For larger batches, at any rate, this method is preferable.   *Organic Syntheses*[84] gives directions for the preparation of n-heptylamine, which may be compared with Goldschmidt's method given above.

The reduction with sodium and alcohol may also be used for other oximes; thus, n-butylamine is obtained from n-butyraldoxime, *sec*-butylamine from methyl ethyl ketone oxime, and cyclohexylamine from cyclohexanone oxime.   The yields amount to 50 to 60% of the theoretical.

This reduction method has been employed especially in the hydroaromatic series; see Forster below for bornylamine.   It was found that the double bonds remain intact when zinc dust and glacial acetic acid are used, but that with sodium and alcohol the double bonds are partially or entirely reduced simultaneously.   Carvone oxime, for instance, when reduced according to Goldschmidt's method,[85] yields carvylamine containing two double bonds.   By the reduction with sodium and alcohol, however, a dihydrocarvylamine is obtained; see Wallach.[86]   For these reductions the position of the double bond relative to the oxime is, of course, important as is also its position in the ring system.   The electro-

[83] Goldschmidt, *Ber.*, 20, 729 (1887).
[84] A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. II, Wiley, New York, 1943, p. 318.
[85] Goldschmidt, *Ber.*, 30, 2069 (1897).
[86] Wallach, *Ann.*, 275, 119 (1893).

lytic reduction of oximes at lead cathodes according to Tafel and Pfeffermann [87] in some cases gives good yields of amines.

Several examples of the various methods follow.

α-Aminocamphor is prepared according to Claisen and Manasse [88] as follows: 9 g. of isonitrosocamphor are dissolved in 50 cc. of glacial acetic acid and 100 cc. of water in a flask with an air condenser. A total of 18 g. of zinc dust is added in small portions and, after the evolution of hydrogen has subsided, the mixture is heated for 1 to 2 hours on a steam bath and then filtered. The filtrate is diluted with water and sodium hydroxide is added to dissolve the zinc hydroxide. The aminocamphor which separates as oil is extracted with ether, and the ether dried with potassium carbonate and evaporated with the exclusion of carbon dioxide. A paraffin-like mass remains which can be purified by distillation, the product boiling at 243° to 245°C.

When camphor oxime is reduced, bornylamine and the stereoisomeric neobornylamine are formed simultaneously; see Forster. [89]

The so called isonitroso ketones also can be reduced to amino ketones; the latter are important for the pyrrole synthesis of Piloty and Hirsch; [90] see also H. Fischer and Kutscher. [91] The amino ketones appear also as intermediates in Knorr and Lange's [92] pyrrole synthesis which consists of simultaneous reduction of isonitroso compounds with keto-enols. The amino ketones which are especially important for the chemistry of pyrroles are aminoacetone, 3-amino-2-butanone, 4-amino-3-pentanone, and ω-aminoacetophenone; see Mannich and Hahn. [93] As an example, we give the preparation of aminobutanone by Diels and Jost [94]; see also Fischer and Orth. [95]

180 g. of isonitroso methyl ethyl ketone (biacetyl monoxime, see p. 267) are slowly added, with ice cooling and shaking, to a solution of 1000 g. of stannous chloride in 1000 cc. of concentrated hydrochloric acid. The cold reaction mixture is diluted with 7 to 8 liters of water and the tin removed by electrolysis. A lead plate is used as cathode, and a carbon rod as anode. The anode, surrounded by a porous cup which is filled with dilute hydrochloric acid, serves as a diaphragm. A current of 16 to 18 atmospheres is used, and the chlorine set free at the anode is sucked out of the porous cup. When, after some time, the evolution of hydrogen becomes stronger and the tin starts to separate at the surface in a mossy and no longer a dense form, the electrolysis is interrupted, the tin is removed by filtration, and the filtrate completely freed from tin with hydrogen sulfide. The solution is filtered again, the filtrate concentrated under reduced pressure in a water bath at 40° to 50°C., and the residue allowed to crystallize in an evacuated desiccator. Thus, 80 g. of aminobutanone hydrochloride are obtained.

[87] Tafel and Pfeffermann, *Ber.*, **35**, 1510 (1902).
[88] Claisen and Manasse, *Ann.*, **274**, 90 (1893).
[89] Forster, *J. Chem. Soc.*, **73**, 390 (1898).
[90] O. Piloty and P. Hirsch, *Ann.*, **395**, 70 (1913).
[91] H. Fischer and W. Kutscher, *Ann*, **481**, 199 (1930).
[92] L. Knorr and H. Lange, *Ber.*, **35**, 3007 (1902).
[93] Mannich and Hahn, *Ber.*, **44**, 1545 (1911).
[94] O. Diels and H. Jost, *Ber.*, **35**, 3292 (1902).
[95] H. Fischer and H. Orth, *Die Chemie des Pyrrols*. Vol. I, Akadem. Verlagsgesellschaft, Leipzig, 1934, p. 410.

The preparation of aminoacetone hydrochloride from isonitrosoacetone according to Fischer, Sturm, and Friedrich [96] is carried out in a similar manner.

Koessler and Hanke [97] improved the method of Kalischer [98] for the preparation of diaminoacetone from diisonitrosoacetone (see page 268) and give the following directions.

To a mixture of 400 g. of crystallized stannous chloride and 110 cc. of concentrated hydrochloric acid, which cools spontaneously, are added 15 g. of diisonitrosoacetone in small portions. A vigorous reaction ensues and sufficient cooling must be applied to keep the temperature below 35°C. Above this temperature decomposition sets in, but if the mixture is kept too cold reduction is incomplete. An additional 110 cc. of concentrated hydrochloric acid are added after 1 hour, almost all the tin chloride passing into solution, and another portion of 18 g. of diisonitrosoacetone is added in the course of another hour. Again 50 cc. of concentrated hydrochloric acid are added to the semi-solid mass of the complex compound of diaminoacetone hydrochloride and tin chloride and the light brown mixture is allowed to stand in the refrigerator overnight. It is then filtered on a Büchner funnel, and the cake washed with concentrated hydrochloric acid and then 95% alcohol until the excess stannous chloride is removed. The complex compound is dissolved in 1.8 liters of water and the solution saturated with hydrogen sulfide under pressure. The precipitated tin sulfide is removed by filtration and the filtrate evaporated to dryness in a vacuum at 60° to 80°C. The residue consists of 37 to 41 g. of colorless or faintly yellow, crystalline diaminoacetone dihydrochloride, which still contains some free hydrochloric acid.

Ruzicka, Goldberg, and Hürbin [99] converted the oximes of higher ring ketones, that is cyclooctanone and cyclopentadecanone oximes as well as the dioxime of cyclotriacontane-1,16-dione, to the corresponding amines with nascent hydrogen. The properties of these compounds are normal.

The catalytic reduction of aldoximes and ketoximes, which has apparently been little used for preparational purposes, is described in detail in Sabatier's book.[100]

(d) By Reduction of Acid Amides

There are few details in the literature on the catalytic hydrogenation of acid amides, which, according to the equation, $R \cdot CONH_2 + 2H_2 \rightarrow H_2O + R \cdot CH_2 \cdot NH_2$, should be a simple means of preparing many valuable products. Mailhe,[101] it is true, stated that acetamide and propionamide can be reduced to a mixture of alkyl and dialkyl amines by Sabatier's method, but the method has not gained any importance. Adkins and Wojcik [102] carry out the reduction under pressure using a copper-

[96] H. Fischer, E. Sturm, and H. Friedrich, *Ann.*, 461, 245 (1928).
[97] K. Koessler and Th. Hanke, *J. Am. Chem. Soc.*, 40, 1718 (1918).
[98] Kalischer, *Ber.*, 28, 1519 (1895).
[99] L. Ruzicka, W. Goldberg, and M. Hürbin, *Helv. Chim. Acta*, 16, 1339 (1933).
[100] Sabatier, P., *Catalysis in Organic Chemistry*. Van Nostrand, New York, 1923, pp. 383–384.
[101] Mailhe, *Bull. soc. chim.*, 35, 614 (1906).
[102] H. Adkins and B. Wojcik, *J. Am. Chem. Soc.*, 56, 247 (1934).

chromium oxide catalyst and dioxane as the solvent. They explain the favorable effect of dioxane by the fact that it takes up the water formed in the reaction, thus cutting down on the amount of hydrolysis. Secondary amines are the main by-products. For instance, 36 g. of α-phenyl-butylamine and 13 g. of di(α-phenylbutyl)amine were obtained from 54 g. of α-phenylbutyramide in 125 cc. of dioxane with 10 g. of catalyst in 2 hours at 250 atmospheres pressure and 250°C.

(e) By Reduction of Nitriles

The reduction of the cyano group does not proceed uniformly at all, either with nascent or with catalytically excited hydrogen. The reason for this is obvious: the extremely reactive aldimines formed by the addition of 1 hydrogen molecule react faster in certain other ways than they can be reduced further to primary amines. The most important of these subsequent reactions is the formation of secondary amines. No simple reaction scheme can be given, for free ammonia is also formed and causes further trouble.

According to Sabatier and Senderens' method [103] secondary amines can be obtained in fairly good yields from aliphatic nitriles, but primary and tertiary amines always have to be expected as by-products. Many attempts have been made, of course, to find such reaction conditions as would produce primary amines in good yield. Other methods, it is true, lead to the common primary amines, e.g. the Hofmann degradation of acid amides, but for some substituted primary amines, such as α-hydroxy-amines, the hydroxy- or ketonitriles are advantageous starting materials. By a method suggested by Kindler [104] β-hydroxyamines may be prepared by reduction of α-hydroxy- or ketonitriles. It deviates from the usual catalytic methods in one principal point; namely, that the solution containing the compound to be hydrogenated is added dropwise to a suspension of the catalyst. The purpose of this procedure is immediately to complete the hydrogenation to the amino step, so that neither unchanged nitrile nor intermediates can accumulate. The yields are very satisfactory. The apparatus used is pictured in Fig. 6. A few examples of the method follow:
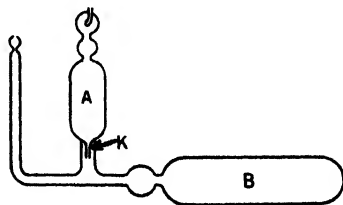
FIG. 6.—Apparatus for the hydrogenation according to Kindler.

Into the reaction bulb B are put 2 g. of palladium black suspended in 100 cc. of glacial acetic acid and 4 cc. of concentrated sulfuric acid. A solution of 20 g. of acetylmandelic nitrile in 100 cc. of glacial acetic acid

[103] Sabatier and Senderens, Compt. rend., 140, 482 (1905).
[104] K. Kindler, Ber. deut. pharm. Ges., 269, 74 (1931).

in funnel A is added dropwise through the capillary K to the suspension during 2 hours. The solution to be hydrogenated must not be added until bulb B is filled with hydrogen. In order to prevent a premature addition of the solution, nitrogen is admitted through the delivery tube of B while A is being filled. Then the entire apparatus is evacuated by a water pump connected to the delivery tube of container A, before hydrogen is admitted.

By means of this apparatus it is also possible to admit the compound to be hydrogenated slowly and under high pressure if both tubes leading to A and B respectively are connected to the same gas holder. Thus, to the hydrogen pressure in A is added the head of the liquid column.

For the reduction of benzoyl cyanide according to Kindler and Peschke [105] 2 g. of palladium black and 75 cc. of glacial acetic acid were put into B; to this suspension a solution of 20 g. of benzoyl cyanide in 250 cc. of glacial acetic acid was added dropwise through K over a period of 2 hours. The addition took place at 18°C. and at 2 atmospheres, with continuous shaking. After the addition was finished, the shaking was continued until no more hydrogen was absorbed. 6 atoms of hydrogen were used for each mole of benzoyl cyanide. The catalyst was removed by filtration, the filtrate evaporated under diminished pressure at 30°C., and the residue was first treated with water and then with an excess of a concentrated solution of potassium hydroxide. The amine, which separated as an oil, was extracted with benzene and the benzene solution, after short drying with potassium hydroxide, was evaporated under diminished pressure. The residue was dissolved in ether and the solution evaporated again in a vacuum. Thus, beautiful crystals of β-hydroxy-β-phenylethylamine were obtained, after filtration and washing with ether, in a yield of 70 to 80% of the theoretical. The melting point was 57°C. and was not changed by recrystallization from benzene.

Rupe and coworkers [106] made extensive, systematic investigations on the catalytic reduction of cyano compounds with a nickel catalyst, without stressing the preparative aspect in their work.

Carothers and Jones,[107] as well as Carothers, Bickford, and Hurwitz,[108] obtained good results with glacial acetic acid and acetic anhydride when they used platinum oxide, prepared according to Adams, as a catalyst. The formation of secondary amines could almost always be thoroughly suppressed especially by the use of acetic anhydride as a solvent, since under these circumstances not the free amines but their acetyl derivatives are obtained. A solution of 23.4 g. of benzyl cyanide in 50 cc. of acetic anhydride, in the presence of 1.2 g. of catalyst (added in two portions), absorbed a total of 115% of the theoretical amount of hydrogen during 22 hours. From the reaction mixture 15.2 g. of β-phenylethylamine could

[105] Kindler and Peschke, *Ber. deut. pharm. Ges.*, 269, 592 (1931).
[106] H. Rupe *et al.*, *Helv. Chim. Acta*, 8, 338 (1925); 10, 859 (1927); 13, 457 (1930); 18, 1190 (1935).
[107] W. H. Carothers and A. Jones, *J. Am. Chem. Soc.*, 47, 3051 (1925).
[108] W. H. Carothers, Bickford, and Hurwitz, *J. Am. Chem. Soc.*, 49, 2912 (1927).

be isolated in the usual manner by hydrolysis with acid. This corresponds to a yield of 63% of the theoretical. Other carboxylic acid anhydrides were also used in place of acetic anhydride, for instance, butyric anhydride. The method proved to be very satisfactory for the preparation of higher homologues of phenylethylamine up to the ε-phenyl-n-amylamine. The amount of catalyst used for this method is still relatively high and it is suggested that fresh portions be added as soon as the speed of hydrogenation decreases.

Graf [109] reported a new chemical method for the conversion of nitriles to primary amines, in which chromous acetate is used as reducing agent. The method has a rather wide range of usefulness and is illustrated by the reduction of benzonitrile.

An aqueous solution of 150 g. of potassium dichromate is first reduced with alcohol and hydrochloric acid to chromic chloride, and then further to chromous chloride by shaking with granulated zinc. Chromous acetate is precipitated with a concentrated aqueous solution of sodium acetate, filtered, washed with water, and placed in a flask equipped with a stirrer and a reflux condenser. The reducing agent is covered with 500 cc. of alcohol, 15 g. of benzonitrile are added, and at boiling temperature, while hydrogen is passed through, an aqueous solution of 80 g. of potassium hydroxide is added dropwise. The red chromous acetate changes to green chromic hydroxide. The mixture is acidified and distilled with steam, thus removing alcohol and unchanged benzonitrile. The residue is rendered strongly alkaline and again distilled with steam as long as any bases pass over. The distillate is acidified with hydrochloric acid and evaporated to dryness on a steam bath. The hydrochlorides are decomposed with strong potassium hydroxide solution, the amines extracted with ether, and the ether extract dried with potassium hydroxide and distilled. 4 g. of benzylamine are obtained, boiling at 65° to 66°C. at 10 mm., and 1 g. of dibenzylamine boiling at 150°C. at the same pressure. Acetonitrile (33 g.) when reduced in a similar manner yielded 6 g. of ethylamine, but no diethylamine.

The yields are not very satisfactory but they are of the same magnitude even in complicated cases. For example, from 12 g. of 2,6-dichloro-4-cyanopyridine a yield of 4.5 g. of 2,6-dichloro-4-pyridylaminoethane was obtained. Thus, the method may be used to advantage when catalytic reduction might remove halogen from the nucleus.

(f) By Reduction of Azo Compounds

This method is especially suited for the preparation of aminonaphthols and is preferable to reduction of nitrosonaphthols. Thus, 1,2-aminonaphthol, the starting material for the preparation of o-naphthoquinone, is prepared from the dye, orange II, according to the following scheme:
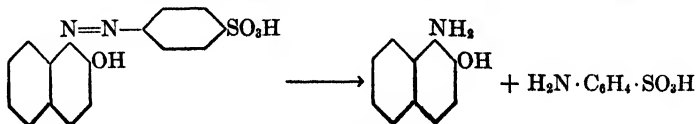
[109] R. Graf, J. prakt. Chem., 140, 39 (1934).

Apparently it is not advantageous to start from the isolated dye. Fieser [110] obtained better results than earlier workers by using a product which was freshly prepared by coupling diazotized sulfanilic acid with β-naphthol. Details of the procedure may be found in *Organic Syntheses.*[111]

1,2-Aminonaphthol can also be prepared from α-nitrosonaphthol, as mentioned above; see for instance, Zincke.[112] The isomeric 1,4-amino-naphthol, however, can be prepared advantageously only from Orange I in a very similar manner; see *Organic Syntheses.*[113]

4. Other Methods

Primary amines of the type of α-phenylethylamine may be prepared by the method of Leuckart [114] which was later improved by Wallach.[115] The reaction proceeds according to the following scheme.

$$R \cdot CO \cdot CH_3 + 2CHOONH_4 \longrightarrow R \cdot CH \cdot CH_3 + 2H_2O + NH_3 + CO_2$$
$$NH \cdot CHO$$
$$R \cdot CH(NHCHO) \cdot CH_3 + H_2O \longrightarrow R \cdot CH(NH_2) \cdot CH_3 + HCOOH$$
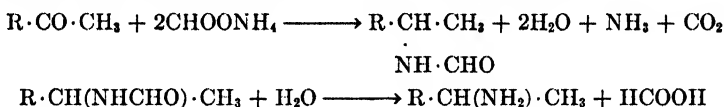
Organic Syntheses [116] gives details for a modern procedure.

A synthesis of ω-amino acids, useful in certain cases, starts from the oximes of alicyclic ketones which change to the lactams when subjected to the Beckmann rearrangement. Cyclohexanone oxime, for instance, yields the lactam of ε-aminocaproic acid, 2-ketohexamethyleneimine:

$$
\begin{array}{ccc}
CH_2 & & CH_2\text{---}CO \\
CH_2 \quad C{=}NHO & \longrightarrow & CH_2 \qquad NH \\
CH_2 \quad CH_2 & & CH_2 \\
CH_2 & & CH_2\text{---}CH_2
\end{array}
$$
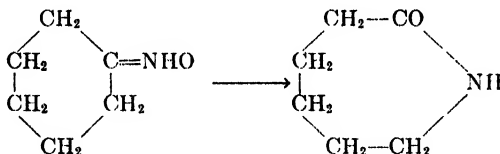
From these lactams the amino acids are obtained by simple hydrolysis. Since cyclohexanone and cyclopentanone are cheap commercial products today, the method is probably superior to all other methods used formerly. Wallach [117] was the first to use it for the preparation of ε-amino-caproic acid. *Organic Syntheses* presents the method in detail.[118]

[110] L. Fieser, *J. Am. Chem. Soc.*, 57, 491 (1935).
[111] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 35.
[112] Th. Zincke, *Ann.*, 278, 188 (1894).
[113] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 39.
[114] Leuckart, *Ber.*, 22, 1409 (1889).
[115] Wallach, *Ann.*, 343, 60 (1905).
[116] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 503.
[117] Wallach, *Ann.*, 312, 188 (1900).
[118] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 28.

Preparation of Methylamine

Gattermann-Wieland [119] gives the following directions, based on a method of Brochet and Cambier.[120]   A mixture of 250 g. of ammonium chloride and 570 g. of a 35% aqueous formaldehyde solution is heated in a distilling flask which has a downward condenser and a thermometer dipping into the liquid.   The temperature is slowly raised to 104°C. and kept there for $4\frac{1}{2}$ hours.   100 to 120 g. of aqueous methanol condense. After the distillation residue has cooled, the crystallized ammonium chloride is removed by filtration and the filtrate concentrated to 0.5 its volume by evaporating on a steam bath.   The solution is filtered again and concentrated until crystallization starts.   The crystallized methylamine hydrochloride is filtered with suction, the filtrate concentrated as far as possible, and the residue allowed to stand in a desiccator over sulfuric acid and sodium hydroxide.   The combined residues are extracted with chloroform to remove secondary and tertiary amine hydrochlorides. Upon filtration by suction and drying, 110 to 125 g. of methylamine hydrochloride are obtained.

Methylamine prepared in this manner (see *Organic Syntheses* [121]) is never entirely free of ammonium chloride; neither is the commercial product.   Sharp and Salomon [122] suggest a purification method suitable for the laboratory.

One-tenth of the amount of methylamine hydrochloride to be purified is treated with alkali and the bases set free are collected in water.   To this solution is added a cold aqueous solution of the remaining nine-tenths and the volatile parts distilled.   This operation is repeated.   One-tenth of the solution containing the hydrochlorides is made alkaline and then distilled and the distillate combined with the residual nine-tenths, etc. If the aqueous solution of the hydrochloride is now concentrated, methylamine hydrochloride, 99.5% pure, is obtained which may be freed from ammonium chloride by recrystallization from water to give a product of any desired degree of purity.   Common methylamine hydrochloride contains about 5% of ammonium chloride and cannot be purified well by recrystallization.   The principle of the purification method described above is based, of course, on the well known fact that ammonium chloride in aqueous solution is hydrolyzed a little more than methylamine hydrochloride.   If the hydrochloric acid present is insufficient, ammonia for the most part distils.   The ratio of the fractional amount, used for the

[119] Gattermann-Wieland, *Die Praxis des organischen Chemikers.*   de Gruyter, Berlin, 1936, p. 269.
[120] A. Brochet and R. Cambier, *Bull. soc. chim.*, **13**, 533 (1895).
[121] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 347.
[122] M. Sharp and W. Salomon, *J. Chem. Soc.*, **1931**, 1477.

alkali treatment, to the total amount of hydrochloride depends on the degree of purity of the starting material. In the example described a contamination of 5% of ammonium chloride was assumed.

B. Secondary Amines [123]

1. By Addition to Ethylene Bond

An example for this reaction, which is important in special cases, is the addition of monoalkyl amines to mesityl oxide, described on page 178 in another connection.

2. By Exchange

(a) From Halides and Amines

If the compounds discussed in the preceding chapter, that is halides, hydroxyl compounds, etc., are made to react with primary amines instead of with ammonia, the reaction mixtures contain secondary amines in varying amounts, depending on the conditions of the reaction. A generally useful method is available for the isolation of the secondary amines with aliphatic, fatty aromatic, or purely aromatic compounds. By treatment with nitrous acid the primary amines are converted to alcohols or diazonium salts, the secondary to nitrosamines, while the tertiary amines remain unchanged. Upon extraction with ether the tertiary amines and the diazonium salts remain in the acid solution. Phenols which may possibly form pass into the ether, while alcohols are distributed between the two phases according to their molecular weights. In the ether extract, therefore, are mainly phenols, alcohols, and the neutral nitrosamines. Phenols can be extracted with alkali. The nitrosamines can readily be converted to secondary amines by elimination of the nitroso group. The secondary amines may then be purified without any difficulty. As an example the preparation of monoethylaniline as described by Erdmann [124] is given.

A mixture of 100 g. of aniline and 130 g. of ethyl bromide is heated gently under a reflux for 2 hours. The reaction mixture becomes almost completely solid on cooling. It is dissolved in water and a small amount of excess ethyl bromide is removed by boiling. 300 cc. of a 20% solution of sodium hydroxide are then added and the oily layer of the mixture of bases is separated. The aqueous layer is extracted with ether and the extract combined with the main crop. The ether is then removed by distillation on a steam bath and the residue is dissolved in a mixture of 200 cc. of concentrated hydrochloric acid and 1000 cc. of water. The mixture is cooled well with ice and 60 g. of sodium nitrite are added. The ethylphenylnitrosamine, which separates as a dark oil, is dissolved in

---

[123] Besides the methods given in this section, there are two recent methods which give excellent results. One is a modified Leuckart synthesis (see page 230) [Novelli, *J. Am. Chem. Soc.*, **61**, 520 (1939)] and the other the reduction of aldimines [Henze and Humphreys, *J. Am. Chem. Soc.*, **64**, 2878 (1942), and Campbell, Sommers, and Campbell, *ibid.*, **66**, 82 (1944)].

[124] H. Erdmann, *Anleitung zur Darstellung organischer Präparate.* Stuttgart, 1894.

ether, leaving the phenyldiazonium salt formed from unchanged aniline in the aqueous solution. As a precautionary measure, the ether may be extracted with a sodium hydroxide solution. The ether is then evaporated and the oily residue added to a solution of 350 g. of stannous chloride in 400 cc. of concentrated hydrochloric acid. Cooling with water is applied when necessary. The mixture is then rendered alkaline with sodium hydroxide and distilled with steam. The distillate is extracted with ether, which, after separation, is dried with potassium hydroxide. Upon distillation 40 to 50 g. of monoethylaniline, boiling at 205°C., are obtained. Pure monoethylaniline shows no color reaction with calcium hypochlorite solution.

Furthermore, secondary fatty aromatic amines may be prepared according to a method quite similar to the phthalimide method of Gabriel. In the monoacyl derivatives of the aromatic series, $R \cdot NH \cdot CO \cdot CH_3$, the hydrogen atom on the nitrogen has an acid nature like that in phthalimide and may be substituted by alkali metal. Sodium acetanilide, to which is ascribed a structural formula derived from a tautomeric form,

$$C_6H_5 \cdot N : C \underset{ONa}{\overset{CH_3}{<}}$$
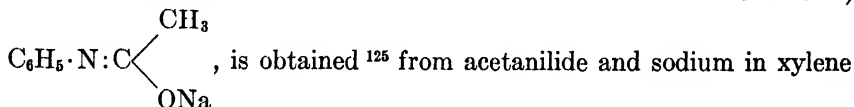
, is obtained [125] from acetanilide and sodium in xylene solution. The sodium compound is treated according to the method of Paal and Otten [126] with an alkyl iodide and the N-alkylacetanilide thus obtained is subsequently saponified.

Hickinbottom [127] gives directions for the preparation of tertiary alkyl anilines which were unknown up to that time; see Nef.[128]

According to Hickinbottom, 80 g. of tertiary butyl iodide are mixed with 81 g. of aniline in a flask equipped with a reflux condenser. The gases generated during the reaction are collected over water. After about 6 minutes a vigorous evolution of gases starts and the flask must be shaken continuously in order to avoid loss of liquid. A total of about 5 liters of isobutylene is collected during 26 minutes. A brownish solid mass remains in the flask which, on addition of a sodium hydroxide solution, yields a mixture of aniline and tertiary butylaniline. The oil layer is dried and fractionated in order to remove the greater part of the aniline.

The high boiling part of the oil is suspended in water and acetic anhydride added, with stirring, until the odor of acetic anhydride persists distinctly for 3 to 4 minutes. After several hours excess sodium carbonate is added and the tertiary butylaniline removed by distillation with steam from the acetanilide. The distillate is extracted with ether, and the ether solution is dried with potassium hydroxide and fractionated. From 5.5 g. of starting material 22 g. of fairly pure tertiary butylaniline distilling at 203° to 206°C. are obtained. It is purified through the hydrochloride or the picrate. The boiling point lies at 214° to 216°C. at 753 mm. (corrected).

A yield of 7.15 g. of tertiary amylaniline was obtained from 27 g. of tertiary amyl iodide and 40 g. of aniline. The boiling point of tertiary amylaniline is 227.5° to 229.5°C. at 744 mm. (corrected).

[125] P. Hepp, *Ber.*, 10, 328 (1877).
[126] C. Paal and G. Otten, *Ber.*, 23, 2587 (1890).
[127] W. J. Hickinbottom, *J. Chem. Soc.*, 1933, 946.
[128] U. Nef, *Ann.*, 309, 164 (1899).

Preparation of Dimethylamine

According to Werner [129] a mixture of 200 g. of ammonium chloride and 400 g. of a 40% solution of formaldehyde is slowly heated in a distilling flask to 104°C. The temperature, taken on an internal thermometer, is kept at 104°C. until nothing more distils (about 4½ hours). The reaction mixture is poured out of the distilling flask and allowed to cool and the crystals of ammonium chloride are filtered with suction. The filtrate is heated anew with 300 g. of formaldehyde solution, this time to 115°C. When no more distillate comes over at this temperature (about 3½ hours), the reaction mixture is concentrated in a vacuum at 100°C. to incipient crystallization. When the material is cooled, a mixture of ammonium chloride and monoethylamine hydrochloride separates and is removed by filtration. The filtrate is heated to 120°C. in an open dish until a sample, when cooled, solidifies almost completely to a crystalline mass. The crystals are allowed to stand for 2 days in a vacuum over sodium hydroxide; they are then completely extracted with chloroform from a small amount of trimethylammonium chloride. On concentration of the chloroform solution 122 g. of almost pure dimethylamine hydrochloride are obtained.

(b) By Hydrolysis of Nitrosamines

A method which is in some cases quite well suited for the preparation of secondary amines of the aliphatic series is based on the fact that *p*-nitrosodialkyl anilines may be split readily and smoothly with aqueous alkali to yield nitrosophenol and dialkyl amines. The reaction is carried out at the boiling point of the solution, the amine distilling out as formed. For the simple members of the series there are more convenient and cheaper methods of preparation. This method is especially good for the preparation of mixed amines, because some of the monoalkyl anilines can be obtained commercially, while others are quite readily available, according to the method described above, and can easily be converted to the desired tertiary amine; see below. For the preparation of nitrosodimethylaniline, see page 260. Only one example follows; that is, the preparation of dimethylamine according to Baeyer and Caro [130]; see also Menschutkin.[131]

75 g. of crude nitrosodimethylaniline hydrochloride and a solution of 100 g. of sodium hydroxide in 4 liters of water with a few zinc chips are boiled in a 6 liter flask. The distillate is collected in two receivers each containing 75 cc. of concentrated hydrochloric acid. The tube connecting the receivers dips into the hydrochloric acid at both ends, so that, when the distillate drips onto the acid, the latter is prevented from backing up.

[129] E. A. Werner, *J. Chem. Soc.*, 111, 850 (1917).
[130] Baeyer and Caro, *Ber.*, 7, 964 (1877).
[131] Menschutkin, *Chem. Zentr.*, 1898, II, 478.

After 2 to 3 hours all the dimethylamine has distilled and the contents of the receivers are evaporated to dryness. The residue is distilled again with sodium hydroxide solution to remove a small amount of dimethylnitrosoaniline, and the distillate is collected in hydrochloric acid as before. Upon concentration, dimethylamine hydrochloride crystallizes, and more is precipitated from the mother liquor with alcohol. The free base is obtained by adding 50% potassium hydroxide solution dropwise to the hydrochloride, the vapors being dried in a calcium oxide tower and condensed in a freezing mixture. The boiling point is 9°C.

From the alkaline solution remaining after the dimethylamine has distilled, p-nitrosophenol may be isolated (see page 260).

C. Tertiary Amines

The preparation of tertiary amines from ammonia and alkyl halides is generally not worth while. A number of better methods of preparation are available for important members of this series. However, the method offers a convenient way through the primary and secondary amines to the desired products. In principle, it is in all respects similar to the method given above for monoethylaniline; therefore it need be discussed only briefly with a few examples. It is not worth while to prepare dimethyl- and diethylaniline in this way in the laboratory. Walter [132] gives details for the manufacture of dimethylaniline on a big scale.

A mixture of 78 kilos of methanol, 80 kilos of aniline, and 8 kilos of concentrated sulfuric acid is heated in an autoclave so that a pressure of 28 to 30 mm. is maintained. The reaction is finished in 9 to 10 hours. After the addition of sodium hydroxide, the amine is distilled with steam from the autoclave.

Commercial dimethylaniline may be purified in different ways: by repeated recrystallization at low temperature (m.p. 2.5°C.),[133] by treating it several times in small portions with concentrated sulfuric acid and removing the separated aniline sulfate by filtration,[134] or by recrystallization of its hydrohalides, especially of dimethylaniline hydriodide.

An interesting commercial method for the preparation of diethylaniline (see Knoevenagel [135]) is given in the following directions adapted for use in the laboratory.

A mixture of 18.6 g. of aniline, 36.8 g. of ethanol, and 0.5 g. of iodine is heated in an autoclave for 10 hours at 220° to 230°C. Upon direct fractionation of the reaction mixture the diethylaniline distils at 213° to 222°C. after a little forerun of ether, ethanol, and water. The crude yield of 28.4 g. is treated with acetic anhydride, whereby any monoethylaniline is converted to N-ethylacetonilide. On refractionation 25.9 g. of diethylaniline, boiling at 213° to 216°C., are obtained, which is a yield of 87% of the theoretical. Diethylaniline is purified, as is dimethylaniline, by treatment with concentrated sulfuric acid.

[132] J. Walter, *Chem.-Ztg.*, **34**, 641 (1910).
[133] Hübner, Tölle, and Athenstädt, *Ann.*, **224**, 347 (1884).
[134] Price, *J. Soc. Chem. Ind.*, **37**, 82 (1918); *Chem. Abstracts*, **12**, 1383 (1918).
[135] Knoevenagel, *J. prakt. Chem.*, **89**, 31 (1914).

The higher alkylation products of aniline, which have no importance for industry, are obtained by treating aniline with excess alkyl halides in a manner similar to that followed for the preparation of monoethylaniline. Zander [136] obtained dipropylaniline by repeated treatment of aniline with n-propyl iodide, monopropylaniline being isolated as an intermediate. He claims a yield of 90% of the theoretical, of a product boiling at 245.4°C. Diisopropylaniline was obtained in a similar manner with a yield of 80% of the theoretical and a boiling point of 221°C.

Skita, Keil, and Havemann [137] describe a method for the preparation of tertiary amines from secondary amines by catalytic hydrogenation in the presence of aldehydes and ketones. Colloidal platinum (see page 16) was used as a catalyst, and a pressure of 3 atmospheres. The carbonyl compound involved was used in excess. The yields were best when aldehydes were used, but only fair even then. However, the method might be useful in certain cases. For details see the original paper.

Preparation of Trimethylamine

Organic Syntheses gives details for the preparation of trimethylamine [138] and its hydrochloride [139] in accordance with a method developed by Koeppen.[140]

Clarke, Gillespie, and Weisshaus [141] often used the method of methylating amines with formaldehyde. They did not succeed, however, in introducing higher alkyl groups with the higher homologues of formaldehyde, because the reaction takes place only at higher temperatures. Aniline cannot be methylated even with formaldehyde, because higher condensation products are formed. In order to obtain tertiary amines, only a little more than the molecular amount of formaldehyde is necessary for each methyl group to be introduced, if formic acid, which acts as a reducing agent according to the equation, $R_2{:}NH + CH_2O + HCOOH \rightarrow R_2{:}N{\cdot}CH_3 + CO_2 + H_2O$, is added. The authors give the following general directions for the methylation of simple amines.

1 mole of a primary amine or 2 moles of a secondary amine are mixed with 5 moles of 90% formic acid. To this mixture are added 2.2 moles of a 35% formaldehyde solution. As soon as the evolution of gases subsides (6 to 8 hours), the solution is boiled under a reflux for 2 to 4 hours on a steam bath. Then a little more than 1 mole of hydrochloric acid is added and the mixture distilled on a steam bath to remove formic acid

[136] A. Zander, *Ann.*, **214**, 168 (1882).
[137] A. Skita, F. Keil, and H. Havemann, *Ber.*, **66**, 1400 (1933).
[138] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 528.
[139] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 533.
[140] Koeppen, *Ber.*, **38**, 882 (1905).
[141] T. Clarke, B. Gillespie, and Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

and excess formaldehyde. The colorless residue is dissolved in water, the solution rendered alkaline with excess 25% sodium hydroxide solution, and the free base is distilled with steam. The amine is salted out with potassium hydroxide, and the oil separated and dried with solid potassium carbonate and finally distilled from sodium. In this manner, dimethyl-*n*-butylamine, dimethylbenzylamine, and methylpiperidine were obtained in yields of 80% of the theoretical.

In a corresponding manner, dimethylamino derivatives were obtained from amino acids with formaldehyde and formic acid; *e.g.*, glycine, alanine, and α-aminoisobutyric acid. Certain complicated amino acids yielded only decomposition and condensation products.

D. Purely Aromatic Secondary and Tertiary Amines

The purely aromatic amines of the type of diphenylamine exhibit a behavior essentially different from that of aliphatic and fatty aromatic amines. In general, they cannot be prepared in a practical way by any of the methods discussed so far, because the halogen on aromatic nuclei is not reactive enough. It is, however, possible to force the reaction with catalysts, such as copper powder. For instance, diphenylamine can thus be obtained from bromobenzene and aniline. Cuprous iodide is also a suitable catalyst.[142]

The practical method of preparing diphenylamine consists of heating aniline and aniline hydrochloride to 140°C., whereby ammonium chloride and diphenylamine are formed. The first method makes possible the preparation of diarylamines with two different substituents, whereas the second method would give a mixture. Thus heating aniline hydrochloride with toluidine would give diphenylamine, methyldiphenylamine, and dimethyldiphenylamine.

The basic properties of the diarylamines are not very pronounced. Their hydrogen is readily substituted by alkali metal, and the metal atom like the potassium in potassium phthalimide reacts readily with aliphatic as well as aromatic bromides and iodides. Thus, it is possible to prepare triphenylamine by heating sodium diphenylamine with bromobenzene. Free diphenylamine also reacts with bromobenzene in the presence of copper powder, with the formation of triphenylamine. This tertiary amine is such a weak base that it forms almost no salts. Weinland,[143] however, prepared an acid fluoride. A very convenient method of preparing triphenylamines was worked out by Goldberg and Nimerovsky,[144] directions for which may be found in *Organic Syntheses.*[145]

[142] German Patent, 187,870.
[143] Weinland, *Ber.*, **41**, 3672 (1908).
[144] Goldberg and Nimerovsky, *Ber.*, **40**, 2452 (1907).
[145] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 544.

Purification of Aromatic Amines

Almost all aromatic amines do not keep well when they are not in a completely pure state. Their color turns to gray, violet, or black, probably due to oxidation. In order to remove the suspected oxidation catalysts, such as traces of heavy metals, Weissberger and Strasser [146] suggest treating the amines in the following manner.

The amine is dissolved in dilute hydrochloric acid at approximately 50°C. and about 5 to 10% of its weight of stannous chloride is added. The solution is treated with hydrogen sulfide completely to precipitate the tin, a little sodium chloride being added at the end to produce a flocculent precipitate of the tin sulfides. The solution is filtered and the filtrate is boiled to remove the hydrogen sulfide and is then rendered alkaline with alkali or sodium sulfide. Solid amines which are slightly soluble in water are filtered off, while those which are easily soluble, or liquid, are extracted with ether.

Compounds treated in this manner, such as p-phenylenediamine, m-phenylenediamine, benzidine, p-aminophenol, ethylaniline, and many others, remain unchanged for weeks even in open bottles if they are protected from dust by a cotton plug.

E. Quaternary Ammonium Compounds

The quaternary ammonium compounds will not be discussed separately here. Details for their preparation will be found where procedures, such as for the cleavage of the carbon-nitrogen bonds, require their use.

II. HYDRAZINES

The methods for the preparation of hydrazines are in part the same as those which were discussed in the preceding section, but important new ones have to be added, especially in the aromatic series. Foremost among them are the reduction of diazonium compounds, of azo compounds, and of nitrosamines. The hydrazines are not classified as are the amines, according to the number of substituted hydrogen atoms, because the chemical properties of hydrazines substituted at one end and having one free amino group differ almost as much from the ones substituted at both ends as the primary, secondary, and tertiary amines differ from one another.

A. Hydrazines with Free Amino Group
1. Formation of Substituted Hydrazines by Addition

The reaction is of little preparational importance, except with such compounds as unsaturated ketones which, however, undergo ring closure to give pyrazolines as the end-product.

[146] A. Weissberger and E. Strasser, *J. prakt. Chem.*, **135**, 209 (1932).

2. By Exchange

Formation of Substituted Hydrazines by Exchange of Acid Radicals for Hydrazine Residue

Hydrazine reacts with halides with the formation of substituted hydrazines. The conditions, however, are much more complicated than in the corresponding reactions with ammonia. In the aliphatic series only one case is known [147] in which the method has preparative usefulness; namely, the preparation of methylhydrazine.

According to Thiele [148] 208 g. of benzalazine are dissolved in 300 cc. of benzene and the solution heated with 100 cc. of dimethyl sulfate (small excess) for 5 hours on a steam bath. A molecular compound of benzalazine and dimethyl sulfate separates as an oil, which occasionally solidifies even while being heated. Water is added to the reaction mixture which hydrolyzes the addition product to methylhydrazine sulfate, benzaldehyde, and methanol. The benzene and benzaldehyde are removed by distillation with steam and the residue allowed to cool. 15 cc. of benzaldehyde are added to remove unchanged hydrazine. After standing overnight, the mixture of separated benzalazine and resinous contaminants is removed by filtration. The filtrate is evaporated to dryness, some absolute alcohol being added towards the end. The residue is mixed with cold absolute alcohol, filtered, and washed with alcohol and ether to give 110 to 120 g. of methylhydrazine sulfate with a melting point of about 142°C. The product is tested for hydrazine sulfate by dissolving in a solution of copper sulfate. If hydrazine is present, hydrazine-copper sulfate slowly precipitates. If necessary, hydrazine sulfate can be removed by recrystallization from methanol.

The free base is obtained [149] by distillation of the sulfate with very concentrated sodium hydroxide solution and powdered sodium hydroxide. The distillate is first treated again with sodium hydroxide powder, distilled, and finally heated with barium hydroxide in a sealed tube; the boiling point of methylhydrazine is at 87°C.

This method fails even for the preparation of ethylhydrazine (see below), since diethyl sulfate apparently cannot form a molecular compound with benzalazine.

In the aromatic series, on the other hand, the exchange of bromine for the hydrazino group proceeds quite readily when the bromine is activated by other substituents. In this manner, the polynitrophenylhydrazines, which are often used for the characterization of carbonyl compounds, may be obtained.

Diels and Fritzsche [150] give the following directions for the preparation of hydrazinecarboxylic acid methyl ester.

A mixture of 12 g. of hydrazine hydrate and 25 cc. of methanol is added rather quickly, with shaking, to an ice-cold solution of 25 g. of ethyl chlorocarbonate in 75 cc.

[147] Westphal, *Ber.*, **74 B**, 759 (1941), reports the preparations of alkyl hydrazines by the direct reaction of the appropriate halide and hydrazine hydrate.
[148] J. Thiele, *Ann.*, **376**, 244 (1910).
[149] Brüning, *Ann.*, **253**, 8 (1889).
[150] Diels and Fritzsche, *Ber.*, **44**, 3022 (1911).

of methanol. Soon hydrazine hydrochloride separates as a by-product, while the hydrochloride of the ester stays in solution. After standing for 30 minutes at room temperature the mixture is filtered, the filtrate is evaporated to dryness on a steam bath, and the residue recrystallized from 50 cc. of absolute ethanol. In all, after concentration of the mother liquor to get a second crop, 15 g. of hydrazinecarboxylic acid methyl ester hydrochloride melting at 160°C. are obtained.

To prepare the free base, the ice-cold solution of 2.25 g. of potassium hydroxide in the same amount of water is added to 5 g. of finely powdered ester hydrochloride and the mixture shaken immediately with 150 cc. of dry ether for 15 minutes.   The extraction with 150 cc. of ether is repeated twice more, until the water has dissolved in the ether and the potassium chloride settles as a powder. The combined, filtered, ether extracts are concentrated on the water bath to 20 cc. and the remainder of the ether allowed to evaporate at room temperature. If the remaining oil does not solidify spontaneously and if no crystals for seeding are available, the material is distilled in a vacuum. The ester distils at 108°C. at 12 mm. and solidifies instantly in the receiver. A yield of 3.3 g. of hydrazinecarboxylic acid methyl ester is obtained, corresponding to 93% of the theoretical. It may be purified by recrystallization from ether or benzene and melts at 63°.

3. By Reduction

(a) By Reduction of Nitrosamines

By this method only hydrazines which have two carbon radicals on the same nitrogen atom may be prepared. Monosubstituted hydrazines, however, may be prepared in an indirect way through nitrosoalkyl urea derivatives by a method similar in principle; see page 241.   The method was originated by E. Fischer.[151]

For the preparation of asymmetrical diphenylhydrazine, 50 g. of diphenylnitrosamine are dissolved in 250 cc. of ethanol, 75 g. of zinc dust are added, and then, with good cooling and continuous shaking, glacial acetic acid is slowly added until no more heat is generated and until a filtered sample shows no bluish green color on the addition of concentrated hydrochloric acid. The mixture is filtered while hot, and the filtrate is concentrated to one-fourth its volume and diluted with the same volume of water. A large excess of concentrated hydrochloric acid is now added with cooling and stirring. Upon cooling, a mixture of the hydrochlorides of diphenylhydrazine and diphenylamine separates in the form of blue needles. The crude product is dissolved in hot, very dilute hydrochloric acid, and the oily diphenylamine, produced by hydrolysis of the hydrochloride, is removed by filtration. The filtrate is mixed with concentrated hydrochloric acid to precipitate the diphenylhydrazine hydrochloride. If necessary, the operation is repeated several times. Finally, by recrystallization from alcohol the hydrochloride is obtained in colorless fine needles. By treating the hydrochloride with excess sodium hydroxide and extracting with ether the free base is obtained as a pale yellow oil. According to Stahel [152] the diphenylhydrazine is best purified by distillation *in vacuo* (b.p.

[151] E. Fischer, *Ann.*, **190**, 175 (1878).
[152] R. Stahel, *Ann.*, **258**, 243 (1890).

220°C. at 40 mm.); the distillate crystallizes in the receiver and is recrystallized from petroleum ether to give colorless plates melting at 34.5°C.

Asymmetrical dimethylhydrazine may be prepared according to the directions of Renouf,[153] an adaptation and improvement of a method used by Fischer [154] for the preparation of diethylhydrazine.

To a solution of 22 g. of dimethylnitrosamine in 300 g. of water are added 150 g. of zinc dust and, with frequent shaking, 150 g. of 50% acetic acid, the temperature being kept below 20° to 30°C. After 2 hours, the temperature is raised to 40° to 50°C. until the odor of nitrosamine has disappeared. If necessary, more zinc dust and hydrochloric acid are added. Basic zinc salts, which render the solution difficult to filter, are dissolved in hydrochloric acid and the hot solution is filtered. The solution is made alkaline with potassium hydroxide and the free base distilled until no more basic material distils over. The distillate is acidified with hydrochloric acid and concentrated to a syrup *in vacuo*. Solid potassium hydroxide is cautiously added to the residue and the mixture distilled on a steam bath. The distillate is dried with potassium carbonate and fractionated. The boiling point of dimethylhydrazine is 62.5°C. *Organic Syntheses* [155] describes a method for preparing a larger batch with 200 g. of nitrosodimethylamine. The hydrazine is isolated as the hydrochloride in a yield of 67 to 73% of the theoretical.

Ethylhydrazine is best prepared according to directions by Fischer.[156] The following directions are somewhat improved and give good results.

To a well cooled solution of 25 g. of symmetrical diethylurea in a mixture of 17.5 g. of concentrated sulfuric acid and 100 cc. of water are added 15 g. of sodium nitrite in small portions. Nitrosoethylurea is separated as a reddish yellow oil, the aqueous layer is extracted with 50 cc. of ether, and the extract is combined with the main portion. The ethereal solution is mixed quickly, with vigorous stirring and ice cooling, with 180 cc. of alcohol and 150 g. of zinc dust, and 79 cc. of glacial acetic acid are added dropwise during 2 hours, the temperature being kept below 10°C. After standing overnight, the reaction mixture is centrifuged and the solids are suspended in a little alcohol and centrifuged again. A solution of 50% sodium hydroxide is added with ice cooling to the combined, clear filtrates until the zinc hydroxide dissolves again. The solution is then extracted with ether until a sample of the extract does not show any reducing action. The ether is evaporated and the residue heated for some time with concentrated hydrochloric acid in an open dish on a steam bath in order to hydrolyze the urea. Finally, 4 times its volume of concentrated hydrochloric acid is added to the residue and the mixture heated for 15 hours over a free flame, the acid lost by evaporation being replaced from time to time. The mixture is allowed to cool and hydrogen chloride is admitted with ice cooling; the separated crystal needles of ethylhydrazine hydrochloride are filtered with suction, dissolved in water, and, after the addition of hydrochloric acid, hydrogen chloride is passed in again. The crystals are filtered again with suction and dried over potassium hydroxide. The yield of ethylhydrazine hydrochloride amounts to 9.6 g., corresponding to 47% of the theoretical.

[153] Renouf, *Ber.*, 13, 2171 (1880).
[154] E. Fischer, *Ann.*, 199, 308 (1879).
[155] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 212.
[156] E. Fischer, *Ann.*, 199, 287 (1879).

(b) By Reduction of Diazonium Compounds

The reduction of nitrosamines can be performed in the aliphatic as well as in the aromatic series, but only for the preparation of disubstituted hydrazines.   The reduction of diazonium compounds, on the other hand, is feasible only in the aromatic series and yields only monosubstituted hydrazines.   Since the reaction discovered by E. Fischer [157] is fully described in all elementary laboratory textbooks, a detailed treatment is not necessary here; some changes and additions, however, may be pointed out.   According to *Organic Syntheses* [158] it is essential that the mixture of sodium sulfite and diazonium salt solution be heated for a longer time than usual after the addition of hydrochloric acid; the heating may require several hours, sometimes even overnight.   Furthermore, the addition of zinc dust, after the reaction is finished, proved superfluous.

Many arylhydrazines substituted in the nucleus can be prepared by the method used for phenylhydrazine; for instance, *p*-nitrophenylhydrazine may be prepared as follows: [159]

A solution of 10 g. of *p*-nitroaniline in 21 g. of concentrated hydrochloric acid is diazotized with 6 g. of sodium nitrite in 10 cc. of water with cooling by ice.   The solution is filtered, neutralized with a solution of sodium carbonate, and diluted with water to 100 cc.   This solution is slowly run, with stirring, into 50 cc. of ice-cold potassium sulfite solution containing 10 g. of potassium carbonate.   The sulfite solution is prepared by saturating the solution of 1 part of potassium hydroxide in 5 parts of water with sulfur dioxide and adding 1.8 parts of potassium carbonate.   The potassium nitrophenyl-disulfonate forms a thick mush of crystals which are filtered with suction and washed with a little cold water.   While still wet, the residue is covered with a mixture of 40 cc. of concentrated hydrochloric acid and an equal volume of water and the mixture is heated for 5 minutes on a steam bath.   Upon cooling, a mixture of potassium chloride and nitrophenylhydrazine hydrochloride separates.   The crystals are recovered by filtration and dissolved in a little water.   To the solution is added, with cooling, first a saturated solution of sodium carbonate, and then sodium acetate.   The free *p*-nitrophenylhydrazine separates in an almost pure state.   More of the hydrazine may be recovered by neutralizing the acid mother liquor with carbonate and acetate as above, giving a total yield that is almost quantitative.   It may be recrystallized from boiling water.

B. Secondary Hydrazines, without Free Amino Group

1. By Exchange

The methods for the preparation of hydrazines substituted at both ends are .in part similar to the methods given above; in part they differ from them, especially in the aromatic series.   The simplest member of the aliphatic series, symmetrical dimethylhydrazine, was formerly pre-

[157] E. Fischer, *Ann.*, 190, 79 (1878).
[158] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 442.
[159] E. Bamberger and E. Kraus, *Ber.*, 29, 1834 (1896).

pared by degradation of 1-methylpyrazole methiodide according to Knorr and Köhler.[160] Harries and Klamt [161] originated another method which was later improved by, Thiele.[162] The starting material is hydrazine which, after conversion to diformylhydrazine, is methylated. The formyl groups are then removed by hydrolysis to give the dimethylhydrazine. Folpmers [163] still later used dibenzoylhydrazine instead of diformyl-hydrazine. *Organic Syntheses* [164] gives details of a method based on Folpmers' suggestions.

Hydrazinedicarboxylic acid dimethyl ester may be obtained [165] as follows:

To a solution of 1 g. of hydrazinecarboxylic acid methyl ester (see above) in 100 cc. of absolute ether is added, dropwise, a solution of 1 g. of methyl chlorocarbonate in 10 cc. of ether. After 1 hour's standing, the hydrazinecarboxylic acid ester hydrochloride formed is removed by filtration and the mother liquor concentrated to 10 cc. The crude product which separates is recrystallized from absolute ether. A yield of 0.8 g. of hydrazinedicarboxylic acid dimethyl ester is obtained, melting at 131°C.

2. By Reduction

By Reduction of Azo Compounds

Aromatic disubstituted hydrazines with the substituents at 2 different nitrogen atoms can be obtained readily through the azo compounds. They may also be prepared by suitable reduction of nitro compounds, which, of course, proceeds through the azo stage. The simplest member of this series, hydrazobenzene, is generally prepared directly from nitro-benzene, either by reduction with zinc dust or electrolytically. Compounds of the type of hydrazobenzene are of practical importance only as starting materials for the preparation of benzidine and its derivatives; therefore, details may be found in the chapter on the benzidine rearrangement.

For the electrolytic preparation of hydrazobenzene from nitrobenzene exactly the same method is used as is given for the preparation of azo-benzene (see page 249). The electrolysis, however, is not stopped 5 minutes after the current was reduced to one-fourth, but is continued until a total of 22.8 ampere hours has passed through the cell. Then another half ampere hour is allowed to pass through at 2 amperes, because in the second phase a small evolution of hydrogen at the cathode cannot be avoided. The cathode liquid which is not red, but yellowish at the end, is cooled during the last stage by setting the beaker in cold water. The

[160] Knorr and Köhler, *Ber.*, **39**, 3257 (1906).
[161] Harries and Klamt, *Ber.*, **28**, 503 (1895).
[162] J. Thiele, *Ber.*, **42**, 2575 (1909).
[163] Folpmers, *Rec. trav. chim.*, **34**, 34 (1915).
[164] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 209.
[165] Diels and Fritzsche, *Ber.*, **44**, 3018 (1911).

main crop of the hydrazobenzene crystallizes and is isolated in the usual manner.   The current is shut off, the porous cup removed, the solution filtered, and the crystals washed with a little water containing sulfur dioxide and then with alcohol and petroleum ether.

Tetraarylhydrazines may be obtained by dehydrogenation of diarylamines according to Wieland and Gambarjan[166] and Busch and Hobein.[167]   Tetraphenylhydrazine can be prepared according to Gattermann-Wieland[168] as follows:

Diphenylamine (34 g.) is dissolved in 200 cc. of acetone in a 400 cc. bottle with a tightly fitting stopper.   The acetone used is specially purified by boiling under a reflux with enough potassium permanganate, so that the color of the permanganate persists for 30 minutes, and then distilling it.   A total of 16 g. of permanganate is added in small portions to the diphenylamine solution while it is cooled with ice-water and shaken vigorously, time being allowed for the disappearance of the color after each addition.   A maximum of 14 g. of additional potassium permanganate is added, without cooling, until the violet color persists for 30 minutes. The reaction mixture contains a certain amount of phenylcarbylamine, as can be detected from its odor.   Excess permanganate is destroyed by the addition of a little alcohol or formaldehyde solution, the manganese dioxide removed by filtration, and the filter cake washed twice with a small amount of warm acetone.   The solvent is then removed under a vacuum (water pump), first on a steam bath at 35°C. and then, towards the end, at room temperature.   The residue in the distilling flask is treated with 25 cc. of ice-cold ether to remove some resinous impurities and the mixture separated by filtration after a short time.   The residue is washed with a little ether, giving 20 to 24 g. of almost colorless crude product.   This corresponds to a yield of 60 to 70% of the theoretical. The product is purified by dissolving it in 50 to 60 cc. of hot benzene, but the solution must not be boiled long.   It is filtered and one-third of its volume of hot alcohol is added and the mixture cooled.   The crystals are filtered and washed first with a mixture of equal parts of alcohol and benzene and then with pure alcohol.   After careful drying in a vacuum, the tetraphenylhydrazine is stable for years if kept in the dark.   Its melting point is 144°C.   From the mother liquors of the recrystallization a residue is obtained which may be treated again, as described above for the crude product.

Tetraphenylhydrazine dissolves in 10 times its weight of xylene in the cold to give a colorless solution; on heating, dissociation takes place

[166] H. Wieland and S. Gambarjan, *Ber.*, **39**, 1500 (1906).
[167] M. Busch and R. Hobein, *Ber.*, **40**, 2100 (1907).
[168] Gattermann-Wieland, *Die Praxis des organischen Chemikers.*   de Gruyter, Berlin, 1936, p. 349.

and the color of the solution turns a deep olive-green. The radical, $(C_6H_5)_2:N$—, however, is unstable. Therefore, the tetraphenylhydrazine cannot be recovered unchanged by cooling. For the fixation of the radical with nitrogen oxide as diphenylnitrosamine see Wieland.[169]

The degree of dissociation of tetraarylhydrazines is determined to a large extent by the substituents, as in the case of hexaarylethanes. Thus, p-tetraanisylhydrazine in a benzene solution dissociates noticeably even at room temperature, the corresponding dimethylamino derivative in benzene up to 10%, in nitrobenzene up to 21%. The radicals, in contrast to the triarylmethyls, are not sensitive to oxygen. However, they disproportionate easily into the corresponding diarylamine and N,N-diarylphenazine derivatives.

III. DIAZOTATES, AZO AND AZOXY COMPOUNDS

The $C \cdot N : N$ group occurs in diazotates and in azo (azoxy) and diazo compounds.

Simple, typical representatives of the three series are:

1. Potassium benzene diazotate, $C_6H_5 \cdot N : NOK$

    Benzene diazocyanide, $C_6H_5 \cdot N : N \cdot CN$

2. Azomethane, $CH_3 \cdot N : N \cdot CH_3$; azobenzene, $C_6H_5 \cdot N : N \cdot C_6H_5$

3. Diazomethane, CH_2N_2, $CH_2 \overset{N}{\underset{N}{\lessgtr\!\!\Vert}}$, $CH_2 : N \vdots N$

    Diazoacetic ethyl ester, $C_2H_5OOC \cdot CH \overset{N}{\underset{N}{\lessgtr\!\!\Vert}}$, or $C_2H_5OOC \cdot CH : N : N$

There is no agreement about the constitution of the diazo compounds.

A. Diazotates

Diazotates occur in the aliphatic as well as in the aromatic series, but only the latter have been thoroughly studied. They may exist in stereoisomeric syn and anti forms. The syn-diazotates are also called normal, the anti-diazotates, iso compounds. They are derived from the hypothetical benzene diazohydroxide, $C_6H_5 \cdot N : N \cdot OH$, which exists only in solution, supposedly as an equilibrium mixture. Hantzsch and Reddelien,[170] in their monograph, prove the constitution of the syn and anti compounds and give details of their theories and experiments.

[169] H. Wieland, *Ann.*, **381**, 211 (1911).

[170] A. Hantzsch and G. Reddelien, *Die Diazoverbindungen.* Springer, Berlin, 1921.

The simplest aliphatic diazotates cannot be prepared, of course, from diazonium compounds, but only by rearrangement of nitrosamines. Only the alkali diazotates of the general formula, $R \cdot N : N \cdot OM$, are known. Thus, potassium methyl diazotate is obtained from nitrosomethylurethane on treatment with potassium hydroxide; Hantzsch and Lehmann.[171] The reaction proceeds according to the following scheme:

$$C_2H_5O \cdot CO \cdot N \overset{NO}{\underset{CH_3}{\diagdown}} \xrightarrow{KOH} CH_3 \cdot N : N \cdot OK + K_2CO_3 + H_2O$$
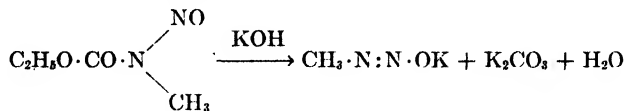
It is a colorless, crystalline, very unstable compound which is decomposed with water in an explosive manner, forming potassium hydroxide and diazomethane. Because of their instability, they are considered to be syn compounds. Considerably more stable are the sodium diazotates. They can be prepared, according to Thiele,[172] from nitrosohydrazines and alkyl nitrites with sodium methylate. The reaction is accompanied by evolution of nitrous oxide. These diazotates form diazomethane only when treated with acids and therefore they are considered to be anti compounds; see also Wieland.[173]

The alkali diazotates of the aromatic series are more stable and may be obtained in isomeric forms. Normal potassium benzene diazotate, $C_6H_5 \cdot N : N \cdot OK$, can be prepared according to Bamberger and Schraube [174] in the following manner.

140 g. of potassium hydroxide are melted in a silver or copper pot with 60 g. of water. The mixture is cooled, with stirring, to 5°C. and to the resulting mush are added dropwise, with continuous stirring, 10 cc. of 15% benzenediazonium chloride solution; see page 108. Each drop causes a yellow precipitate which changes on stirring to colorless normal potassium benzene diazotate. After the addition is finished, the temperature is allowed to rise to about 20°C. and the reaction mixture spread on a porous plate. After being dried on a clay plate in a desiccator, the product may be purified by dissolving it in 1 g. portions in 3 cc. of alcohol at −5°C., filtering to remove inorganic substances, and precipitating the potassium salt with 8 to 10 volumes of absolute ether. The diazotate is very hygroscopic and changes easily even with well cooled alcohol into diazo ester. It is fairly stable towards heat, but explodes above 30°C.

The preparation of the isomeric potassium benzene isodiazotate by Schraube and Schmidt [175] was described on page 109.

The diazosulfonates [176] of the general formula, $R \cdot N : N \cdot SO_3K$, are formed from benzenediazonium nitrate solution with carbonate-alkaline

[171] A. Hantzsch and Lehmann, *Ber.*, **35**, 901 (1902).
[172] J. Thiele, *Ber.*, **41**, 2810 (1908); *Ann.*, **376**, 252 (1910).
[173] H. Wieland, *Die Hydrazine.* Enke, Stuttgart, 1913, p. 115.
[174] Bamberger and Schraube, *Ber.*, **29**, 461 (1896).
[175] Schraube and Schmidt, *Ber.*, **27**, 514 (1894).
[176] Error in the original.

sulfite solution, which gives the normal syn-diazotates. The isomeric anti-diazosulfates separate from the solutions of the normal ones on standing, the color changing from dark yellow to light yellow.

In a similar manner syn- and anti-diazocyanides are obtained from suitable diazonium salt solutions in the cold with potassium cyanide, which gives the normal syn compounds. These change slowly in the solid state, faster in alcoholic solution, to the stable anti compounds. The latter are obtained directly from diazonium salt solutions with potassium cyanide at an elevated temperature.

B. Azo Compounds

Azo compounds may be formed by dehydrogenation of disubstituted hydrazines according to the following scheme.

$$R \cdot NH \cdot NH \cdot R \longrightarrow H_2 + R \cdot N : N \cdot R$$
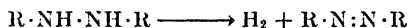
They also occur as intermediates in the aromatic series during the reduction of nitro compounds, presumably as secondary condensation products of the nitroso and amino stages: $R \cdot NO + H_2N \cdot R \rightarrow H_2O + R \cdot N : N \cdot R$, or as reduction products of azoxy compounds: $R \cdot \overset{..}{N} : N \cdot R \rightarrow$
$$\overset{|}{O}$$
$R \cdot N : N \cdot R$, which in turn are formed from the intermediate nitroso and hydroxylamino compounds: $R \cdot NO + HONH \cdot R \rightarrow H_2O + R \cdot N : \overset{..}{N} \cdot R$.
$$\overset{|}{O}$$

Another and the most important method of formation is the coupling of diazonium salts with aromatic phenols, amines, or their derivatives, and also with reactive methylene compounds, especially enols. The azo compounds thus formed, in contrast to the compounds mentioned above, possess the characteristics of dyes.

1. Dehydrogenation of Hydrazines

The dehydrogenation of hydrazines of the type, $R \cdot NH \cdot NH \cdot R$, proceeds most readily in the aromatic series. Hydrazobenzene, symmetrical diphenylhydrazine, and its derivatives are even susceptible to air oxidation, particularly if accelerated by alkali.

Aliphatic hydrazines are more stable; for their dehydrogenation, chromates, nitric acid, nitrous acid, and hydrogen peroxide are used.

Azomethane, $CH_3 \cdot N : N \cdot CH_3$, is prepared according to Thiele [177] in the following manner.

To a concentrated aqueous solution of 30 g. of potassium chromate in a distilling flask is added a concentrated solution of 12 g. of symmetrical dimethylhydrazine hydrochloride, $CH_3 \cdot NH \cdot NH \cdot CH_3 \cdot 2HCl$, dropwise,

[177] J. Thiele, *Ber.*, **42**, 2575 (1909).

considerable heating being avoided.   Azomethane, which is formed instantly, starts to distil towards the end.   It is passed over calcium chloride and collected in a flask cooled in solid carbon dioxide.   After all the dimethylhydrazine hydrochloride has been added, the azomethane is recovered from the aqueous solution by distillation *in vacuo* until nothing more distils over at 20 mm.   A yield of 2.5 g. of azomethane is obtained as a yellow liquid boiling at 1.8°C. at 756 mm.

Thiele [178] also prepared ω-azotoluene, $C_6H_5 \cdot CH_2 \cdot N : N \cdot CH_2 \cdot C_6H_5$.

To a solution of 10 g. of dibenzylhydrazine in 300 cc. of hot water are added 100 cc. of 20% ammonia.   The milky mixture is treated on the steam bath with 250 cc. of 3% hydrogen peroxide for 5 minutes.   Upon cooling with ice, the ω-azotoluene formed crystallizes.   The crude product (6.9 g.) is recrystallized from methanol, giving colorless leaflets melting at 31.5°C.

Azodicarboxylic acid dimethyl ester was obtained by Diels and Fritzsche [179] in the following manner.

2 g. of hydrazinedicarboxylic acid dimethyl ester are dissolved in 2 cc. of concentrated nitric acid and treated with 4 cc. of fuming nitric acid while cooled with ice.   The color of the reaction mixture slowly turns orange with evolution of nitrogen oxide.   After 30 minutes ice water is added and the azo ester which separates as a heavy oil is extracted with ether.   The ethereal solution is shaken with ice water three times and once with a little sodium carbonate solution and then dried with calcium chloride.   Upon distillation *in vacuo*, an almost theoretical yield of azodicarboxylic acid ester is obtained as an orange-yellow oil which boils at 96°C. at 25 mm.

Often azo compounds may also be obtained by dehydrogenation of primary aromatic amines according to the scheme, $2R \cdot NH_2 \rightarrow 2H_2 + R \cdot N : N \cdot R$.   Hypohalides, permanganate, and lead dioxide are used as dehydrogenating agents.   The method is especially successful for heterocyclic and polysubstituted aromatic amines, in which the reduction of the corresponding nitro compounds does not give good results.   Thiele,[180] for instance, prepared azomethyltriazole and azotetrazole in this way from the corresponding heterocyclic amines.

Meigen and Nottebohm [181] obtained p-azobenzoic acid from p-aminobenzoic acid by treatment with an aqueous solution of sodium hypobromite with cooling.   Meigen and Normann [182] prepared the dinitroazobenzenes by vigorously mixing a benzene solution of nitroaniline with 2- to 3-fold excess of aqueous sodium hypochlorite solution, or better yet, with a 20% solution of hypobromite.   The reaction is complete when no more nitroaniline can be extracted with hydrochloric acid from the benzene

[178] J. Thiele, *Ann.*, **376**, 265 (1910).
[179] Diels and Fritzsche, *Ber.*, **44**, 3026 (1911).
[180] J. Thiele, *Ber.*, **26**, 2600 (1893); *Ann.*, **303**, 57 (1898).
[181] W. Meigen and E. Nottebohm, *Ber.*, **39**, 745 (1906).
[182] W. Meigen and W. Normann, *Ber.*, **33**, 2711 (1900).

solution.   The layers are separated and the benzene solution concentrated to crystallize the azo compounds.   Thus, o-, m-, and p-dinitroazobenzenes as well as m-dinitro-p-azotoluene were obtained.

Occasionally, however, the dehydrogenation of amines yields azines:

$$2\text{R} \cdot \text{NH}_2 \rightarrow \text{R} \underset{\diagdown \text{NH} \diagup}{\overset{\diagup \text{NH} \diagdown}{\bigg\langle\bigg\rangle}} \text{R}.$$ This reaction takes place especially in the
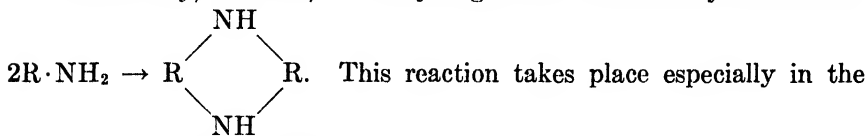
naphthalene series, as Meigen and Normann state in their paper mentioned above.

2. By Direct Reduction of Nitrogen Compounds

Azo compounds are formed from nitro compounds either directly or through the azoxy compounds as intermediates.   Azoxy compounds, which are known only in the aromatic series, are obtained by chemical reduction of nitro compounds or by electrolysis.

The reduction of nitrobenzene to azobenzene is carried out according to Witt [183] in the following manner.

2 moles of stannous chloride are dissolved in water and the solution added to an excess of sodium hydroxide.   The mixture is stirred with 1 mole of nitrobenzene on a steam bath until the odor of nitrobenzene has disappeared.   The crude product which solidifies on cooling is collected on a funnel, dried, and recrystallized from ligroin.   Coal, saw dust, and iron powder have been suggested to take the place of the expensive stannous chloride.

In the laboratory, however, azo hydrocarbons are prepared best by electrolytic reduction.   The following directions for the electrochemical preparation of azobenzene are taken from Müller.[184]

The apparatus consists of a porous cylinder of 5 mm. wall thickness, 18 cm. high, and 6 cm. in diameter, and of a beaker 22 cm. high and 8 cm. in diameter.   The cathode is a nickel screen (0.1 mm. wire thickness, 225 mesh per square centimeter) which is wound around the porous cylinder.   The current connection is made with a strong nickel wire (4 mm.) which is used to braid the ends of the screen together.   The screen extends a little below the edge of the bottom of the cell and is folded under.   The anode is a lead cylinder (sheet lead of 1 mm. thickness) which is put inside the cup and is connected with the current by a lead strip.   The cathode and anode are of about equal height and cover the cylinder walls to four-fifths of its height.   A rubber tubing of moderate wall thickness is wrapped around the beaker from the top down to two-

[183] Witt, *Ber.*, **18**, 2912 (1885).
[184] E. Müller, *Elektrochemisches Praktikum.*   Steinkopf, Dresden, 1913, p. 186.

thirds of its height in close windings which are held in place by a string. The porous cup is filled with a completely saturated solution of sodium carbonate. The space between the cell and beaker is filled with a solution of 20 g. of nitrobenzene and 5 g. of crystallized sodium acetate in 200 cc. of 70% alcohol. The anode as well as the cathode liquids are preheated to 70°C. and the level of the sodium carbonate solution is a little higher than that of the nitrobenzene solution. It is advantageous first to allow the porous cup to become saturated with the sodium carbonate solution in order to decrease the initial resistance. Cold water is now passed through the rubber tubing and the electrolysis is started with 16 to 20 amperes. When the necessary amount of current (17.5 ampere hours) has passed through, evolution of hydrogen at the nickel cathode is observed. The current is then reduced to one-fourth and shut off after 5 minutes. The heat generated by the current keeps the nitrobenzene solution boiling gently during the electrolysis. The greater part of the alcohol is condensed at the cooling surface, but it is advisable from time to time to replace the amount lost by evaporation by the addition of 96% alcohol. When the electrolysis is finished, the cathode liquid is poured into an Erlenmeyer flask. The small amount of hydrazobenzene formed is dehydrogenated by blowing a current of air through the solution, which also cools the solution so that most of the azobenzene crystallizes. The yields are almost quantitative.

Azobenzene may also be obtained by distillation of azoxybenzene with 3 times its weight of fine iron filings (Schmidt and Schultz [185]). The materials must be completely dry lest an explosion occur on heating. The distilled azobenzene is contaminated by a little aniline, which is extracted with hydrochloric acid. The azobenzene is then isolated in the usual manner, in a yield of about 73% of the theoretical, when 60 g. batches of azoxybenzene are employed.

p-Azoxyphenol ethers of the type, $RO \cdot C_6H_4 \cdot \overset{\cdot\cdot}{N} : N \cdot C_6H_4 \cdot OR$, which
$$O$$
are important because of their ability to yield liquid crystals, are best prepared electrolytically. Elbs [186] gives good directions for the preparation of the lower members. As an example, the following directions are suggested by C. Weygand for the preparation of di-(p-propoxy)-azoxybenzene, $CH_3 \cdot CH_2 \cdot CH_2 \cdot O \cdot C_6H_4 \cdot \overset{\cdot\cdot}{N} : N \cdot C_6H_4 \cdot O \cdot CH_2 \cdot CH_2 \cdot CH_3$, from
$$O$$
p-nitrophenyl-n-propyl ether; see page 165.

[185] Schmidt and Schultz, *Ann.*, **207**, 329 (1881).
[186] Elbs, *Z. Elektrochem.*, **5**, 108 (1898); **7**, 133, 141 (1900); *J. prakt. Chem.*, **43**, 39 (1891).

The apparatus used is the same as that described in the preparation of azobenzene, except that it is cooled in ice. A cold, saturated sodium carbonate solution serves as anode liquid, alcohol saturated with sodium acetate as cathode liquid. 10 g. of p-nitrophenyl-n-propyl ether are dissolved in 200 cc. of the cathode liquor. The electrolysis is started with 3 amperes at 36 volts; during 8 to 9 hours the current is increased to 4.5 amperes. The greater part of the reaction product crystallizes from the cathode liquor and is filtered. The mother liquor yields another portion by careful precipitation with water. The yield is 3.4 g. of di-(p-propoxy)-azoxybenzene, corresponding to 39% of the theoretical. After recrystallization from alcohol it forms yellow crystals melting at 118°C. to cloudy liquid crystals and, further, at 121°C. to a clear amorphous liquid.

IV. IMINES AND SCHIFF BASES

The unsubstituted imino group, $:C:NH$, plays no important rôle either from a practical or a theoretical view-point. The imines may be prepared by the reaction of carbonyl compounds with ammonia, under suitable conditions, according to the equation, $R_2CO + NH_3 \rightarrow H_2O + R_2C:NH$.

As an example, the preparation of benzophenoneimine, Mignonac,[187] is described.

Benzophenone vapors and excess ammonia are passed over thorium oxide heated to 380° to 390°C., to give a yellowish oil boiling at 170° to 171°C. at 17.5 mm.

Ketimines also are formed, according to Moureu and Mignonac,[188] from the addition compounds of Grignard reagents and nitriles of the general formula, $R_2C:N \cdot MgBr$, by hydrolysis with ice, but this method is somewhat inconvenient. For the preparation of benzophenoneimine, for instance, the reaction product of benzonitrile with phenylmagnesium bromide must be isolated and then decomposed with a mixture of ice and ammonium chloride at $-15°C$. The mixture must be extracted immediately with ether and the imine precipitated with dry hydrogen chloride as hydrochloride from the mixture of ketone and imine obtained. The free imine is obtained by treating an ether suspension of the hydrochloride with ammonia.

The imides of benzoquinone played an important rôle in the evolution of the theory of the chromophores. Willstätter and Pfannenstiel [189] obtained benzoquinonemonoimine from p-aminophenol by shaking it in an ether suspension with dry silver oxide, which yielded colorless very unstable needles.

For the preparation of quinonediimine, which is described in Willstätter and Pfannenstiel's paper, the ether solution of p-phenylene-diamine is shaken with 2 moles of silver oxide (twice the theoretical amount) for 2 hours in the presence of ignited sodium sulfate to bind the

[187] G. Mignonac, *Compt. rend.*, **169**, 239 (1919).
[188] Ch. Moureu and G. Mignonac, *Compt. rend.*, **156**, 1803 (1913).
[189] Willstätter and Pfannenstiel, *Ber.*, **37**, 4607 (1904).

water of the reaction.   The silver precipitate is removed by filtration, and the filtrate concentrated on a steam bath to incipient crystallization and cooled to a low temperature.   The diimine crystallizes in the form of entirely colorless needles which, however, become discolored soon after filtration.   The compound melts at 124°C. with decomposition.

More important are the substituted imines, the so called Schiff bases, especially the derivatives of aromatic amines.

Primary aromatic amines react very readily with any aldehyde accompanied by the splitting off of water.   According to Schiff [190] benzalaniline (m.p. 54°C.) forms, even when heated only gently, from molecular amounts of benzaldehyde and aniline.   According to Hantzsch and Schwab [191] benzalaniline is polymorphous and shows varying melting points.   The melting points given in the literature lie between 42° and 56°C.   Aniline and formaldehyde react in a quite similar manner, but the so called anhydroformaldehyde aniline is known only as a polymer.

According to Vanino,[192] aniline is mixed with 5 times its volume of alcohol and a moderate excess of commercial 40% formaldehyde solution is added.   The mixture is shaken mechanically until nothing more crystallizes; the crystals are filtered, washed with alcohol, dried, and recrystallized from ligroin.   The melting point is 143°C.

Anhydroformaldehyde aniline is known for its importance in the new fuchsin process.   Many derivatives are described in the patent literature, all of which react with aromatic amines according to the monomolecular formula; that is, with the formation of secondary aromatic amines, according to the general scheme, $R \cdot N : CH_2 + C_6H_5 \cdot NH_2 \rightarrow R \cdot NH \cdot CH_2 \cdot C_6H_5 \cdot NH_2$.   The Schiff bases may also be used advantageously for the characterization of aldehydes as well as for primary aromatic amines.   Sometimes the condensation products thus formed may also be used quite conveniently for the preparation of secondary amines by hydrogenation.   The great stability of the Schiff bases proper, which are derived from purely aromatic aldehydes, is remarkable compared with the condensation products of aromatic amines and aliphatic or fatty aromatic ketones.   Thus, the condensation product of aniline and acetophenone could be obtained only with difficulty and in impure form, until Reddelien [193] discovered a method of preparation which consists of the use of the double salts of aromatic amines with zinc chloride instead of the usual means of splitting off water, such as zinc chloride or hydrogen chloride.   As an example directions are given for the preparation of acetophenone anil according to Reddelien.[194]

[190] Schiff, *Ann., Supplement*, **3**, 353 (1864–1865).
[191] A. Hantzsch and O. Schwab, *Ber.*, **34**, 828 (1901).
[192] L. Vanino, *Handbuch der präparativen Chemie.*   Vol. II, Enke, Stuttgart, 1937, p. 477.
[193] G. Reddelien, *Ber.*, **43**, 2476 (1910).
[194] G. Reddelien, *Ber.*, **43**, 2477 (1910); **47**, 1366 (1914); *Ann.*, **388**, 185 (1912).

20 g. of acetophenone and 20 g. of aniline are heated with 1 g. of aniline-zinc chloride to 160°C. (best in a current of carbon dioxide). The reaction proceeds vigorously and steam escapes. The mixture is heated 30 minutes longer, the temperature being raised at the end to 180°C. Then it is allowed to cool and a little chloroform is added to precipitate the zinc chloride-aniline. After filtration the chloroform is evaporated *in vacuo*. The acetophenone anil (13 g.) distils at 166° to 167°C. at 12 mm. The oil soon solidifies as colorless crystals melting at 41°C., which are recrystallized from petroleum ether by cooling in an ice-salt mixture.

In Reddelien's paper the preparation of numerous other compounds of similar constitution is described.

The keto anils are, as mentioned above, much less stable than the corresponding aldehyde anils. This may seem strange at first, but it can be explained by the fact that the former may exist in tautomeric forms as eneamines which are inclined to autoxidation and other subsequent reactions.

$$C_6H_5 \cdot \overset{\cdot\cdot}{C} \cdot CH_3 \; \rightleftharpoons \; C_6H_5 \cdot \overset{\cdot}{C} : CH_2$$
$$\overset{\cdot\cdot}{N} \cdot C_6H_5 \qquad\qquad \overset{\cdot}{N}H \cdot C_6H_5$$
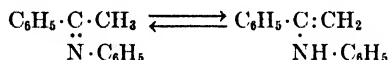
They do not keep well in sealed glass bottles, but are quite stable in inert containers even when exposed to the air. Many other sensitive compounds, such as unstable keto-enols, show a similar behavior.

V. HYDRAZONES, SEMICARBAZONES, PHENYLHYDRAZONES

The simple hydrazones of carbonyl compounds have little importance as such, except, under certain conditions, as starting materials for the Wolff-Kishner reaction; see page 52. Hydrazine can react with 1 as well as with 2 molecules of a carbonyl compound.

In accordance with the method of Curtius and Pflug [195] acetone hydrazone is obtained by mixing 15 g. of acetone with 15 g. of hydrazine hydrate to which a few pieces of barium oxide have been added. The reaction mixture becomes quite hot. After several days standing it is fractionated, the acetone hydrazone boiling at 124° to 125°C. Acetone hydrazone is quite unstable and decomposes when stored, with evolution of nitrogen and ammonia.

Dimethyl ketazine, $(CH_3)_2 : C : N \cdot N : C(CH_3)_2$, is prepared according to the method of Curtius and Zinkeisen [196] by mixing 1 mole of hydrazine sulfate with 2 moles of acetone and adding a little more than 2 moles of a 20% solution of sodium hydroxide, added in small portions with shaking until the reaction mixture is alkaline. The ketazine formed is extracted with ether, and the solution dried and distilled. The boiling

[195] Curtius and Pflug, *J. prakt. Chem.*, **44**, 543 (1891).
[196] Curtius and Zinkeisen, *J. prakt. Chem.*, **58**, 315 (1898).

point is 131°C.   Other ketazines are obtained in a similar manner.   This method is not recommended for the preparation of aldazines of the aliphatic series.

While alkaline condensation reagents are used in these examples for the formation of aliphatic hydrazones, benzalazine may be formed, according to Curtius and Jay,[197] from 1 mole of hydrazine hydrochloride or sulfate with 2 moles of benzaldehyde in alcoholic solution.   But the reaction is catalyzed by alkali also.

In place of the monohydrazones, the semicarbazones are a better derivative and are more conveniently prepared.   In most cases they crystallize well, have sharp melting points, and may readily be split into their components by boiling with dilute acids.   Their preparation is very simple.   According to Thiele,[198] semicarbazide hydrochloride is dissolved in as little water as possible, then the corresponding amount of alcoholic potassium acetate solution is added, and finally the carbonyl compound is involved.   The mixture is rendered homogeneous by the addition of a minimum amount of water or alcohol.   The velocity of formation varies greatly, from a few minutes to several days, when the reaction is carried out at room temperature.   For the slower ones, the duration of the reaction may be shortened by heating the mixture.

The semicarbazide does not always react with the carbonyl compound, but may add to reactive double bonds in a manner similar to that of hydroxylamine.   This fact must be kept in mind when unsaturated ketones and aldehydes are involved.   Strange to say it sometimes makes a difference whether the hydrochloride or the sulfate of semicarbazide is used.   A further variation is suggested by the use of thiosemicarbazide, because the thiosemicarbazones form very slightly soluble compounds with heavy metal salts; for details see the original paper of Neuberg.[199]

In sugar chemistry phenylhydrazine and its derivatives played a classic rôle in the preparation and purification of the individual sugars. When phenylhydrazine hydrochloride is used, the preparation of derivatives is, in principle, exactly the same as that described for the semicarbazones.   The reaction is carried out in aqueous alcoholic solution and the acidity reduced by potassium or sodium acetate.   If free phenylhydrazine is used as the starting material, a procedure which shows certain advantages, the components are mixed in alcoholic solution or, if the reaction is to be performed in aqueous solution, the phenylhydrazine is dissolved in an equal amount of 50% acetic acid.   With either method the purity of the starting material is important.   Phenylhydrazine hydro-

[197] Curtius and Jay, *J. prakt. Chem.*, 39, 44 (1889).
[198] J. Thiele, *Ber.*, 27, 1918 (1894).
[199] Neuberg, *Ber.*, 35, 2049 (1902).

chloride must be recrystallized from alcohol if it is not completely colorless. The free base may be distilled in a vacuum, or it may be recrystallized from an equal amount of ether by cooling in a freezing mixture. For the many derivatives of phenylhydrazine, such as p-bromophenylhydrazine, methylphenylhydrazine, benzylphenylhydrazine, diphenylhydrazine, and β-naphthylphenylhydrazine, which played a part in sugar chemistry, the special literature on this subject must be studied. Today, for the most part, the various nitrophenylhydrazines, such as 4-nitro- and 2,4-dinitrophenylhydrazine, are used for the identification of carbonyl compounds.

VI. NITRILES

In this chapter are discussed only those methods for the preparation of nitriles by which the carbon chain is not lengthened. The formation of cyanohydrins from aldehydes and hydrocyanic acid is dealt with on page 345, while the formation of cyanides from halides and alkali cyanides is discussed on page 367 in Chapter Eleven. A special method of formation for the aromatic series was described with the Sandmeyer reactions on page 115.

The two main reactions which lead to nitriles from nitrogen-containing compounds, without change of the carbon skeleton, consist of the removal of water from the acid amides and aldoximes, which are isomeric with one another. The acid amides may be replaced in some cases by the ammonium salts of carboxylic acids; the acid amides appear as intermediates, of course. In other cases, however, it is more advantageous to proceed from the free carboxylic acids through the acid chlorides and the amides.

Phosphorus pentoxide, phosphorus pentasulfide, phosphorus pentachloride, and thionyl chloride are the most important reagents for removing water from acid amides. The method is seldom important for preparative work in the aliphatic series, because the simple aliphatic nitriles are usually obtained better by one of the condensation methods. For the higher molecular fatty acids, with which the reaction proceeds very readily, it is usually advantageous to start with the amides. As an example the directions of Krafft and Stauffer [200] for the preparation of lauric nitrile from lauramide are given.

Lauramide is heated with half its weight of phosphorus pentoxide in a retort made of high melting, chemically resistant glass, under the vacuum of a water pump. The mixture foams considerably at the start, while the nitrile distils into the receiver. The crude product is purified by rectification in a vacuum and boils at 198°C. at 100 mm. Its melting point is 4°C. In a corresponding manner the nitriles of myristic, stearic, and palmitic acid were prepared.

[200] Krafft and Stauffer, *Ber.*, **15**, 1729 (1882).

The conversion of aldoximes to nitriles is important in sugar chemistry as the first step in the Wohl degradation of aldoses to the next lower homologue.   According to the scheme,

$$CH_2OH \cdot CH \cdot (CHOH)_3 \cdot CHNHOH \longrightarrow CH_2OAc \cdot (CHOAc)_4 \cdot CH:N \cdot OAc \longrightarrow$$
$$\underset{|\underline{\hspace{2em}O\hspace{2em}}|}{}$$

$$CH_2OAc \cdot (CHOAc)_4 \cdot C:N + CH_3 \cdot COOH \quad (Ac = acetyl)$$
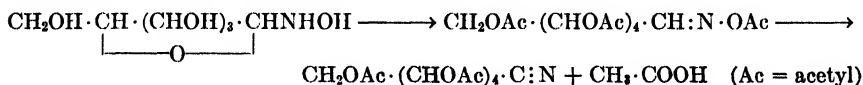
pentaacetyl compounds of aldonic acid nitriles are obtained from the oximes upon treatment with acetic anhydride and sodium acetate. Wolfrom and Thompson [201] showed that the oximes react in their tautomeric hydroxylamino forms.

According to Wohl [202] 25 g. of well dried glucose oxime (see page 266) are mixed with 25 g. of freshly melted sodium acetate and the mixture covered in a 2 liter flask with 100 cc. of acetic anhydride. The flask is connected to a long, wide, air-cooled reflux condenser and then carefully heated with continuous shaking until the reaction mixture starts boiling at one point. The very vigorous reaction proceeds to the end in a short time without further external heating. After the reaction has subsided, the dark liquid is poured immediately, with stirring, into 250 cc. of cold water. The cooled mixture is almost neutralized with sodium hydroxide (about 60 g.) and the aqueous solution is decanted from the tarry mass at the bottom of the flask. The dark product is washed with water by decantation and then dissolved by heating in 50 cc. of alcohol. On standing in the cold for several hours, 17 to 20 g. of pentaacetylglucononitrile crystallize. The crystals are filtered with suction, washed with pure then with aqueous alcohol, and dried in the air. From the mother liquor a few more grams are recovered. The crude product may be recrystallized from aqueous alcohol and decolorized with carbon; the melting point is 80° to 81°C. The yield of not quite colorless product which is sufficiently pure for further processing amounts to 40% of the theoretical. If the reaction is made to proceed less violently, the reaction product is less colored from decomposition products, but the acetylation remains incomplete and the yield decreases.

In a corresponding manner, tetraacetylarabononitrile can be obtained from arabinose oxime in a yield of 60% of the theoretical.

VII. NITROSO COMPOUNDS

A. Nitroso Groups Attached to Carbon

The nitroso group, in general, may be prepared only in two ways: by direct introduction into the aromatic nucleus when it contains certain groups, such as hydroxyl, $N(CH_3)_2$, or in the aliphatic as well as in the aromatic series, by dehydrogenation or oxidation, respectively, of hydroxylamino compounds and primary amines. The numerous isonitroso derivatives of compounds containing active methylene groups are discussed under oximes.

[201] M. Wolfrom and A. Thompson, *J. Am. Chem. Soc.*, 53, 622 (1931).
[202] A. Wohl, *Ber.*, 26, 732 (1893).

(a) Aliphatic Nitroso Compounds

The simple aliphatic nitroso compounds isomerize spontaneously into the corresponding oximes, and only the tertiary nitroso compounds have been isolated in a pure state. The nitroso group is stable at the nontertiary carbon atom in the pseudonitriles of the general formula,

$$R_2C\begin{matrix} \diagup NO_2 \\ \diagdown NO \end{matrix}$$

. Tertiary aliphatic nitroso compounds can be obtained by oxidation of primary amines of the type of tertiary butylamine, by monopersulfuric acid. Thus, tertiary nitrosobutane is prepared according to the method of Bamberger [203] in the following manner.

A solution of 1 g. of tertiary butylamine in 5 cc. of ether is shaken in a closed bottle with 10 g. of ice and 20 cc. of a solution of sodium monopersulfate (see below), containing the equivalent of 0.18 g. of oxygen. After a few minutes a light blue color appears in the ether, which becomes darker and finally fades again. After 6 minutes the ether is separated, shaken with a little sulfuric acid, and dried with calcium chloride. The ether solutions of sixteen such single batches are united. On heating in a water bath, the nitrosobutane distils with the ether. To isolate the nitroso compound, the ether is blown off with dry air, but the losses are high and only a few tenths of a gram of the colorless crystalline nitroso compound remains. The melting point must be determined in a sealed tube on account of the high vapor pressure of the nitrosobutane. It lies at 76° to 76.5°C. Nitrosobutane dissolves readily in organic solvents. The solutions are at first colorless, but after some time they turn deep blue because of depolymerization.

Monopersulfuric acid is prepared according to Caro,[204] see also Baeyer,[205] as follows:

18 g. of finely powdered sodium persulfate are mixed with 18 cc. of concentrated sulfuric acid and cooled with ice. The mixture is allowed to stand for 1 hour. It is then poured onto 100 g. of ice and neutralized with crystallized sodium carbonate while being cooled.

When one tries in the same way to oxidize primary amines, the amino group of which is attached to a primary or secondary carbon atom, one does not obtain the nitroso compounds, but the isomeric oximes of aldehydes or ketones. On the other hand, halogenated nitroso compounds which carry a halogen atom and a nitroso group at a secondary carbon atom, such as bromonitrosopropane, $(CH_3)_2 : C\begin{matrix} \diagup Br \\ \diagdown NO \end{matrix}$, are stable, because a rearrangement to an oxime is impossible. The bromonitrosopropane may be obtained according to Piloty [206] by treating acetoxime with

[203] Bamberger, Ber., 36, 686 (1903).
[204] Caro, Angew. Chem., 11, 845 (1898).
[205] Baeyer, Ber., 34, 855 (1901).
[206] Piloty, Ber., 35, 3113 (1902).

bromine in aqueous pyridine solution. In a corresponding manner, chloronitrosoethane, $CH_3 \cdot CHCl \cdot NO$, is obtained from acetaldoxime and chlorine. In this case, the chlorine stabilizes the nitroso group and no rearrangement to the oxime takes place, despite the fact that a hydrogen atom is available.

The numerous compounds of the type of isonitrosoacetone, $CH_3 \cdot CO \cdot CH : NOH$, which are designated isonitroso compounds, are really oximes and, therefore, are treated under that heading. However, some compounds, the nitroso group of which is attached to a secondary carbon atom, exist, such as α-nitrosopropionic acid ester. In common with the halogenated nitroso compounds mentioned above, they have a nitroso group stabilized by a negative substituent on the same carbon atom. The preparation of ethyl α-nitrosopropionate from ethyl methyl acetoacetate may serve as an example.

According to Schmidt and Widmann [207] nitrous gases are passed into 10 g. of ethyl methyl acetoacetate with ice cooling. The color of the liquid soon becomes light blue and after about 25 minutes turns dark bluish green. At this point the nitrous gases are shut off and the liquid allowed to stand in ice for several hours until the evolution of gases stops and the solution is of a dark blue color. The solution is put in a vacuum desiccator over sulfuric acid. Upon the reduction of the pressure a large volume of nitrogen oxides escapes, if they have previously been admitted long enough. After 4 hours of evacuation the nitroso ester is considered pure, because it cannot be purified in any other way. After long storage, the color disappears, partly because of polymerization, partly because of isomerization.

Nitroso compounds of this kind must be prepared without solvents; otherwise isonitroso compounds are obtained.

Nitroso compounds may be prepared by oxidation of hydroxylamines as well as aliphatic amines. According to Harries and Jablonski,[208] see also Bamberger and Seligmann,[209] diacetonehydroxylamine, which is obtained by addition of hydroxylamine to mesityl oxide, yields nitrosoisopropylacetone on oxidation with mercuric oxide:

$$(CH_3)_2 : C \cdot CH_2 \cdot CO \cdot CH_3 + HgO \longrightarrow (CH_3)_2 : C(NO) \cdot CH_2 \cdot CO \cdot CH_3 + H_2O + Hg$$
$$NHOH$$
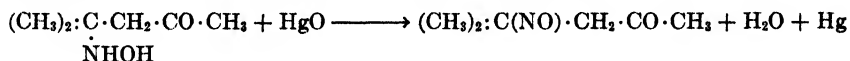
The colorless, very volatile compound can be recrystallized from petroleum ether; it melts at 75° to 76°C. to give a blue liquid.

(b) Aromatic Nitroso Compounds

Nothing in particular need be said about the preparation of aromatic nitroso compounds from aromatic amines with monopersulfuric acid, as the reaction proceeds in exactly the same manner as with aliphatic amines.

[207] Schmidt and Widmann, Ber., 42, 497, 1886 (1909).
[208] Harries and Jablonski, Ber., 31, 1371, 1809 (1898).
[209] Bamberger and Seligmann, Ber., 36, 697 (1903).

The oxidation of hydroxylamines in the aromatic series, however, may · conveniently be carried out with strong oxidation reagents, such as dichromates, because of the greater stability of the aromatic nitroso compounds.

According to Gattermann-Wieland,[210] for instance, 12 g. of phenylhydroxylamine are dissolved as quickly as possible, in portions, in an ice-cold solution of 50 cc. of concentrated sulfuric acid in 250 cc. of water. The solution is diluted with 500 cc. of ice water and an ice-cold solution of 12 g. of sodium dichromate in 200 cc. of water is added at 0°C. with stirring. Nitrosobenzene separates as flocculent crystals which are collected on a filter, washed with water, and immediately distilled with steam. The nitrosobenzene distils very readily as a green vapor and forms colorless crystals in the condenser. In order to get as stable a product as possible, the distillation must be stopped as soon as no more green vapors pass over. The distillation flask is removed and the nitrosobenzene is melted with steam after two-thirds of the cooling water has been drained from the condenser. If steam is blown through the dark, liquid residue in the distilling flask, decomposition products apparently pass over which contaminate the product and spoil its stability. The distilled product is filtered off and recrystallized from a little alcohol, to give colorless crystals which melt at 68°C. It may then be stored for quite some time if it is kept in tightly stoppered bottles.

The phenomenon, that the colorless solid gives a green melt and green vapors, is explained by assuming a dimolecular compound to be present in the solid nitrosobenzene; see Drucker and Flade.[211]

The phenomenon, that compounds which crystallize in colorless forms yield colored melts, is not limited, however, in the aromatic series to nitrosobenzene. Some nitro compounds, such as m-nitroacetotoluide,

$$CH_3-\!\!\!\!\!<\!\!\!\!\boxed{}\!\!\!\!>\!\!\!\!-NH\cdot CO\cdot CH_3,$$ are colorless substances when solid, but

$$NO_2$$
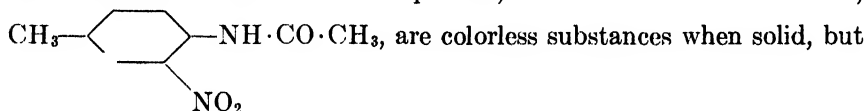
always yield yellow melts; see Gattermann [212] and Schaum.[213] However, depending on the circumstances and on the manner in which crystallization is induced, the melts crystallize in colorless or yellow forms, which are chemically identical and, therefore, to be considered polymorphous.

(c) *Formation of Aromatic Nitroso Compounds by Replacement of Hydrogen by Nitroso Group*

The reaction is successful with phenols and with tertiary amines, as mentioned above, while secondary amines yield nitrosamines and primary ones are diazotized. The nitroso group almost always takes the p position in benzene derivatives; in the naphthalene series, however, isomers

[210] Gattermann-Wieland, *Die Praxis des organischen Chemikers*. de Gruyter. Berlin, 1936, p. 182.
[211] C. Drucker and Th. Flade, *Z. wiss. Phot.*, 29, 29 (1930).
[212] Gattermann, *Ber.*, 18, 1482 (1885); 23, 1733 (1890).
[213] Schaum, *Ann.*, 300, 224 (1898).

are frequently formed simultaneously. Thus, α-naphthol yields about equal amounts of 1-hydroxy-2-nitrosonaphthalene and 1-hydroxy-4-nitrosonaphthalene. Nitrosophenol and nitrosonaphthol are tautomeric with the corresponding quinone oximes.

p-Nitrosophenol is prepared according to the method of Bridge [214] as follows:

60 g. of phenol, 27 g. of sodium hydroxide, and 54 g. of sodium nitrite are dissolved in 1500 cc. of water. To this solution is added slowly at 7° to 8°C., with cooling, a mixture of 150 g. of concentrated sulfuric acid and 400 cc. of water. After 2 hours, the precipitated nitrosophenol is collected on a filter, washed with water, and dissolved in ether. The ethereal solution is shaken with animal charcoal at room temperature. After evaporation of the filtered ether solution *p*-nitrosophenol is obtained in yellowish needles which, when quickly dried, melt at 125°C. with decomposition. The compound may be purified by recrystallization from benzene or toluene.

Nitrosophenol may also be recovered from the alkaline distillation residue which remains in the preparation of dimethylamine; see page 235. Directions are as follows:

The residue is filtered while hot and to the filtrate are added, with stirring, 250 g. of sodium chloride for each liter of liquid. When cooled with ice, a very voluminous precipitate of red, crystalline sodium nitrosophenolate precipitates. This is filtered with suction, dissolved in as little water as possible, and the solution shaken with animal charcoal at room temperature. The filtrate is run slowly and with stirring into ice-cold dilute sulfuric acid. The precipitate is filtered, dissolved in ether, and the ether solution treated as described above. The yield is 35 to 40% of the theoretical, on the basis of the nitrosodimethylaniline. The product is less pure than that obtained according to the first method.

Organic Syntheses [215] gives directions for the preparation of large amounts of α-nitroso-β-naphthol; this was first prepared by Fuchs [216] and is important in analytical chemistry.

While in the preparation of α-nitroso-β-naphthol the nitroso group takes the place adjacent to the hydroxyl group in a quantitative reaction, α-naphthol yields a mixture of isomers; see Ilinski and Henriques [217] and Harden.[218] The directions of Ilinski and Henriques follow:

A solution of 100 g. of α-naphthol and 100 g. of anhydrous zinc chloride in 600 cc. of alcohol is boiled under a reflux while a concentrated aqueous solution of 50 g. of sodium nitrite is added. The mixture is boiled for 2 to 3 hours longer and then allowed to stand for some time. The red zinc salt of 1-hydroxy-2-nitrosonaphthalene crystallizes together with free yellowish 1-hydroxy-4-nitrosonaphthalene. The mixture is filtered with suction, washed with a little cold alcohol, and suspended in water. Upon addition of

[214] Bridge, *Ann.*, 277, 85 (1893).
[215] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 411.
[216] Fuchs, *Ber.*, 8, 1026 (1875).
[217] Ilinski and Henriques, *Ber.*, 18, 706 (1885).
[218] Harden, *Ann.*, 255, 151 (1889).

hydrochloric acid 1-hydroxy-2-nitrosonaphthalene also separates in a free state. The mixture is again filtered with suction and washed well with cold water. To separate the two isomers, the mixture is treated with a solution of 30 g. of potassium hydroxide in 300 cc. of alcohol, the 1-hydroxy-4-nitrosonaphthalene passing into solution as the potassium salt. After some time, the undissolved potassium 2-nitroso-1-naphtholate is removed by filtration and washed with cold alcohol. The salt is dissolved in hot water and precipitated with hydrochloric acid. 50 g. of crude product are obtained, which may be recrystallized from water. The melting point is 162° to 164°C. with decomposition. 1-Hydroxy-4-nitrosonaphthalene is recovered from the original mother liquor as well as from the alkaline filtrates. The original mother liquor is diluted with 3 to 4 volumes of water, which precipitates the nitrosonaphthol at first, while unchanged α-naphthol still remains in solution. The mixture is therefore filtered as quickly as possible and the filter cake washed with water. From the aqueous alcoholic filtrate from the potassium 2-nitroso-1-naphtholate, more of the 1,4 compound is obtained by dilution with 4 to 5 volumes of water and acidifying with hydrochloric acid. The precipitate, filtered and washed with cold water, is united with the first fraction. After the hydroxynitrosonaphthalene has been dried, traces of α-naphthol and colored contaminants are extracted with benzene and the residue crystallized from dilute alcohol. Thus, 40 g. of 1-hydroxy-4-nitrosonaphthalene are obtained as shiny bronze leaflets melting at 193° to 194°C.

B. Nitroso Group Attached to Nitrogen

Nitrosomethylurea is prepared, according to Arndt and coworkers [219] (see also *Organic Syntheses* [220]), from methylamine hydrochloride or from methylamine which has been prepared from ammonia and dimethyl sulfate.

1. 100 g. of methylamine hydrochloride (1.48 moles) and 150 g. of potassium cyanate (1.85 moles) are dissolved in 600 cc. of warm water in a 1500 cc. flask. After the salts have been dissolved, the mixture is boiled moderately for 10 minutes and vigorously for 5 minutes more. The solution is filtered while hot and poured into a solution of 100 g. of 95% sodium nitrite (1.38 moles) in 200 cc. of water. The mixture is cooled to $-5°C$. and added in small portions and with stirring to a mixture of 600 g. of ice and 100 cc. of concentrated sulfuric acid in a 3 liter beaker which is cooled in a freezing mixture. The temperature must not exceed 0°C. while the solution of methylurea is added. This operation takes about 45 minutes. The foamy, crystalline powder of nitrosomethylurea is filtered at once, pressed well, slurried with 30 cc. of ice water, and again filtered with suction and pressed as dry as possible. A sample of the crude product must give a clear solution with boiling methanol. If a residue remains, the treatment with a little ice water must be repeated, which causes considerable loss. The yield amounts to 84 to 98% of the theoretical; that is, 120 to 140 g. of dry material.

Gattermann-Wieland [221] gives an analogous method, in which the dried nitrosomethylurea is recrystallized from 2 parts of methanol. The solvent is warmed, but not brought to a boil, and then the solution is cooled to $-15°C$. in a freezing mixture.

[219] F. Arndt *et al.*, *Angew. Chem.*, **43**, 444 (1930); **46**, 47 (1933).
[220] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 461.
[221] Gattermann-Wieland, *Die Praxis des organischen Chemikers.* de Gruyter, Berlin, 1936, p. 269.

2. 400 cc. of 28% ammonia (6 moles) are cooled in a 2 liter flask to −5°C. and 220 cc. of dimethyl sulfate (2.38 moles) added dropwise with continuous stirring, the temperature being kept below 20°C. This takes about 35 minutes. The mixture is then heated on a steam bath for 2 hours and finally boiled vigorously for 15 minutes. The hot solution is poured into a solution of 150 g. of potassium cyanate in 250 cc. of water in a 3 liter flask. This mixture is boiled 20 minutes and then filtered. To the filtrate is added a solution of 120 g. of 95% sodium nitrite in 200 cc. of water, and the mixture cooled to below 0°C. and added to a mixture of 600 g. of ice and 120 g. of concentrated sulfuric acid as above. Nitrosomethylurea (60 to 65 g.) can be isolated in the manner described above, which corresponds to a yield of 35 to 38% of the theoretical.

Nitrosomethylurea is not very stable if not recrystallized. It decomposes slowly above 20°C. and sometimes explodes suddenly with evolution of gas. Heavy explosions have not been observed thus far, but it is not advisable to store large amounts. The stability of the recrystallized product is better, but even in this case it is still well to be cautious.

VIII. HYDROXYLAMINES

1. By Addition to Ethylene Bond

Hydroxylamine derivatives are easily obtained by addition of the parent substance to double bonds, especially those of α,β-unsaturated ketones.

According to Harries and coworkers [222] 20 g. of mesityl oxide are boiled under a reflux with 15 g. of hydroxylamine hydrochloride and 100 cc. of water for 90 minutes. The diacetonehydroxylamine is set free with potassium carbonate from the brown, homogeneous solution. It is then extracted with ether and precipitated from the ethereal solution with an ether solution of anhydrous oxalic acid, which contains the calculated amount for the formation of the neutral oxalate. A yield of 24 g. of oxalate is obtained, corresponding to 67% of the theoretical. The free hydroxylamine is prepared by treating the aqueous solution of the oxalate with potassium carbonate and extracting the separated colorless oil with ether. Upon being dried and fractionated *in vacuo* at 9 to 10 mm., the diacetonehydroxylamine boils at 94° to 95°C. It solidifies at once on cooling, and melts at 52°C. after recrystallization from petroleum ether.

2. By Reduction and Oxidation

The hydroxylamines of the aliphatic series have no special significance. They are obtained by reduction of nitro or nitroso compounds or oximes which occur, as mentioned above, as intermediates during the reduction of aliphatic nitro compounds. The oxidation of amines to the hydroxylamino stage is only successful if the nitrogen atom is attached to a tertiary carbon atom; otherwise oximes are formed. Bamberger and Seligmann [223] carried out the oxidation of aliphatic amines with a tertiary carbon atom by the use of Caro's acid. Details may be found in the original paper.

[222] Harries *et al.*, *Ber.*, **31**, 1808 (1898).
[223] Bamberger and Seligmann, *Ber.*, **36**, 701 (1903).

The different reducing agents may be used for the preparation of aliphatic hydroxylamine derivatives.   In most cases zinc dust is used, but electrochemical reduction is also advantageous.   Beckmann [224] gives the following directions for the preparation of N-methylhydroxylamine.

Zinc dust (275 g.) is slowly added with vigorous stirring to a mixture of 100 g. of nitromethane, 60 g. of ammonium chloride, and 800 g. of water during 2 to 3 hours, the temperature being kept between 0° and 15°C. by suitable cooling.   The zinc dust is removed by filtration, and the filtrate acidified with hydrochloric acid and concentrated on a steam bath until a sample solidifies on cooling.   The residue is dissolved in alcohol, filtered from undissolved ammonium chloride, and the methylhydroxylamine hydrochloride precipitated from the alcoholic solution with ether.   When dry, it may be stored in a desiccator.

The free base, however, is not stable; see Brühl.[225]   According to V. Meyer [226] methylhydroxylamine may also be prepared by reduction of nitromethane with 1 mole of stannous chloride.

Aromatic hydroxylamine derivatives are obtained by reduction of nitro compounds.   The success of the method, which is almost exclusively carried out with zinc dust, depends considerably on the quality of the zinc dust and on the temperature.   In this respect the individual directions differ greatly from each other.   Zinc dust rich in zinc is not always especially reactive.   Bamberger [227] furthermore stated that one grade of zinc dust with about 70% zinc gave good yields of phenylhydroxylamine, while another grade with a similar metal content (67%) was entirely without effect.

Wohl [228] suggests suspending 100 parts of zinc dust in a sufficient quantity of water so that, on stirring, complete suspension of the material results.   To this mixture is then added a concentrated solution of 4 parts of copper sulfate and the mixture stirred until the aqueous solution appears colorless.   The coppered zinc dust is collected on a filter, washed, and dried *in vacuo.*

Weygand frequently made the observation that, for some reason difficult to understand, the preparation of phenylhydroxylamine from nitrobenzene with zinc dust and ammonium chloride does not proceed satisfactorily at the low temperatures (15°C. maximum) often prescribed. *Organic Syntheses* [229] gives good directions which are based on a German patent.[230]

[224] Beckmann, *Ann.*, **365**, 205 (1909).   J. Scheiber, *Ann.*, **365**, 225 (1909).
[225] Brühl, *Ber.*, **26**, 2514 (1893).
[226] V. Meyer, *Ber.*, **24**, 3531 (1891).
[227] E. Bamberger, *Ber.*, **27**, 1548 (1894).
[228] Wohl, German Patent, 84,891.
[229] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 445.
[230] German Patent, 89,978.

The phenylhydroxylamine thus prepared may, according to Wohl, be purified after drying by recrystallization from benzene. The melting point is 81°C. Absolutely pure phenylhydroxylamine is stable for some weeks.

Directions for the preparation of phenylhydroxylamines by reduction of nitrobenzene with sodium sulfide and hydrochloric acid, that is with hydrogen sulfide, were given by Lapworth and Pearson.[231] The method is not described here, because it offers no particular advantages. It dates back to a suggestion of Willstätter [232] who prepared α-naphthylhydroxylamine with excellent yield in the following manner.

A cooled solution of 20 g. of α-nitronaphthalene in 500 cc. of alcohol is saturated with ammonia and then with a rapid stream of hydrogen sulfide. After standing for 24 hours, the reaction mixture is added to 1200 cc. of cold water. The α-naphthylhydroxylamine crystallizes in a yield of 82% of the theoretical.

IX. OXIMES

Oximes are prepared either by the reaction of aldehydes and ketones with hydroxylamine, or as so called isonitroso compounds, by the reaction of compounds containing reactive methylene groups with nitrous acid or nitrous acid esters. In the first place one must decide whether hydroxylamine or its hydrochloride or sulfate is to be chosen. In place of free hydroxylamine a mixture of a mineral acid salt of hydroxylamine and the calculated amount of alkali hydroxide may frequently be used. In the aromatic series especially, α-oximes are often formed in neutral or alkaline solutions, while the stereoisomeric β-oximes are obtained in hydrochloric acid solution. A few examples follow to illustrate the methods.

Formaldoxime is prepared, according to Dunstan and Bossi,[233] as follows:

A solution of formaldehyde is mixed with a solution of hydroxylamine hydrochloride which has been neutralized exactly with the calculated amount of sodium hydroxide and the mixture, while still warm, is at once extracted several times with ether. The extract is dried with calcium chloride and the ether is removed by distillation at low temperature. The residual formaldoxime forms a colorless liquid boiling at 84°C. Formaldoxime is unstable, polymerizing at room temperature to form a gel.

Acetaldoxime, which is more stable, is prepared by Wieland [234] as follows: .

A solution of 325 g. of hydroxylamine hydrochloride in 300 cc. of water is mixed with a solution of 255 g. of crystallized sodium carbonate in 600 cc. of water. To this mixture is slowly added, with cooling by an ice-salt bath, a mixture of 200 g. of acetal-

[231] Lapworth and Pearson, *J. Chem. Soc.*, 119, 767 (1921).
[232] R. Willstätter, *Ber.*, 41, 1937 (1908).
[233] Dunstan and Bossi, *J. Chem. Soc.*, 73, 353 (1898).
[234] H. Wieland, *Ber.*, 40, 1677, foot-note 1 (1907).

dehyde and 100 g. of water. After standing 15 hours the solution is saturated with sodium chloride and extracted eight times with 1500 cc. each of ether. The ether solution is dried with calcium chloride and fractionated through a short column. Thus, a yield of 80% of the theoretical of acetaldoxime is obtained, boiling at 112° to 114°C. The ether extraction could be more easily accomplished in a continuous extraction apparatus.

Benzaldoxime, which exists in two forms, can be obtained according to Beckmann [235] in the following manner.

Benzaldehyde (1 mole) is mixed with an excess of 25% sodium hydroxide solution and 1 mole of hydroxylamine hydrochloride with shaking. The solution becomes warm. As soon as the benzaldehyde has passed into solution and the odor of it has disappeared, the solution is allowed to cool. If a part of the sodium compound of the oxime has crystallized, the crystals are dissolved by the addition of a little water, and the solution is then extracted several times with a little ether. Carbon dioxide is now passed into the solution, thus precipitating a mixture of much α- and a little β-aldoxime. By treatment of the mixture with a concentrated solution of sodium ethylate, the sodium compound of the α-oxime separates, while the β-oxime remains in solution. The crystals are filtered, washed with a solution of sodium ethylate, and dissolved in water. Upon treatment with carbon dioxide as above the α-oxime is obtained as an oil which soon crystallizes. It melts at 35°C. and boils at 123° to 124°C. at 14 mm.

The α-oxime may be converted to the β-oxime by passing hydrogen chloride into the ethereal solution of the former. The crystals formed are filtered with suction, washed with ether, and suspended in ether. This suspension is shaken at once in a separatory funnel with concentrated sodium carbonate solution. The ether solution is separated and the ether removed as quickly as possible *in vacuo* in the cold. The residue of β-oxime is mixed with benzene in order to render it stable. Upon filtration the β-oxime is obtained in thin shiny needles which melt at 128° to 130°C. when quickly heated. β-Oxime which has not been washed with benzene is sometimes reconverted to α-oxime very rapidly.

Benzophenone oxime is obtained according to Beckmann [236] by heating a solution of 30 g. of benzophenone in 150 g. of 90% alcohol with 20 g. of hydroxylamine hydrochloride and a little hydrochloric acid. The mixture is boiled under a reflux for 24 hours, the alcohol is then removed by distillation, and the residue which soon crystallizes is recrystallized from aqueous alcohol. The melting point is 139.5° to 140°C.

Camphor oxime is prepared according to Auwers [237] (see also Lenz [238]), in the following manner.

To a solution of 10 parts of camphor in 20 parts of alcohol is added a concentrated aqueous solution of 10 parts of hydroxylamine hydrochloride and 17 parts of sodium

[235] Beckmann, *Ber.*, **23**, 1684 (1890).
[236] Beckmann, *Ber.*, **19**, 989 (1886).
[237] K. v. Auwers, *Ber.*, **22**, 605 (1889).
[238] Lenz, *Arch. Pharm.*, **249**, 293 (1911).

hydroxide. If a cloudy liquor is obtained, the mixture is rendered homogeneous with alcohol and heated on a steam bath for about 1 hour, until the solution stays clear on addition of water or clarifies if it is made alkaline. When all the camphor has reacted, as shown by this test, the reaction mixture is diluted with water, filtered if necessary, and cautiously neutralized with dilute hydrochloric acid. The camphor oxime precipitates in fine white needles in a crude yield of 75% of the theoretical. It may be purified by recrystallization from aqueous alcohol and then melts at 120°C. Further amounts may be extracted with ether from the mother liquor.

Because of their importance in the Wohl degradation of sugars and in the preparation of amino sugars, a few examples of the preparation of sugar oximes will be described. Glucose oxime is prepared according to Wohl [239] as follows:

Hydroxylamine hydrochloride (77 g.) is dissolved in 25 cc. of hot water and to this solution is added a warm solution of 25 g. of sodium in 300 cc. of absolute alcohol, at first slowly and then fast enough to keep the solution just below its boiling point. After the solution has cooled, the separated sodium chloride is filtered off and washed with 300 cc. of dry alcohol. The filtrate is heated on a steam bath almost to its boiling point and mixed with 180 g. of finely powdered glucose which passes rapidly into solution. After the solution has cooled to 35° to 40°C., it is inoculated with glucose oxime crystals, or the crystallization is brought about by scratching. After several days 110 g. of glucose oxime crystallize, melting at 137.5°C. Upon concentration of the filtrate, first 26 g. of a product, almost as pure as the first crop, are obtained and from the mother liquor an additional 70 g. of a product which melts a little lower. The total yield, on the basis of glucose used, amounts to 80% of the theoretical.

If ordinary alcohol is used, only a little oxime crystallizes out and most of the crop is obtained as a syrup which crystallizes slowly. If larger amounts of anhydrous alcohol are used or less pure glucose, the oxime also separates as a sticky syrup. The same thing occurs if the solution is allowed to stand at room temperature, instead of at the given temperature of 35° to 40°C., when the maximum speed of crystallization is apparently approached.

Arabinose oxime is obtained in a similar manner, directions for which may also be found in the paper of Wohl mentioned above. He recommends using an excess of hydroxylamine (150% of the theoretical) and twice the amount of alcohol. The oxime crystallizes at once in an almost theoretical yield, melting at 132° to 133°C.

Mannose oxime was prepared by E. Fischer and Hirschberger [240] in an aqueous solution. Wolfrom and Thompson [241] modified the method as follows:

To a solution of 10 g. of mannose in 15 cc. of water are added 15 g. of potassium acetate and 7 g. of hydroxylamine hydrochloride, and the mixture heated gently for a

[239] A. Wohl, *Ber.*, **26**, 730 (1893).
[240] E. Fischer and J. Hirschberger, *Ber.*, **22**, 1155 (1889).
[241] M. Wolfrom and A. Thompson, *J. Am. Chem. Soc.*, **53**, 629 (1931).

few minutes. It is then placed in a freezing mixture for 30 minutes. The oxime crystallizes immediately upon scratching with a glass rod. It is filtered and washed with ice water to give 7.8 g. of mannose oxime melting at 175° to 177°C.

The conversion of these oximes into the acetylated nitriles was described on page 256. The acetyl compounds which occur as intermediates were prepared and closely studied by Wolfrom and Thompson; see their paper cited above. The pentaacetates of sugars which contain a free aldehyde group were used as starting materials.

Of the isonitroso compounds, which must be designated as oximes, those with the general formula, $R \cdot CO \cdot C : (NOH) \cdot R \rightleftarrows R \cdot CO \cdot CHNO \cdot R$, are the ones most often used for preparative purposes. On hydrolysis they yield α-diketones or, in some cases, vicinal triketones, while on reduction they give α-amino ketones. The reaction of ketones with nitrous acid cannot always be carried out, while the condensation with nitrous acid esters and alcoholate may be used in every case. Saponification does not always succeed readily (see page 159), but reduction to amino ketones, however, can apparently be carried out without exception. A special use of isonitroso ketones consists of their condensation to isatin and isatin derivatives.

In the aliphatic series, the simplest method is used frequently; namely, the reaction with free nitrous acid. For instance, isonitroso-acetone is prepared according to Küster [242] in the following manner.

To a solution of 5.8 g. of acetone in 30 cc. of glacial acetic acid, which is cooled to 0°C., is added slowly dropwise a concentrated aqueous solution of 15 g. of sodium nitrite. After 45 minutes; 100 cc. of water are added and the mixture extracted with ether. The ethereal solution is washed several times with 10 cc. portions of water and dried with sodium sulfate, and the ether is removed by distillation. The residual crystal mush is spread on a porous plate and then recrystallized from benzene. 6 g. of isonitrosoacetone are obtained, melting at 65°C.

The preparation of nitroso methyl ethyl ketone has been studied very carefully in recent times, because its saponification product, biacetyl, has become important as an aromatic. Semon and Damerell [243] examined the conditions for the preparation of biacetyl monoxime very thoroughly; see *Organic Syntheses*.[244]

There are various patents for the preparation of biacetyl through biacetyl monoxime, according to which the latter is obtained with free nitrous acid instead of a nitrous acid ester; see page 268.

Isonitrosoacetophenone is prepared according to Claisen and Manasse [245] as follows:

[242] W. Küster, *Z. physiol. Chem.*, **155**, 174 (1926).
[243] W. Semon and R. Damerell, *J. Am. Chem. Soc.*, **47**, 2033 (1925).
[244] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 204.
[245] L. Claisen and O. Manasse, *Ber.*, **20**, 2194 (1887).

To the solution of 1 mole of sodium dissolved in 20 times its weight of ethanol are added in portions, with good cooling, first 1 mole of amyl nitrite and then 1 mole of acetophenone. The mixture is allowed to stand in a well stoppered bottle, but it is advisable to keep the bottle cool; otherwise the mixture may explode. After 1 to 2 days the separated brown sodium salt of the isonitroso ketone is filtered off, washed with ether, and dried in air. The yield amounts to about 70% of the theoretical. To convert the sodium salt to the free isonitroso ketone, it is dissolved in ice water and the calculated amount of glacial acetic acid is added. The precipitated yellow isonitroso-acetophenone is filtered with suction, dried, and recrystallized from chloroform or ethyl acetate. The yield amounts to 50% of the theoretical of material melting at 126° to 128°C.

Organic Syntheses[246] gives details for the preparation of isonitroso-propiophenone.

If the molecule of the ketone contains a reactive methylene group at each side of the carbonyl group, as is the case with acetone, the reaction with nitrous acid or with nitrites may take place twice. However, it is better to use acetonedicarboxylic acid than acetone for the preparation of diisonitrosoacetone.

According to Pechmann and Wehsarg,[247] a concentrated aqueous solution of 40 g. of sodium nitrite is added, with cooling by ice, to a mixture of 50 g. of acetonedicarboxylic acid (see page 449) and 100 cc. of water. The mixture is slowly acidified with dilute nitric acid and cooled thoroughly. The crystallized diisonitrosoacetone is filtered with suction and washed with cold water. Koessler and Hanke[248] found that 30 g. of 93% sodium nitrite are sufficient. Also, the free sulfuric acid present in the crude acetonedicarboxylic acid is essential for the success of the reaction. As soon as this is bound as sodium sulfate, the evolution of carbon dioxide stops and the color of the reaction mixture turns brownish blue. Upon addition of nitric acid the color of the solution changes yellow again; thus, one can tell whether sufficient acid has been added.

Diisonitrosoacetone is important as the starting material for diamino-acetone, which in turn is used for imidazole syntheses.

The methylene group between the two carbonyl groups of 1,3-di-ketones and of β-keto esters reacts with nitrous acid in a similar manner, surprisingly enough even though the compound is stable only in the enol form.

For the preparation of isonitrosoacetylacetone, according to Wolff,[249] 50 g. of acetyl-acetone are suspended in 500 cc. of 7% aqueous sulfuric acid and a solution of 35 g. of sodium nitrite in 150 cc. of water is added with shaking. The mixture is extracted with

[246] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 363.
[247] v. Pechmann and Wehsarg, *Ber.*, **19**, 2465 (1886).
[248] K. Koessler and M. Hanke, *J. Am. Chem. Soc.*, **40**, 1717 (1918).
[249] Wolff, *Ann.*, **325**, 139 (1902).

ether, and the ethereal solution washed with water and dried. Upon evaporation of the ether, the remaining oil crystallizes. After recrystallization from ethyl acetate, the compound melts at 75°C.

For the preparation of isonitrosodibenzoylmethane, according to Neufville and Pechmann,[250] to a solution of 20 g. of dibenzoylmethane in 40 g. of chloroform are added, with cooling, 12 g. of amyl nitrite and 2 cc. of alcoholic hydrochloric acid. After some time, an equal volume of ligroin is added, thus precipitating 18 g. of isonitrosodibenzoylmethane. Upon recrystallization from chloroform or ligroin the compound melts at 146°C.

The action of nitrous gases on dibenzoylmethane, according to Wieland and Bloch,[251] at first leads to the bimolecular bisnitrosodibenzoylmethane of the formula,

$$\begin{array}{ccc} C_6H_5 \cdot CO & & CO \cdot C_6H_5 \\ & \diagdown \quad \diagup & \\ & CH \cdot N_2O_2 \cdot CH & \\ & \diagup \quad \diagdown & \\ C_6H_5 \cdot CO & & CO \cdot C_6H_5 \end{array}$$
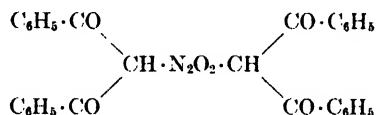
5 g. of dibenzoylmethane are dissolved in absolute ether and dry nitrous gases are admitted with good cooling. Bisnitrosodibenzoylmethane soon starts to crystallize. As soon as the color of the solution has turned olive-green, the admission of gases is discontinued and the mixture allowed to stand in a freezing mixture with exclusion of moisture for several hours. The crystals are filtered with suction and washed with ether; thus, 50 to 60% of the weight of dibenzoylmethane used is recovered as analytically pure bisnitrosodibenzoylmethane melting at 125°C. with decomposition. This compound is dissolved in alcoholic potassium hydroxide or ammonia. Upon acidifying with sulfuric acid the isonitrosodibenzoylmethane precipitates.

These isonitroso ketones are apparently not suited for the preparation of the basic triketones; see Lemaire.[252] The condensation products of keto-enols with nitrosodimethylaniline are better suited for this purpose and, therefore, their preparation is described at this point.

According to Sachs and Röhmer,[253] 4.4 cc. of 33% aqueous sodium hydroxide are added in one portion to a boiling solution of 24 g. of acetylacetone and 36 g. of nitrosodimethylaniline in 120 cc. of alcohol. After about 1 minute the color changes. The mixture is removed from the water bath and the reaction, which continues, must be moderated by occasional cooling. When the color of the solution has become pure red, it is cooled to a low temperature and diluted with about 400 cc. of ether. The separated sodium acetate (from acetylacetone by hydrolysis) is re-

[250] R. de Neufville and H. v. Pechmann, *Ber.*, **23**, 3378 (1890).
[251] H. Wieland and S. Bloch, *Ber.*, **37**, 1530 (1904).
[252] J. Lemaire, *Rec. trav. chim.*, **29**, 32 (1910).
[253] F. Sachs and A. Röhmer, *Ber.*, **35**, 3310 (1902).

moved by filtration and the filtrate decomposed in a separatory funnel with a mixture of 150 cc. of sulfuric acid ($D = 1.16$) and 50 cc. of water. The sulfuric acid layer is separated and extracted six times with 500 cc. portions of ether. The ether is removed from the combined ether-alcohol extracts by distillation at ordinary pressure, and then the alcohol is removed in a vacuum and the residue fractionated. Thus, 15 g. of triketo-pentane are obtained, boiling at 54° to 55°C. at 12 mm. Triketopentane is hygroscopic and changes on standing in moist air to a monohydrate.

X. NITROGEN DERIVATIVES OF CARBOXYLIC ACIDS

Acid Amides

The unsubstituted acid amides can be obtained in some cases by de-hydration of the ammonium salts. They are also prepared by addition of water to nitriles. The substituted amides, especially the acetyl and benzoyl compounds used for the characterization of amines, as well as some unsubstituted amides are best prepared by the reaction of the carboxylic acid halides or anhydrides with the respective amines.

1. By Removal of Water from Ammonium Salts

Formamide is prepared commercially in many different ways, which need not be discussed here. For the purification of commercial forma-mide, Willstätter and Wirth [254] recommend passing ammonia through the mixture until a slightly alkaline reaction is obtained. The ammonium formate, thus formed from excess formic acid, is precipitated by the addition of acetone and the filtrate, after drying, is distilled *in vacuo*.

For the preparation of formamide in the laboratory the very careful directions of Brann [255] seem to be the most suitable.

In a 3 liter flask equipped with a gas inlet tube running close to the bottom of the flask and with a downward condenser are placed 1500 cc. of pure formic acid. This is saturated with dry ammonia while being cooled with running water. The lower end of the condenser is connected to a suction flask through the side outlet of which the excess ammonia is removed. The ammonia is admitted at such a speed that the formic acid is neutralized in 15 to 20 minutes. Crystals of ammonium formate appear at the cold upper part of the flask, while the main portion remains melted. The stream of ammonia is now reduced and the flask heated in an oil bath. At 150°C. water starts to distil. If the heating is continued too long, the reaction mixture turns dark; normally, it is only brown. The temperature is increased during 4 to 5 hours to 180°C. until nothing more distils. The distillate is allowed to cool in a stream of ammonia and is finally distilled *in vacuo*. According to Willstätter and Wirth, the boiling point at 11 mm. is 105° to 106°C. The melting point of the amide is variously given as 1.8° to 4°C.

While an excess of ammonia hinders the hydrolysis of ammonium formate during the preparation of formamide, acetamide is obtained

[254] Willstätter and Wirth, *Ber.*, 42, 1911, foot-note (1909).
[255] A. Brann, *J. Am. Chem. Soc.*, 40, 793 (1918).

under opposite conditions, ammonium acetate being distilled through a column with an excess of acetic acid; see Gattermann-Wieland.[256]

Organic Syntheses [257] gives directions for the preparation of larger amounts of acetamide. It suggests that acetamide be purified by recrystallization from a mixture of 1 part of benzene and 0.3 part of ethyl acetate or by dissolving 1 part by weight of acetamide in 0.8 part by volume of methanol and diluting with 8 to 10 parts of ether; the crystallization is artificially started.

2. Addition of Water to Nitriles

Generally it is not difficult to catch the amide stage during the hydrolysis of nitriles with acids: $R \cdot CN + H_2O \rightarrow R \cdot CO \cdot NH_2$. Frequently the amides are obtained merely by dissolving the nitriles in cold concentrated sulfuric acid, when, upon standing in the air, they separate spontaneously at the rate at which the acid absorbs water. Generally applicable directions for the reaction cannot be given. Hydrolysis with concentrated acids may frequently be hastened by short heating to moderate temperatures, without the formation of noticeable amounts of carboxylic acids.

Thus for the formation of phenylacetamide from benzyl cyanide, according to Purgotti,[258] 2 parts of benzyl cyanide are mixed with 3 parts of sulfuric acid ($D = 1.82$), the temperature being kept below 70°C. The mixture is cooled and when poured onto ice solid phenylacetamide is obtained. It melts at 157°C. when pure. Since the acid amides are almost without exception well crystallized compounds, their preparation in this way is very simple.

If the saponification is carried out with alkalies, the amide step cannot be caught so well. However, according to Radziszewski,[259] it is possible to convert nitriles to acid amides in slightly alkaline medium with good results according to the scheme, $R \cdot CN + 2H_2O_2 \rightarrow R \cdot CO \cdot NH_2 + H_2O + O_2$. It is an open question what course the reaction follows. Using this method, Rupe [260] prepared the piperonylamide in the following manner.

To a mixture of 600 to 650 cc. of 3% hydrogen peroxide and 6 to 7 g. of aqueous potassium hydroxide are added very slowly, with gentle heating, 20 g. of piperonylonitrile. After about 30 to 40 minutes everything is dissolved. On cooling, the amide (m.p. 169°C.) crystallizes. A little piperonylic acid remains in the alkaline solution.

[256] Gattermann-Wieland, *Die Praxis des organischen Chemikers.* de Gruyter, Berlin, 1936, p. 134.
[257] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 3.
[258] Purgotti, *Gazz. chim. ital.,* 20, 173, 593, foot-note 2 (1890–1891).
[259] Radziszewski, *Ber.,* 18, 355 (1885).
[260] Rupe, *Ber.,* 33, 3403 (1900).

In *Organic Syntheses*[261] Buck and Ide also describe the method, incidental to the preparation of 3,4-dimethoxyaniline (4-aminoveratrole).

3. From Carboxylic Acid Halides, Anhydrides, and Esters

The preparation of unsubstituted carboxylic acid amides from acid chlorides, anhydrides, and esters is simple. The acid chloride or anhydride involved is mixed with an excess of ammonium carbonate and the reaction completed by heating on a steam bath. The ammonium salts are extracted with cold water and the remaining amide isolated in the usual manner. The esters of the carboxylic acids are made to react with alcoholic ammonia.

Thus, according to Weddige,[262] ethyl oxamate is obtained from diethyl oxalate by mixing 1 mole of ammonia in alcohol with a solution of 1 mole of oxalic ester in 2 to 3 volumes of alcohol, while the mixture is cooled carefully with ice. Most of the ethyl oxamate crystallizes out. This, with a further amount recovered from the mother liquor, is recrystallized from hot alcohol. An almost theoretical yield of ethyl oxamate is obtained, melting at 114° to 115°C. Only traces of oxamide, which is insoluble in alcohol, are formed.

Oxamide, oxalic acid diamide, is formed in an analogous manner from ethyl oxalate and an excess of ammonia in alcohol upon standing for several hours with occasional shaking. When washed with water and alcohol, the product is practically pure, but may be recrystallized from hot water in which it is slightly soluble.

In the same manner, malonamide may be obtained from diethyl malonate with excess concentrated aqueous ammonia.

The exchange of the alkoxy group of the esters for —NH_2, however, does not always take place. For instance, according to E. Fischer and Dilthey,[263] diethylmalonamide cannot be prepared from diethyl diethyl malonate, but may be obtained from diethylmalonic acid chloride as follows:

To a solution of 300 cc. of ether, saturated with dry ammonia at 0°C., 10 g. of diethylmalonyl chloride are added dropwise while ammonia is admitted cautiously, the mixture being shaken and kept cold. Ammonia must always be present in excess. The mixture of diethylmalonamide and ammonium chloride which separates is filtered, dried, and then extracted with cold water, and the residue is recrystallized from hot water. A yield of 55% of the theoretical of diethylmalonamide is obtained, melting at 224°C.

[261] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 44.
[262] Weddige, *J. prakt. Chem.,* 10, 196 (1874).
[263] E. Fischer and Dilthey, *Ber.,* 35, 854 (1902).

Organic Syntheses [264] gives directions for the preparation of cyano-acetamide from ethyl cyanoacetate.

The preparation of the substituted acid amides from primary or secondary amines is carried out in a manner quite similar to that of the unsubstituted ones. The free carboxylic acids as well as their chlorides or esters may be made to react with the amines. The reaction is frequently accelerated by the addition of a catalyst. Thus, acetanilide is obtained from aniline and glacial acetic acid only after many hours boiling under a reflux, whereas the time may be shortened very much by the addition of small amounts of sulfuric acid or sodium pyrosulfate.

According to Odell and Hines,[265] a mixture of 25 g. of aniline, 30 g. of glacial acetic acid, and 25 g. of sodium pyrosulfate is heated for 1 hour at 130° to 140°C. The solid cake obtained on cooling is powdered and dissolved in 300 cc. of boiling water. On cooling, an almost quantitative yield of acetanilide, melting at 113°C., is obtained.

Manicke and Grigel [266] recommend the addition of concentrated sulfuric acid for the preparation of acetanilide, phenacetin, and other acetyl compounds even when acetic anhydride, which is itself more reactive, is used instead of acetic acid. Under these conditions the reaction takes place even without any external heating.

For the preparation of substituted acid amides Bodroux [267] used a method in which carboxylic acid esters react according to the following equation:

$$R \cdot COOC_2H_5 + R' \cdot NH \cdot MgX \longrightarrow R \cdot CO \cdot NH \cdot R' + C_2H_5O \cdot MgX$$
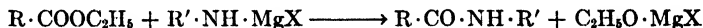
It has recently become important for the synthesis of natural polyenes; see page 431. Thus, Kuhn and Morris [268] converted β-ionylideneacetic ester into the corresponding *o*-toluide as follows:

A Grignard solution (see page 368) is prepared from 35 g. of methyl iodide and 5.9 g. of magnesium with 180 cc. of ether. The solution is cooled to 0°C. and to it is added dropwise a solution of 25.5 g. of pure *o*-toluidine in 50 cc. of ether. By continuous stirring the precipitate which appears first is dissolved after 30 minutes. Without isolation of the *o*-toluidinemagnesium iodide, the cooling bath is removed and a solution of 32 g. of β-ionylideneacetic ethyl ester in 50 cc. of ether is added dropwise. The reaction mixture then starts to boil. It is stirred for 15 minutes more and cooled in an ice-salt mixture. The solution is then decomposed with 100 cc. of ice-cold 0.1 N hydrochloric acid and the ether layer washed with 0.1 N hydrochloric acid until the aqueous layer is acid to Congo paper. The ether layer is then finally shaken six times with 200 cc. portions of water, then with a 0.05 N solution of sodium carbonate, and again with water.

[264] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 179.
[265] A. Odell and C. Hines, *J. Am. Chem. Soc.*, 35, 83 (1913).
[266] P. Manicke and P. Grigel, *Arch. Pharm.*, 264, 322 (1926).
[267] F. Bodroux, *Compt. rend.*, 138, 1427 (1904).
[268] R. Kuhn and C. Morris, *Ber.*, 70, 856 (1937).

After the material is dried over sodium sulfate in an atmosphere of nitrogen, the ether is carefully removed by distillation.   41 g. of a sticky, yellowish oil remain, which is used without further purification in the next step; see page 436.

For the purpose of characterization, amines are acylated in the same manner as are alcohols; see page 180.   Benzoyl derivatives are prepared most often because they usually crystallize well.   When acetic anhydride is used, the amine or its hydrochloride is dissolved in aqueous acetic acid, sodium acetate or potassium hydroxide is added, and then the anhydride, without cooling, often with heating to 60°C., and with shaking.

For the benzoylation of sensitive amines Étard and Vila [269] recommend adding crystallized barium hydroxide to the aqueous solution and then, slowly, benzoyl chloride; see also Biehringer and Busch.[270]

[269] Étard and Vila, *Compt. rend.*, **135**, 699 (1902).
[270] Biehringer and Busch, *Ber.*, **36**, 139 (1903).

Cleavage of Carbon-Nitrogen Bonds

The removal of nitrogen from its linkages to carbon has already been treated in the preceding chapter at different points whenever the reactions involved were important elements in the methods discussed.

A few more reactions must be mentioned here which are chiefly used for the degradation of heterocyclic compounds in such a manner that no degradation of the carbon skeleton takes place. These reactions do not belong in Chapter Twelve and, for this reason, are discussed in a short summary at this point.

The oldest method, discovered by Hofmann,[1] consists of the dry distillation of the quaternary ammonium bases. According to the scheme, $R_4 \cdot NOH \rightarrow R_3N + ROH$, one of four organic radicals of the quaternary hydroxyl compound is split off as alcohol, or, with loss of water, as an ethylenic hydrocarbon, thus breaking a C—N linkage. Which one of the radicals is eliminated depends on many circumstances. As an example of the opening of nitrogen-containing rings, the degradation of piperidine proceeds as follows:

$$CH_2-CH_2 \diagdown CH_2 \diagup NH \longrightarrow CH_2-CH_2 \diagdown CH_2 \diagup N \cdot (CH_3)_2OH \longrightarrow$$

$$CH_2=CH_2 \diagdown CH_2 \diagup N \cdot (CH_3)_2 + H_2O$$
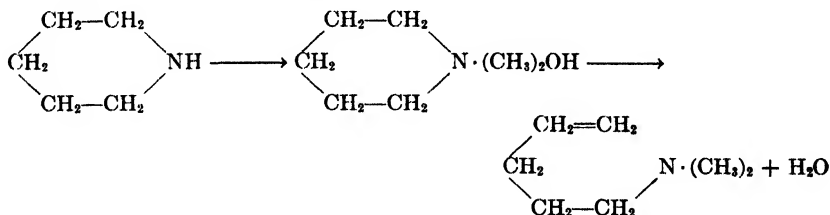
In this case the longest chain is split off. The unsaturated tertiary amines thus formed may be converted anew into a quaternary ammonium base which, on dry distillation, decomposes according to the equation:

$$CH_2:CH \cdot (CH_2)_3 \cdot N(CH_3)_3 \cdot OH \longrightarrow CH_2:CH \cdot CH_2 \cdot CH:CH_3 + N(CH_3)_3 + H_2O$$

The hydrocarbon, piperylene, contains the original carbon chain of the hetero ring.

For the conversion of piperidine to dimethylpiperidinium hydroxide Hofmann[2] recommends the following procedure.

[1] A. W. Hofmann, *Ber.*, 14, 494, 659 (1881).
[2] A. W. Hofmann, *Ber.*, 14, 660 (1881).

Methyl iodide is added dropwise to piperidine under a reflux and the mixture heated for a short time on the steam bath as soon as the vigorous reaction has subsided. The solution is allowed to cool, and the crystals filtered and recrystallized from alcohol. Thus, piperidine hydriodide and N-methylpiperidine are removed. The free base is obtained from the quaternary iodide with moist silver oxide. The characteristics of this base have never been investigated. Upon distillation it yields the so called dimethylpiperidine, $CH_2:CH\cdot CH_2\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$.

A simpler method of preparation was given by Ladenburg.[3]

To a mixture of 16 parts of piperidine and 25 parts of potassium hydroxide in 132 parts of alcohol are slowly added dropwise 84 parts of methyl iodide. The crystals are filtered with suction, dried, mixed with solid sodium hydroxide, and distilled from a copper retort. A yield of 70% of the theoretical of the so called dimethylpiperidine is obtained boiling at 116° to 118°C.

This is treated again with methyl iodide according to Hofmann's method above. The resulting salt mixture is extracted with hot alcohol from which, upon cooling, the quaternary iodide crystallizes. This is again treated with moist silver oxide, the silver iodide filtered, and the filtrate distilled to give a basic liquid as well as a light oil. The latter is separated after neutralization with hydrochloric acid, and rectified. It boils at 42°C. and consists of piperylene, 1,3-n-pentadiene. Trimethylamine and another base are formed as by-products. The degradation does not proceed at all quantitatively in the desired direction, even in such favorable cases.

A classical application of the method is the elucidation of the constitution of coniine, 2-propylpiperidine, which yields conylene, an octadiene, upon degradation according to Hofmann [4]; see also Mugdan [5] and Merling.[6] For the theory of the reaction see Braun.[7]

Further degradation methods were suggested by Braun. When acylated cyclic amines are treated with phosphorus pentachloride,[8] either chlorinated imide chlorides or ω,ω'-dichlorides are obtained. From benzoylpiperidine, for instance, the benzimide chloride of ϵ-chloro-n-amylamine is formed according to the scheme:

$$C_5H_{10}N\cdot CO\cdot C_6H_5 \longrightarrow C_6H_5\cdot CCl:N\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2Cl$$

or 1,5-dichloropentane according to the scheme:

$$C_5H_{10}N\cdot CO\cdot C_6H_5 \longrightarrow C_6H_5\cdot CN + Cl\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot Cl$$
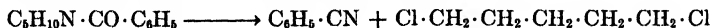
The benzimide chloride yields on hydrolysis with hydrochloric acid under pressure first the N-benzoyl-ϵ-chloroamylamine and this in turn the chloroamylamine itself. An example of the formation of the ω,ω'-

[3] Ladenburg, *Ann.*, **247**, 56 (1888).
[4] A. W. Hofmann, *Ber.*, **14**, 710 (1881).
[5] Mugdan, *Ann.*, **298**, 134 (1897).
[6] Merling, *Ann.*, **264**, 310 (1891); **278**, 1 (1894).
[7] J. v. Braun, *Ber.*, **42**, 2532 (1909).
[8] J. v. Braun, *Ber.*, **37**, 2915 (1904).

dihalogeno compound has already been described on page 212 for the preparation of pentamethylenediamine.

The second method of degradation by Braun consists of the action of cyanogen bromide, BrCN, upon cyclic amines. Tertiary amines react with cyanogen bromide according to the scheme:

$$R_3N + BrCN \longrightarrow R_2N \cdot CN + RBr$$
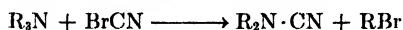
The tendency of the different radicals to split off varies. Tertiary cyclic amines, such as N-substituted piperidines, can react either according to the scheme:

$$C_5H_{10}N \cdot R + BrCN \longrightarrow C_5H_{10}N \cdot CN + RBr$$

or according to the equation:
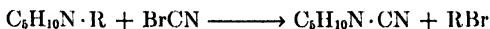
$$C_5H_{10}N \cdot R' + BrCN \longrightarrow Br \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NR' \cdot CN$$

The cyanamides formed in the latter case may be saponified to brominated secondary amines.

The reaction follows the first scheme generally, according to Braun,[9] only if R is a radical of low molecular weight; that is, with methyl-, ethyl-, and propylpiperidine. Even butylpiperidine reacts in the main according to the second scheme. Phenyl- and p-tolylpiperidine show a similar behavior. The latter two, however, cannot readily be prepared from piperidine; therefore, their reaction with cyanogen bromide, which has been studied thoroughly, has no special significance for the degradation problem proper. The readily available N-methyl derivatives of some bases, such as the ones of tetrahydroisoquinoline, narcotine, as well as hydrocotarnine and hydrohydrastinine and tetrahydroisoindoles, may also be split. Tropidine, which contains a double bond in the ring, can be subjected to the degradation according to the second scheme.[10]

On the basis of these experiences, Braun used his cyanogen bromide method mainly for comparative studies on the stability of heterocyclic systems.[11]

No such method for splitting the C—N bond, which is always successful, is known for the aromatic systems. In most cases the C—C bonds are split by the severe reactions.

The cleavage of pyrrole and its homologues by hydroxylamine is important for preparative work. It proceeds according to the scheme:

$$\begin{array}{c} CH=CH \\ | \qquad\qquad \diagdown \\ \qquad\qquad NH + 2NH_2OH \longrightarrow \\ | \qquad\qquad \diagup \\ CH=CH \end{array} \quad \begin{array}{c} CH_2-CH:NOH \\ | \qquad\qquad\qquad + NH_3 \\ CH_2-CH:NOH \end{array}$$
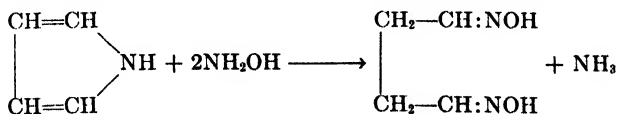
[9] J. v. Braun, *Ber.*, **40**, 3916 (1907).
[10] J. v. Braun, *Ber.*, **49**, 2624 (1916).
[11] J. v. Braun, *Ber.*, **42**, 2221 (1909); **49**, 2629 (1916).

The reaction yields succinaldehyde dioxime and its homologues.   It can also be successfully carried out with pyrroles carrying an aliphatic substituent at the nitrogen, but not with N-phenylpyrrole.   For the preparation of succinaldehyde dioxime numerous directions have been given since Ciamician and Dennstedt first described [12] this reaction.   Willstätter and Heubner [13] give the following details.

Pyrrole (33.5 g.) and 70 to 72 g. of hydroxylamine hydrochloride are dissolved in 500 cc. of alcohol, 53 g. of sodium carbonate are added, and the mixture is boiled under a reflux for 24 hours.   The solution, while still hot, is decanted from the separated sodium chloride, the alcohol removed by distillation in a vacuum, and the residue mixed with as little water as possible.   The undissolved dioxime is filtered with suction and washed with a little ice-cold water and 60% alcohol.   Thus, 26.8 g. of almost pure dioxime remain, corresponding to a yield of 46% of the theoretical.   After recrystallization from water or alcohol the melting point is 171°C.   From the alcoholic distillate a part of the unchanged pyrrole may be recovered, according to Harries,[14] by fractional distillation.

The method has played a rôle in explaining the constitution of pyrrole homologues; see H. Fischer and Zimmermann.[15]

For the conversion of succinaldehyde dioxime to succinaldehyde see page 160.

[12] Ciamician and Dennstedt, *Ber.*, **17**, 533 (1884).
[13] Willstätter and Heubner, *Ber.*, **40**, 3871 (1907).
[14] Harries, *Ber.*, **35**, 1184 (1902).
[15] H. Fischer and W. Zimmermann, *Z. physiol. Chem.*, **89**, 163 (1914).

Formation of Carbon-Pentavalent Nitrogen Linkages

NITRO COMPOUNDS

A. Nitro Groups by Addition

From the purely theoretical view-point nitro compounds could be obtained by addition of nitrous acid to the double bond. This reaction has not been observed, because nitrous acid reacts with unsaturated compounds, forming pseudonitrosites. Nitro compounds, however, can be obtained by addition of nitric acid or nitrogen dioxide to ethylene compounds. The addition of nitric acid to aliphatic double bonds is of little preparative importance; see Wieland and Sakellarios.[1]

According to Wieland, the addition of nitric acid is the first step in nitration of aromatic compounds. These intermediates have never been isolated, a fact that is not surprising. For preparational work the problem has little meaning.

The addition of nitrogen dioxide to double bonds very likely proceeds according to the scheme

$$-CH{=}CH{-} + 2NO_2 \longrightarrow \begin{array}{c} -CH{-}CH{-} \\ | \quad\ | \\ ONO\ NO_2 \end{array}$$
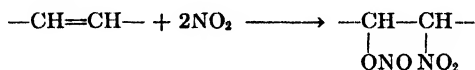
Thus, nitrous acid esters of saturated nitro alcohols are formed. From these, unsaturated nitro compounds but not alcohols can be obtained in satisfactory yields. These nitro alcohol nitrites are regular by-products whenever unsaturated compounds are treated with nitrogen oxides generated from arsenic trioxide and nitric acid. The so called pseudonitrosites are usually formed as the main product. These crystalline products thus far have usually been the source of unsaturated nitro compounds. If the pseudonitrosites as such are not desired, presumably it might be better to treat the ethylene compounds with pure nitrogen dioxide instead of with a mixture of nitrogen oxides. The preparation of the pseudonitrosite of cyclohexene, according to the directions of Wieland and

[1] H. Wieland and E. Sakellarios, *Ber.*, **53**, 201 (1920).

Blümich,[2] is as follows: Nitrous gases are passed into 100 g. of well cooled cyclohexene, diluted with 1.5 volumes of a mixture of equal parts of ether and petroleum ether, until the precipitation of crystals ceases. The nitrous gases are generated from coarse pieces of arsenic trioxide and nitric acid ($D = 1.23$), the moisture is partially removed in a reflux condenser on top of the reaction flask, and then the gases are dried over calcium chloride and finally over phosphorus pentoxide. All parts of the apparatus are connected by means of ground glass joints. A cock is provided at the bottom of the calcium chloride tower to drain the liquid which collects there. After the gases have been admitted for several hours, 30 g. of cyclohexene pseudonitrosite are obtained. Corresponding yields are obtained with smaller batches.

For a method of preparing nitroethylenes of the general formula, $R \cdot CH : CH \cdot NO_2$, accompanied by lengthening of the chain, see page 436.

B. Nitro Compounds by Replacement

1. By Substitution of Nitro Group for Hydrogen

Nitration

Just as halogenation does not stop when 1 halogen atom has been introduced, so even when only small quantities of nitrating agent are used, nitration does not stop after the introduction of one nitro group. During the reaction, however, the formation of mono- or polysubstituted products may be controlled by the temperature more readily than is the case during halogenation. While the introduction of chlorine and bromine generally proceeds without any side reactions even at high temperatures, during nitration at high temperatures oxidation effects predominate.

Catalysts for nitration are hardly known; nor does light play any part. The action of nitric acid differs from the reaction of the halogens in that it depends on the concentration. Only at high temperatures and in a dilute state does it preferably attack the aliphatic residues; the concentrated acid substitutes in the nucleus.

Nitrating Agents

1. Nitric Acid. Nitric acid of different degrees of concentration and of a very high grade of purity is commercially available. It is not worth while to prepare highly concentrated nitric acid in the laboratory from a dilute acid. Almost anhydrous nitric acid may be obtained by distilling fuming commercial acid ($D = 1.5$, not to be mistaken for red, fuming acid) with twice its weight of concentrated sulfuric acid. The distillation is best performed *in vacuo*. When the material is distilled at ordinary pressure, the distillate has a yellowish color owing to its content of nitro-

[2] H. Wieland and Blümich, *Ann.*, **424**, 86 (1921).

gen oxides.   These oxides may be removed by passing dried dust-free air or carbon dioxide through the liquid at 70° to 80°C. until it becomes colorless.   For the removal of the last traces of nitrous acid see below.   In many cases it will not be necessary to remove the nitrous acid, but, if it is not removed during the nitration of amines, trouble can be expected because of the possible formation of diazonium compounds.   The acid distilled *in vacuo* at 15 mm. is colorless.

If concentrated nitric acid should not be available, a mixture of sodium nitrate and one-third of the calculated amount of concentrated sulfuric acid is distilled *in vacuo* on the water bath from a tubulated retort or from an all-glass apparatus with ground joints.   The rest of the calculated amount of sulfuric acid is added at the same rate at which the pure acid distils.   The distillate is colorless and free of nitrogen oxides; its density is about 1.53.

If sodium nitrate is distilled with about 3 times its volume of concentrated sulfuric acid at ordinary pressure, the nitric acid obtained contains nitrogen oxides.

In order completely to free nitric acid of nitrous acid, it is boiled for a short time with 0.5 to 1% of urea while a strong current of dry air or carbon dioxide is passed through.   Carbon dioxide, nitrogen, and water are formed and the acid is somewhat diluted.   Urea nitrate may be substituted for urea.   Nitric acid entirely free of nitrous acid is less active in some special cases than the regular acid.   For instance, it does not attack phenols in ethereal solution; see Klemenc and Ekl.[3]

2. Red, Fuming Nitric Acid.   The red, fuming nitric acid is also a commercial product.   If necessary, it may be prepared in the laboratory by passing nitrogen oxides into concentrated acid, or by distilling ordinary concentrated acid from an equal weight of concentrated sulfuric acid and 3 to 4% of vegetable starch.   The specific gravity, of course, does not indicate nitric acid content.   This is always lower.   The content of nitrogen dioxide may exceed 12%.

3. Mixed Acid.   By far the most important of all nitrating agents is the so called mixed acid which consists of concentrated or anhydrous nitric acid and varying amounts of sulfuric acid.   Its preparation is very simple, consisting of mixing the components; for instance, for the nitration of 100 g. of benzene, 110 g. of nitric acid ($D = 1.456$) and 143 g. of sulfuric acid ($D = 1.842$); or 73.5 g. of nitric acid and 157 g. of sulfuric acid for 50 g. of toluene; or 17.5 parts of nitric acid, 78 parts of sulfuric acid, and 4.5 parts of water for the nitration of nitrotoluenes to trinitrotoluene.

Mixed acid was used for the first time by Hofmann and Muspratt.[4]

---

[3] A. Klemenc and Ekl, *Monatsh.*, **39**, 641 (1918).
[4] Hofmann and Muspratt, *Ann.*, **57**, 214 (1846).

It suppresses the harmful (oxidation) side reactions caused by intermixed nitrogen oxides. Under certain conditions it also hinders the oxidation caused by nitric acid itself, because of the formation of salts (nitration of amines and aldehydes).

4. Other Nitrating Mixtures. Nitric acid is sometimes mixed with glacial acetic acid or with acetic anhydride instead of with sulfuric acid. The effect of these mixtures is similar to that of dilute nitric acid. Finally, a mixture of nitric acid, sulfuric acid, and glacial acetic acid is used occasionally.

Because of its chemically reactive nature nitric acid is not used very often in organic solvents. Besides glacial acetic acid, alcohol [5] may be considered as solvent; also acetone, ether, and chloroform. The last mentioned was first recommended by Willstätter [6] for diluting 100% nitric acid, and was recently suggested again by Darzens [7] for commercial use.

5. Nitration with Nitrates. The method of nitrating with an alkali nitrate and sulfuric acid is used if nitration with mixed acid is not successful; for instance, according to Nägeli,[8] 100 g. of benzoic acid are mixed with 200 g. of potassium nitrate, and 300 g. of 100% sulfuric acid are slowly added, with stirring. The mixture is gently heated until the nitrobenzoic acids separate as an oil. After the mixture has cooled, the solidified product is mechanically separated from potassium bisulfate and purified through the barium salts. Besides m-nitrobenzoic acid, there are obtained, as by-products, 20% of o- and 2% of p-nitrobenzoic acids. 2,3,4,6-Tetranitroaniline is obtained from aniline with mixed acid and potassium nitrate according to Flürscheim.[9] A mixture of potassium nitrate and concentrated sulfuric acid is used at high temperatures in a sealed tube; see Kaufmann and Decker.[10] Instead of potassium nitrate, barium nitrate is occasionally mentioned in patents. Copper, nickel, iron, and cobalt nitrates, and others, have been recently introduced. According to Menke,[11] these nitrates work well, because they have a low decomposition temperature. In combination with acetic anhydride they show reactions similar to the generally inaccessible and harmful acetyl nitrate (see items 6 and 7). Bacharach [12] confirmed the observations of Menke. He states that the nitrates mentioned above nitrate at low temperatures like acetyl nitrate and, therefore, preferably yield o substitution products; while lithium nitrate, which he was the first to use, at

[5] French Patent, 345,441.
[6] R. Willstätter, *Ber.*, 42, 4151 (1909).
[7] G. Darzens, *Chem. Abstracts*, 28, 5671 (1934).
[8] E. Nägeli, *Bull. soc. chim.*, 21, 786 (1899).
[9] Flürscheim, *Z. ges. Schiess- u. Sprengstoffw.*, 8, 185 (1913); *Chem. Abstracts*, 7, 2685 (1913).
[10] Kaufmann and H. Decker, *Ber.*, 39, 3649 (1906).
[11] J. B. Menke, *Rec. trav. chim.*, 44, 141, 269 (1925).
[12] G. Bacharach, *J. Am. Chem. Soc.*, 49, 1522 (1927).

higher temperatures yields for the most part p derivatives. This specific o or p effect is so pronounced that benzene derivatives with second class substituents, such as benzoic acid, benzaldehyde, and nitrobenzene, cannot be nitrated according to this method.

6. Acetyl Nitrate. Acetyl nitrate is prepared by adding nitrogen pentoxide to an equal amount of acetic anhydride. The mixture hardly warms; the acetyl nitrate formed distils at 22°C. at 70 mm. Working with acetyl nitrate may be dangerous; see Pictet and Khotinsky.[13] In many cases the distillation of the mixture is not necessary. Acetyl nitrate must not be heated, because decomposition and explosions occur on quick heating. The advantage of this nitrating agent lies in the fact that it directs the nitro group to the o position of substituted benzene derivatives, such as toluene, benzyl chloride, and acetanilide. Furthermore, it almost exclusively yields mononitro derivatives. Acetyl nitrate is very sensitive to moisture.

7. Benzoyl Nitrate. Benzoyl nitrate whose effect is similar to that of acetyl nitrate is prepared by adding very finely powdered and absolutely dry silver nitrate (20% excess) to benzoyl chloride at −15°C. The silver nitrate is added in small portions. After the first portions have reacted, the mixture may be cooled to a lower temperature without freezing the benzoyl chloride. The moisture in the air must be carefully excluded. The mixture is allowed to stand for 1 hour at this low temperature, and then is filtered through dry asbestos. The oil obtained contains about 15 to 20% benzoic anhydride. It must be carefully protected from moisture. On filtration through a wet filter, it may decompose with great violence.

8. Nitrogen Oxides. It was mentioned above that nitrations with pure nitric acid free of nitrogen oxides proceed with difficulty or not at all. According to Klemenc,[14] the presence of nitrogen pentoxide in mixed acid must be assumed for physicochemical reasons. Schaarschmidt[15] states that it is this nitrogen pentoxide which adds to aromatic compounds. The decomposition of this addition compound produces nitric acid from which, in turn, nitrogen pentoxide is produced. The course of the nitration with the lower nitrogen oxides is quite analogous regardless of whether a mixture of NO–NO₂ or whether pure nitrogen di- or tetraoxide is used. In each case only the tetraoxide is active. The addition compound decomposes spontaneously to the nitro derivative and nitrous acid according to the scheme, $C_6H_6 + N_2O_4 \rightarrow C_6H_5 \cdot NO_2 + HNO_2$. Schaarschmidt made the existence of complex compounds of the formula,

[13] Pictet and Khotinsky, *Ber.*, **40**, 1163 (1907).
[14] Klemenc, *Chem.-Ztg.*, **48**, 717 (1924).
[15] Schaarschmidt, *Angew. Chem.*, **39**, 1457 (1926).

$2AlCl_3(C_6H_6N_2O_4)_3$, appear probable. Despite numerous experiments, especially by Schaarschmidt,[16] to substitute the relatively expensive mixed acid by cheap nitrogen tetraoxide, no success was encountered and the use of nitrogen oxides as nitrating agent is restricted to a few special cases.

9. Aluminum Nitrate. $Al(NO_3)_3 \cdot 9H_2O$ was used long ago for the nitration of alicyclic hydrocarbons; see Nametkin.[17] In principle, this is similar to the nitration with dilute nitric acid, since the salt is partially hydrolyzed at 73°C. and decomposes completely at 140°C. into nitric acid and hydrated aluminum oxide. When a mixture of 100 g. of cyclohexane and 240 g. of aluminum nitrate was heated to 110° to 120°C., more than 56% yield of nitrocyclohexane was obtained; from methylcyclohexane, a 72% yield of nitro products was obtained.

Nitration Methods

In the following paragraphs, the nitration of the most important aromatic and heterocyclic systems will be briefly outlined.

The course of the nitration of benzene is known; only three nitro groups can be introduced directly. 1,2,3,5-Tetranitrobenzene, which was supposedly obtained by oxidation of a 1,3-dinitro-4,5-dinitrosobenzene, is non-existent according to Will.[18] It is not practical to prepare trinitrobenzenes by direct nitration, as they may be prepared more readily by indirect methods. The direct nitration of naphthalene is not difficult; however, it yields α-nitronaphthalene exclusively. β-Nitronaphthalene is obtained in indirect ways. The higher nitrated naphthalenes are formed in part by direct nitration, in part by indirect methods. More than two nitro groups have apparently never been observed in the nucleus of naphthalene. The nitration of anthracene is considerably more difficult; it yields products substituted in the 9 and 10 positions exclusively. Phenanthrene gives various isomeric nitrophenanthracenes, one of which has been identified as 3-nitrophenanthrene.

Of the 5-membered heterocyclic compounds, thiophene and pyrrole may be nitrated as easily as benzene. Thiophene has to be treated with care, lest decomposition products or dinitrothiophene be formed. The oxidizing effect of nitric acid becomes more noticeable with pyrrole, which is apparently nitrated but immediately undergoes a radical change. Indirect ways must be selected for the preparation of nitropyrroles. It is surprising that furane may be converted into the monoacetate of nitrosuccinaldehyde with nitric acid and acetic anhydride. The reaction takes place quite readily without decomposition although with rearrangement

[16] Schaarschmidt, *Ber.*, **57**, 2065 (1924).
[17] Nametkin, *Angew. Chem.*, **24**, 1250 (1911).
[18] Will, *Ber.*, **47**, 714 (1914).

to the dialdehyde.   From nitrosuccinaldehyde, 3-nitrofurane is formed by removal of acetic acid with dry pyridine.

The 6-membered heterocyclic compounds show a different behavior. Pyridine can be converted to β-nitropyridine only with great difficulty and with very poor yields. This resistance to nitration is found in quinoline, of which only the benzene nucleus can be nitrated. Pyrazole may be nitrated as readily as a normal aromatic compound. The pyrazole ring has as high a stability towards chemical reagents as the pyridine ring. The NH group is apparently responsible for the ease with which the system reacts. Isoxazoles which are substituted in the 3,5 position also readily yield nitro derivatives.

Influence of Substituents on Nitration of Aromatic and Heterocyclic Compounds

Substituents in the aromatic or heterocyclic nucleus may facilitate direct nitration or they may make it more difficult. Methyl groups have relatively little influence; longer chains have more effect, since the oxidizing action of the nitric acid becomes more apparent. Most reactive of all are the phenols and amines. The halogen substitution products are also very reactive. Carboxylic acids, sulfonic acids, and the nitro compounds themselves are difficult to nitrate. As far as the formation of isomers is concerned, some deviations and regularities can be observed which are unusual.

Acetophenone yields varying amounts of *o*- and *m*-nitro substitution products simultaneously; their ratio depends on the temperature. This is one of the rare cases in which the directing effect of a substituent is very abnormal as far as Holleman's substitution rules are concerned.

A similar behavior is exhibited by benzoic acid, which yields more than 20% *o*-nitrobenzoic acid besides about 75% *m*-nitrobenzoic acid. Data on this nitration and on the dependency of the ratio of isomers upon the composition of the nitrating acid are given by Holleman.[19] Benzal chloride and benzotrichloride yield *m* substitution products when nitrated, while halogen directs to *o* and *p* positions. Nitration occupies a peculiar position, as can be seen from the relatively high content of *m*-nitrotoluene (1 to 2%) which occurs during the direct nitration of toluene; in this case the *m* compound is formed besides the *o* and the preferred *p* compound. The *p* isomer of acetophenone is not formed at all. The nitro group can at least to a limited extent be redirected to the *m* position in another way. This is accomplished by nitrating amines in the presence of a large excess of sulfuric acid. The formation of *m*-nitroaniline in this way is not an important method, because *m*-nitroaniline is much more conveniently obtained by partial reduction of dinitrobenzene.

[19] Holleman, *Ber.*, **39**, 1716 (1906).

It is possible to influence the ratio of *o* and *p* substitution products. Phenol almost always yields *o*- and *p*-nitrophenols in nearly equal amounts when ordinary nitric acid is used. Toluene when treated with mixed acid or with nitric acid alone gives a yield of 40 to 60% *p*-nitrotoluene, while the reaction of acetyl nitrate with toluene produces 90% of the *o*-nitro compound. Phenol also gives more *o*-nitrophenol, but the shifting is not so conspicuous in this case. Acetanilide with acetyl nitrate yields *o*-nitroacetanilide exclusively. Benzoyl nitrate reacts in a similar fashion with anisole and phenetole; it produces almost theoretical yields of *o*-nitro compounds.

If benzenesulfonic acid phenyl ester is prepared from phenol and benzenesulfonyl chloride, nitration takes place only in the *p* position. Upon saponification, pure *p*-nitrophenol and benzenesulfonic acid are obtained. It is remarkable that in this case a redirection towards the *m* position does not occur, such as can be observed in the salt formation of amines. The method, however, has not gained any practical importance.

A similar effect is found in the case of cinnamic acid. It yields *p*-nitrocinnamic acid as main product, while the cinnamic ester gives up to 70% *o*-nitrocinnamic acid ester.

Special precautions are necessary for the nitration of sensitive compounds, such as amines and aldehydes. The nitration of the free amines is performed best with nitric acid free of nitrogen oxides (see page 280) and in the presence of much sulfuric acid. Since with this method the formation of isomeric mixtures must be expected, owing to the formation of *m* substitution products, the amino group is advantageously protected by acylation. But the different acyl groups have very different effects. According to Noelting and Collin [20] *p*-nitroacetanilide with less than 5% of the *o* compound is obtained on treatment of acetanilide with mixed acid. Benzanilide, on the other hand, gives a mixture of *o*- and *p*-nitrobenzanilide. The above mentioned method of preparing *o*-nitroacetanilide with acetyl nitrate is expensive and inconvenient. *o*-Nitroacetanilide, and through it *o*-nitroaniline, is better prepared in indirect ways; see page 288. A protective effect similar to acylation is obtained with boric acid; according to a patent [21] boric acid is used in the nitration of diaminoanthraquinonesulfonic acids.

Aromatic aldehydes are decomposed by mixed acid even at room temperature. In the cold with pure nitric acid they yield crystalline, well defined molecular compounds, the so called aldehyde nitrates which change easily to nitrated benzaldehydes; see Reddelien.[22] At lower temperatures, nitro aldehydes may be prepared with mixed acid.

[20] Noelting and Collin, *Ber.*, **17**, 262 (1884).
[21] German Patent, 108,873.
[22] G. Reddelien, *J. prakt. Chem.*, **91**, 213 (1915).

Special Methods for Preparation of Nitro Compounds

In the preparation of nitro compounds two special methods are of prime importance:

1. Certain places in the molecule where the nitration is not desired are protected by the temporary introduction of auxiliary substituents; subsequently these may readily be replaced by hydrogen. Usually it is the sulfonic acid group which may easily be eliminated, but occasionally amino and carboxyl groups are used.

2. Certain substituents which may be introduced more readily and under milder conditions than nitro groups are exchanged subsequently for such groups. The ease with which substituents, sulfonic acid groups, halogen, and amino groups may be exchanged depends essentially on their position relative to other substituents. In nitrations this substitution is less effective than it is in the exchange of halogens for other groups; see page 294.

The Sandmeyer reactions also belong to these methods; in these reactions the nitro compounds are prepared from the corresponding aromatic amines by treating the diazonium compounds with cupric nitrite. It seems paradoxical to prepare a nitro compound from an amine; this is contrary to the usual reaction procedure. In two cases this is the only successful method. First, β-nitronaphthalene, as mentioned above, cannot be prepared by direct nitration or indirectly through intermediary substitution products. But β-nitronaphthalene can readily be prepared from β-naphthol. Second, there is no practical way known for the preparation of o- and p-dinitro compounds by direct nitration unless one wishes to work in a tedious manner with relatively large batches. o- and p-nitroanilines can easily be obtained; their amino groups can be replaced by the nitro group through the Sandmeyer reaction, as mentioned above, or oxidized to the nitro group with hydrogen peroxide or perbenzoic acid.

The fact that aromatic amines form nitramines with nitrogen pentoxide gives some idea about the mechanism of the nitration of amines. Bamberger and coworkers [23] and Hoff [24] made a thorough investigation of this matter. They found that nitramines may be obtained from nitrates. This reaction, too, may be used in the aliphatic series. The aromatic nitramines rearrange more or less readily into nitro-substituted amines.

The influences which affect nitration may be explained by a few typical examples. The first one is the nitration of aniline. The purpose of this reaction is the preparation of the technically important o- and p-nitroanilines as free from isomers as possible and with the best possible yields.

[23] Bamberger *et al.*, *Ber.*, **26**, 477, 490 (1893); **27**, 584 (1894); **28**, 537 (1895).
[24] Hoff, *Ann.*, **311**, 101 (1900).

Such a preparation must be cheap and the use of expensive apparatus must be avoided.

1. The direct nitration of aniline in the presence of much sulfuric acid gives no reaction product of practical usefulness. According to Holleman's substitution rules only *o*- and *p*-nitroanilines should be expected. Since the nitration can be carried out well only in the presence of a high concentration of sulfuric acid, considerable quantities of *m*-nitroaniline are formed simultaneously. *m*-Nitroaniline is obtained much more conveniently by reduction of *m*-dinitrobenzene.

2. Theoretically it is possible to prepare *o*- as well as *p*-nitroaniline in a convenient way from the relatively cheap acetanilide. Acetyl nitrate readily yields *o*-nitroacetanilide (see Pictet and Khotinsky [25]); by the use of mixed acid only *p*-nitroacetanilide is obtained according to Noelting and Collin.[26] The method of Pictet and Khotinsky is too expensive and inconvenient. Noelting's method is not well suited for commercial application because of the low temperature which must be maintained during the reaction.

3. Of practical methods for the manufacture of *o*-nitroaniline the following were used, or are still in use.

According to Nietzki and Benckiser,[27] see also Wülfing,[28] acetyl-sulfanilic acid was used as the starting material. This can be obtained either by acetylation of sulfanilic acid or by sulfonation of acetanilide. For the sulfonation fuming sulfuric acid with 20% sulfur trioxide must be used. Subsequently, the reaction mixture is treated with nitrating acid at low temperature, thus forming 2-nitro-4-sulfoacetanilide. The acetyl group of the latter compound can be removed even with water, but its sulfonic acid group is attached very strongly and is eliminated only at higher temperatures with concentrated hydrochloric acid. The method, therefore, is not at all satisfactory. It was replaced by another one in which the dianilide of oxalic acid is used as starting material.[28] The oxanilide is obtained according to Perkin [29] from oxalic acid and aniline by removal of water at 200°C. It is hydrolyzed with much greater difficulty than acetanilide, a fact which is advantageous as far as the subsequent reactions are concerned. Furthermore, it may be sulfonated with ordinary concentrated sulfuric acid, forming the *p*-disulfonic acid. This is conveniently nitrated in one operation in the sulfonation mixture. The nitration is carried out in the following manner.

24 parts of finely powdered oxanilide are stirred into 144 parts of

[25] Pictet and Khotinsky, *Ber.*, **40**, 1164 (1907).
[26] Noelting and Collin, *Ber.*, **17**, 262 (1884).
[27] Nietzki and Benckiser, *Ber.*, **18**, 294 (1885).
[28] Wülfing, German Patent, 65,212.
[29] Perkin, *J. Chem. Soc.*, **61**, 459 (1892).

concentrated sulfuric acid and the mixture heated on a steam bath until a sample in water forms a clear solution, thus indicating that sulfonation is complete. The mixture is allowed to cool to 40° to 50°C. Then a mixture of 17 parts of nitric acid ($D = 1.44$) and 17 parts of concentrated sulfuric acid is added slowly. The dinitrodisulfonic acid of oxanilide can be salted out of the solution with sodium chloride after dilution with water. The isolation of the disulfonic acid is not necessary for further processing to o-nitroaniline. Boiling the mixture with enough added water so that the boiling point lies between 120° and 150°C. first splits off oxalic acid which decomposes further into carbon dioxide, formic acid, or carbon monoxide. Then the sulfonic acid groups are eliminated. The latter reaction is finished in 2 to 4 hours, depending on the temperature. The reaction mixture is poured into water completely to precipitate the nitroaniline; about a 75% yield, calculated on the basis of oxanilide, of the theoretical o-nitroaniline is obtained.

4. For the preparation of p-nitroaniline, benzalaniline may be used as starting material according to Schwalbe.[30] This yields only p-nitrobenzalaniline when treated with mixed acid at low temperature. From the latter p-nitroaniline is obtained by hydrolysis. On treatment of the benzalaniline with a mixture of glacial acetic acid, acetic anhydride, and nitric acid, however, some o-nitrobenzalaniline is also obtained. The method is expensive, because only a part of the benzaldehyde can be recovered, and because it requires much attention.

A more convenient method was given by Lesser.[31] It consists of the nitration of cheap phthalanil instead of expensive benzalaniline. The amount of the phthalic anhydride used can always be recovered as product.

Phthalanil (2.23 parts) is dissolved by means of low heat in 14 parts of concentrated sulfuric acid. After being cooled with ice, the reaction mixture becomes cloudy. 2.55 parts of a mixture of sulfuric acid monohydrate containing 25% of nitric acid are added at a temperature below 3°C. The mixture is then poured onto ice, and the precipitated nitrophthalanil is filtered off, dried, and heated with 1.1 parts of aniline for 1 hour at 170° to 180°C. Thus, a mixture of phthalanil, p-nitroaniline, and excess aniline is obtained. The aniline is removed from this mixture by distillation with steam. From the residue p-nitroaniline is extracted with hot water and the remaining undissolved phthalanil may be used for a new batch. A little o-nitroaniline distils with steam.

Another method which leads to nitroanilines consists of the replacement of chlorine in o- and p-nitrochlorobenzenes by the amino group by means of ammonia or ammonium compounds; see page 205. The methods described above were apparently not all tested for their usefulness in the laboratory. For the preparation of o-nitroaniline (see *Organic Syn-*

[30] Schwalbe, *Ber.*, **35**, 3301 (1902).
[31] Lesser, German Patent, 141,893.

theses [32]), Nietzki's method is usually relied upon. The hydrolysis of 2-nitro-4-sulfoaniline can be performed at high temperature and at relatively moderate temperature in open vessels. For the preparation of *p*-nitroaniline the method of Noelting and Collin [33] is commonly used. This method is not particularly suited for commercial application because of the necessary cooling. The directions are as follows:

1 kilo of acetanilide is dissolved in 4 kilos of concentrated sulfuric acid and the solution cooled in an ice-salt bath. As acetanilide dissolves only with difficulty in sulfuric acid, it is advisable to dissolve it first in an equal amount of glacial acetic acid and then to add this solution, after cooling to incipient crystallization, to the concentrated sulfuric acid. The sulfuric acid solution of acetanilide is then definitely cooled while 590 g. of 85% nitric acid ($D = 1.478$) are slowly added. After the mixture has been allowed to stand for some time, it is poured into a large amount of ice water. The nitroacetanilide is filtered, washed, and recrystallized from alcohol. 950 g. of almost pure *p*-nitroacetanilide with a melting point of about 200°C. are obtained. When pure, it melts at 207°C. The acetyl group is removed by boiling for 20 minutes 50 parts of *p*-nitroacetanilide with a solution containing 125 parts by volume of concentrated hydrochloric acid and 125 parts by volume of water. After the reaction mixture has been cooled, it is diluted with 1250 parts of water. From the carefully neutralized mother liquor an additional amount of *p*-nitroacetanilide can be obtained. The compound may be purified by recrystallization from benzene; it melts at 147°C.

Witt and Utermann [34] give directions for the isolation of *o*-nitroacetanilide which is formed as a by-product in the above reaction.

The nitration of alizarin may serve as another example.

Alizarin could be readily nitrated only as a diacetyl compound, at first. Thus, according to Perkin [35] α-nitrodiacetylalizarin is formed. By splitting off the acetyl group and by oxidation, nitropurpurin is obtained as a by-product. The method was later improved [36] by the use of dibenzoylalizarin. The crude product, obtained by heating equal amounts of benzoyl chloride and alizarin to 180°C., may be used directly. It is much more difficult to remove the benzoyl group than it is to remove the acetyl group; also the nitration must be carried out at low temperature. Another method of preparing α-nitroalizarin by the use of fuming sulfuric acid [37] is more convenient.

240 parts of alizarin are dissolved in 2000 parts of 20% oleum. To this solution at −10°C. is slowly added a solution of 96 parts of potassium nitrate in 190 parts of sulfuric acid monohydrate. The mixture is poured into water after standing several hours.

Another patent [38] discloses how α-nitroalizarin may be prepared with concentrated sulfuric acid in the presence of arsenic acid.

[32] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 388.
[33] Noelting and Collin, *Ber.*, **17**, 202 (1884).
[34] Witt and Utermann, *Ber.*, **39**, 3903 (1906).
[35] Perkin, *Jahresber.*, 1877, 586.
[36] German Patent, 66,811.
[37] German Patent, 70,515.
[38] German Patent, 74,598.

To a solution of 10 kilos of alizarin in 200 kilos of concentrated sulfuric acid are added 10 kilos of arsenic acid. To this mixture at 0°C. are then added 3 liters of nitric acid ($D = 1.41$). After several hours, the solution is poured into water and the precipitate is filtered and dissolved in a solution of sodium hydroxide. The boiling solution is mixed with a large excess of sulfuric acid and the solution boiled to hydrolyze the arsenic ester of α-nitroalizarin. The reaction is complete when a sample of the precipitate dissolves in sodium hydroxide solution with a pure violet color.

It is remarkable that β-nitroalizarin is obtained by nitration in the presence of concentrated sulfuric acid instead of oleum. A more satisfactory preparation is according to a patented method [39] with the boric acid ester which, in contrast to the arsenic acid ester, directs the nitro group to the β position.

10 kilos of alizarin are dissolved in 200 kilos of concentrated sulfuric acid, and 10 kilos of boric acid are mixed with this solution. The mixture is then cooled and at 0°C. 3 liters of nitric acid ($D = 1.41$) are added. After standing for several hours, the solution is poured into cold water and the precipitate is filtered and then dissolved in sodium hydroxide solution. The addition of strong mineral acid to the boiling solution precipitates β-nitroalizarin.

The preparation of picric acid is an example showing the advantage gained by the temporary introduction of sulfonic acid groups and their subsequent replacement by nitro groups. Phenol is directly nitrated only with considerable formation of resin; however, it is readily sulfonated. Phenoltrisulfonic acid, obtained from phenol and pyrosulfuric acid, readily exchanges all three sulfonic acid groups for nitro groups, if the reaction mixture is treated with sodium nitrate. It is not even necessary to prepare the trisulfonic acid, since the monosulfonic acid, unlike phenol, may readily and smoothly be nitrated to dinitrophenolsulfonic acid. The sulfonic acid group in the latter may then readily be replaced by the nitro group.

According to Köhler [40] 100 parts of phenol and 110 parts of concentrated sulfuric acid are heated to 80°C. The solution is then cooled, and 192 parts of potassium nitrate are added in small portions. During this operation the temperature is slowly raised to 140°C. The reaction mixture is cooled and diluted with 320 parts of water. Then 148 parts of potassium nitrate are added at 80° to 90°C., and the solution is heated to 140°C. for 2 hours. After the material is cooled, the crystal mixture of potassium bisulfate and picric acid is separated from the mother liquor. The bisulfate is extracted with water from the residue, and the latter recrystallized from water.

The directions of Stettbacher [41] also give good results.

200 g. of phenol are mixed with 800 g. (436 cc.) of concentrated sulfuric acid ($D = 1.84$) in an 800 cc. beaker. On being stirred the mixture grows warm (65° to 70°C.), producing a greenish or brownish solution. After being cooled to room temperature, the solution

[39] German Patent, 74,562.
[40] Köhler, German Patent, 67,074.
[41] A. Stettbacher, *Die Schiess- und Sprengstoffe.* Barth, Leipzig, 1933, p. 282.

is added with mechanical stirring to 1000 cc. of nitric acid (D = 1.38 to 1.40). The temperature rises slowly and nitrous gases are evolved. Towards the end of the reaction the temperature should reach 90° to 100°C. The mixture is then heated with stirring on a water bath until the evolution of gases subsides; then the temperature is increased to 112°C. After about 15 minutes the nitration is complete and picric acid starts to crystallize. The reaction product is poured into 6 to 7 times its volume of ice water, and the precipitate is filtered with suction and washed with a little water. Thus, 360 g. of picric acid, melting at 120° to 121°C., are obtained.

2. Replacement of Halogen in Aliphatic Compounds by Nitro Group

In some aliphatic compounds halogen may be quite readily replaced by the nitro group by treatment with silver nitrite. According to V. Meyer and Locher [42] the reaction proceeds very smoothly with methyl, ethyl, propyl, and isopropyl iodide. With the halides of higher molecular weight, however, side reactions take place. The reaction has little preparative importance, but it may be useful under certain conditions for analytical work. The reaction is carried out by mixing dry silver nitrite with an equal amount of dry sand. This mixture is placed in a small distilling flask and methyl iodide is added in an amount equal to about one-quarter of the total weight of the mixture. After the reaction, which proceeds with evolution of heat, has taken place, the nitro hydrocarbon may be distilled directly. An example of the preparation of a nitro hydrocarbon by this method is given by Meyer [43] for nitroethane.

A mixture prepared from separate warm water solutions of 2400 g. of silver nitrate and 1500 g. of potassium nitrite is cooled and the crystals of silver nitrite are washed with water and dried. The silver nitrite (2090 g.) is placed in a large flask equipped with an efficient reflux condenser and dropping funnel, and 1700 g. of ethyl iodide are added slowly, without shaking, at such a rate that the reaction mixture continues to boil. The reaction is completed by heating the flask for a short time on a water bath. On fractionation of the reaction mixture, a yield of about 50% of the theoretical amount of nitroethane is obtained; it boils at 111° to 113°C. Ethyl nitrite is presumably formed as a by-product, most of which escapes on account of its low boiling point (17°C.).

Kissel and Götting [44] slowly add the calculated amount of silver nitrite to ethyl iodide at a low temperature; any heating must be avoided. The mixture is allowed to stand for 1 day in cold water and is then fractionated in a current of carbon dioxide. The fractions boiling below 100°C. yield additional amounts of nitroethane if treated again with silver nitrite. No yield is given, but according to V. Meyer it amounts to 50% of the theoretical.

The method can be carried out only with iodides. Bromides do not react with silver nitrite even at higher temperatures. As mentioned above, the yields with the high molecular weight iodides are lower. It is an open question whether the low molecular weight nitro hydrocarbons may be prepared advantageously in this way. Much cheaper and more

[42] V. Meyer and Locher, *Ber.*, **7**, 1510 (1874); **9**, 539 (1876); *Ann.*, **180**, 140 (1876).
[43] V. Meyer, *Ann.*, **171**, 23 (1874).
[44] Kissel, *Ber.*, **15**, 1574 (1882). Götting, *Ann.*, **243**, 115 (1888).

productive for the simple members of the series is the method in which α-nitrocarboxylic acids are easily decomposed into nitro hydrocarbons and carbon dioxide. This method, although it really belongs in the chapter on degradation, is discussed at this point. It was originated by Kolbe (see Preibisch [45]). The following directions for the preparation of nitromethane are those of Steinkopf.[46]

A 2 liter round bottom flask is equipped with a dropping funnel, a glass tube connected to a condenser, and another glass tube, one end of which almost touches the bottom of the flask and the other end of which is connected to a water pump. The connection can be shut off by a stop-cock. The lower end of the downward condenser is attached to the apparatus shown in Fig. 7, by means of which a continuous and convenient separation of nitromethane and water is possible. The water distilling with the nitromethane overflows into a second receiver.

500 g. of chloroacetic acid are dissolved in 1 liter of water in a 2 liter flask. The solution is neutralized with 250 to 300 g. of calcined soda ash. Then 300 g. of sodium nitrite are dissolved in 500 cc. of water and one-fourth of this solution is poured into the flask. The mixture is brought to a boil and the remaining portion of the sodium nitrite solution is added at such a rate that nitromethane distils continuously. After all the nitrite solution has been added, the mixture is boiled as long as nitromethane steam distils and then an additional 250 cc. of water are collected. All but 100 cc. of the distillation residue is removed through the water pump. Another 500 g. of chloroacetic acid can now be added and the operations repeated as desired. The nitromethane is separated from the bulk of the water and dried over calcium chloride. 30 to 35 g. of sodium chloride are added to each 100 cc. of the water, and the aqueous solution concentrated to two-thirds the original volume. The distillate is treated in the manner described above. The nitromethane is finally purified by distillation from a little mercuric oxide. The yield is 50% of the theoretical; the boiling point is 102°C.

FROM CONDENSER
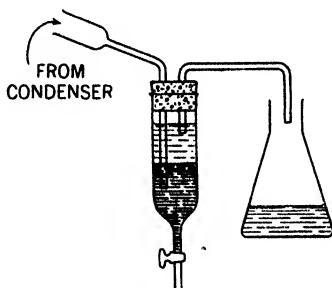
FIG. 7.—Apparatus for the separation of nitromethane and water.

Organic Syntheses [47] presents a more recent method.

Auger [48] gives directions for an analogous method of preparing nitroethane.

20 g. of α-bromopropionic acid are neutralized with potassium carbonate. To this solution are added 20 g. of sodium nitrite and the volume brought to 100 cc. with water. On distillation the mixture gives a 50% yield of nitroethane, boiling at 114°C. The yield is the same as that obtained with V. Meyer's method (see above) but the cost is much less.

[45] Kolbe, *J. prakt. Chem.*, **5**, 427 (1872). Preibisch, *ibid.*, **8**, 310 (1874).
[46] Steinkopf, *Ber.*, **41**, 4458 (1908); **42**, 3438 (1909).
[47] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 401.
[48] Auger, *Bull. soc. chim.*, **23**, 333 (1900).

To what extent this method might be used for the preparation of the higher members of the series, and whether secondary nitro hydrocarbons might also be prepared, apparently has not been established.

Tertiary nitro compounds cannot be obtained in this way. Tscherniak [49] succeeded in obtaining tertiary nitrobutane in small amounts from tertiary butyl iodide and silver nitrite by the method of V. Meyer. The preparation of tertiary nitrobutane from bromonitropropane, $CBr(NO_2)(CH_3)_2$, and zinc ethyl is given by Bewad.[50]

Occasionally, halogen in aliphatic compounds may be replaced by treatment with a large excess of nitric acid; see Biltz.[51]

3. Replacement of Alkyl Group by Nitro Group

When p-cymene is treated with fuming nitric acid, not only is it nitrated in the ortho position, but simultaneously the isopropyl group is replaced by a nitro group producing 2,4-dinitrotoluene; see Alfthan.[52] In an analogous manner the isopropyl group in thymol ethers may be replaced by the nitro group during nitration. Giua [53] obtains trinitro-m-cresyl ether in this way.

4. Replacement of Sulfonic Acid Group by Nitro Group

The replacement of the sulfonic acid group by the nitro group has considerable importance. It is most successful with phenol- and naphtholsulfonic acids. For example, α-naphthol may be converted with an equivalent amount of concentrated sulfuric acid to the 2,4-disulfonic acid. If the reaction mixture is then heated with dilute nitric acid, 2,4-dinitro-α-naphthol, Martius' yellow, is obtained. Instead of nitric acid, nitrous gases are occasionally used in this reaction. The 3- and 4-sulfonic acids of o-cresol yield 2,4-dinitro-o-cresol; from o-cresol-3,5-disulfonic acid, 3,5-dinitro-o-cresol is obtained by saturation of the aqueous solution with nitrous gases.

5. Replacement of Carboxyl Group by Nitro Group

Isobutyric acid treated with concentrated nitric acid yields dinitro-isopropane. Thus, not only is the carboxyl group replaced, but the tertiary hydrogen atom is substituted by the nitro group. The replacement of carboxyl for the nitro group in the aromatic series is just as complicated. The reaction was studied with the dialkylaminobenzoic acids, for which it is successful with nitric as well as with nitrous acids.

[49] Tscherniak, *Ann.*, 180, 155 (1876).
[50] Bewad, *J. prakt. Chem.*, 48, 359 (1893).
[51] H. Biltz, *Ber.*, 35, 1528 (1902).
[52] J. Alfthan, *Ber.*, 53, 78 (1920).
[53] M. Giua, *Gazz. chim. ital.*, 49, 158 (1919).

It·is accompanied, of course, by direct nitration, also by elimination of the alkyl groups on the nitrogen atom.   With p compounds, simple replacement of carboxyl by the nitro group takes place.

As an example, the directions of Jackson and Earle [54] follow for the preparation of trinitroanisol.

10 g. of anisic acid are slowly added to a mixture of 80 cc. of nitric acid ($D = 1.5$) and an equal amount of concentrated sulfuric acid (98.7% H_2SO_4).   The solution is heated for 2 hours at 70°C. and, after being cooled, poured into ice water.   The separated compound is filtered off and washed with water until it is free of acid.   14 g. of crude product are obtained, which corresponds to a yield of 88% of the theoretical.   After recrystallization from ethanol the melting point is 65°C.   A by-product which melts at 76°C. can be isolated from the mother liquor.   This is not di- or tetranitroanisole.

6. Replacement of Diazonium Group by Nitro Group

The reaction, discovered by Sandmeyer,[55] gives poor yields if the original directions are followed.   Hantzsch and Blagden [56] substitute cupric sulfite-potassium nitrite for cuprous oxide.   Since aromatic amines are usually obtained from nitro compounds, the importance of the method is not immediately evident.   Therefore, two points are stressed again:

1. If several nitro groups are successively introduced, they take up the m position in relation to one another almost without exception. p-Dinitrobenzene, for instance, cannot be prepared practically by nitration of nitrobenzene.   Aniline, however, yields p-nitroaniline readily, and from this p-dinitrobenzene is conveniently prepared through nitrobenzenediazonium chloride.

2. β-Nitronaphthalene cannot be prepared at all by direct nitration. β-Naphthylamine is easily prepared from β-naphthol with ammonium sulfite.   Sandmeyer [57] was the first to obtain β-nitronaphthalene from β-naphthylamine through its diazonium salt.   The following directions are those of Meisenheimer and Witte.[58]

105 g. of β-naphthylamine are dissolved in a mixture of 350 cc. of nitric acid ($D = 1.4$) and 3.5 liters of water.   The solution is cooled to 0°C. and diazotized with a solution of 360 g. of sodium nitrite in a liter of water.   The reaction liquid is allowed to stand for 2 days over cuprous oxide.   This is prepared from 750 g. of copper sulfate by treatment with sodium hydroxide and glucose.   The β-nitronaphthalene is recovered by steam distillation.

Sandmeyer [59] gave the following directions for the preparation of cuprous oxide.

[54] C. L. Jackson and R. B. Earle, *J. Am. Chem. Soc.*, **29**, 104 (1903).
[55] Sandmeyer, *Ber.*, **20**, 1494 (1887).
[56] A. Hantzsch and J. Blagden, *Ber.*, **33**, 2544 (1900).
[57] Sandmeyer, *Ber.*, 1497 (1887).
[58] Meisenheimer and Witte, *Ber.*, **36**, 4157 (1903).
[59] Sandmeyer, *Ber.*, **20**, 1494 (1887).

50 g. of copper sulfate and 15 g. of glucose are dissolved in 100 cc. of warm water. The solution is brought to a boil and a cold solution of 20 g. of sodium hydroxide in 60 cc. of water is added. The precipitated hydroxide changes quickly to cuprous oxide. As soon as the reaction is completed, the blue hydroxide having completely changed to yellow cuprous oxide, the reaction mixture is cooled quickly and neutralized with acetic acid.

Hantzsch and Blagden [60] add the solution of diazotized β-naphthylamine sulfate to a mixture of cuprous-cupric sulfite and potassium nitrite solutions.

β-Nitronaphthalene steam-distils with difficulty even with superheated steam. It may be recrystallized from dilute alcohol and melts at 78°C. The yield is about 25% of theory.

The preparation of β-nitronaphthalene by removal of the amino group from 1-amino-2-nitronaphthalene is given by Lellmann and Remy.[61]

7. Replacement of Hydroxyl by Nitro Group

The tertiary nitro compounds, which are difficult to prepare in other ways, can be obtained from carbinols with nitric acid. The yields are very poor. As an example, tertiary isobutanol may be converted to tertiary nitrobutane; see van Duin.[62]

[60] A. Hantzsch and J. Blagden, *Ber.*, **33**, 2544 (1900).
[61] Lellmann and Remy, *Ber.*, **19**, 237 (1886).
[62] van Duin, *Rec. trav. chim.*, **37**, 111 (1918).

Carbon-Divalent Sulfur Bonds

The great similarity between divalent sulfur and oxygen is responsible for the fact that the methods of preparation of sulfur compounds are often very similar to those of the corresponding oxygen compounds.

The importance of the sulfur compounds in physiological chemistry is great, but only a few of the many possible types are encountered. The mercaptans and disulfides are represented by cysteine and cystine; the thiazole ring forms a part of the antineuritic vitamin B_1.

1. Sulfhydryl Compounds, Mercaptans

(a) By Reduction of Sulfonyl Chlorides and of Disulfides

The reduction of sulfonyl chlorides has practical importance only in the aromatic series; it is so simple that one example will illustrate it.

According to Bourgeois,[1] 100 parts of benzenesulfonyl chloride are added with stirring to a mixture of 400 parts of concentrated sulfuric acid, 1200 parts of water, and 200 parts of zinc dust, the temperature being maintained at 0°C. After several hours standing in the cold, the solution is boiled until it is no longer milky. It is then steam-distilled. The distillate is extracted with ether, and the ether extract is dried and fractionated. A yield of 80 to 85% of thiophenol is obtained. It boils at 169.5°C. at 760 mm. (corrected).

The zinc dust and sulfuric acid may be replaced by granulated zinc and hydrochloric acid. Gebauer-Fuelnegg [2] recommends aluminum amalgam.

The disulfides can be successfully reduced with many reagents.

l-Cysteine is prepared from *l*-cystine according to Baumann [3] in the following manner.

Tin foil is added to a solution of *l*-cystine in hydrochloric acid. The tin, at first, passes into solution without evolution of hydrogen. As soon as a distinct evolution of gas starts, the solution is diluted, the tin precipitated with hydrogen sulfide, and the liquid evaporated to dryness. *l*-Cysteine hydrochloride is obtained as the residue.

[1] Bourgeois, *Ber.*, **28**, 2319 (1895); *Rec. trav. chim.*, **18**, 432 (1899).
[2] E. Gebauer-Fuelnegg, *J. Am. Chem. Soc.*, **49**, 1361 (1927).
[3] E. Baumann, *Z. physiol. Chem.*, **8**, 300 (1884).

To isolate *l*-cysteine, the hydrochloride is dissolved in alcohol, and the cysteine carefully precipitated with ammonia. An excess of ammonia must be avoided. The precipitate is filtered, washed with alcohol, and quickly dried in a vacuum. The melting point is, according to Gabriel,[4] about 175° to 178°C. Bergmann and Michalis [5] prepared cysteine by catalytic hydrogenation with palladium black. They crystallized it from air-free water and found a decomposition temperature of about 240°C. after they had dried their product in a desiccator filled with hydrogen. For the reduction Gebauer-Fuelnegg recommends [6] aluminum amalgam or sodium metal in liquid ammonia. Free cysteine is very unstable.

An example of the reduction of a disulfide to a sulfhydryl compound is the reduction of dithiosalicylic acid. Directions can be found in *Organic Syntheses.*[7]

(b) By Replacement of Hydroxyl Group

The replacement of the hydroxyl group by the mercapto group can be accomplished with phosphorus sulfides, but it is not a good preparative method.

According to Sabatier and Mailhe [8] thorium oxide alcoholates can readily be made to react with hydrogen sulfide to give mercaptans. Kramer and Reid,[9] using pumice-thorium oxide as catalyst, observed the formation of mercaptans from alcohols and hydrogen sulfide.

(c) By Replacement of Halogen

This method is of prime importance in the aliphatic series. A large excess of alkaline hydrosulfide is used. According to Klason,[10] methylmercaptan is prepared in the following manner.

Dry methanol (500 cc.) is slowly added to 750 cc. of anhydrous sulfuric acid. The mixture is cooled. After the addition of ice, an aqueous solution of 2750 g. of sodium carbonate is added. The weakly alkaline solution is concentrated to a small volume, from which, upon cooling, sodium sulfate separates. The mother liquor is further concentrated and mixed with a solution of 500 g. of potassium hydroxide in 1000 cc. of water which has been saturated with hydrogen sulfide. When this mixture is heated on a water bath, a reaction starts at 30°C. The gases evolved are passed through 50 cc. of concentrated aqueous potassium hydroxide solution and are collected in a solution of 350 g. of potassium hydroxide in 700 cc. of water. Methyl sulfide separates at the surface

[4] Gabriel, *Ber.*, **38**, 638 (1905).
[5] M. Bergmann and G. Michalis, *Ber.*, **63**, 987 (1930).
[6] E. Gebauer-Fuelnegg, *J. Am. Chem. Soc.*, **52**, 4610 (1930).
[7] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 581.
[8] Sabatier and Mailhe, *Compt. rend.*, **150**, 1217, 1569 (1910).
[9] Kramer·and·Reid, *J. Am. Chem. Soc.*, **43**, 880 (1921).
[10] P. Klason, *Ber.*, **20**, 3407 (1887).

as a volatile, oily by-product. A solution of lead acetate is added as long as a lead precipitate is formed. The methylmercaptan is set free by passing into the mixture hydrogen sulfide or concentrated hydrochloric acid. The mercaptan is condensed in a freezing mixture. The distillate is dried with potassium carbonate and distilled. Methylmercaptan boils at 5.8°C. About 200 g. of methylmercaptan and 40 g. of methyl sulfide are obtained. Methyl sulfide, even in small concentrations, raises the boiling point of methylmercaptan.

Another method of preparing methylmercaptan was suggested by Arndt.[11] He starts with thiourea.

Aromatic mercaptans can be obtained from halides with potassium hydrosulfide in the presence of copper powder. The reduction of sulfonyl chlorides is often more convenient in the laboratory; see page 297. In a patent [12] the preparation of thiosalicylic acid, $HS \cdot C_6H_4 \cdot COOH$, from o-chlorobenzoic acid is described. In the laboratory the method of preparation with anthranilic acid is a better method; see page 301.

2. Thio Ethers

There is no useful method for the preparation of thio ethers by replacement of oxygen by sulfur in ethers. Neither is it possible to remove hydrogen sulfide from mercaptans although it is theoretically conceivable.

In the aliphatic series the reaction between halides or alkyl sulfates and potassium sulfide is generally suitable. By replacement of an alkali atom in a mercaptide, $R \cdot SNa$, by an alkyl residue, mixed thio ethers can be obtained in a similar manner. It will suffice to cite only two papers. Klason's [13] directions for the preparation of dimethyl and diethyl sulfide have apparently not been improved; Krüger [14] prepared mixed ethers especially.

Aromatic sulfides can be obtained from the sodium salts of thiophenols and aromatic iodides; diphenyl sulfide, for instance, is prepared according to Mauthner [15] in the following manner.

To a solution of 1.2 g. of sodium in 7 cc. of alcohol are added 7 g. of thiophenol. The alcohol is removed by distillation and 0.2 g. of copper powder and 12.9 g. of iodobenzene are added. The mixture is heated for 2.5 hours in an oil bath at 235° to 240°C. A little alcohol is added to the cooled mixture. The solution is then acidified with dilute sulfuric acid. After the addition of zinc dust, the unchanged iodobenzene is removed by steam distillation, and the diphenyl disulfide formed as by-product distils as thiophenol. After the distillation residue has cooled, the zinc is filtered off and extracted with ether. The ethereal solution is dried with calcium chloride and fractionated. Thus, 6.1 g. of diphenyl sulfide boiling at 295°C. are obtained.

[11] F. Arndt, *Ber.*, **54**, 2236 (1921).
[12] German Patent, 204,450.
[13] P. Klason, *Ber.*, **20**, 3407 (1887).
[14] Krüger, *J. prakt. Chem.*, **14**, 206 (1876).
[15] Mauthner, *Ber.*, **39**, 3593 (1906).

This method may be used quite generally; for diphenyl sulfide itself other methods are perhaps more convenient; see below.

Schaarschmidt [16] suggested a method in which thiocyanates not thiophenols are used as the starting material. The thiocyanates can be saponified to thiophenols with potassium carbonate. The method is of importance in the anthraquinone series.

The method of allowing elementary sulfur to act on aromatic systems in which aluminum chloride is used as catalyst is also important.

Diphenyl sulfide is prepared, according to Dougherty and Hammond,[17] as follows:

A mixture of 250 cc. of benzene and 134 g. of aluminum chloride is boiled under a reflux with stirring while 32 g. of sulfur are slowly added in 3 hours. After an additional 3 hours boiling, the cooled reaction mixture is decomposed with water, dried with calcium chloride, and the benzene removed by distillation. The residue is dissolved in 500 cc. of absolute alcohol. A little thianthrene is removed by filtration, and the alcohol removed by distillation. Upon fractionation 65 g. of diphenyl sulfide boiling at 115°C. at 3 mm are obtained.

3. Disulfides

The disulfides, $R \cdot S \cdot S \cdot R$, analogous in formula to the derivatives of hydrogen peroxide, are readily obtained by dehydrogenation of mercaptans. It is an accepted theory that glutathione is a compound which in an organism plays the part of a hydrogen donor as well as, in the disulfide phase, the part of acceptor. The reaction may be written:

$$2R \cdot SH \rightleftharpoons R \cdot S \cdot S \cdot R + H_2$$
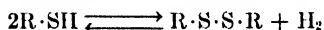
Other reactions, however, must be considered for preparative work. Otto and Tröger [18] use elementary iodine on alkali mercaptides. Alkyl halides react with sodium disulfide according to Blanksma.[19] Price and Twiss [20] discovered a method in which the alkali salts of thiosulfuric acid semiesters are used; these react with elementary iodine according to the following equation:

$$2R \cdot S \cdot SO_3K + 2H_2O + I_2 \longrightarrow R \cdot S \cdot S \cdot R + 2KHSO_4 + 2HI$$
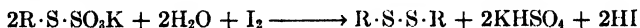
It is not necessary to isolate the esters. The following directions for the preparation of dimethyldithioglycolate are taken from the paper of Price and Twiss.

A mixture of methyl bromoacetate (15 g.), 25 g. of sodium thiosulfate, and 100 cc. of 50% alcohol is heated for 45 minutes on a steam bath. Then the solution of 12 g. of

[16] Schaarschmidt, *Ann.*, **409**, 65 (1915).
[17] G. Dougherty and P. D. Hammond, *J. Am. Chem. Soc.*, **57**, 118 (1935).
[18] R. Otto and J. Tröger, *Ber.*, **24**, 1146 (1891).
[19] Blanksma, *Rec. trav. chim.*, **20**, 133 (1901).
[20] T. S. Price and D. F. Twiss, *J. Chem. Soc.*, **95**, 1489 (1909).

iodine in 50 cc. of alcohol is added in portions. The reaction takes place at once. Excess iodine is removed with sulfurous acid and the ester is precipitated with water. It is recovered by extraction with ether in the usual manner.

In a quite similar fashion dibenzyl disulfide is obtained in a 99% yield from 5 g. of benzyl chloride, 10 g. of thiosulfate, and 60 cc. of 50% alcohol. After the mixture has been boiled for 1 hour, an excess of iodine is added and the procedure given above is followed.

The numerous methods for the preparation of disulfides show a great similarity and cannot be discussed here in detail; see also Otto, Lecher, and Price and Twiss.[21]

However, there remains the reaction of diazonium compounds with sodium disulfide, Na_2S_2. It is of practical importance and proceeds as follows:

$$2R \cdot N_2Cl + Na_2S_2 \longrightarrow R \cdot S \cdot S \cdot R + 2NaCl + 2N_2$$
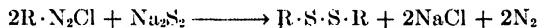
The preparation of dithiosalicylic acid serves as an example; directions for this method can be found in *Organic Syntheses*.[22]

4. Thio Aldehydes and Thio Ketones

The most general method of preparation of this type of compound consists of the reaction of hydrogen sulfide with the analogous oxygen compounds in the presence of hydrochloric acid or of other condensation agents. The thio aldehydes recently acquired importance, because they undergo a reaction analogous to the Wurtz synthesis. Ethylene compounds are yielded according to the reaction, $2R \cdot CHS \rightarrow R \cdot CH:CH \cdot R$; see Kuhn and coworkers.[23] The tendency of $>C=S$ compounds to polymerize is more pronounced than with the ordinary aldehydes. Thio ketones yield trimers which presumably have a constitution similar to that of paraldehyde; the same is true for the trimeric thio aldehydes. Only one form of trimeric thioformaldehyde and of trimeric symmetrical thio ketones exists. Homologous thio aldehydes and asymmetrical thio ketones exist in α and β forms. The explanation of this has not been ascertained as yet.

α-Trithioacetaldehyde forms according to Baumann and Fromm[24] when hydrogen sulfide is passed into a mixture of equal parts of water, acetaldehyde, and concentrated hydrochloric acid. An oil separates which solidifies slowly. The product is filtered after 24 hours and recrystallized several times from acetone; it melts at 101°C.

[21] R. Otto, *J. prakt. Chem.*, **37**, 207 (1888). H. Lecher, *Ber.*, **53**, 584 (1920); **55**, 1474 (1922). T. S. Price and D. F. Twiss, *J. Chem. Soc.*, **91**, 2021 (1907).
[22] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 580. See also German Patent, 204,450.
[23] R. Kuhn *et al.*, *Angew. Chem.*, **50**, 703 (1937).
[24] E. Baumann and E. Fromm, *Ber.*, **22**, 2600 (1889).

β-Trithioacetaldehyde can be prepared by saturating a mixture of 1 part of acetaldehyde and 3 parts of alcohol (that first has been saturated with hydrogen chloride) with hydrogen sulfide. After recrystallization from alcohol, the product melts at 125° to 126°C.

β-Trithiobenzaldehyde is obtained by passing hydrogen sulfide into a mixture of benzaldehyde and alcoholic hydrochloric acid. The precipitate is extracted with boiling benzene. When the mixture cools, β-trithiobenzaldehyde crystallizes with 1 molecule of benzene. This is removed by heating to 140°C. The product melts at 225°C.

Evaporation of the benzene mother liquor produces a mixture of β- and γ-thiobenzaldehyde. The residue is treated with cold benzene; the β-aldehyde is undissolved and is removed by filtration. The filtrate is allowed to evaporate, and γ-trithiobenzaldehyde free of benzene is obtained in pointed needles melting at 166° to 167°C.

The monomeric thio aldehydes occur as intermediates. They have not been studied closely because of their unbearable odor; see Baumann and Fromm.[25]

Trithioacetone is known only as a trimer. Acetophenone, according to Baumann and Fromm,[26] yields besides trithioacetophenone, the monomeric thioacetophenone as a blue, very unstable oil. This is also formed by heating the trimer. Numerous by-products are formed, however, during this reaction.

Purely aromatic thio ketones are prepared from the anil of the ketones by treatment with hydrogen sulfide. Reddelien and Danilof obtained thiobenzophenone [27] in the following manner.

7 g. of benzophenone anil dissolved in 50 cc. of benzene are treated in a shaking bulb with dry hydrogen chloride; the yellow hydrochloride precipitates. The hydrogen chloride is displaced by hydrogen sulfide and the bulb is shaken for 6 days under the pressure of a Kipp apparatus. The resulting dark blue solution is filtered under carbon dioxide from aniline hydrochloride and unchanged benzophenone anil hydrochloride. The benzene is evaporated in a current of carbon dioxide and the residue fractionated. 3 g. of thiobenzophenone distils at 176° to 178°C. at 18 mm. This dark blue oil solidifies when cooled. It melts at body temperature; see Gattermann and Schulze.[28]

Thiobenzophenone is oxidized in air and must be stored in a sealed tube. Apparently no polymers of purely aromatic thio ketones have been observed.

5. Thiocarboxylic Acids and Dithiocarboxylic Acids

Thio acids are the sulfhydryl derivatives of normal carboxylic acids. Thiocarboxylic acids are compounds with oxygen replaced by sulfur in

[25] E. Baumann and E. Fromm, *Ber.*, 22, 2593 (1889).
[26] E. Baumann and E. Fromm, *Ber.*, 28, 895 (1895).
[27] G. Reddelien and H. Danilof, *Ber.*, 54, 3141 (1921).
[28] Gattermann and Schulze, *Ber.*, 29, 2944 (1896).

the carbonyl group:

$$R \cdot C \overset{O}{\underset{SH}{\diagup}} \quad \rightleftharpoons \quad R \cdot C \overset{S}{\underset{OH}{\diagup}} \quad \text{and} \quad R \cdot C \overset{SH}{\underset{S}{\diagup}}$$
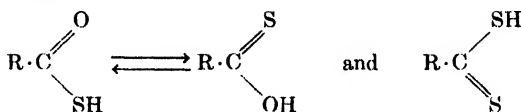
The derivatives with the grouping $-C \overset{O}{\underset{SH}{\diagup}}$ are called carbothiolic

acids, the ones with $-C \overset{S}{\underset{OH}{\diagup}}$ carbothionic acids. For the tautomerism

of the simple acids see Hantzsch and Scharf.[29]

1. Thiocarboxylic Acids

Brief mention of the methods of preparation will suffice. Kekulé [30] heated carboxylic acids with phosphorus pentasulfide.

Thiocarboxylic acid esters of the aromatic series are obtained, according to Seifert,[31] from phenyl esters of aromatic carboxylic acids according to the equation

$$R \cdot COOC_6H_5 + NaSC_2H_5 \longrightarrow R \cdot CO \cdot SC_2H_5 + C_6H_5ONa$$
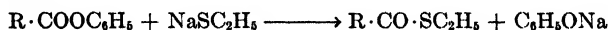
A method given by Delépine [32] is generally useful.

$$Cl \cdot CS \cdot OR + R' \cdot MgX \longrightarrow R' \cdot CS \cdot OR + MgXCl$$
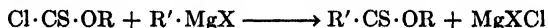
Chlorothioformic O esters are used as intermediates. Thionic esters are obtained as end-products. Seifert's method, on the other hand, gives the isomeric carbothiolic acid esters.

2. Dithiocarboxylic Acids

Houben and coworkers [33] obtained the dithiocarboxylic acids from carbon disulfide and Grignard compounds according to the general equation, $RMgX + CS_2 \rightarrow R \cdot CS \cdot SMgX + H_2O \rightarrow R \cdot CS \cdot SH + MgXOH$. They can readily be dehydrogenated and often change to thioacyl disulfides with the oxygen of air.

$$2R \cdot CS \cdot SH \xrightarrow{D_2} H_2O + R \cdot CS \cdot S \cdot S \cdot CS \cdot R$$
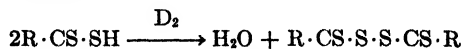
The formula of the thioacyl disulfides shows that they are similar to compounds of the type of benzoyl peroxide.

[29] A. Hantzsch and E. Scharf, Ber., 46, 3570 (1913).
[30] Kekulé, Ann., 90, 309 (1854).
[31] R. Seifert, J. prakt. Chem., 31, 462 (1885).
[32] M. Delépine, Compt. rend., 153, 279 (1911); Bull. soc. chim., 9, 901, 904 (1911).
[33] J. Houben et al., Ber., 35, 3696 (1902); 39, 3221, 3503 (1906); 40, 1303, 1725 (1907).

3. Thio Derivatives of Carbonic Acid

By replacement of the oxygen atoms in carbonic acid, H_2CO_3, one can expect two thio acids, the thiolcarbonic acid, $HO \cdot CO \cdot SH$, and the thioncarbonic acid, $HO \cdot CS \cdot OH$, two dithiocarbonic acids, namely $HS \cdot CO \cdot SH$ and $HO \cdot CS \cdot SH$, and the trithiocarbonic acid, $HS \cdot CS \cdot SH$. Only the trithiocarbonic acid can be isolated; the others are known only as salts or esters.

Of most importance are the xanthates, salts of the esters of the dithiocarbonic acid of the formula $RO \cdot CS \cdot SH$. They are formed from carbon disulfide and alcoholic alkalies according to the equation $R \cdot ONa + CS_2 \rightarrow R \cdot O \cdot CS \cdot SNa$. They contain the organic residue bound to oxygen.

Viscose is a colloidal solution of cellulose xanthate.

6. Sulfur-Containing Heterocyclic Compounds

Thiophene can be prepared in the laboratory either by Steinkopf's method of passing acetylene over pyrites,[34] or by the reaction of sodium succinate with phosphorus trisulfide. The first method requires rather complicated apparatus; the second calls for special apparatus only with larger batches. It can be performed quite conveniently on a small scale.

It is quite instructive to compare the different directions given for this method. Volhard and Erdmann [35] obtained yields of 50% when they used a mixture of sodium succinate and phosphorus trisulfide in a ratio of 1:2 in a very simple set-up. Erdmann [36] uses a mixing ratio of 3:4, and obtains a yield of 27 to 33% of the theoretical. *Organic Syntheses* [37] recommends the distillation in a current of carbon dioxide, with a ratio of 3:4, which yields 25 to 30%. Erdmann distilled batches of 350 g. of the mixture, while in *Organic Syntheses* about 3 times this amount is used. The directions for proper drying are different also. Volhard and Erdmann dehydrate the sodium succinate at the temperature of the steam bath; Erdmann heats to 140°C. After the different directions were thoroughly checked, the following method proved to be the most advantageous.

Sodium succinate is dried to constant weight at 140°C. and then ground well in a ball mill with technical phosphorus trisulfide which was preground in a mortar; the ratio should be 3:4. Less than 700 g. of this mixture is placed in a long necked distilling flask with a ground joint made of Jena or Pyrex glass. The flask must be less than half full. The flask is connected to a downward condenser with wide inside diameter. The condenser is followed by 2 or 3 receivers of 500 cc. capacity, each of which contains about

[34] W. Steinkopf, *Ann.*, **403**, 1 (1914).

[35] Volhard and Erdmann, *Ber.*, **18**, 454 (1885).

[36] Erdmann, *Anleitung zur Darstellung organischer Präparate.* Stuttgart, 1894.

[37] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 578.

200 g. of ice and 50 cc. of 40% sodium hydroxide solution. The receivers must be well cooled; the outlet of the last one is vented to a fume duct. In the lower part of the apparatus cork or rubber stoppers may be used. When the flask is carefully heated with a free flame, the reaction starts at one point and the mass puffs up. It turns black, and rapid evolution of hydrogen sulfide takes place. The reaction then proceeds to completion without external heating, but subsequent heating is recommended to distil the last traces of thiophene. If an apparatus with interchangeable ground joints is used, the reaction flask, after cooling, may be replaced with another one filled with new reaction mixture. After the reaction of this second batch is completed, the first flask may be attached again with another batch. This method of operation proved to be more convenient and productive than the use of large single batches.

The contents of the receivers are steam-distilled. The thiophene is dried over potassium hydroxide and distilled over sodium. The yield amounts to more than 30% of theory; each 700 g. batch of the mixture yields at least 50 g. of pure thiophene boiling at 84°C.

Carbon-Hexavalent Sulfur Bonds

I. ALIPHATIC SULFONIC ACIDS

The aliphatic sulfonic acids were first prepared by Strecker [1] from alkyl halides and alkali sulfites. Hemilian [2] used ammonium sulfite. For the preparation of the lower members of the series, the alkyl halide is advantageously replaced by dimethyl or diethyl sulfates; see below.

Wagner and Reid [3] checked the method of Hemilian, but they did not obtain the almost theoretical yields claimed. However, they obtained very satisfactory results with alkyl bromides. The method could not be used with *sec*-amyl, *n*-hexyl, and *sec*-hexyl bromides.

Hemilian prepared barium ethanesulfonate by heating 20 g. of ethyl iodide and a solution of 20 g. of ammonium sulfite in 40 cc. of water under a reflux for 6 hours. Upon cooling the mixture, ammonium ethanesulfonate crystallizes out. The mixture is diluted with water and heated with lead oxide as long as ammonia escapes. The excess lead oxide is removed by filtration and the filtrate treated with hydrogen sulfide to precipitate the lead. The filtrate is finally treated with barium carbonate, filtered again, and the clear solution evaporated to dryness to yield the product.

A method set forth in a Swiss patent [4] gives good results.

Pure dimethyl sulfate (126 g.) is added slowly at 10°C. to 600 cc. of 26% ammonium sulfite solution. As soon as the dimethyl sulfate has passed into solution, 75 g. of crystalline ammonium sulfite, mixed with 75 cc. of water to form a paste, are added and the solution heated for several hours on a steam bath. The hot solution is diluted to 3 times its volume, the small excess of sulfite decomposed with sulfuric acid, and the ammonia boiled off after the addition of the calculated amount of barium hydroxide. Any excess of barium hydroxide is cautiously removed with sulfuric acid, and the solution neutralized with barium carbonate. The filtrate, upon evaporation, yields barium methanesulfonate.

The calcium salt may be prepared in a corresponding manner. The barium hydroxide is replaced by a suspension of lime. Lime is also used for the final neutralization.

[1] Strecker, *Ann.*, **148**, 90 (1868).
[2] Hemilian, *Ann.*, **168**, 145 (1873).
[3] F. C. Wagner and E. E. Reid, *J. Am. Chem. Soc.*, **53**, 3409 (1931).
[4] Swiss Patent, 105,845.

The free alkylsulfonic acids can be obtained according to a Swiss patent [5] by mixing the calcium salts with concentrated sulfuric acid and distilling the mixture. For instance, 200 parts of calcium ethanesulfonate and 100 parts of concentrated sulfuric acid are mixed. Distillation at 3 to 5 mm. pressure and at a bath temperature of 210° to 235°C. yields 130 parts of a 95% ethanesulfonic acid distilling at 150° to 165°C. This is then fractionated.

II. AROMATIC SULFONIC ACIDS

Direct Introduction of Sulfonic Acid Group

The sulfonic acid group may replace hydrogen in a great variety of organic compounds. In the simplest case, a hydroxyl of the sulfuric acid and a hydrogen atom are split off as water. The greatest significance of the reaction, as is the case with nitration, is in the aromatic and hetero-cyclic series. The reaction products, the sulfonic acids, are without exception very strong acids, the dissociation constant being greater than that of dibasic sulfuric acid if both hydrogen atoms of the sulfuric acid are taken into consideration.

Special Factors Influencing Sulfonation

· Compared with nitration, the possibilities of changing the course of sulfonation is less. In the sulfonic acid group, the substitution rules are followed almost without exception; only the ratio of ortho and para isomers can successfully be changed. The temperature is much more of a determining factor here than in the case of nitration. In general it can be stated that at lower temperatures the sulfonic group prefers the neighborhood of substituents already present. At higher temperatures more distant hydrogen atoms are replaced. Thus, naphthalene, when sulfonated in the cold with fuming sulfuric acid, yields a preponderant amount of α-naphthalenesulfonic acid. The β-sulfonic acid, on the other hand, is obtained almost exclusively if, according to Witt,[6] sulfuric acid is added to naphthalene heated to 160°C. In a corresponding manner phenol can be sulfonated in the ortho position. The reaction does not proceed exclusively in this direction, but the reaction mixture contains more o-phenolsulfonic acid when the sulfonation is carried out with cooling than when it takes place with heating.

Of great technical importance is the sulfonation of toluene to produce o-toluenesulfonic acid. This is used as a starting material for the manu-facture of saccharin. Up to date no successful method has been developed for preparation of o-toluenesulfonic acid without the simultaneous forma-

[5] Swiss Patent, 104,907.
[6] Witt, *Ber.*, 48, 743 (1915).

tion of considerable amounts of *p*-toluenesulfuric acid. The latter still constitutes a by-product of little use.

Furthermore, it is not possible, as it is in nitration, to protect the para position by means of an intermediate substituent. Therefore, one must rely on indirect methods for the preparation of isomers, unless simple methods of separating the isomer mixture are available; this is often the case.

In contrast to nitration, sulfonation may be directed in some cases by catalysts. Anthraquinone with sulfuric acid alone almost exclusively yields β-anthraquinonesulfonic acid. On the addition of small amounts of mercury, α-monosulfuric acid is obtained almost exclusively. Iljinsky[7] found 0.5% of mercury sufficient. That such cases are rare is true. Systematic investigations of Holdermann[8] show that other examples are scarce. An observation by Dimroth and Schmädel[9] indicates that benzoic acid with sulfuric acid alone yields a mixture of *m*- and *p*-sulfonic acids, while in the presence of mercuric sulfate *o*-sulfobenzoic acid is formed.

The speed of sulfonation can be influenced by catalysts only in rare cases. An English patent[10] states that small amounts (less than 1%) of iodine facilitate considerably the sulfonation of benzene. Thümmler[11] says vanadium salts exert a similar effect.

Sulfonating Agents

"Sulfonation" refers to the methods used for the introduction of the SO_3H group, the sulfonic acid group.

1. Sulfuric acid which boils at a constant temperature at atmospheric pressure contains 98.3% H_2SO_4. It is a liquid at ordinary temperature as is the so called monohydrate of the composition H_2SO_4, which has a melting point of 10°C. In these liquids, however, an equilibrium must be assumed between water, sulfuric acid, pyrosulfuric acid, and its anhydride.

The ordinary commercial sulfuric acid contains 96% of the acid. A very convenient qualitative method for testing the water content was given by Vorländer and Schilling.[12] If a few cubic centimeters of acid are heated with a few tenths of a gram of potassium perchlorate, the acid exhibits a dark orange color in 96 to 98% H_2SO_4. If the acid tests better than 99%, it turns brown and chlorine dioxide is evolved copiously even though the flame is removed.

[7] Iljinsky, *Ber.*, **36**, 4197 (1903).
[8] Holdermann, *Ber.*, **39**, 1250 (1906).
[9] Dimroth and Schmädel, *Ber.*, **40**, 2411 (1907).
[10] Heinemann, English Patent, 12,260 (1915).
[11] Thümmler, German Patent, 214,156.
[12] Vorländer and Schilling, *Ann.*, **310**, 377 (1900).

2. Fuming sulfuric acid, oleum, is commercially available in many different concentrations. It is not practical to prepare it in the laboratory. Fuming sulfuric acid of definite anhydride content is obtained most conveniently by mixing oleum with ordinary acid according to the mixing rule of Küster and Thiel.[13]

3. Alkali bisulfates are used occasionally as sulfonating agents. By melting the compound together with bisulfate high temperatures can conveniently be reached.. Pyrosulfates may also be used.

4. Chlorosulfonic acid may be obtained by saturating 40% oleum with hydrochloric acid; it boils at 149° to 151°C.

5. Other sulfonating reagents. A mixture of manganese dioxide and sulfurous acid has the same effect as sulfuric acid.

Examples of Sulfonation of Hydrocarbons

1. H. Meyer [14] gives the following directions for the preparation of benzenesulfonic acid.

The U-tube *C*, Fig. 8, contains small pieces of glass in leg *K*. The top of the leg is closed with a calcium chloride tube *L* for equalizing pressure. At *M* a pinch-cock is provided to drain the collected water.
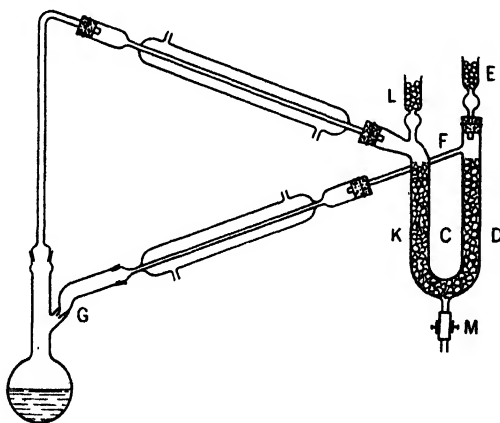
FIG. 8.—Apparatus for the preparation of
benzenesulfonic acid.

The bent part of *C* is filled with glass pieces, while leg *D* contains calcium chloride topped with glass-wool and some glass beads to prevent the calcium chloride from rising in the liquid. The outlet of the U-tube above the tube *F*, which is connected to a downward condenser, is closed with a

[13] F. W. Küster and A. Thiel, *Logarithmische Rechentafeln für Chemiker, Pharmazeuten, Mediziner und Physiker.* de Gruyter, Berlin, 1929, Table 23.
[14] H. Meyer, *Ann.,* **433,** 330 (1923).

second calcium chloride tube E.   At point G a restriction is provided in order to prevent the vapors from backing up.

The U-tube C is filled completely with benzene.   The distilling flask is filled with 200 cc. of benzene and 20 cc. of concentrated sulfuric acid. After the mixture has been boiled for 90 to 100 hours, all of the sulfuric acid has changed.   The benzene is removed by distillation and the residue allowed to solidify in a desiccator.   The yield is 55 to 56 g. of crude product melting at 53°C. · This corresponds to 94% of the theoretical amount.   The product is purified by solution in water, a small amount of diphenylsulfone separating as a by-product.   The filtrate is evaporated to dryness and the residue recrystallized from benzene.   The monohydrate melting at 45° to 46°C. is obtained.

2. p-Toluenesulfonic acid is prepared in the apparatus shown in Fig. 9.   The directions are those of H. Meyer.

Toluene (200 g.) and 40 cc. of concentrated sulfuric acid are boiled in the flask for 5 hours. The moist toluene vapors pass into the condenser, condense, and pass through the funnel to the bottom of the water catcher, the lower part of which is enclosed by a lead pipe through which cooling water runs.   The water of reaction is drained from the bottom.   After the reaction is completed, the excess toluene is removed by distillation and 12.5 cc. of water are added to the residue.   The mixture grows warm and solidifies. The solid is pressed on a porous plate and recrystallized from a little water.

FIG. 9.—Apparatus for the preparation of toluenesulfonic acid.

3. For the preparation of β-naphthalenesulfonic acid Witt [15] places 100 g. of naphthalene in a flask equipped with a thermometer, a dropping funnel, and a stirrer.   To the melt at 160°C. are added dropwise, during 15 minutes, 160 g. of concentrated sulfuric acid.   Stirring is continued for 5 more minutes at 160°C.   The solution is poured into 120 cc. of cold water and after 24 hours the crystals are collected on a Büchner funnel and dried on a porous plate.

To purify the crude product 10 g. are dissolved in 5 cc. of water, the solution filtered hot, and about 2 cc. of concentrated hydrochloric acid added to the hot (>70°) filtrate.   Upon cooling, the filtrate yields the trihydrate of the sulfonic acid.· A total of 160 g. of sulfonic acid tri-

[15] Witt, *Ber.*, **48**, 751 (1915).

hydrate is obtained.   Drying is effected by spreading the material on porous plates, or in a desiccator over sodium hydroxide.

4. The sulfonation of anthracene is complicated.   On treatment with moderately concentrated sulfuric acid at 120° to 135°C., the β-sulfonic acid is obtained along with disulfonic acids.[16]

5. The sulfonation of phenanthrene was studied recently by Fieser [17] and Cohen and Cormier.[18]   Fieser's directions for preparing 2- and 3-phenanthrenesulfonic acids can be found in *Organic Syntheses*.[19]

In industry, there is little interest in pure sulfonic acids.   Sodium salts are usually produced.   These, as well as the potassium salts, can be salted out of aqueous solutions with alkali chlorides; see the above reference on the sulfonation of phenanthrene.   The alkali salts of the monosulfonic acids are considerably less soluble than the salts of di- or polysulfonic acids.

Sulfonation of Heterocyclic Compounds

Thiophene, one of the 5-membered heterocyclic compounds, may be converted to α-thiophenesulfonic acid by shaking with concentrated sulfuric acid in petroleum ether solution; see Biedermann.[20]   Furane- and pyrrolesulfonic acids, apparently, are unknown.

Only the β-pyridinesulfonic acid can be obtained directly from pyridine.   It was described by E. Fischer.[21]   From quinoline, Fischer [22] prepared, by varying the reaction temperature, several reaction products in which the benzene nucleus had been substituted.

Knorr [23] found that pyrazole may be directly sulfonated, as might be expected, but details for the method are lacking.

Sulfonation of Other Compounds

The sulfonation of phenol proceeds readily.   In no way, as mentioned above, can the *o*- and *p*-phenolsulfonic acids be directly obtained free of isomers.   Obermiller [24] showed that a higher content of one or the other isomer in the reaction product can be secured according to the following method.

1. *o*-Phenolsulfonic Acid.   200 g. of phenol are just melted and 100 g. of sulfuric acid monohydrate are added with stirring.   The mixture, which does not easily crystal-

[16] German Patent, 77,311.
[17] L. Fieser, *J. Am. Chem. Soc.*, **51**, 2460, 2471 (1929).
[18] Cohen and Cormier, *J. Am. Chem. Soc.*, **52**, 4363 (1930).
[19] A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. II, Wiley, New York, 1943, p. 482.
[20] Biedermann, *Ber.*, **19**, 1615 (1886).
[21] E. Fischer, *Ber.*, **15**, 62 (1882).
[22] E. Fischer, *Ber.*, **20**, 731 (1887).
[23] L. Knorr, *Ann.*, **279**, 230 (1894); *Ber.*, **28**, 715 (1895).
[24] Obermiller, *Ber.*, **40**, 3637 (1907).

lize, is cooled and 200 g. more of sulfuric acid monohydrate are added, while the mixture is stirred and the temperature is kept below 20°C. The stirring is continued at the same temperature for 6 to 8 hours, and then the mixture is poured into 1.5 liters of water. The large excess of sulfuric acid is neutralized with lead carbonate. About 1.8 moles, 500 g., are necessary. Then barium carbonate is added with caution until the solution just changes Congo red paper from blue to red. This is in order to keep the sulfonic acids in solution as acid barium salts. During this operation long boiling with excess carbonate must be avoided, because otherwise the neutral barium sulfonates, which are slightly soluble, precipitate. The precipitated lead and barium sulfates are removed by filtration, the cake washed well, and the filtrate if necessary cleared by another filtration. The liquid is concentrated until its specific gravity over the precipitated crystals is 1.18 to 1.20 (determined in the cold). Care must be taken that none of the fine, felty needles of the isomer appear with the coarse crystals of the o-sulfonate which combine to form clusters. The fine crystalline isomer must be redissolved by adding cold water. The crude product thus obtained is filtered and washed with cold water, until the washings show a specific gravity of 1.08 to 1.09.

The final yield amounts to about 25% of the theoretical amount of crude barium phenol-o-sulfonate.

2. p-Phenolsulfuric Acid. The reaction mixture obtained according to the above directions (1) consists of about two-fifths of o- and three-fifths of p-sulfonic acid. After removal of the crude barium o-sulfonate, the mother liquor contains about 80% p-sulfonate which crystallizes upon addition of magnesium sulfate as the magnesium sulfonate. If the p-sulfonate alone is desired, 200 g. of phenol are heated to 90° to 100°C. with 220 g. of 95% sulfuric acid for 6 to 8 hours with stirring. The solution is allowed to cool to 70° to 75°C., and 50 cc. of water are added to prevent the solution from solidifying. Then the temperature is lowered to room temperature. The reaction mixture now contains more than 80% of p-sulfonic acid which may be isolated directly from it. For details see the original paper.

An example of the preparation of sulfonyl chlorides by sulfonation with chlorosulfonic acid may be found in *Organic Syntheses*.[25] This method for the preparation of benzenesulfonyl chloride is based on a German patent.[26]

It has been known for a long time that the sulfonation of anthraquinone takes place in the α position if mercury is present. Lauer [27] studied the conditions thoroughly. His recent [28] studies deal with the problem of the reaction mechanism with such catalysts applied to simple benzene monosubstitution products. He found that the directing effect of the mercury is based on the formation of metal-organic intermediates. The ratio of the sulfonic compounds formed in sulfonation can be shifted by the addition of mercury, whenever the substituent present is negative. For instance, with 5% mercury, from nitrobenzene in 20% oleum up to 25% of the p-sulfonic acid can be obtained, as compared to a yield of 3%

[25] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 85.
[26] German Patent, 224,386.
[27] K. Lauer, *J. prakt. Chem.*, **135**, 173 (1932).
[28] K. Lauer, *J. prakt. Chem.*, **138**, 81 (1933).

of the same acid when mercury is not used.   Lauer succeeded in clarifying the contradictory statements found in the literature on the sulfonation of phthalic anhydride.   In the absence of mercury only 4-sulfonic acid is formed.   By a technical method [29] in which mercury is used still better yields are claimed.   This statement is erroneous.   If a sufficient amount of mercury is present, the 3,5-disulfonic acid is formed exclusively in accordance with the statements of Waldmann and Schwenk.[30]   The 3,5-sulfonic acid is presumably formed through the 3-sulfophthalic acid which cannot be isolated.   3-Sulfophthalic acid prepared in another way, see Zincke and Greune,[31] can easily be further sulfonated.   In this case the presence of mercury exerts no noticeable influence.   The circumstances, therefore, are quite similar to those bearing on anthraquinone: 3-sulfophthalic acid corresponds to the α-anthraquinonesulfuric acid and 4-sulfophthalic acid to the β-anthraquinonesulfonic acid.   These theories are confirmed by experiments with the isolated mercurihalogen compounds of phenol, toluene, nitrobenzene, and benzoic acid.

Huber [32] carried out systematic investigations on the so called Back process.   It is essential in this process to start with pure materials. Furthermore, it is necessary in certain cases to promote the formation of the acid sulfates by the addition of an indifferent solvent.   The base to be sulfonated is dissolved in glacial acetic acid and this solution added to the calculated amount of concentrated sulfuric acid.   After evaporation *in vacuo* of the glacial acetic acid the residue consists quantitatively of the acid sulfate.   Additions such as oxalic acid are not recommended.   A laboratory apparatus for heating the acid sulfate *in vacuo* is described; it consists of an enameled dish of 100 g. capacity which is inserted in a steel chamber; see Holleman.[33]

[29] German Patent, 500,914.
[30] H. Waldmann and E. Schwenk, *Ann.*, **487**, 287 (1931).
[31] Th. Zincke and G. Greune, *Ann.*, **427**, 232 (1922).
[32] W. Huber, *Helv. Chim. Acta*, **15**, 1372 (1932).
[33] A. F. Holleman, *Helv. Chim. Acta*, **16**, 245 (1933).

Unsaturated Carbon Bonds

I. ETHYLENE LINKAGES

A distinction between two types of ethylene bonds must be made. The newly formed double bond may be part of a conjugated or of an aromatic or heterocyclic system, or it may be isolated; that is, adjacent to at least 2 saturated carbon atoms. While aromatic systems can be obtained directly from saturated or partially unsaturated systems by dehydrogenation, it is not possible to prepare isolated double bonds in this manner. Indirect ways have to be found in which substitution products of saturated systems are used.

A. Isolated Ethylene Bonds

The most important reactions as far as preparative work is concerned are the following:

1. $R \cdot CHX \cdot CHX \cdot R \longrightarrow R \cdot CH:CH \cdot R + X_2$

2. $R \cdot CH_2 \cdot CHX \cdot R \longrightarrow R \cdot CH:CH \cdot R + HX$

3. $R \cdot CH_2 \cdot CHOH \cdot R \longrightarrow R \cdot CH:CH \cdot R + H_2O$

4. $R \cdot CH_2 \cdot CHNH_2 \cdot R \longrightarrow R \cdot CH:CH \cdot R + NH_3$

The third reaction, that is the cleavage of water from alcohols, is the most important. The first one, namely the removal of halogen from 1,2-dihalides, is used in some cases for the preparation of ethylene compounds. The fourth reaction is important, because it can be used with many naturally occurring amino compounds.

In addition to these typical and generally used methods, there are many others which can be employed in special cases. A remarkable version of the removal of halogen is the following reaction.

$$-CHBr-CH(OCH_3)- \longrightarrow -CH=CH-$$
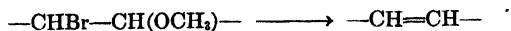
An example of this is described in the following section.

1. Removal of Halogen

The formation of the ethylene bond by removal of halogen from 1,2-dihalides is of almost no importance in synthesis, since the dihalides in-

volved are obtained almost without exception by addition of halogen to the double bond. However, the method is important for the reason that the halogen substitution products frequently crystallize well, are slightly soluble, and may be used for isolation and separation.

Metals are used almost exclusively to effect the removal of halogen. In most cases zinc in the form of zinc dust or shavings is used; copper-zinc, that is coppered zinc, is frequently suitable.

Pure ethylene is prepared in the laboratory by heating on a steam bath an alcoholic solution of ethylene bromide with an excess zinc dust.

It is remarkable that the halogen in 1,2-dihalides is not replaced by hydrogen when they are treated with zinc and glacial acetic acid or with sodium amalgam. An ethylene bond is formed by removal of halogen.

Occasionally derivatives of sensitive ethylene compounds are obtained by first adding bromine, then preparing the derivative, and finally removing the bromine. In the esterification of acrylic acid, $CH_2\!:\!CH\cdot COOH$, for instance, it is converted into its dibromide; this is esterified with alcohol and hydrochloric acid as usual and the α,β-dibromopropionic ester is boiled in alcoholic solution with zinc shavings. Instead of acrylic acid, acrolein dibromide may be used as a starting material and the dibromide oxidized to dibromopropionic acid.

Only the stable form of the two possible stereoisomers of the ethylene compounds is formed when halogen is removed from dihalides. Dibromosuccinic acid and isodibromosuccinic acid, for instance, both yield fumaric acid. From dibromocinnamic ester, however, Liebermann [1] obtained besides the ordinary ester about 10% of the total ester formed as allo-(cis)-cinnamic ester.

Small amounts of butadiene may be prepared conveniently in the laboratory from the tetrabromide by the method of Thiele.[2] The preparation of the tetrabromide is described on page 63.

A Soxhlet extraction apparatus, filled with 100 g. of butadiene tetrabromide, is attached to a flask containing 200 g. of zinc dust and 250 cc. of alcohol. The alcohol is brought to a boil to dissolve the tetrabromide and to react with the zinc dust slowly so that the speed of reaction does not get out of control. The escaping gases are passed through an efficient condenser, dried with calcium chloride, and condensed in a freezing mixture. If the dead spaces of the apparatus are reduced to a minimum, 80 to 90% of the theoretical amount of butadiene is obtained. It boils at $-5°$ to $-4°C$. at 713 mm.

The formation of the naturally occurring unsaturated fatty acids is difficult, because the double bond cannot be present in the chain at the start. Noller and Bannerot [3] used an olefin synthesis recommended by Shoemaker and Boord [4] for the preparation of oleic and elaidic acids. A

[1] C. Liebermann, *Ber.*, **24**, 1108 (1891).
[2] J. Thiele, *Ann.*, **308**, 339 (1899).
[3] R. Noller and A. Bannerot, *J. Am. Chem. Soc.*, **56**, 1563 (1934).
[4] Shoemaker and Boord, *J. Am. Chem. Soc.*, **53**, 1505 (1931).

sketch of the course of the reaction is as follows: ω-chlorononaldehyde is converted with bromine to α-bromo-ω-chlorononaldehyde and treated with methanol-hydrobromic acid.   According to the equation,

$$Cl(CH_2)_7 \cdot CHBr \cdot CHO + HBr + CH_3OH \longrightarrow$$
$$Cl(CH_2)_7 \cdot CHBr \cdot CHBr \cdot OCH_3 + H_2O$$
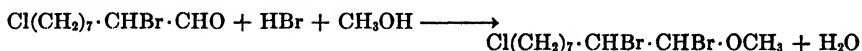
8,9-dibromo-9-methoxynonyl chloride is thus obtained which with n-octyl-magnesium chloride gives 8-bromo-9-methoxy-ω-heptadecyl chloride: $Cl(CH_2)_7 \cdot CHBr \cdot CH(OCH_3) \cdot (CH_2)_7 \cdot CH_3$.   Reduction with zinc dust in boiling butanol yields 8-heptadecenyl chloride, $Cl(CH_2)_7 \cdot CH:CH \cdot (CH_2)_7 \cdot CH_3$; the chlorine is replaced by the nitrile with potassium cyanide.   On saponification of the nitrile a mixture of one-third oleic acid and two-thirds elaidic acid is obtained.   From 86 g. of ω-chlorononaldehyde there are obtained 30.6 g. of the unsaturated condensation product, and from this about an equal amount by weight of the acid mixture is obtained.

The critical points in the sequence of the reaction are in the formation of the group —CHBr—CH(OCH₃)— and the removal of bromine and the methoxyl group with nascent hydrogen.   It has been observed that vinyl ethers, —CH=C·(OCH₃)—, yield ethylene derivatives with catalytically excited hydrogen by exchanging OCH₃ for hydrogen.

2. Removal of Hydrogen Halide

The method is entirely analogous to the removal of the elements of water from alcohols.   Since many halides are obtained only from the corresponding hydroxy compounds, this reaction frequently constitutes a round about method, but often this indirect procedure is of advantage.

The agents for removal of hydrogen halide are almost always of basic nature.   Generally potassium and sodium hydroxides are sufficient; sometimes the alcoholates are more useful.   In the first case the side reaction, $RX + KOH \rightarrow ROH + KX$, must be considered, while in the second case, ethers may form:

$$RX + KOCH_3 \longrightarrow ROCH_3 + KX$$
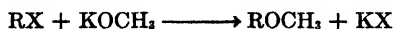
The removal of the hydrogen halide is easier the less hydrogen there is on the carbon atom which carries the halogen.   Tertiary halides are converted to unsaturated compounds with pyridine.   Pyridine may be replaced in the hydroaromatic series by aniline, dimethylaniline, or quinoline.   Thus, Wallach [5] obtained dipentene from dipentene hydrochloride; see also Crossley.[6]

Eltekow [7] obtained good results with lead oxide, but the olefins he prepared are more conveniently derived from the alcohols.

[5] O. Wallach, *Ann.*, **245**, 196 (1888).
[6] W. Crossley, *J. Chem. Soc.*, **85**, 1403 (1904
[7] Eltekow, *Ber.*, **30**, 2404 (1880).

The rule for the removal of hydrogen halide is the same as that governing the removal of water from alcohols. This fact makes possible, under certain conditions, the planned shifting of the double bond by addition and subsequent removal of hydrogen halide.

$$(CH_3)_2:CH \cdot CH:CH_2 + HI \longrightarrow (CH_3)_2:CH \cdot CHI \cdot CH_3$$
$$\longrightarrow (CH_3)_2:C:CH \cdot CH_3 + HI$$
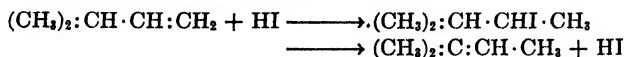
The preparation of trimethylethylene in this way has no importance, because it is more conveniently prepared from amyl alcohol. The rule, however, is only qualitative. Tertiary amyl iodide yields 1-methyl-1-ethylethylene besides the expected trimethylethylene:
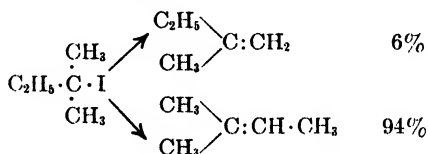
Another application of the method, which is important only from a theoretical standpoint, is the preparation of unsaturated monocarboxylic acids. When hydrogen halides are added to α,β-unsaturated olefin carboxylic acids according to the equation,

$$R \cdot CH_2 \cdot CH:CH \cdot COOH + HX \longrightarrow R \cdot CH_2 \cdot CHX \cdot CH_2 \cdot COOH$$
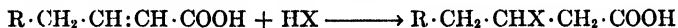
β-halogenocarboxylic acids are obtained, because the halogen takes the position farthest from the carboxyl group. These acids, when treated with agents which split off hydrogen halides, are reconverted only to the α,β-unsaturated acids.

In some exceptional cases, for example, cyclic carboxylic acids, the double bond is established at different places, depending on the nature of the agent used for the removal. In general, unsaturated acids are obtained by removal of water from hydroxycarboxylic acids. Dicarboxylic acids of the maleic-fumaric acid type are readily obtained from halogen-substituted succinic acids. Fumaric acid is easily formed from monobromosuccinic acid which splits off 1 mole of hydrogen bromide when boiled with water or when heated above its melting point. The crude product may be recrystallized from water. The melting point in a sealed tube is 286° to 287°C. At atmospheric pressure fumaric acid sublimes at about 200°C., with decomposition.

Fumaric acid may also be obtained from malic acid by removal of water (see page 321), but the best method of preparation today is by oxidation of furfural (see page 464).

G. Bryant Bachman [8] reported on the removal of hydrogen bromide

[8] G. Bryant Bachman, *J. Am. Chem. Soc.*, **55**, 4279 (1933).

from the dibromide of α,β-unsaturated aliphatic carboxylic acids. He discussed the possibilities of cleavage under different conditions and gave directions for the preparation of 1-bromoölefins which may be used to obtain acetylene hydrocarbons.

The preparation of β-methylcrotonaldehyde acetal is an example of difficulty in the removal of hydrogen bromide. G. Fischer and Löwenberg [9] gave the procedure that is briefly described.

960 g. of bromomethylbutanal diethyl acetal, α-bromoisovaleraldehyde acetal (see page 86), are stirred well under nitrogen with 200 g. of powdered potassium hydroxide for 6 hours at 150° to 160°C., in a copper vessel equipped with a copper agitator. Then the unsaturated acetal formed is distilled completely *in vacuo*. The accompanying water is separated, and the remainder of the distillate is treated in the same manner with 200 g. of potassium hydroxide two more times. Thus 500 g. of bromine-free β-methylcrotonaldehyde acetal are obtained, boiling at 163° to 165°C., a yield of 88% of the theoretical. The hydrolysis of the acetal is referred to on page 201.

3. Dehydration of Alcohols

In many cases water may be removed directly. Sometimes, especially with complicated compounds, the alcohol is converted into an ester, and acetic acid or other carboxylic acid is split off.

The removal of water may be effected catalytically, with water-removing agents. It does not always proceed uniformly, if the possibility of the formation of different isomers is present.

In the case of a secondary or tertiary carbinol, the equation below is valid:

$$R'\cdot CH{:}CH\cdot CH_2\cdot R'' \longleftarrow R'\cdot CH_2\cdot CHOH\cdot CH_2\cdot R'' \longrightarrow R'\cdot CH_2\cdot CH{:}CH\cdot R''$$

The shifting of the double bond has to be considered under the conditions of the reaction. Molecular rearrangements accompanied by the shifting of radicals take place even in simple aliphatic systems.

When water is removed, the so called rule of Saytzev [10] applies: the hydrogen atom split off is taken from the carbon atom with the least number of hydrogen atoms. Thus, secondary isoamyl alcohol with concentrated sulfuric acid yields, not isopropylethylene, $(CH_3)_2{:}CH\cdot CH{:}CH_2$, but trimethylethylene according to the equation

$$(CH_3)_2\cdot CH\cdot CHOH\cdot CH_3 \longrightarrow (CH_3)_2{:}C{:}CH\cdot CH_3 + H_2O$$
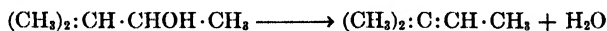
It has been mentioned on page 124 that, if water is added again, the hydrogen atom adds to the carbon atom richest in hydrogen. Thus, in this case secondary isoamyl alcohol is not recovered but tertiary amyl alcohol, $(CH_3)_2{:}C(OH)\cdot C_2H_5$.

[9] G. Fischer and K. Löwenberg, *Ann.*, **494**, 272 (1932).
[10] Saytzev, *Ann.*, **179**, 300 (1875).

The rule of Saytzev is not quantitative. Thoms and Mannich [11] obtained from methylnonylcarbinol 1-ethyl-2-octylethylene and about 4% of the isomeric nonylethylene.

The shifting of the double bond always takes place in such a way that a symmetrical molecule is formed. Amyl alcohol from fermentation processes with zinc chloride yields trimethylethylene according to the equation

$$(CH_3)_2 : CH \cdot CH_2 \cdot CH_2OH \longrightarrow (CH_3)_2 \cdot CH \cdot CH : CH_2 \longrightarrow (CH_3)_2 : C : CH \cdot CH_3$$
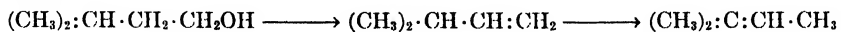
The final product must be formed from isopropylethylene which is produced first.

No general rule can be established for the direction in which radicals shift. In the case of the removal of water from isobutanol with sulfuric acid, the yield is about two-thirds isobutylene, $(CH_3)_2 : C : CH_2$, and, by rearrangement, one-third n-butylene-2, $CH_3 \cdot CH : CH \cdot CH_3$. The formation of a symmetrical molecule apparently is determinant in the rearrangement.

Isoamyl alcohol with zinc chloride yields besides trimethylethylene 1-methyl-1-ethylethylene and an amylene with a normal chain; see also Kondakov.[12]

On the whole the reaction is very valuable from a preparative point of view. The removal of water is successful with fairly active reagents. Tertiary carbinols split off water with the greatest ease; secondary and then primary carbinols follow.

The chief reagents for dehydration are the following.

1. Sulfuric acid
2. Metaphosphoric acid
3. Oxalic acid, formic acid
4. Zinc chloride, phosphorus oxychloride, acetyl chloride
5. Grignard's reagents

The use of sulfuric acid in the laboratory is very simple. High temperatures must be avoided, because the acid exerts an oxidation effect. The reaction takes the following course proceeding through the sulfuric acid esters.

$$R \cdot CH_2 \cdot CH_2OH + H_2SO_4 \longrightarrow R \cdot CH_2 \cdot CH_2 \cdot O \cdot SO_3H \longrightarrow R \cdot CH : CH_2$$
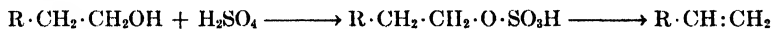
However, the use of sulfuric acid for the removal of water is restricted by many circumstances.

The preparation in the laboratory of ethylene from ethanol in this way is not very practical. It is better to dehydrate ethanol by means of metaphosphoric acid or catalytically. Pure ethylene is conveniently obtained from ethylene bromide (see page 315), but this method is ex-

[11] Thoms and Mannich, *Ber.*, **36**, 2544 (1903).
[12] Kondakov, *Chem. Zentr.*, **1893**, I, 383.

pensive. An example of the use of the method in the aliphatic series is the preparation of 1-methyl-2-ethylethylene. Directions can be found in *Organic Syntheses*.[13]

Organic Syntheses [14] gives directions for the preparation of cyclohexene from cyclohexanol, illustrating the application of the method in the isocyclic series; see also Senderens.[15]

A convenient laboratory method for the preparation of ethylene makes use of metaphosphoric acid.

120 g. of syrupy phosphoric acid ($D = 1.7$) are stirred in a porcelain dish and heated to 160°C. As soon as the evolution of steam subsides, the temperature is raised to 200°C., heating being continued until only a little water escapes. The metaphosphoric acid, while still warm, is placed in a 200 cc. flask equipped with a dropping funnel, a thermometer, and a gas outlet tube. After the flask with the metaphosphoric acid has been heated to 210° to 220°C., ethanol is added dropwise. The ethylene obtained is not very pure, as it contains by-products of higher molecular weight. The method may be used for similar reactions. It has the advantage that practically any desired amount of alcohol can be dehydrated with a small amount of metaphosphoric acid. The water formed distils off with the gases.

The removal of water with oxalic acid is preferred for terpene alcohols, as rearrangements easily take place. Wallach [16] boiled terpineol with an aqueous solution of oxalic acid, producing mainly terpinolene. Sulfuric acid isomerizes the terpinolene to terpinene.

The water-removing action of Grignard solutions is frequently disturbing, but it may be used for the preparation of ethylene derivatives. If the alcohols are available, the method is not convenient and is better replaced by one of the methods mentioned above. But frequently the preparation of a hydroxy compound can be followed by its dehydration. The preparation of 1-methyl-1-phenylethylene, $C_6H_5 \cdot C(CH_3):CH_2$, from acetophenone and 2 moles of methylmagnesium iodide by the method of Klages [17] serves as an example.

The reaction product obtained in the usual manner from 2 moles of methylmagnesium iodide and 1 mole of acetophenone is heated to 100°C. for 6 hours after removal of the ether by distillation. The residue is decomposed with ice water and the product extracted with ether. After drying and distillation, there are obtained from every 10 g. of acetophenone 5 to 6 g. of the unsaturated hydrocarbon. The boiling point of the product is 162°C. It is formed according to the following equation.

$$C_6H_5 \cdot CO \cdot CH_3 + 2CH_3MgI \longrightarrow C_6H_5 \cdot C(CH_3):CH_2 + MgI_2 + MgO + CH_4$$
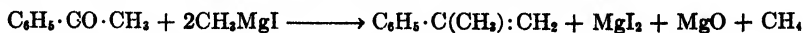
Inflammable methane escapes, a fact which must be kept in mind.

[13] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 430.
[14] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 183.
[15] Senderens, *Compt. rend.*, **154**, 1169 (1912).
[16] Wallach, *Ann.*, **275**, 106 (1893).
[17] L. Klages, *Ber.*, **35**, 2640 (1902).

For complex hydroxy compounds and also for higher alcohols the method involving the esterification of the hydroxy group is useful. Many tertiary alcohols when acetylated under the usual conditions do not yield esters but only olefins, especially if a little zinc chloride is added.

The cleavage of acetic acid from nitro alcohols with potassium bicarbonate will be described on page 437; acetates of polyene alcohols split off acetic acid with potassium ethylate (see page 435).

High molecular weight alcohols are advantageously esterified with palmitic acid. Thus, Krafft [18] reports that palmitic acid n-dodecyl ester when distilled at 600 mm. decomposes to dodecylene and palmitic acid.

Some ketoles split off 1 molecule of water with ease; thus, diacetone alcohol, $(CH_3)_2:COH \cdot CH_2 \cdot CO \cdot CH_3$ (see page 341), is converted into mesityl oxide. Many experiments show that traces of elementary iodine constitute a good catalyst. Conant and Tuttle give directions for this preparation in *Organic Syntheses*.[19]

α-Hydroxy acids, as a rule, are not converted to α,β-unsaturated acids, but for the most part give lactides or aldehydes by removal of formic acid. However, Henry [20] found that from α-hydroxynitriles, cyanohydrins, which are obtained by addition of hydrogen cyanide to aldehydes, α,β-unsaturated nitriles are obtained on treatment with phosphorus pentoxide. The unsaturated nitriles can be saponified to unsaturated acids.

It is easier to split out water from β-hydroxy acids. This reaction has no particular importance, because in many cases the unsaturated acids themselves are obtained more easily than the hydroxy acids which might be used for the preparation.

In a few special cases α,β- or β,γ-unsaturated acids can be obtained, depending on the choice of the agent employed for the removal of water. Thus, according to Wallach,[21] the cyclohexanolacetic acid (I) with potassium bisulfate yields the Δ[1]-cyclohexeneacetic acid (II); with acetic anhydride, on the other hand, it yields the isomeric α,β-unsaturated acid (III).
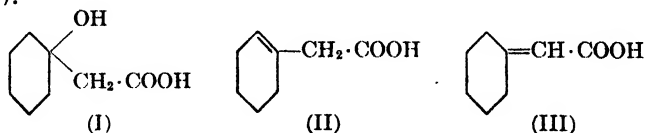
This method is more important for the preparation of unsaturated acids of the type of maleic-fumaric acids.

Baeyer [22] obtained fumaric acid by heating malic acid to 140° to 150°C.

[18] Krafft, *Ber.*, **16**, 3020 (1883).
[19] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 345.
[20] L. Henry, *Bull. classe sci. Acad. roy. Belg.*, **36**, 31 (1898); *Chem. Zentr.*, 1898, II, 662.
[21] O. Wallach, *Ann.*, **365**, 257 (1909).
[22] Baeyer, *Ber.*, **18**, 676 (1885).

in open vessels.   In a batch of 500 g., the solidified reaction product is dissolved after treatment for 40 hours in hot water and the crystallized fumaric acid is filtered off after the solution has been cooled.   The filtrate is evaporated to dryness and the residue of malic acid is treated again in the same manner.

The preparation of fumaric acid from furfural is given on page 464. For the preparation of maleic acid, Anschütz [23] also used malic acid.

Malic acid, at room temperature, is mixed with an excess of acetyl chloride and the mixture heated under a reflux on a water bath.   The reaction mixture is distilled at ordinary pressure; acetyl chloride, acetic acid, and hydrogen chloride distil, while crude maleic anhydride remains.   It is purified by mixing with phosphorus pentoxide and subliming *in vacuo* at 10 to 15 mm.   The anhydride comes over at 120° to 130°C.   Its aqueous solution when carefully evaporated yields pure maleic acid melting at 130°C.

The catalytic dehydration of alcohols can be successfully performed with clay at high temperatures.

The powdered, unignited, pure clay is mixed with a little water by the method of Kesting [24] so as to form beads.   These are then dried on a sand bath at moderate temperature.   The product is packed loosely in a combustion tube and held in place by means of asbestos or glass-wool plugs.   The tube so prepared is put on a slightly inclined combustion furnace.   The neck of a tubulated retort protrudes into the lower end of the tube, a rubber tubing being slipped over the joint to effect a tight seal.   A downward condenser is connected to the upper end.   A little silica sand is placed in the retort and the tubulure is equipped with a dropping funnel.   The furnace is then heated to maintain a temperature of 230°C. directly above the combustion tube.   At the same time the retort is heated well in the sand bath and alcohol dropped into it at a steady rate.   Unchanged alcohol and the water of reaction are liquefied in the condenser.

In a similar manner propylene and butylene can be prepared.   Higher boiling alcohols can be dehydrated by another method with better results.

High boiling tertiary alcohols, such as methyldiphenylcarbinol, split off 1 molecule of water without a catalyst when heated just below their boiling points.   The equation for the reaction is $(C_6H_5)_2$: C(OH)·CH$_3$ → $(C_6H_5)_2$: C: CH$_2$.   It is practically complete at 210°C.   If the carbinol is heated, as Stadnikov [25] directs, in an oil bath of 210°C., the water distils into the receiver.   During subsequent distillation at 30 mm. pressure, a little water is obtained as forerun, then comes the main run consisting of very pure 1,1-diphenylethylene boiling at 164°C.   At 2 mm. the boiling point is 113°C.

4. Removal of Ammonia from Amines

While water may be split out directly or indirectly from alcohols by water-binding agents, there are no real ammonia-removing agents.

[23] Anschütz, *Ber.*, **14**, 2791 (1881).
[24] Kesting, *Angew. Chem.*, **38**, 362 (1925).
[25] Stadnikov, *J. Russ. Phys. Chem. Soc.*, **47**, 2037, 2115 (1915); *Chem. Abstracts*, **10**, 1355 (1916).   H. Gilman and A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 226.

A remote similarity can be seen between salts of amines with hydrogen halides which yield olefins, with the loss of ammonium salts, and the decomposition of sulfuric acid esters of the alcohols. The chief importance of the reaction for preparatory work is in the hydroaromatic series. Wallach [26] found that thujone, which can be obtained from thuja oil, when treated with ammonium formate yields a thujonamine, the hydrochloride of which forms thujene on dry distillation. Harries and Antoni [27] in a corresponding fashion obtained 1,3-dihydrotoluene from 1,3-diamino-1-methylcyclohexane.

The removal of ammonia from amines indirectly by use of the quaternary ammonium bases obtained by complete alkylation has already been discussed on page 275.

B. Conjugated Double Bonds

The methods used for the preparation of isolated double bonds, that is the removal of water, of hydrogen halides, etc., may be employed singly and together for the preparation of conjugated double bonds. The following simple possibilities exist:

1. Removal of water from unsaturated alcohols (H_2O)
2. Removal of water from glycols ($2H_2O$)
3. Removal of hydrogen halides from unsaturated halides (HX)
4. Removal of hydrogen halides from dihalides (2HX)
5. Removal of halogen from tetrahalides ($2MeX_2$)

The removal of water from unsaturated alcohols has considerable importance only in special cases, since olefin alcohols themselves are usually very difficult to prepare. Scheiber [28] obtained from ricinoleic acid the octadecadienecarboxylic acid, the conjugated double bond of which renders it a valuable starting material for the manufacture of synthetic drying oils of the synourin oil type.

1,4-Glycols are readily dehydrated. The glycols are obtained from 1,4-dicarboxylic acid esters. Recently 1,3-butylene glycol became important as starting material for the manufacture of butadiene. Directions for the laboratory preparation have not been published. The patent literature is too vast to be discussed here. An older patent [29] gives as an example the method of dropping 1,3-butylene glycol onto phosphoric acid at 300°C. to prepare butadiene. In general, the methods suggested for technical use are the same as the usual laboratory procedures.

The removal of hydrogen halides from unsaturated halides has no special rôle. The cleavage of halogen from 1,2,3,4-tetrahalides has preparational importance only in the case of butadiene. It leads,

[26] Wallach, *Ann.*, **286**, 99 (1895).
[27] Harries and Antoni, *Ann.*, **328**, 88 (1903).
[28] Scheiber, *Farbe u. Lack*, 1929, 153; 1936, 361; *Angew. Chem.*, **46**, 643 (1933).
[29] German Patent, 261,642.

for instance, from erythritol, $CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CH_2OH$, through 1,2,3,4-tetrabromobutane (see Colson [30]), to butadiene; see Thiele [31] and also page 452.

The removal of hydrogen halide from 1,4-dihalides is for practical purposes insignificant.

A good example of the formation of three conjugated double bonds within one ring system is the synthesis of cycloheptatriene, or tropilidene, given by Willstätter.[32] The first step is the introduction of an ethylene bond into suberane, cycloheptane. Suberone (I) is used as starting material. From this, suberene (II) may be obtained in two ways. Either suberyl alcohol is first prepared by reduction, the alcohol converted to the iodide, and then hydrogen iodide removed with alcoholic potassium hydroxide; or, suberone oxime is prepared which, after reduction to suberylamine, is completely methylated and trimethylamine is split off. The cycloheptene thus prepared is converted to its dibromide (III). When this is treated with dimethylamine in indifferent solvents, 1 molecule of hydrogen bromide is removed and the second bromine atom is replaced by a dimethylamino group. 1-Dimethylaminocycloheptene (IV) is obtained. Upon addition of methyl iodide, the quaternary ammonium iodide is obtained which yields the base with silver oxide. The base, when heated, is decomposed to cycloheptadiene (V), trimethylamine, and water. The addition of bromine to cycloheptadiene is to the ends of the conjugated system. The dibromocycloheptene (VI) thus formed loses 2 molecules of hydrogen bromide on treatment with quinoline, yielding cycloheptatriene (VII) or tropilidene.

$$
\begin{array}{ccc}
CH_2\text{—}CH_2\text{—}CO & CH_2\text{—}CH_2\text{—}CH & CH_2\text{—}CH_2\text{—}CHBr \\
\qquad\quad CH_2 \longrightarrow & \qquad\quad CH \longrightarrow & \qquad\quad CHBr \longrightarrow \\
CH_2\text{—}CH_2\text{—}CH_2 & CH_2\text{—}CH_2\text{—}CH_2 & CH_2\text{—}CH_2\text{—}CH_2 \\
(I) & (II) & (III)
\end{array}
$$

$$
\begin{array}{cc}
CH_2\text{—}CH_2\text{—}CH \cdot N(CH_3)_2 & CH_2\text{—}CH =CH \\
\qquad\quad CH \longrightarrow & \qquad\quad CH \longrightarrow \\
CH_2\text{—}CH_2\text{—}CH & CH_2\text{—}CH_2\text{—}CH \\
(IV) & (V)
\end{array}
$$

$$
\begin{array}{cc}
CH_2\text{—}CHBr\text{—}CH & CH =CH\text{—}CH \\
\qquad\quad CH \longrightarrow & \qquad\quad CH \\
CH_2\text{—}CH_2\text{—}CHBr & CH_2\text{—}CH=CH \\
(VI) & (VII)
\end{array}
$$
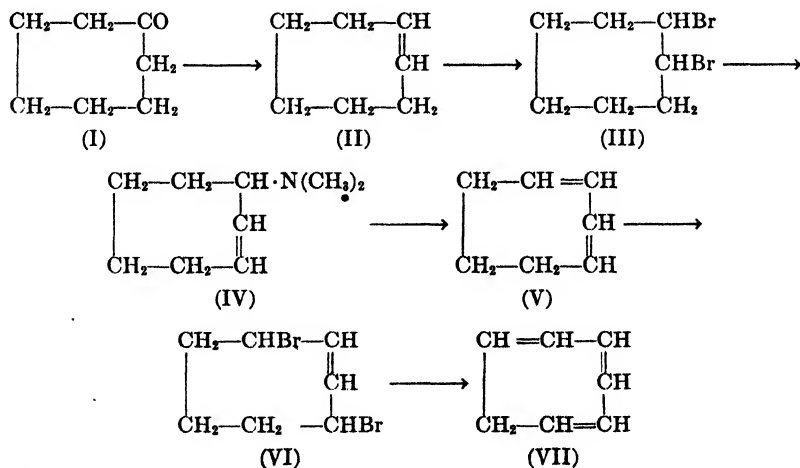
[30] Colson, *Bull. soc. chim.*, **48**, 52 (1887).
[31] J. Thiele, *Ann.*, **308**, 339 (1899).
[32] R. Willstätter, *Ann.*, **317**, 204 (1901).

It is doubtful whether or not the above reaction sequence might be applied to the formation of conjugated double bonds in open chains. This, or a similar principle, suggests the theoretical possibility of converting saturated chains into polyene chains, a problem which is of interest in consideration of the synthesis of the carotenoids. Willstätter [33] succeeded in obtaining cyclooctatetraene by a similar method. Cyclooctatetraene contains four conjugated double bonds.

II. FORMATION OF THE ACETYLENE LINKAGE

The introduction of the acetylene bond into a carbon chain is almost without exception through an ethylene bond. The only reaction of preparative significance is the following:

$$R \cdot CH{:}CX \cdot R \longrightarrow R \cdot C{:}C \cdot R$$
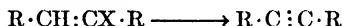
It is usually subsequent to the reaction,

$$R \cdot CHX \cdot CHX \cdot R \longrightarrow R \cdot CH{:}CX \cdot R$$
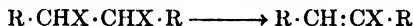
Both reactions may be performed in the same run.   When unsaturated halogen compounds of the type, $R' \cdot CH{:}CX \cdot R''$, are treated, R' and R'' being different radicals, the two stereoisomers usually differ considerably in the ease with which they undergo the hydrogen halide cleavage.   When hydrogen halide is split off from dihalides, mixtures of both isomers are frequently formed.

Another method of obtaining unsaturated halides consists of the removal of hydrogen halides from dihalides of the type, $R \cdot CX_2 \cdot CH_2 \cdot R$, ketone halides.

The halogen atom attached to a double bond distinctly resembles in chemical behavior that in aromatic halides.   Therefore, strong reagents or higher temperatures are necessary for the removal of hydrogen halide in the final stage. When alcoholates are used, the side reaction, $R \cdot CH{:}CX \cdot R + KOCH_3 \rightarrow R \cdot CH{:}C(OCH_3) \cdot R + KX$, becomes annoying and prominent.   The preparation by Nef [34] of phenylacetylene from 1-phenyl-2-bromoethylene ω-bromostyrene was for a long time rather unproductive because the styrene methyl ether, $C_6H_5 \cdot CH{:}CH \cdot OCH_3$, was formed as a by-product in large amounts.   Hessler [35] suggested a simple improvement of the method, thus making the product, which is important for syntheses, readily available.

Besides cheap ω-bromostyrene, which is commercially available as a perfume, styrene dibromide may be used as a starting material.   The directions of Bourguel [36] offer few advantages, as do the older ones of

[33] R. Willstätter, *Ber.*, **46**, 517 (1913).
[34] U. Nef, *Ann.*, **308**, 265 (1899).
[35] J. Hessler, *J. Am. Chem. Soc.*, **44**, 425 (1922).
[36] Bourguel, *Ann.*, **3**, 225 (1925).

Brühl.[37] Because of poor results with these methods the oldest method of preparation was reinvestigated. Weger [38] prepared phenylacetylene by decarboxylation of phenylpropiolic acid, $C_6H_5 \cdot C \vdots C \cdot COOH$. The method gives good yields, but the price of sodium phenylpropiolate which serves as starting material is high; see Straus.[39]

Organic Syntheses [40] gives the latest directions by Hessler's method. He made use of a non-alcoholic medium which Bourguel studied with styrene dibromide. However, he employed sodium hydroxide in place of sodium amide and started with inexpensive bromostyrene. He took advantage of the fact that reaction flasks made of relatively alkali-resistant and high melting glass became available. Since phenylacetylene is a relatively sensitive compound, Hessler took care to remove it as quickly as possible from the influence of the alkali, by allowing bromostyrene to drop onto a highly concentrated alkali melt heated above the boiling point of phenylacetylene.

An example of the use of sodium amide for the removal of hydrogen halide from olefin halides is given in the preparations of 3-cyclohexyl-propine from cyclohexylbromopropene, and of decine from 2-bromodecine (see Bourguel [41]). Directions may be found in *Organic Syntheses*.[42]

The preparation of simple acetylene hydrocarbons is not difficult when these methods are used. The acetylenedicarboxylic acids, such as the propiolic acid and its derivatives, are relatively easy to obtain. Propiolic acid is formed by decarboxylation of acetylenedicarboxylic acid. The latter may be prepared from dibromosuccinic acid according to the method of Baeyer; see also *Organic Syntheses*.[43]

Dibromosuccinic acid is dissolved in the smallest possible amount of hot alcohol. To the cooled solution are added in small portions 4 moles of an alcoholic solution of potassium hydroxide and then the mixture is boiled on a steam bath for 1 hour. If the solution becomes cloudy or milky when cooled, a little more potassium hydroxide in alcohol is added and the boiling repeated. The potassium salt of the acid which crystallizes on cooling is washed with cold alcohol and then dissolved in a little water. A dilute solution of sulfuric acid containing 4.75 g. of H_2SO_4 for each 50 g. of dibromosuccinic acid used is added to the filtered solution. The acid potassium salt of the acetylene-dicarboxylic acid which crystallizes is filtered off, dissolved in 40% sulfuric acid, and extracted with ether in an extraction apparatus. The free acid crystallizes from water-containing ether with 2 moles of water. If the ether solution is dried with calcium

[37] Brühl, *Ann.*, **235**, 13 (1886).
[38] Weger, *Ann.*, **221**, 70 (1883).
[39] Straus, *Ann.*, **342**, 220 (1905).
[40] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 438.
[41] Bourguel, *Ann. chim. phys.*, **3**, 231 (1925).
[42] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 191.
[43] Baeyer, *Ber.*, **18**, 677, 2269 (1885). A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 10. •

chloride and diluted with petroleum ether, it is obtained free of water, melting at 178° to 179°C. The dihydrate effloresces easily and loses its water quantitatively over sulfuric acid.

Bandrowski [44] found that acetylenedicarboxylic acid is converted to propiolic acid when boiled with water. Perkin and Simonsen [45] suggest using the crude potassium salt of the acetylenedicarboxylic acid. The preparation from magnesium acetylide is described by Straus and Voss. [46]

Phenylpropiolic acid is best prepared from cinnamic acid dibromide in two steps: A mixture of the stereoisomeric monobromocinnamic acids, $C_6H_5 \cdot CH:CBr \cdot COOH$, is first prepared and then the allo-α-bromocinnamic acid is converted to the ordinary bromocinnamic acid by heating above its melting point. Finally, the second molecule of hydrobromic acid is removed. Michael [47] describes this method.

Cinnamic acid dibromide (95 g.) is slowly added to 2.5 moles of dilute potassium hydroxide solution. After the solution has been allowed to stand for several hours, a small amount of bromostyrene is removed by filtration and the filtrate is acidified. The mixture of the crystallized α-bromocinnamic acids (65 g., corresponding to 85% of the theoretical amount) is dried and then fused by heating to 130°C. for 1 minute. By this treatment the low melting allocinnamic acid is converted to the higher melting, ordinary acid.

The solidified melt is finely powdered and treated for 4 hours on a steam bath with 2.5 moles of 20% aqueous potassium hydroxide solution. Phenylacetylene, which is formed as a by-product, is extracted with ether. The ether is removed by blowing air through the alkaline solution. The product is precipitated with sulfuric acid. The yield is supposedly 85% of the theoretical, but experiments show it to be lower. The melting point of pure phenylpropiolic acid is 137°C.

Sudborough [48] recommends the removal of hydrogen bromide by shaking the cinnamic acid dibromide with cold alcoholic potassium hydroxide and separating the stereoisomeric α-bromocinnamic acids through the barium salts. The allo acid is then rearranged by heating 15 to 20 minutes at 205° to 210°C.

The preparation of the phenylpropiolic acid by the elaborate method of Sudborough is hardly practical, because Nef's method gives at least a 50% yield of pure phenylpropiolic acid. Sudborough at best obtains only a 68 to 70% yield. The observations of Sudborough are important, however, when applied to cinnamic acid derivatives. p-Tolylpropiolic acid, for instance, can be obtained free of halogen only with difficulty and poor yield. The reason for this apparently is the fact that in this case also an allobromo-p-methylcinnamic acid is present which possesses little tendency to split off hydrogen halide under the reaction conditions. The

[44] Bandrowski, *Ber.*, **15**, 2699 (1882).
[45] Perkin and Simonsen, *J. Chem. Soc.*, **91**, 834 (1907).
[46] F. Straus and W. Voss, *Ber.*, **59**, 1681 (1926).
[47] Michael, *Ber.*, **34**, 3648 (1901).
[48] Sudborough, *J. Chem. Soc.*, **83**, 1155 (1903).

rearrangement by merely heating is not always possible as in the case of the parent compounds. In such cases, therefore, it is advisable to separate the stereoisomers.

The acid dibromides can sometimes be replaced advantageously by the dibromides of the esters. It cannot be predetermined with certainty whether or not this is an advantage. If the ester is obtained first by synthesis, the ester may either be saponified and bromine added subsequently, or the ester dibromide may be prepared, and this then treated with alcoholic potassium hydroxide to saponify the ester and remove the hydrogen bromide simultaneously. But even this procedure often yields halogen-containing products. The contaminations involved can only be separated with considerable loss of product.

Considering these difficulties, one might suggest preparing the aryl-propiolic acids, which are difficult to obtain in the manner discussed, by synthesis from the arylacetylides, $R \cdot C : CNa$ or $R \cdot C : C \cdot MgBr$, and carbon dioxide.

A peculiarity of the acetylene bond is the fact that formerly it was neither encountered nor could it be formed in a ring system. However, recently Ruzicka, Hürbin, and Boekenoogen [49] prepared 15- and 17-membered carbon rings with an acetylene bond. According to the theory of the tetrahedric carbon it would have been possible from a stereochemical view-point to prepare such rings with ten members and Ruggli [50] had already described heterocyclic systems in which acetylene bonds very likely occur. For preparative purposes, however, Ruzicka and coworkers chose the readily available cyclopentadecene and cyclo-heptadecene as starting materials. From these the dibromides were prepared in the usual manner. These did not react uniformly with potassium hydroxide solution, but the unsaturated, cyclic bromides which were formed by removal of 1 molecule of hydrogen bromide could be detected and isolated from the reaction mixture. The cleavage of the second molecule of hydrogen bromide was unusually difficult. Thus, 4.4 g. of bromocyclopentadecene were heated for 4 hours in a sealed tube to 150°C. with 5 g. of potassium hydroxide and 30 cc. of alcohol. After that time the reaction product still contained much bromine. Therefore, the treatment with potassium hydroxide and alcohol was continued for 15 hours at a higher temperature (170° to 175°C.). After repeated distillation from potassium metal, a main fraction was obtained boiling at 158° to 159°C. at 14 mm. This constitutes the cyclopentadecine which is a sticky oil which did not crystallize.

[49] L. Ruzicka, M. Hürbin, and A. Boekenoogen, *Helv. Chim. Acta*, **16**, 498 (1933).
[50] Ruggli, *Ann.*, **392**, 92 (1912); **399**, 174 (1913).

III. FORMATION OF THE ALLENE BOND

The formation of the allene bond is interesting only from a theoretical standpoint; therefore, only the simplest cases will be discussed. The seemingly obvious reaction consisting of the removal of water from acetone or acetone derivatives according to the equation,

$$R \cdot CH_2 \cdot CO \cdot CH_2 \cdot R \rightarrow R \cdot CH : C : CH \cdot R$$
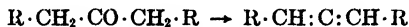
cannot be realized.

According to Vorländer,[51] the following method yields a product which is unexpected.

Barium diphenyl acetate on dry distillation (see page 439) yields besides diphenylmethane not the tetraphenylacetone which we would expect and which was later prepared by Vorländer and Rack,[52] but tetraphenylallene which has a molecule of water less. Tetraphenylallene cannot be prepared from tetraphenylacetone. This method of preparation is not generally applicable. Two methods of general usefulness have been developed, the last stage of which consists of the removal of water or hydrogen bromide. The first method is an imitation of the one given by Gustavson and Demjanov [53] for the parent hydrocarbon, $CH_2 : C : CH_2$. The reaction proceeds as follows:

$$CH_2Br \cdot CHBr \cdot CH_2Br \longrightarrow CH_2BrCBr : CH_2 \longrightarrow CH_2 : C : CH_2$$

First 1 molecule of hydrogen bromide is split off from tribromohydrin and then both bromine atoms are removed from the 2,3-dibromopropylene formed with zinc. 2 moles of potassium hydroxide are heated to 145° to 150°C. in a flask equipped with a dropping funnel and a downward condenser, and 1 mole of tribromohydrin is added dropwise. Water and dibromopropylene distil. The temperature is allowed to fall to 130°C., water is added through the dropping funnel, and the remainder of the oil is distilled with steam. Dibromopropylene, boiling at 139° to 141°C., can be isolated in about one-fifth of the amount of tribromohydrin used. This is allowed to drop into a flask containing zinc dust and 80% alcohol. The gas formed is collected over water. From 10 g. of dibromopropylene 900 to 1000 cc. of gaseous allene are obtained.

In the preparation of tetraphenylallene Vorländer [54] used benzalacetophenone as starting material. With phenylmagnesium bromide, according to the method of Kohler [55] this yields tetraphenylpropyl alcohol; see page 377. The alcohol yields tetraphenylpropylene when boiled with

[51] D. Vorländer, *Ber.*, **39**, 1024 (1906).
[52] Vorländer and Rack, *Ber.*, **56**, 1125 (1923).
[53] S. Gustavson and N. Demjanov, *J. prakt. Chem.*, **38**, 201 (1888).
[54] D. Vorländer, *Ber.*, **39**, 1025 (1906).
[55] Kohler, *Am. Chem. J.*, **31**, 651 (1904).

acids. With bromine, this in turn, probably through an unstable dibromide, gives monobromotetraphenylpropylene which splits off hydrogen bromide with alcoholic potassium hydroxide.

$$(C_6H_5)_2:CH \cdot CH_2 \cdot COH:(C_6H_5)_2 \longrightarrow (C_6H_5)_2:CH \cdot CH:C:(C_6H_5)_2 \longrightarrow$$
$$(C_6H_5)_2CH \cdot CBr:C:(C_6H_5)_2 \longrightarrow (C_6H_5)_2:C:C:C:(C_6H_5)_2$$
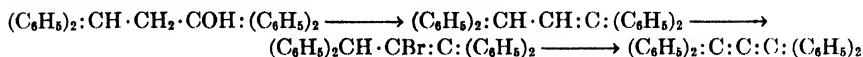
Vorländer's directions for the preparation of tetraphenylallene follow.

Tetraphenylpropyl alcohol is dehydrated by boiling under a reflux either for 4 hours with 20 times its weight of 20% hydrochloric acid, or for 6 to 8 hours with 3 times its weight of acetic anhydride. When the mixture is cooled, tetraphenylpropylene crystallizes directly from acetic anhydride. The melting point is 127° to 128°C. after recrystallization from alcohol. The tetraphenylpropylene is mixed with chloroform and then a solution of 1 mole of bromine in chloroform is added. The reaction mixture at first is colorless; then its color turns reddish and hydrogen bromide is evolved. The chloroform is allowed to evaporate and the residue is recrystallized from a mixture of alcohol and chloroform. The melting point of the tetraphenylmonobromopropylene is at 124°C. 4 g. of the bromide are boiled under a reflux for 30 to 60 minutes with a solution of 6 g. of potassium hydroxide in 70 cc. of alcohol. During this operation part of the tetraphenylallene crystallizes. The reaction mixture is diluted with water, the precipitate washed with water, and, after drying, crystallized from dilute acetone or from alcohol. The melting point is 164° to 165°C. From 94 g. of tetraphenylpropyl alcohol, 81 g. of tetraphenylpropylene, 86 g. of bromopropylene, and 55 g. of pure tetraphenylallene are obtained.

The second generally useful method for preparing allene derivatives starts with benzalacetophenone and leads through tetraphenylpropylene alcohol: $(C_6H_5)_2:C:CH \cdot COH:(C_6H_5)_2 \rightarrow (C_6H_5)_2:C:C:C:(C_6H_5)_2$. This also yields tetraphenylallene when boiled for 3 hours with excess acetic anhydride. Details for this and similar allene syntheses can be found in the original papers; see Ziegler and coworkers.[56] Recently the preparation of optically active allene derivatives was accomplished. The existence of such compounds had been predicted in accordance with vant' Hoff's theory; see Mills and Maitland, and Kohler, Walker, and Tischler.[57]

For the preparation of allene derivatives by rearrangement of polyacetylenes see page 474.

Solutions of carbon suboxide are prepared according to Staudinger and Bereza[58] in the following manner.

A solution of 30 g. of dibromomalonyl chloride in 300 cc. of ether is added through a dropping funnel to 20 g. of zinc turnings at such a rate that the reaction mixture boils well. The ether distilled is condensed in a downward condenser and collected in a receiver cooled in a freezing mixture. The condensate contains 80% of the theoretical amount of carbon suboxide.

[56] K. Ziegler et al., Ann., 443, 161 (1925); Ber., 63, 1851 (1930).
[57] Mills and Maitland, Nature, 135, 994 (1935). P. Kohler, T. Walker, and M. Tischler, J. Am. Chem. Soc., 57, 1743 (1935).
[58] Staudinger and Bereza, Ber., 41, 4461 (1908).

Formation of Carbon-Carbon Bonds

Part One: by Addition
SINGLE BONDS
A. Only Hydrogen at New Bond
1. Addition to Ethylene Bond

Hydrocarbons

The simplest addition is the reversal of the so called cracking process: $CH_2:CH_2 + CH_3 \cdot CH_3 \rightarrow CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_3$. To date, the reaction is not important for laboratory work in the aliphatic series. It proceeds successfully, as shown by Ipatieff,[1] under the catalytic influence of aluminum chloride. It is not surprising that under the reaction conditions addition and cracking occur simultaneously. Rather complicated hydrocarbon mixtures are obtained.

On the other hand, the addition of olefins to aromatic compounds is a method of alkylation that is extensively used. It has been shown that the use of aluminum chloride, as recommended in the Friedel-Crafts method, really offers no advantages. By the use of sulfuric acid or phosphoric acid the same results are obtained more cheaply. Brochet,[2] presumably, was the first to obtain 2-phenyl-*n*-hexane from benzene and *n*-hexene with concentrated sulfuric acid. This showed at the beginning that normal chains are never formed in this reaction, since the addition always takes place at the carbon atom with the least hydrogen. Truffault[3] did experiments with phosphoric acid and found that polymerization of the ethylene hydrocarbons becomes very prominent. Benzene reacts quite smoothly and readily with cyclohexene, giving a good yield of cyclohexylbenzene. Truffault treated cyclohexene and an excess of benzene with a molecular amount of sulfuric acid for 30 minutes. From 83 g. of cyclohexene, 115 g. of phenylcyclohexene were isolated (70% yield) along with 30 g. of C_{18} hydrocarbons the greater part of which consisted of *p*-dicyclohexylbenzene.

Corson and Ipatieff[4] studied the reaction between cyclohexene and benzene more thoroughly.

[1] Ipatieff, *J. Am. Chem. Soc.*, **58**, 913 (1936).
[2] A. Brochet, *Compt. rend.*, **117**, 115 (1893).
[3] R. Truffault, *Compt. rend.*, **202**, 1268 (1936).
[4] Corson and Ipatieff, *J. Am. Chem. Soc.*, **59**, 645 (1937).

200 g. of cyclohexylbenzene are obtained (b.p. 239° to 245°C.) when 164 g. of cyclohexene are added with stirring to an ice-cold mixture of 408 g. of benzene and 92 g. of concentrated sulfuric acid during a period of 2 hours. The reaction mixture is worked up by washing the oily layer, before distillation, with two portions of 50 cc. each of cold concentrated sulfuric acid, then with water, dilute sodium hydroxide solution, and again with water. Thus, esters are removed which would be decomposed during distillation, producing tarry substances. The distillation residues contain dicyclohexylbenzenes and higher substitution products of benzene; the preparation of these by-products is described in the paper of Corson and Ipatieff.

Truffault [5] mentions a reaction by which allyl chloride and benzene are condensed under the conditions described to form ω-chlorocumene, $C_6H_6 + CH_2:CH \cdot CH_2Cl \rightarrow C_6H_5 \cdot CH(CH_3) \cdot CH_2Cl$. A reactive atom is thus introduced into the side chain, forming a useful intermediate.

2. Polymerization of Ethylene Derivatives

The polymerization of ethylene compounds has recently become exceedingly important in the manufacture of synthetic materials. It was found that certain substituents in the ethylene molecule greatly increase the velocity of polymerization as well as the attained rate of polymerization. Such substituents are aromatic radicals (styrene), oxygen-containing groups (acrolein, acrylic acid, and its esters, vinyl ethers and vinyl esters), and halogens (vinyl chloride). It is remarkable that an accumulation of such substituents decreases the tendency of polymerization very much (1,1-diphenylethylene) or makes it disappear almost completely. Stilbene yields a dimer only when irradiated in a benzene solution; see Ciamician and Silber.[6]

The early papers on the polymerization of styrene to polystyrene have been the starting point for all the later investigations. Above all, Stobbe's [7] investigations must be mentioned. He differentiates between the dark polymerization of freshly distilled styrene compounds at 100°C. and the photopolymerization in the light of a mercury vapor lamp. The essence of his investigations lies in the observation that pretreated, that is either preirradiated or preheated samples, polymerize faster than untreated ones under the same conditions. Therefore, polymerization accelerators must have been formed during the pretreatment. Moureu in particular made the observation that in the presence of the so called antioxidants ethylene compounds which otherwise polymerize readily remain in the monomeric state for some time. Phenols are especially

[5] R. Truffault, *Compt. rend.*, **202**, 1268 (1936).
[6] Ciamician and Silber, *Ber.*, **35**, 4129 (1902).
[7] H. Stobbe, *Ann.*, **409**, 1 (1915); *Ber.*, **47**, 2701 (1914).

efficient antioxidants; hydroquinone has proved to be a good stabilizer in the laboratory. The rôle of the antioxidants is not exactly known. It is certain that the ethylene polymerizations take place only in the presence of oxygen, but it must not be thought that the phenols act only as oxygen acceptors.

On the basis of these observations, peroxides are used as so called promoters for polymerization in commercial applications.

Formerly only the initial phases of the polymerization reactions involved were discussed in the scientific literature. The process frequently stops at the dimer, as with cinnamic acid, with unsaturated ketones of the type of benzalacetophenone, and with stilbene. The dimeric products are cyclobutane derivatives and this explains the fact that no higher molecular compounds are obtained. In other cases, for instance with styrene, a different course of reaction takes place. Chains are formed the length of which cannot be ascertained by the usual methods of investigation. Many details can be found in Staudinger's numerous papers; see also K. H. Meyer and Mark.[8]

3. Polymerization of Butadiene and of Butadiene Derivatives

The tendency of ethylene to polymerize is slight; that of butadiene and of many of its derivatives, however, is extraordinarily great. The behavior of isoprene, of 2,3-dimethylbutadiene, and, recently, of butadiene has been thoroughly studied. Of the many polymerization catalysts, metallic sodium apparently is used the most frequently. According to investigations of Ziegler,[9] the sodium is added to the unsaturated system in the first step, alkali organic compounds are formed, and these are the real polymerization carriers.

By introduction of halogen into the butadiene molecule (2-chlorobutadiene, chloroprene) the tendency to polymerize is increased still more. Klebansky and Wassiljewa[10] reported on the constitution of polychloroprene. Cleavage of α-polychloroprene with ozone yielded 80 to 95% of the calculated amount of succinic acid, fixing the structural type of the molecule within certain limits. Succinic acid can be formed in such a high yield only if the chlorine is attached to an ethylene bond. Branched chains are thus eliminated and the chloroprene molecule supposedly contains mostly normal carbon chains. In ethylene polymerizations, rings with relatively few members and long, essentially unbranched carbon chains should be expected.

[8] K. H. Meyer and H. Mark, *Chem.-Ztg.*, **58**, 561, 581 (1934); H. Staudinger, *Naturwissenschaften*, **17**, 141 (1929); *Chem.-Ztg.*, **58**, 225 (1934).

[9] K. Ziegler, *Angew. Chem.*, **49**, 455, 499 (1936).

[10] A. Klebansky and W. Wassiljewa, *J. prakt. Chem.*, **144**, 251 (1936).

4. Diene Syntheses

Diels [11] called the addition reaction between the ethylene bond and a conjugated system the diene synthesis. The simplest equation serves as a general example:

$$
\begin{array}{ccc}
\overset{CH\cdot R}{\underset{\displaystyle\parallel}{C}H} & \overset{R}{\underset{\displaystyle\parallel}{CH}} & \\[-1ex]
\overset{CH}{\underset{\displaystyle\parallel}{CH\cdot R}} + \overset{CH}{\underset{R}{CH}} & \longrightarrow &
\end{array}
$$
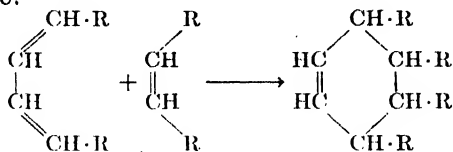
In the course of the numerous investigations of Diels and Alder, the possible variations of the synthesis were clarified.

The conjugated system which gave the name to the method may be varied practically without limitation. Butadiene and its aliphatic as well as aromatic derivatives add to the 1,4 position, according to the above equation, also ring systems, such as cyclopentadiene, cyclohexadiene, and even heterocyclic compounds such as furane.

The second component cannot be varied as desired. The ethylene bond present in it must be activated, usually by oxygen-containing groups. The typical ethylene components of the diene synthesis are maleic anhydride, acrolein, crotonaldehyde, cinnamaldehyde, and acrylic acid. Nitrogen-containing heterocyclic compounds such as pyridine may also on occasion be active. The ethylene bond may be activated by unsaturated bonds; thus, a true diene synthesis may take place between 2 moles of diene and, in general, between polyenes.

Finally an acetylene derivative such as acetylenedicarboxylic acid ester may take the place of the ethylene component; then the ring structure formed contains two double bonds instead of one at the start.

A significant characteristic of the diene synthesis is the fact that the two reaction components combine without a catalyst, frequently even without a solvent. Often room temperature is sufficient; occasionally higher temperatures must be used. The reactions proceed to completion vigorously. The above equation shows that a 6-membered ring must be formed in every diene synthesis. If one starts with aliphatic dienes, derivatives of tetrahydrobenzene are obtained. From butadiene and maleic anhydride, for instance, tetrahydrophthalic anhydride is obtained, or from butadiene and acrolein, tetrahydrobenzaldehyde.
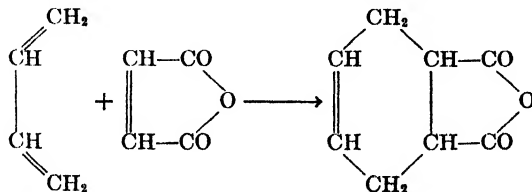
[11] O. Diels, *Angew. Chem.*, **42**, 911 (1929).

or

$$\begin{array}{ccc}
\begin{array}{c}
CH_2 \\
\parallel \\
CH \\
| \\
CH \\
\diagdown \\
CH_2
\end{array}
&
+
&
\begin{array}{c}
CH \cdot CHO \\
\parallel \\
CH_2
\end{array}
&
\longrightarrow
&
\begin{array}{c}
CH_2 \\
CH \quad CH \cdot CHO \\
\parallel \quad | \\
CH \quad CH_2 \\
CH_2
\end{array}
\end{array}$$
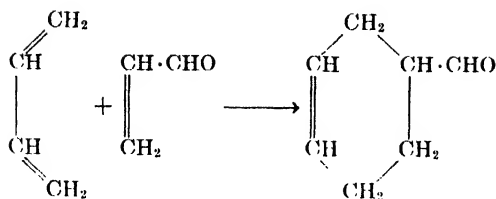
By reaction of cyclic dienes with maleic anhydride, for example cyclopentadiene, compounds of the type of norcamphor, endomethylene compounds, are obtained. Cyclohexadiene yields endoethylene compounds of a tension-free type.

$$\begin{array}{c}
CH \\
\parallel \\
CH \\
| \\
CH_2 \\
| \\
CH \\
\parallel \\
CH
\end{array}
+
\begin{array}{c}
CH-CO \\
\parallel \qquad O \\
CH-CO
\end{array}
\longrightarrow
\begin{array}{c}
CH \\
CH \quad CH \quad CO \\
\parallel \quad | \qquad O \\
CH \quad CH-CO \\
CH
\end{array}$$

or

$$\begin{array}{c}
CH \\
| \\
CH \; CH_2 \\
| \\
CH \; CH_2 \\
| \\
CH
\end{array}
+
\begin{array}{c}
CH-CO \\
\parallel \qquad O \\
CH-CO
\end{array}
\longrightarrow
\begin{array}{c}
CH \\
CH \; CH_2 \; CH \; -CO \\
\qquad \qquad O \\
CH \; CH_2 \; CH-CO \\
CH
\end{array}$$
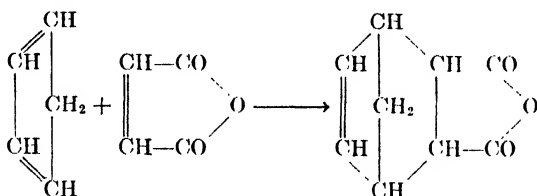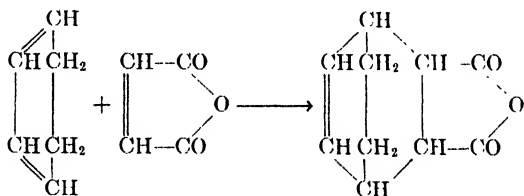
The combination of furan with maleic anhydride leads to endoxo systems of the cantharidin type. N-Methylpyrrole reacts also, yielding ring systems which could possibly be derived from tropine.

$$\begin{array}{c}
CH \\
\parallel \\
CH \\
| \qquad O \\
CH \\
\parallel \\
CH
\end{array}
+
\begin{array}{c}
CH-CO \\
\parallel \qquad O \\
CH-CO
\end{array}
\longrightarrow
\begin{array}{c}
CH \\
CH \quad CH-CO \\
\parallel \quad O \qquad O \\
CH \quad CH-CO \\
CH
\end{array}$$

or

$$\begin{array}{c}
CH \\
\parallel \\
CH \\
| \\
N \cdot CH_3 \\
| \\
CH \\
\parallel \\
CH
\end{array}
+
\begin{array}{c}
CH-CO \\
\parallel \qquad O \\
CH-CO
\end{array}
\longrightarrow
\begin{array}{c}
CH \\
CH \qquad CH-CO \\
\parallel \qquad \qquad O \\
N \cdot CH_3 \\
CH \qquad CH-CO \\
CH
\end{array}$$
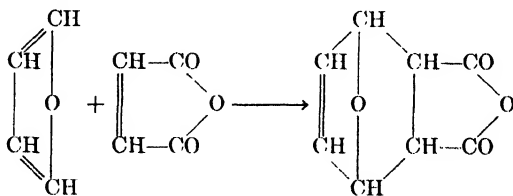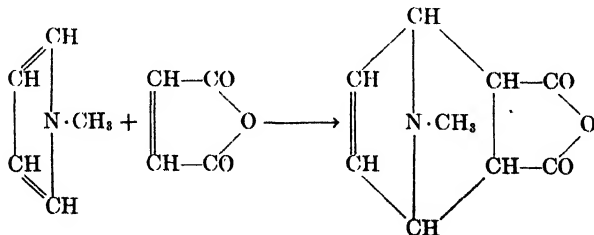
The variations in the ethylene component have been briefly mentioned. Another variation possible is the use of quinone. Its reaction with cyclopentadiene was the starting point of the investigations of Diels and Alder. With benzoquinone the diene synthesis takes place twice. 2 moles of cyclohexadiene react, leading to a bisendoethylene ring system that is closely related to anthraquinone.

$$
\begin{array}{ccc}
\text{CH} & \text{CO} & \text{CH} \\
\text{CH CH}_2\ \text{CH} & \text{CH} & \text{CH}_2\ \text{CH} \\
\text{CH CH}_2 & \text{CH} & \text{CH} & \text{CH}_2\ \text{CH} \\
\text{CH} & \text{CO} & \text{CH}
\end{array}
\longrightarrow
\begin{array}{cc}
\text{CH} & \text{CO} & \text{CH} \\
\text{CH CH}_2\ \text{CH} & \text{CH CH}_2\ \text{CH} \\
\text{CH CH}_2\ \text{CH} & \text{CH CH}_2\ \text{CH} \\
\text{CH} & \text{CO} & \text{CH}
\end{array}
$$
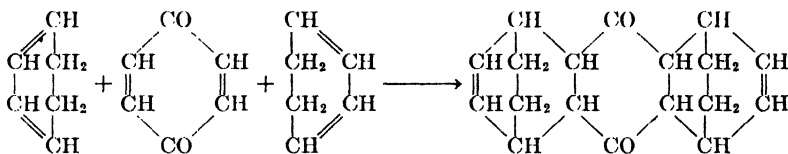
The addition product readily loses 4 atoms of hydrogen and the dehydrogenation product (I) in turn splits off 2 moles of ethylene on heating and is thus converted into anthraquinone (II).

$$
\text{(I)} \longrightarrow \text{(II)} + 2\text{CH}_2\!=\!\text{CH}_2
$$

(I)   (II)
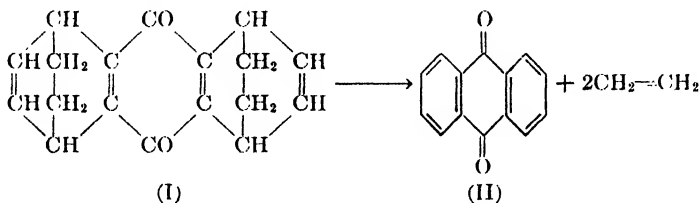
It can be seen that in this way anthraquinone homologues may be obtained if derivatives of cyclohexadiene are employed. 1,4-Naphthoquinone may also be used as a starting material. The endoethylene bridge may carry a substituent without interfering with its removal as an ethylene derivative. In the final step of the synthesis of β-methylanthraquinone such a product is removed.

(III) $\longrightarrow$

$$
\text{(IV)} + \text{CH}_2\!:\!\text{CH}\cdot\text{CH(CH}_3)_2
$$

(IV)
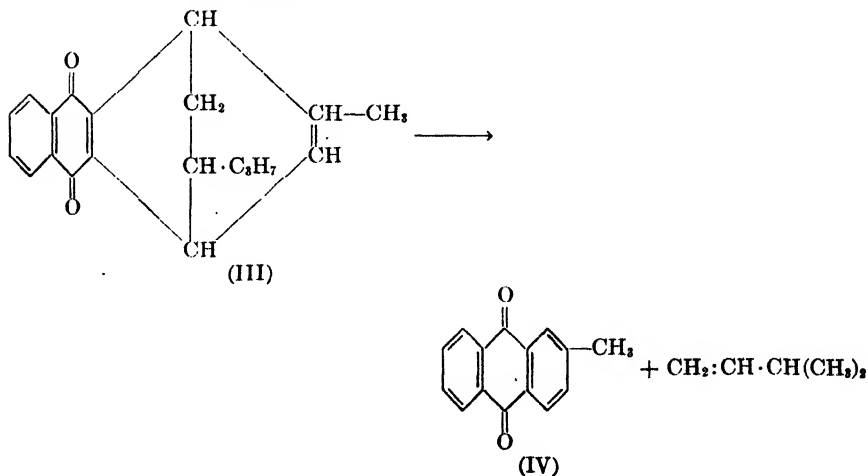
1,4-Naphthoquinone first is combined with phellandrene. The primary reaction product loses a mole of hydrogen and is converted to a product with the formula (III); when heated, isopropylethylene is split off and the desired β-methylanthraquinone (IV) remains.

Acetylenedicarboxylic acid esters react normally with dienes according to the following equation.
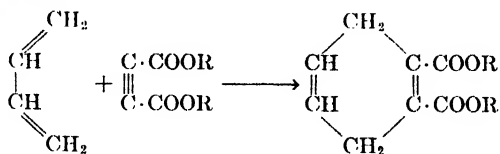
The dihydrophthalic acid esters thus formed readily lose hydrogen to give aromatic compounds.

A more complex reaction occurs with heterocyclic compounds of the pyridine type. The individual steps cannot be discussed here. The final product of the reaction which leads to a ring system, quinolizine, is as yet slightly known.
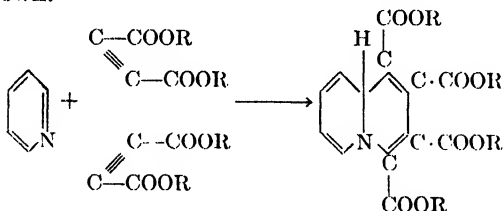
These examples in no way exhaust the possible variations of the synthesis. They are the ones which form the basis of those fields of study which have to date been most thoroughly investigated. Directions for the diene syntheses by Diels and Alder [12] follow.

1 mole of cyclopentadiene is slowly added, with cooling, to a suspension of 1 mole of maleic anhydride in 5 times its weight of benzene. The maleic anhydride passes into solution with the evolution of much heat. During this reaction the cis-endomethylene-tetrahydrophthalic anhydride crystallizes in an almost theoretical yield. After recrystallization from ligroin, its melting point is 164° to 165°C.

Butadiene reacts less readily with maleic anhydride. The following directions are taken from the same paper of Diels and Alder.

To a solution of 2 to 2.5 g. of butadiene in 10 cc. of benzene are added 4 g. of maleic anhydride and the mixture sealed into a tube. After standing for 12 hours, the solution is heated to 100°C. for 5 hours. The contents then consist of tetrahydrophthalic anhydride in quantitative yield. After recrystallization from ligroin, the melting point is 103° to 104°C.

Diels and Alder [12] give the following directions for the preparation of tetrahydrobenzaldehyde.

[12] Diels and Alder, *Ann.*, **460**, 11 (1928).

Freshly distilled butadiene (3 to 4 g.) is heated to 100°C. in a sealed tube with an equal amount of acrolein for not longer than 1 hour. The reaction product is then distilled in a carbon dioxide atmosphere. The forerun consists mostly of acrolein. The foamy mass remaining as residue is apparently a polymer. The aldehyde boils at 51° to 52°C. at 13 mm. It is a colorless, strongly refractive oil which possesses no great tendency to polymerize when pure.

Norcantharidin is prepared according to Diels and Alder [13] as follows:

2 g. of maleic anhydride are suspended in ether and the calculated amount of furan is added. The reaction takes place slowly while the mixture warms slightly. If the solution is allowed to stand for several hours in the cold, most of the reaction product, endoxotetrahydrophthalic anhydride, crystallizes. Upon removal of the ether, the yield is theoretical. The melting point is 125°C., with decomposition into the components. The addition product was converted into norcantharidin by hydrogenation in a sodium carbonate solution with colloidal palladium as a catalyst.

Endoethylenetetrahydrobenzaldehyde is obtained according to Diels and Alder [14] in the following manner.

7 g. of $\Delta^{1,2}$-dihydrobenzene, cyclohexadiene, are heated in a sealed tube with 10 g. of acrolein for 3.5 hours at 100°C. On fractionation, 3 g. of aldehyde distil at 84° to 85°C. at 12 mm. It was purified by forming the semicarbazide (m.p. 176° to 177°C.) from which the pure aldehyde was recovered by treatment with oxalic acid and steam distillation of the mixture.

When anthracene is used as diene component, the addition takes place at carbon atoms 9 and 10.

Diels and Alder [15] heat 12 g. of anthracene and 8 g. of maleic anhydride in an oil bath until the reaction occurs. It proceeds rapidly from the outside to the center of the mixture. The heating is continued for 15 to 20 minutes longer. The bath temperature must not exceed 260°C. From the cooled and powdered reaction mixture, the unchanged maleic anhydride is extracted with ether. Upon recrystallization from malonic ester coarse, colorless crystals are obtained which melt, when rapidly heated, at 262° to 263°C.

If the reaction is performed in a corresponding manner with dibromomaleic anhydride, the reaction product may be freed of bromine by reduction with platinum black and hydrogen. The product then contains a bridge with a double bond and possesses the following formula.
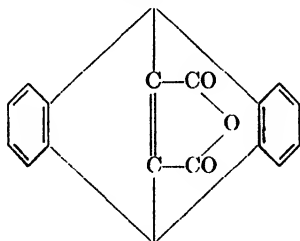
[13] Diels and Alder, *Ber.*, **62**, 557 (1929).
[14] Diels and Alder, *Ann.*, **478**, 144 (1930).
[15] Diels and Alder, *Ann.*, **486**, 196 (1931).

With dimethyl acetylene dicarboxylate and butadiene, Diels and Alder [16] obtained dimethyl $\Delta^{1,4}$-3,6-dihydro-o-phthalate,

$$
\begin{array}{c}
CH_2 \\
CH \qquad\quad C\cdot COOCH_3 \\
CH \qquad\quad C\cdot COOCH_3 \\
CH_2
\end{array}
$$
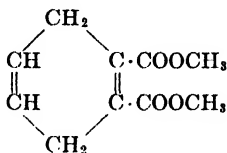
in the following manner.

An equimolecular mixture of butadiene and dimethyl acetylene dicarboxylate is heated in a sealed tube for 20 hours at 100°C. The oily reaction product is freed from easily volatile constituents in a vacuum on a water bath. The structure is then proved by hydrogenation over colloidal palladium in an acetone solution. A little more than the theoretical amount of hydrogen is absorbed. The resulting ester is saponified with a small amount of alcoholic potassium hydroxide. The melting point of the crude product is 175° to 180°C. It is heated without further purification with 2 moles of bromine to 200°C., thus producing o-phthalic acid.

Furan and dimethyl acetylene dicarboxylate give an addition product with the following formula:

$$
\begin{array}{c}
CH \\
CH \qquad\quad C\cdot COOCH_3 \\
\quad O \\
CH \qquad\quad C\cdot COOCH_3 \\
CH
\end{array}
$$
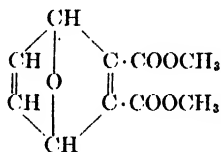
It is named dimethyl 3,6-endoxo-3,6-dihydro-o-phthalate.

20 g. of dimethyl acetylene dicarboxylate and 10 g. of furan are heated in a sealed tube at 100°C. for 10 hours. The tube is opened and after the addition of 1 g. more of furan heated for another 6 hours. An oil is isolated from the reaction product. This is converted to the corresponding crystalline tetrahydro ester by the addition of 1 mole of hydrogen by catalytic hydrogenation. Its melting point is 51° to 52°C.

The addition of acetylenedicarboxylic acid ester to pyridine leads, as mentioned above, to the quinolizine ring system. Details can be found in the original paper of Diels and Alder.[17]

That the polymerization of cyclopentadiene also proved to be a diene synthesis was discovered by Alder and Stein,[18] who, while pursuing these investigations,[19] were able to clarify the stereochemical part of the diene syntheses.

The formation of aromatic hydrocarbons from polyenes was first observed during the distillation of bixin with zinc dust and during the

[16] Diels and Alder, *Ann.*, 490, 242 (1931).
[17] Diels and Alder, *Ann.*, 510, 87 (1934).
[18] Alder and Stein, *Ann.*, 504, 216 (1933).
[19] Alder and Stein, *Ann.*, 514, 1 (1934); 515, 165, 185 (1935); 525, 221, 247 (1936).

dry heating of the dye. These treatments produced *m*-xylene, the manner of formation of which was obscure for a long time. Kuhn and Deutsch [20] studied the reactions occurring in decarboxylation with barium hydroxide of low molecular dienecarboxylic acids, specifically vinylacrylic acid and sorbic acid. Döbner [21] had already described similar experiments.

He thoroughly mixed 20 g. of sorbic acid and 60 g. of anhydrous barium hydroxide and distilled the mixture. During 1 hour he obtained 10 g. of a hydrocarbon mixture from which 4.55 g. of 1-methyl-2-propylbenzene could be isolated.

Kuhn and Deutsch explained this result by assuming as a first step a diene synthesis between 2 moles of sorbic acid. Of the four possible ways in which 2 moles of sorbic acid might add to each other, apparently only the following addition takes place.

$$
\begin{array}{ccc}
& \text{CH—CH} & \\
\text{CH}_3\cdot\text{CH} & \quad\quad \text{CH}\cdot\text{COOH} & \\
\quad\quad + & \text{COOH} & \\
\text{CH}_3\cdot\text{CH}=\text{CH} & & \\
& \text{CH}=\text{CH} & \\
\end{array}
\quad\longrightarrow\quad
\begin{array}{ccc}
& \text{CH}=\text{CH} & \\
\text{CH}_3\cdot\text{CH} & \quad\quad \text{CH}\cdot\text{COOH} & \\
& \text{CH—CH} & \\
\text{CH}_3\cdot\text{CH}=\text{CH} & \quad\quad \text{COOH} & \\
\end{array}
$$
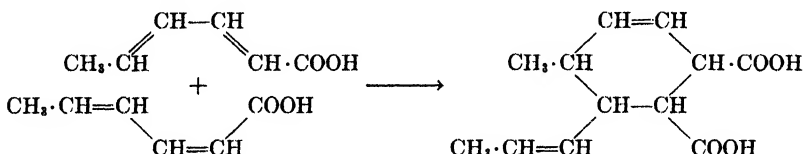
During the subsequent course of the reaction the primary product, that is a cyclohexenedicarboxylic acid with one unsaturated and one saturated side chain, is decarboxylated, the ring dehydrogenated, while the side chain is hydrogenated. Since hydrogen is not evolved in the reaction, the excess molecule of hydrogen liberated when 1 molecule of 1-methyl-2-propylbenzene is forming must be used for the hydrogenation of another molecule of the primary product. Aromatic as well as hydro-aromatic hydrocarbons occur simultaneously; these may be separated by careful fractionation. The experiments with vinylacrylic acid and with cinnamenylacrylic acid proceed in a similar manner.

5. Polymerization of Acetylene and Its Derivatives

Acetylene and its derivatives polymerize in several different ways. From 2 moles of acetylene, vinylacetylene, $CH:C\cdot CH:CH_2$, is first formed. This was prepared in another way by Willstätter and Wirth.[22] Further polymerization leads either to ring systems of aromatic character, such as benzene and naphthalene, with the possible formation of side chains (styrene), or the chains may be lengthened, the products being divinylacetylene, $CH_2:CH\cdot C:C\cdot CH:CH_2$, or butadieneacetylene, $CH_2:CH\cdot CH:CH\cdot C:CH$, depending on how an acetylene molecule is added; see Nicodemus.[23]

[20] R. Kuhn and A. Deutsch, *Ber.*, **65**, 43 (1932).
[21] O. Döbner, *Ber.*, **40**, 146 (1907).
[22] Willstätter and Wirth, *Ber.*, **46**, 538 (1913).
[23] O. Nicodemus, *Angew. Chem.*, **49**, 791 (1936).

Higher polymerization products of this kind apparently cannot be isolated by chemical means. The compounds are so unsaturated that they must be treated with special care, as their polymerization to compounds of very high molecular weight proceeds in an explosive manner.

B. Oxygen at New Bond

The formation of aldols is one of the most versatile reactions treated in this chapter. Aldols are used frequently as intermediates in the synthesis of unsaturated compounds, as they are readily dehydrated. In many cases, for example the Perkin's syntheses, they are not isolated at all. Only primary products that can be isolated are described here. Their reaction products obtained by removal of water are discussed on page 318. The reactions in which the aldols are important only as intermediates are discussed on page 419 together with the preparation of other unsaturated condensation products. That the above separation is justified as far as methodic aspects are concerned is shown by the following example. Mesityl oxide may be obtained directly from acetone. Its preparation in this manner is still advantageous, although large amounts are obtained by removal of water from diacetone alcohol.

Doubts may arise about the classification of Grignard reactions of the type

$$R_2CO + MgXR' \longrightarrow R_2C(OMgX) \cdot R'$$
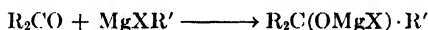
If written in this form they are certainly addition reactions and might be discussed at this point. However, it seems preferable to consider them with exchange reactions, because the primary products are almost never isolated, and it follows customary practice. There is probably a good reason for this, since the key group MgX has already separated from the organic linkage proper in the addition compounds. They appear to be similar to condensations with removal of halogen: $R'X + XMgR'' \rightarrow R' \cdot R'' + MgX_2$.

1. Aldol Type

The formation of aldols from aldehydes, or the formation of ketols from ketones, proceeds under the influence of alkaline reagents. The classical example of the formation of sugars from aqueous formaldehyde solutions has no practical importance; therefore, a further discussion at this point is omitted.

The acetaldol, $CH_3 \cdot CHOH \cdot CH_2 \cdot CHO$, was prepared by Claisen [24] from an aqueous solution of acetaldehyde and potassium cyanide.

100 g. of acetaldehyde, freshly prepared from paraldehyde, are added slowly to 200 cc. of ice-cold water. After the solution has been cooled to $-12°C$., an ice-cold solution

[24] L. Claisen, *Ann.*, **306**, 323 (1899).

of 2.5 g. of potassium cyanide in 100 cc. of water is cautiously added. The temperature must not exceed −8°C. After 2 hours more in a freezing mixture, and 30 hours in the cold, sodium chloride is added to saturation and the solution extracted with ether. The ethereal solution is dried and fractionated. Aldol is obtained in a 40 to 45% yield, boiling between 80° and 90°C. at 20 mm. The pure aldol boils at 83°C.

Grignard and Reif [25] add, with shaking, 75 cc. of cold 15% sodium carbonate solution to an ice-cold mixture of 200 g. of ether and 200 g. of acetaldehyde. The temperature must not exceed 10°C. After the addition is completed, the temperature of the solution is allowed to rise. It is kept at 25° to 28°C. for 5 minutes and then increased with steady shaking to 30° to 32°C. Stirring is better than shaking. The ethereal layer is separated and the aqueous part extracted with an equal volume of ether. The ether solutions are washed with saturated bicarbonate solution, dried, and fractionated. The yield amounts to 48 to 50% of the theoretical.

Acetaldol polymerizes, on standing, to the dimeric paraldol, Nowak [26] reports. The higher molecular aliphatic aldehydes yield analogous addition products: $2R \cdot CH_2 \cdot CHO \rightarrow R \cdot CH_2 \cdot CHOH \cdot CH(R) \cdot CHO$. The propionaldol ($R=CH_3$) was described by Franke, Kohn, and Zwiauer.[27]

An example of the reaction of an aldehyde with a ketone is the preparation of acetylisopropyl alcohol, $CH_3 \cdot CO \cdot CH_2 \cdot CHOH \cdot CH_3$, from acetone and acetaldehyde. The directions are taken from Claisen and Rupe.[28]

105 g. of acetone are cooled to −12°C. and a solution of 5 g. of potassium cyanide in 10 cc. of water is added. Then 40 g. of freshly prepared acetaldehyde are added while the cooling is continued. The mixture is allowed to stand for 8 hours in the cold. It is then extracted with ether, and the ether solution shaken with saturated sodium chloride solution, dried with sodium sulfate, and fractionated *in vacuo*. The ketole boils at 77° to 78°C. at 19 mm.

The condensation product of 2 moles of acetone is called diacetone alcohol; it is best prepared according to Conant and Tuttle's directions given in *Organic Syntheses*.[29]

2. Benzoin Type

Acyloin Condensation

The acyloin condensation proceeds according to the equation

$$2R \cdot CHO \longrightarrow R \cdot CHOH \cdot CO \cdot R$$
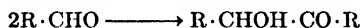
This reaction is most important in the preparation of aromatic compounds. In the aromatic series it is called benzoin condensation because of the simple case of benzaldehyde. The reaction can be performed in the aliphatic series only in very special cases. The aliphatic acyloins of the above constitution can be obtained much more conveniently in other ways. One of the few cases in which the acyloin condensation proceeds

[25] Grignard and Reif, *Bull. soc. chim.*, 1, 114 (1907).
[26] Nowak, *Monatsh.*, 22, 1140 (1901).
[27] Franke, Kohn, and Zwiauer, *Monatsh.*, 27, 1118 (1906).
[28] L. Claisen, *Ann.*, 306, 324 (1899). A. Rupe, *Ber.*, 40, 4766 (1907).
[29] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 199.

smoothly with aldehydes that are not purely aromatic is that of the glyoxals of the type of phenylglyoxal; see Söderbaum.[30]

The action of potassium cyanide in the benzoin condensation is not clearly understood. The method is generally known, and therefore will be discussed only briefly.

The alcoholic or aqueous alcoholic solution of the aldehyde with about one-tenth its weight of potassium cyanide is boiled under a reflux. When the mixture is cooled, the benzoin crystallizes. Benzoin with a slight yellow tint is usually obtained. The coloring is difficult to remove. A. Weissberger [31] obtained completely colorless benzoin by recrystallization from diisoamyl ether. Its melting point is 137°C.

Potassium cyanide may be replaced by sodium or barium cyanide, but not by free hydrogen cyanide or by complex cyanogen compounds. Therefore, the cyanide ion is considered responsible for the catalytic effect in the condensation. The slight dissociation of free hydrogen cyanide and of the complex compounds causes these to be ineffective. The homologues of benzaldehyde and the ethers of hydroxy aldehydes, such as anisaldehyde, condense readily. Free hydroxy aldehydes, also halogenated nitro and amino aldehydes, do not form any benzoins. With cinnamaldehyde the yield is very small.

3. Pinacol Type

The preparation of pinacol from acetone may be made with a great many reducing agents; e.g., magnesium amalgam, aluminum amalgam, sodium, and sodium amalgam, or electrolytically. Holleman's [32] method is well suited for the laboratory; he used magnesium activated with mercuric chloride. Detailed directions are given in *Organic Syntheses*.[33]

Anhydrous pinacol is best obtained from the hydrate by distillation with benzene. King and Stewart [34] who devised the method describe an apparatus for continuous dehydration in their paper. The benzene is separated from the distillate and returned to the distillation flask. After the water is removed, the mixture is distilled up to 170°C. and pinacol is obtained as the residue. The boiling point of the pure pinacol is 171° to 172°C.; its melting point is about 38°C.

The preparation of benzopinacol from benzophenone described by Vanino [35] serves as an example of the formation of a pinacol in acid solution.

[30] Söderbaum, *Ber.*, 25, 3468 (1892).
[31] A. Weissberger, *Ber.*, 62, 1952 (1929).
[32] F. Holleman, *Rec. trav. chim.*, 25, 206 (1906).
[33] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 459.
[34] H. King and W. Stewart, *Chem. Abstracts*, 25, 1799 (1931).
[35] Zagumenny, *J. Russ. Phys. Chem. Soc.*, 12, 429 (1880). L. Vanino, *Handbuch der präparativen Chemie*, Vol. II, Enke, Stuttgart, 1937, p. 560.

1 part of benzophenone, 2 parts of zinc, and 10 parts of 80% acetic acid are boiled for 15 minutes with vigorous agitation. The crystals that separate when the material is cooled are removed by filtration. The filtrate is treated with zinc as above several times. The separated benzopinacol is washed with dilute acetic acid and recrystallized from boiling acetic acid. It melts at 185° to 186°C., decomposing into benzophenone and benzhydrol.

4. Addition of Carbon Dioxide

Kinney and Ward [36] studied the influence of catalysts on the formation of carboxylic acids from substituted aromatic hydrocarbons and carbon dioxide under pressure. After many experiments the following preparation of an effective catalyst was developed. A solution of 20 g. of nickel nitrate hexahydrate and 24 g. of cobaltous nitrate hexahydrate in a little water is mixed in a mortar with 15 g. of dry asbestos. The mixture is dried and heated until nitrous oxides are no longer evolved. Another effective catalyst is obtained by mixing the hydroxides prepared from 99 g. of zinc nitrate and 93.5 g. of copper nitrate and ammonia, with 7.7 g. of chromium oxide and 40 g. of asbestos. This mixture is then treated as described above. The effectiveness of the catalysts soon diminishes. A few grams of simple aromatic hydrocarbons, such as phenols, phenol ethers, or other substituted benzene derivatives, are sealed into 200 cc. Carius combustion tubes together with 0.1 mole of solid carbon dioxide and with an unspecified amount of the catalyst. On heating, pressures of 20 to 30 atmospheres are built up. The temperatures used are between 100° and 300°C. The amount of the carboxylic acid formed is below 1%. Only resorcinol gives a yield of about 10% of 2,4-dihydroxybenzoic acid.

C. Halogen at the Bond

Halogen substitution products of unsaturated hydrocarbons show an affinity for saturated halides. Prins [37] recently investigated such condensations and the reaction products obtained. Substitution products of ethylene react if their double bonds are adjacent to CCl_2 or CCl_3 groups. Chloromethanes, especially chloroform, but also methylene chloride, and chloroethanes may be added, but the latter more slowly. Chloropropanes with low chlorine content are not added, but pentachloropropane is. As an example, directions for the preparation of 1,1,2,3,3-pentachloropropane [38] follow.

120 g. of pure chloroform are boiled for a few minutes with about 1% of this weight of aluminum chloride, while 97 g. of dichloroethylene are heated to 40°C. with the same amount of aluminum chloride. The two reaction components thus saturated with aluminum chloride are mixed

[36] C. Kinney and O. Ward, *J. Am. Chem. Soc.*, **55**, 3796 (1933).
[37] H. J. Prins, *Rec. trav. chim.*, **51**, 1065 (1932); **54**, 307 (1935).
[38] H. J. Prins, *Rec. trav. chim.*, **54**, 309 (1935).

when cool. The mixture is warmed and the temperature held for 5 minutes at 50°C. until it begins to rise spontaneously. By cooling with running water the temperature of the reaction mixture is kept between 50° and 55°C. If it exceeds this temperature, the reaction gets out of control. After 30 minutes the temperature begins to fall. The mixture is then heated for 10 minutes at 55° to 60°C. and unchanged starting material is removed by steam distillation. During this distillation the ratio of distilled water and oil must be watched constantly. If the volume of oil in 10 cc. of the distillate drops to 3 cc., the receiver is changed. Pentachloropropane now distils in a practically constant mixture of 2.5 cc. in 10 cc. of distillate. When 10 cc. of the distillate contain only 0.5 cc. of oil, the distillation is stopped. Thus 70 to 75% of the theoretical amount of pentachloropropane is obtained. Influences which hinder the reaction are discussed in the original paper.

D. Nitrogen at the Bond

1. Addition of Hydrogen Cyanide to Carbonyl Group

The so called cyanohydrin synthesis consists of the addition of hydrogen cyanide to carbonyl compounds: $R_2 \cdot CO + HCN \rightleftarrows R_2 \cdot C(OH) \cdot CN$. It can be performed successfully with aldehydes as well as with ketones and produces an equilibrium mixture. This equilibrium is reached quite slowly if no catalysts are present. Small amounts of alkalies, also potassium cyanide, have a catalytic effect; see Ultée.[39] The general procedure with free hydrogen cyanide is as follows:

To the equimolecular mixture of aldehyde and hydrogen cyanide (for ketones a 10% excess of hydrogen cyanide is used) a few drops of a concentrated potassium cyanide solution are carefully added. Since the mixture soon comes to a boil, an efficient reflux condenser must be provided; in some cases cooling is necessary. After the reaction has subsided, the mixture is well cooled and acidified with sulfuric acid. Unchanged hydrogen cyanide and excess aldehyde or ketone are removed by distillation and the residue fractionated *in vacuo*.

A solution of potassium cyanide added to the mixture of acetaldehyde and hydrogen cyanide produces explosions. The mixture is allowed to flow slowly onto a few granules of potassium cyanide covered by ether; see Meerwein.[40]

This simple method may be replaced by other methods because hydrogen cyanide is poisonous. Bucherer and Grolée [41] let the bisulfite compounds of aldehydes or ketones react with aqueous potassium cyanide solution. Frequently it is not even necessary to isolate the bisulfite compounds.

[39] Ultée, *Rec. trav. chim.*, 28, 1, 248 (1909).

[40] J. Houben, *Die Methoden der organischen Chemie.* Vol. II, Thieme, Leipzig, 1925, p. 583.

[41] H. Bucherer and A. Grolée, *Ber.*, 39, 1225 (1906).

1 mole of acetone is shaken with a concentrated aqueous solution of 1 mole of sodium bisulfite. The mixture is allowed to cool and a concentrated aqueous solution of potassium cyanide is added dropwise with shaking. The solution grows warm again. It is cooled and the oily acetone cyanohydrin is separated from the aqueous layer. The latter is extracted several times with ether and the ether extract combined with the main portion. The ether solution is shaken with bisulfite solution to remove the acetone, then shaken with concentrated sodium chloride solution, and dried. Ultée found that the cyanohydrin can be distilled *in vacuo* if the last traces of alkali are removed. It is desirable to dry and distil the ethereal solution Bucherer obtained, which may contain 95% of acetone cyanohydrin. The boiling point is 82°C. at 23 mm., the melting point −19°C.

In the preparation of aromatic cyanohydrins, *e.g.* mandelic nitrile, the bisulfite compound of the aldehyde is usually isolated.

15 g. of freshly distilled benzaldehyde are shaken with 50 cc. of a concentrated solution of sodium bisulfite, according to Gattermann-Wieland.[42] The addition product is filtered off by suction and washed with a little ice-cold water. Then the crystals are mixed to a thick mush with water, and a solution of 12 g. of potassium cyanide in 25 cc. of water added. The crude mandelic nitrile is an oil.

For the preparation of mandelic acid the nitrile must be hydrolyzed immediately, as it is unstable. Pure mandelic nitrile cannot be obtained in this manner. The changes that take place when mandelic nitrile is allowed to stand are discussed by Stollé.[43] Ultée[44] obtained crystals when he cooled the reaction mixture from equimolecular amounts of acid-free benzaldehyde and hydrogen cyanide by the above procedure. The melting point of the crystals after repeated recrystallization was 21.5° to 22°C. ·

The cyanohydrin synthesis is of special significance in sugar chemistry. E. Fischer converted pentoses to hexoses, etc., by reducing the lactones of the aldonic acids. The method was first described by Kiliani[45] who later improved it. The nitriles formed as intermediates in the course of the reaction just sketched have not been isolated as such in most cases. This is not necessary for the preparation of the aldonic acid lactones when these are of interest. However, the carboxylic acid amides involved have been isolated in pure form on numerous occasions. The following directions are taken from the report of Kiliani.[46]

A solution of 30 g. of finely powdered galactose in 6 cc. of water is mixed with the calculated amount of 50% hydrocyanic acid and a drop of ammonia is added. Alkalies are catalysts for the cyanohydrin synthesis. The reaction flask is closed and thoroughly shaken. On standing, the sugar turns yellow and liquefies. After 6 to 8 hours fine

[42] Gattermann-Wieland, *Die Praxis des organischen Chemikers*. de Gruyter, Berlin, 1936, p. 227.
[43] Stollé, *Ber.*, 35, 1590 (1902).
[44] Ultée, *Rec. trav. chim.*, 28, 254 (1909).
[45] H. Kiliani, *Ber.*, 19, 3033 (1886).
[46] H. Kiliani, *Ber.*, 21, 916 (1888).

colorless needles start to separate. The mixture at times becomes quite warm. After an additional 12 hours standing the same volume of water is added, and the mixture is shaken and filtered. The dark colored mother liquor is discarded. 40 to 50% of the weight of the galactose is obtained as the crude heptanoic acid amide.

Haworth and Peat [47] changed the method by treating partially methylated sugars simultaneously with potassium cyanide and methyl chlorocarbonate. They obtained nitriles which carry a carbomethoxy group on a hydroxy group. On subsequent hydrolysis the carbomethoxy group is removed. Details are given in the original paper.

The best method for preparing aldonic acid nitriles involves the removal of water from oximes; see page 255.

2. Addition of Formaldehyde and Amines

Mannich and Chang [48] discovered a new method for lengthening the carbon chain. According to the equation, $C_6H_5 \cdot C : CH + CH_2O + HN \cdot R_2 \rightarrow C_6H_5 \cdot C : C \cdot CH_2 \cdot NR_2 + H_2O$, arylacetylenes react with formaldehyde and secondary amines to form unsaturated bases. This new type of compounds allows many reactions because of the reactivity of the acetylene bond. The bases may be hydrogenated in stages. With concentrated sulfuric acid, ketones are formed. The preparation of 1-phenyl-3-diethylamino-1-propine serves as an example.

Phenylacetylene (10.2 g.), 8 g. of diethylamine, 3.6 g. of paraformaldehyde, and 15 cc. of dioxane are heated under a reflux on a water bath for 15 hours. After the solution has been cooled, it is acidified, diluted with water, and the non-basic components (1 g.) extracted with ether. The bases are liberated with potassium hydroxide solution. 15 g. of an oil can be isolated, boiling at 137°C. at 18 mm. This represents an 80% yield.

Nitro- and methoxyphenylacetylenes were treated in the same way with dimethylamine and piperidine as basic components.

Part Two: by Replacement

I. FORMATION OF SINGLE BONDS WITHOUT CONDENSING AGENTS

A. Removal of Hydrogen

1. Pyrogenic Reactions (Autocondensations)

The formation of uniform products at high temperatures can be expected only if very stable systems are obtained. Such systems are, with a few exceptions, always aromatic compounds with several nuclei. This reaction has practical preparative importance only occasionally.

Saturated hydrocarbons cannot be obtained in this manner, because

[47] W. Haworth and St. Peat, *J. Chem. Soc.*, **1929**, 354.
[48] C. Mannich and F. Chang, *Ber.*, **66**, 418 (1933).

they are cracked at these temperatures, but the formation of hydrocarbons of the aliphatic series with multiple unsaturation has been observed.

Thus, Norton and Noyes [1] found that at dark red heat butadiene is formed from ethylene as well as numerous highly condensed systems: $2CH_2:CH_2 \rightarrow CH_2:CH\cdot CH:CH_2 + H_2$. Apparently the yield of butadiene could not be increased enough so that this temptingly simple reaction could be used in a practical way.

However, the reaction has considerable importance for the preparation of biphenyl from benzene. The preparation of biphenyl by pyrogenic decomposition of benzene has been known for a long time, but not until recently have the best conditions for its formation been studied thoroughly. This has happened since biphenyl has become an industrial product. The main products of the reaction are hydrogen, biphenyl, carbon, decomposition gases, and biphenylbenzenes.

The older methods agreed in the use of red-hot iron tubes, but exact data on the most advantageous temperature were not given. Zanetti and Egloff [2] found 750°C. to be a suitable temperature. At higher temperatures more carbon and more biphenylbenzene are formed. C. Smith and Lewcock [3] investigated several conditions. They varied the temperature, the velocity of flow, and the length and the diameter of the iron tube, and studied the effect of addition compounds such as barium peroxide, aluminum oxide, zinc oxide, and minium. Grant and James [4] report on the use of red-hot metal wires for the decomposition. Low and James [5] describe an apparatus for preparing biphenyl in the laboratory. Hixson and coworkers [6] describe a pressure apparatus in which molten lead is used to transmit the heat; the apparatus is rather elaborate and not intended for preparative purposes. Many recent publications are available which suggest reaction mechanisms but apparently the theories have not been proved.

If it is a question of occasionally preparing biphenyl in the laboratory, one of the older simple set-ups, described by E. Fischer, [7] may be used.

The apparatus described by Low and James for the preparation of biphenyl is of the very simple construction given here.

A 12 liter round bottom flask is equipped with an ordinary reflux condenser. Into the flask there projects a heating element consisting of a nichrome ribbon which is protected from short circuit on the support in a manner similar to that of an isoprene lamp; see page 451. Details for the diameter and length of the heating ribbon are lacking, although one that is made of 8 strands, that is braided from eight single wires, is recom-

[1] Norton and Noyes, *Ber.*, 20, 200 (Ref.) (1887).
[2] J. Zanetti and G. Egloff, *Ind. Eng. Chem.*, 9, 350 (1917).
[3] C. Smith and W. Lewcock, *J. Chem. Soc.*, 101, 1453 (1912).
[4] J. Grant and C. James, *J. Am. Chem. Soc.*, 39, 934 (1917).
[5] H. Low and C. James, *J. Am. Chem. Soc.*, 45, 2666 (1923).
[6] A. W. Hixson *et al.*, *Ind. Eng. Chem.*, *Anal. Ed.*, 3, 289 (1931).
[7] E. Fischer, *Anleitung zur Darstellung organischer Präparate*. Vieweg, Braunschweig, 1905, p. 63.

mended. It is arranged in such a manner that it can be replaced in 10 minutes if it burns through. The heating element almost touches the surface of the benzene without dipping into it; the upper part ends at the neck of the flask. Details can be found on page 452, where the preparation of butadiene is described. At the beginning of the experiment the benzene in the flask is brought to a boil before the current is turned on in order to displace all the air in the flask. The heating wire is brought to moderate red heat (yellowish red) by a current of about 10 to 12 amperes. During the experiment the benzene is kept boiling by the radiant heat of the heating element. A mist is formed and the benzene returning from the condenser is yellowish. Biphenyl condenses at the wall of the flask. If carbon forms at the heater, the temperature is too high. The surface usually becomes covered with tar during the run; this must be removed frequently. 1 kilo of biphenyl can be obtained during 24 hours. No very large amount of by-products is found during the fractionation. The boiling point of biphenyl is 254°C.; its melting point 70.5°C.

The formation of fluorene from biphenylmethane proceeds in a manner entirely analogous to the formation of biphenyl. It was first described by Graebe.[8] Recently Zelinskii[9] gave details on the formation of fluorene by passing biphenylmethane vapors over platinized carbon at 300°C. The method is not suitable for preparative purposes. The formation of phenanthrene from bibenzyl and that of carbazole from diphenylamine belong in this series. These compounds were also prepared by Zelinskii with platinized carbon. This catalyst permits the reaction temperature to be lowered, thus avoiding much decomposition.

All pyrogenic reactions discussed here are certainly of a catalytic nature even if only the wall of the reaction flasks represents the active catalyst. There is no basic difference between pyrogenic and catalytic reactions of this kind. In a strict sense, the commercially important dehydrogenations with aluminum chloride belong to the same group. These reactions, in almost all cases, yield condensed aromatic or heterocyclic ring systems.

2. Catalytic Removal of Hydrogen

The catalytic removal of hydrogen with the formation of new carbon linkages is most successful with aluminum chloride. The main importance of this reaction lies in the preparation of condensed ring systems in the aromatic series. 2 molecules can react with one another; for instance, perylene is formed from naphthalene or 1,1'-binaphthyl.
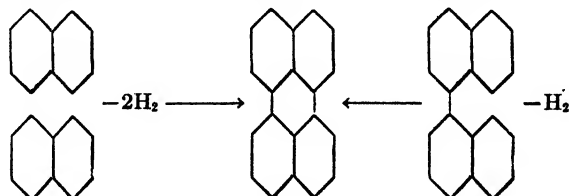
[8] C. Graebe, *Ann.*, 174, 194 (1874).
[9] N. Zelinskii, *Ber.*, 59, 2591 (1926).

Scholl did most of the work on this reaction; therefore, it is called Scholl's synthesis.   A recent account can be found in Kränzlein's book.[10]

The operation is very simple; therefore, only a few examples are given. For the preparation of perylene, Scholl [11] gives the following directions.

10 g. of 1,1'-binaphthyl (see page 351) are thoroughly mixed in a mortar with 40 g. of anhydrous aluminum chloride.   The mixture is heated for 1 hour at 140°C. in a flask equipped with a calcium chloride tube.   The reaction product is decomposed with water and the brown powder extracted repeatedly with boiling hydrochloric acid and then dried at 110°C.   On sublimation of the dried residue, perylene appears at 350° to 400°C. and is deposited in the form of shiny yellow leaflets.   After recrystallization, first from benzene, then from much glacial acetic acid, perylene is obtained as bronze-colored leaflets which melt at 264° to 265°C. on rapid heating.   The yield is 1.5 g.

Perylene is also obtained from naphthalene but in a much poorer yield. The following are Scholl's directions.

20 g. of naphthalene and 80 g. of aluminum chloride are thoroughly mixed and heated for 1 hour at 180°C.   The reaction mixture is treated as described above.   The dried residue is heated to 300°C. in a Pyrex retort until everything which is easily volatilized has distilled with strong foaming.   If the heating is continued to the softening point of the glass, the perylene distils as a thick red oil which slowly solidifies.   It is purified according to the directions given above.   0.2 g. of pure perylene is obtained.

In most cases Scholl's reaction yields 6-membered rings, but occasionally 5-membered rings with a keto group are also obtained.   Fierz-David [12] described the formation of 6-hydroxy-7,8-benzofluorenone from 2-hydroxybenzanthrone.

Prior to Scholl's, similar reactions were frequently reported although without ring formation.   Friedel and Crafts obtained [13] biphenyl from benzene.   Nenitzescu and Jonescu [14] later found that cyclohexane is converted into 2,2'-dimethyldicyclopentyl.

The examples discussed thus far involve connections of nuclei of the same kind, or intramolecular reactions.   Pummerer [15] obtained p-diphenylquinone from quinone and benzene.   Free hydrogen cannot be observed during this reaction, because part of the quinone is hydrogenated.   Pummerer and Binapfl [16] discovered another reaction of this kind; namely, the formation of p-aminobiphenyl from azobenzene.   The yield is 70 to 80%, and proceeds according to the equation,

$$\langle\ \rangle\!-\!N\!\!=\!\!N\!-\!\langle\ \rangle + 2C_6H_6 \longrightarrow 2\langle\ \rangle\!-\!\langle\ \rangle\!-\!NH_2$$
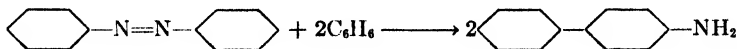
[10] G. Kränzlein, *Aluminiumchlorid in der organischen Chemie.* Verlag Chemie, Berlin, 1932, p. 73.
    [11] R. Scholl, *Ber.*, **43**, 2204 (1910).
    [12] Fierz-David, *Helv. Chim. Acta*, **11**, 1046 (1928).
    [13] Friedel and Crafts, *Bull. soc. chim.*, **39**, 306 (1883).
    [14] Nenitzescu and Jonescu, *Ann.*, **491**, 189 (1931).
    [15] R. Pummerer, *Ber.*, **55**, 3105 (1922); **60**, 1439, 1442 (1927).
    [16] Pummerer and Binapfl, *Ber.*, **54**, 2768 (1921).

3. Oxidation, Removal of Hydrogen

The reactions falling under this heading are very numerous and are difficult to summarize and an attempt at systematic treatment would require much space. The reaction in which 2 hydrogen-containing molecules are oxidized under the influence of oxidizing reagents to form a compound is probably one of the most common reactions, even though its practical importance is slight. In general it may be stated that aromatic nuclei may be connected under the influence of oxidizing agents and that aliphatic methyl or methylene groups may take part in these reactions. Saturated as well as unsaturated bonds can be formed.

While the synthesis of biphenyl proceeds without oxidizing agents, 1,1'-binaphthyl is obtained from naphthalene, as Lossen [17] found, by treatment with manganese dioxide and sulfuric acid. This method is not suited for preparative purposes. The compound is more conveniently obtained from the readily available α-bromonaphthalene. H. Meyer and Hofmann [18] found that 2,2'-binaphthyl is formed predominantly if naphthalene is passed over a red-hot platinum wire. It is remarkable that the 2,2' compound may be partially converted into 1,1'-binaphthyl, as Weitzenböck [19] reports, if it is boiled with aluminum chloride and sulfuric acid. Smith [20] gives the following directions for the preparation of 1,1'-binaphthyl.

Naphthalene is boiled with manganese dioxide and 50% sulfuric acid; boiling water is then added, the mixture filtered, and the residue is extracted completely with alcohol. On distillation, the fraction boiling above 360°C. is collected and repeatedly recrystallized from alcohol and ligroin. The melting point of the product is 160.5°C.

Phenols may be condensed readily by oxidation to give dihydroxybiphenyl derivatives, as has been shown by Barth and Schreder.[21] When hydroquinone is melted with alkalies, tetrahydroxy- and hexahydroxybiphenyl are formed, besides hydroxyhydroquinone. The method is important mainly for the preparation of dinaphthols.

According to Julius [22] 100 g. of β-naphthol and 30 g. of sodium hydroxide are dissolved in 4 liters of water and the solution brought to a boil. Then 160 g. of crystalline ferric chloride, 100 cc. of hydrochloric acid, and 200 cc. of water are added. The mixture is boiled for 30 minutes, filtered, and the filter cake washed with hot water. This is recrystallized from alcohol; see also Eckstein.[23]

The isomeric α-dinaphthol is obtained in the following manner.

[17] Lossen, *Ann.*, **144**, 78 (1867).
[18] H. Meyer and Hofmann, *Monatsh.*, **37**, 708 (1916).
[19] Weitzenböck, *Monatsh.*, **32**, 998, foot-note (1911).
[20] Smith, *J. Chem. Soc.*, **35**, 225 (1879).
[21] Barth and Schreder, *Monatsh.*, **5**, 589 (1884).
[22] Julius, *Chemische Industrie*, **10**, 98 (1887).
[23] Eckstein, *Ber.*, **38**, 3662 (1905).

To a boiling solution of 80 g. of ferric chloride and 50 cc. of hydrochloric acid in 1 liter of water is added, in portions and with stirring, a solution of 50 g. of α-naphthol and 15 g. of sodium hydroxide in 3.5 liters of water. The mixture is filtered, and the residue washed with much hot water and recrystallized from alcohol. The melting point is 300°C.

Tertiary aromatic amines such as dimethylaniline are condensed to biphenyl derivatives still more easily than phenols.

Michler and Pattison [24] dissolved dimethylaniline in 3 to 4 times its weight of concentrated sulfuric acid and heated the solution to 180° to 210°C. Water and sulfur dioxide are evolved. After 6 to 8 hours the syrup is poured into water, the mixture is made alkaline with sodium hydroxide, and excess dimethylaniline removed by steam distillation. The distillation residue is filtered, the filter cake is dissolved in hydrochloric acid, and the solution evaporated to incipient crystallization. After the material has cooled, the hydrochloride is decomposed with ammonia; thus, 4,4'-tetramethyldiamido-biphenyl is obtained. Its melting point is above 360°C.

Phenol requires stronger oxidizing agents.

Dianin [25] mixes 100 g. of phenol with 20 g. of sodium bicarbonate and 200 cc. of water. To this mixture is added, with shaking, a solution of 20 g. of potassium permanganate in 1500 cc. of water and 150 g. of concentrated sulfuric acid. The reaction mixture is further diluted with water, and the separated oil is collected and washed with 500 cc. of cold water. It is boiled several times with 100 cc. portions of water. From the hot aqueous filtrate the 4,4'-dihydroxybiphenyl, or p-biphenol, crystallizes; it melts at 272°C.

Hirsch [26] reports that this compound is more conveniently obtained from benzidine by diazotizing and boiling with water.

The examples discussed show that the method is used mostly for the preparation of diphenyl and dinaphthyl derivatives. In rare cases it may also be used for the preparation of diphenylethane derivatives; see Green.[27]

Likewise, in a few cases ring closures may be effected; an example of this reaction is the formation of quinoline from allylaniline and lead oxide (Koenigs [28]).

Heterocyclic compounds may be condensed in a similar manner. Hein and Schwedler [29] prepared α,α'-bipyridine [30] as follows:

In a glass beaker immersed in an autoclave of 750 cc. capacity a mixture of 165 g. of pyridine and 135 g. of sublimed ferric chloride is heated for 4 hours at 320° to 340°C.

[24] W. Michler and S. Pattison, Ber., 14, 2161 (1881).
[25] A. Dianin, Jahresber., 1883, 875. J. Houben, Die Methoden der organischen Chemie, Vol. II, Thieme, Leipzig, 1925, p. 781.
[26] Hirsch, Ber., 22, 335 (1889).
[27] A. Green, Chem. Zentr., 1908, I, 642.
[28] W. Koenigs, Ber., 12, 453 (1879).
[29] F. Hein and H. Schwedler, Ber., 68, 682 (1935).
[30] F. Hein and W. Retter, Ber., 61, 1790 (1928).

The reddish black reaction product, which must not be carbonized, is coarsely pulverized and mixed with water. A concentrated sodium hydroxide solution is added to make the solution strongly alkaline. The mixture is steam-distilled until the distillate shows only a slight red coloration when tested with ferrous sulfate. This distillation takes a long time. The distillate is acidified with concentrated sulfuric acid and evaporated to 500 cc. After the mixture has cooled, it is made strongly alkaline. The main portion of the bipyridine separates as an oil along with unchanged pyridine. The oil layer is dried with potassium hydroxide, while the aqueous layer is extracted with ether. The ether extract is dried with potassium hydroxide and combined with the main portion. This mixture is then fractionated. The fraction distilling at 265° to 280°C. solidifies. It is pressed on a porous plate. The compound is purified by recrystallization from low boiling petroleum ether with the addition of decolorizing carbon. When the material cools in a freezing mixture, colorless crystals of bipyridine separate; they melt at 71° to 72°C. A second crop of almost the same purity may be obtained from the mother liquor.

The classical example of condensation by oxidation was the synthesis of triphenylmethane dyes. In the older commercial method toluidine-containing mixtures of aromatic bases were used. At this point it must suffice only to mention this historically important method.

B. Removal of Halogen

1. Spontaneous Removal of Halogen and Halogen Halide

In some cases new carbon bonds are formed with spontaneous removal of halogen from halides. Ethanetetracarboxylic acid ester, for instance, is formed by the action of sodium iodide upon bromomalonic ester through the iodo ester which must be assumed as intermediate.

Finkelstein [31] directs that 2.4 g. of bromomalonic ester be boiled for 3 hours with 16 cc. of N sodium iodide in acetone. The reaction mixture is diluted with water and decolorized with sulfur dioxide. Ethanetetracarboxylic acid ester (1.3 g.) crystallizes. This corresponds to an 80% yield.

The cleavage of hydrogen halides can be easily observed if the halogen atom of one component is reactive as well as a hydrogen atom of the other. Aromatic compounds, phenols, and tertiary amines are usually involved. The reactions that occur are similar to the Friedel-Crafts synthesis. They lead to di- or triphenylmethane derivatives and to ketones. According to Döbner,[32] benzotrichloride reacts with phenol according to the equation

$$C_6H_5 \cdot CCl_3 + 2C_6H_5OH \longrightarrow C_6H_5 \cdot C(Cl)(C_6H_4OH)_2 + 2HCl$$
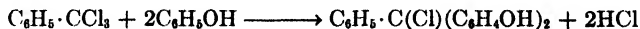
The p-dihydroxydiphenylphenylmethyl chloride hydrolyzes to benzaurin.

1 mole of benzotrichloride is heated on a water bath with 2 moles of anhydrous phenol. Hydrogen chloride is evolved and the reaction mixture turns red. The reaction mixture is heated until hydrogen chloride is no longer evolved. Then hot water is added

[31] H. Finkelstein, *Ber.*, **43**, 1532 (1910).
[32] O. Döbner, *Ann.*, **217**, 227 (1883).

and the unchanged phenol is removed by steam distillation. The cooled mixture is filtered, and the residue pulverized and extracted with a bisulfite solution. A resin is left undissolved. The aqueous extract is boiled with hydrochloric acid to separate the benzaurin in the form of metallic crusts. It can be purified by repeated treatment with bisulfite as described.

The reaction with dimethylaniline proceeds in a very similar manner. Döbner recommends adding zinc chloride so that the malachite green formed may be obtained as the zinc chloride double salt.

The reactions of some of the highly condensed aromatic ring systems with acid chlorides, such as phosgene or oxalyl chloride, may be looked upon as a transition to the reactions of the Friedel-Crafts type. Acid chlorides, phosgene, also oxalyl chloride, benzoyl chloride, and phthalyl chloride react in an entirely analogous manner with dimethylaniline. These reactions are known and need not be described in detail. Gräbe and Liebermann [33] used phosgene for the carboxylation of anthracene. Liebermann and Zsuffa [34] found later that phosgene may frequently be replaced by oxalyl chloride. The reactions take place in a sealed tube and were carried out on a small scale. Anthracene, fluorene, indene, acenaphthene, phenanthrene, and chrysene could be converted into carboxylic acids with only fair yields. The difference between the products obtained by this method and the method in which aluminum chloride is used is that the latter gives better yields but the products are less pure.

2. Catalytic Removal of Halogen

Recently Busch and coworkers [35] thoroughly investigated a previously neglected reaction which produces an effect similar to that of the Wurtz-Fittig reaction. It proceeds according to the equation, $2RX + H_2 \rightarrow R \cdot R + 2HX$. Palladium is used as a catalyst and hydrazine as a source of hydrogen. The method is simple. The compound involved is dissolved in methanol, ethanol, or dioxane, the solution made alkaline, and the palladium-calcium carbonate catalyst and hydrazine added. The mixture is boiled or heated to a higher temperature in an autoclave.

Bromobenzene, thus, can be converted to biphenyl in an 80% yield. p-Bromoaniline yields 60% of the theoretical amount of benzidine, p-bromobenzoic acid a 40% yield of biphenyl-p,p'-dicarboxylic acid. Bipyridine compounds can also be obtained in good yields.

Of special interest are the experiments with aromatic dihalogen compounds. p-Dibromobenzene gave a series of polyphenyls; details of this reaction as an example of the method follow.

[33] C. Gräbe and C. Liebermann, *Ber.*, 2, 678 (1869).
[34] C. Liebermann and M. Zsuffa, *Ber.*, 44, 202 (1911).
[35] M. Busch *et al.*, *J. prakt. Chem.*, 146, 1 (1936).

p-Dibromobenzene (25 g.) is mixed with 370 cc. of 5% potassium hydroxide-methanol solution, 30 cc. of water, 12 g. of catalyst (containing 0.5 g. of palladium), and 4 g. of hydrazine hydrate. This mixture is heated with stirring in an autoclave for 5 hours at 150°C. (about 12 atmospheres pressure). The following compounds can be isolated: 21% biphenyl, 14% terphenyl, 10% quaterphenyl, 2% quinquiphenyl, 0.7% sexiphenyl, 0.2% septiphenyl.

Similar runs with m-dibromobenzene yielded a series of m-polyphenyls supposedly containing products as high as sedeciphenyl, $C_{96}H_{66}$, with a molecular weight of 1218.

This method gives the possibility of synthesizing quite remarkable chains from compounds that are simple and comparatively easy to obtain. Thus, 4,4'-dibromodiphenylmethane yields mixed chains: $C_6H_5 \cdot CH_2 \cdot C_6H_4 \cdot CH_2 \cdot C_6H_4 \cdot CH_2$.

The condensation may also take place within the molecule; from 2,2'-diiododibenzyl, about equal yields (30%) of dihydrophenanthrene and bibenzyl are obtained according to the equation:
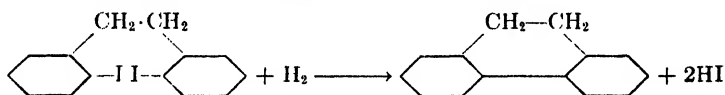
In general it may be stated that the condensation reaction becomes the more prominent the more difficult it is to split off the halogen. This is illustrated clearly by the difference between the behavior of benzyl chloride, $C_6H_5 \cdot CH_2Cl$, which was for the most part saponified by the alkaline medium, and that of ω-bromostyrene, $C_6H_5 \cdot CH:CHBr$, which gave a 50% yield of diphenylbutadiene.

Finally, high melting hydrocarbon mixtures were obtained from symmetrical tribromobenzene, the molecular weight of which was determined to be 1200 to 2300, which probably contain novel polyphenyl compounds with branched chains.

3. Spontaneous Removal of Halogen as Halide

The ideal reaction for combining hydrocarbon residues is expressed by the following scheme: $RMe + X \cdot R' \rightarrow R \cdot R' + MeX$. However, to effect syntheses in accordance with this equation it is only rarely desirable to use metallo-organic compounds. The preparation of these compounds is still quite difficult. The following reaction of Grignard compounds with halides resembles the above scheme most closely:

$$R \cdot MgX + XR' \longrightarrow R \cdot R' + MgX_2$$
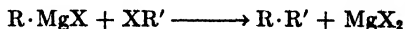
But this reaction, too, is not advantageous for preparational purposes; it can compete with other methods only in a few cases. This is true, however, only for the syntheses of hydrocarbons. Whenever oxygen or

nitrogen is attached to the metal or halogen component the Grignard reaction is one of the most productive synthetic methods of all organic chemistry.

(a) Hydrocarbons

As has been indicated, the Grignard synthesis seldom offers any advantages for the preparation of hydrocarbons (for the directions and details see page 368). This is especially true if unsaturated side chains are to be introduced into aromatic nuclei. According to Tiffeneau,[36] allylbenzene, boiling at 156° to 157°C., is obtained from phenylmagnesium bromide and allyl bromide, while ω-bromostyrene with phenylmagnesium iodide gives only a small yield of the isomeric propenylbenzene. Ramart-Lukas and Amagat [37] have described the preparation of allylbenzene and higher unsaturated benzene homologues with an end vinyl group. They recommend adding allyl bromide slowly to the ethereal solution of phenylmagnesium bromide at a temperature below 0°C. The reaction mixtures are worked up as usual; yields are not given. Allylbenzene is rearranged to propenylbenzene by alkaline reagents.

The more recent procedure of Hershberg [38] is known to have given poor yields (10 to 11% instead of the stated yield of 82%). The reason for the low yield can apparently be found in the excessive magnesium used. Bredereck's improved method, by which good yields are obtained, is as follows:

A phenylmagnesium bromide solution is prepared in the usual fashion from 50.3 g. of magnesium (activated with a little iodine), 324 g. of bromobenzene, and 800 cc. of ether. To the mixture, cooled externally in ice water, is added a solution of 250 g. of allyl bromide and 300 cc. of ether dropwise during 90 minutes. After 2 hours of boiling on a water bath the flask, which contains two layers, is cooled in ice water and 500 cc. of water are added slowly. The layers are separated and the aqueous part is extracted twice with ether. The combined ether solutions are dried over sodium sulfate and the ether removed by distillation. The residue is distilled over sodium. 213 g. of a crude product, boiling at 150° to 170°C., are obtained. This is a yield of 87% of the theoretical amount. On fractionation over sodium through a Widmer column pure allylbenzene, boiling at 158° to 160°C., is obtained. The yield is 153 g. (62.7% of the theoretical amount).

In special cases this method may offer advantages for the preparation of benzene homologues with saturated side chains. These compounds are usually obtained conveniently and in good yield by the method of Fittig. Special cases are encountered whenever an aliphatic bromide is difficult to obtain, as was the n-amyl bromide for a long time. The Wurtz synthesis, which would have to start with benzyl bromide and

[36] Tiffeneau, Compt. rend., 139, 482 (1904).
[37] Ramart-Lukas and Amagat, Bull. soc. chim., 51, 967 (1932).
[38] Hershberg, Helv. Chim. Acta, 17, 352 (1934).

n-butyl bromide, is then better replaced by the Grignard synthesis; see Schramm.[39] *Organic Syntheses*[40] gives the directions of Gilman and Heck; according to them benzylmagnesium chloride and butyl-*p*-toluene-sulfonate are used.

Inasmuch as *n*-amyl bromide has become readily available, *n*-amyl-benzene can be prepared according to Fittig's method (see page 382) from bromobenzene and *n*-amyl bromide more conveniently, more cheaply, and in better yield than by the Grignard method.

The Wurtz synthesis fails quite generally in the aliphatic series with tertiary halides. On the other hand, the preparation of highly branched paraffin hydrocarbons, such as hexamethylethane, by the Grignard method gives satisfactory yields only when special techniques are exercised. Whitmore, Stehman, and Herndon[41] have discussed the methods of preparation of hexamethylethane. They found that, with the exception of the reaction between pentamethylethyl bromide and zinc methyl, only the reaction of a tertiary butylmagnesium chloride solution with silver bromide gave a yield of more than 10%[42] (see also page 368).

The silver bromide necessary for the reaction was prepared according to the method of Gardner and Borgstrom.[43]

A warm solution of silver nitrate is precipitated with sodium bromide, the precipitate then being washed with water and acetone. The silver bromide is dried below 80°C. Drying the silver bromide even at 90°C. impairs its reactivity.

The reaction proceeds according to the following equation:

$$2R \cdot MgX + 2AgBr \longrightarrow 2Ag + MgX_2 + MgBr_2 + R \cdot R$$

According to Gardner and Borgstrom, other hydrocarbons can be synthesized in a similar way.

Flood and Calingaert[44] prepared hexamethylethane without the use of silver bromide. The yield was only 10%, but the method was simpler and cheaper.

In the case of certain condensed aromatic hydrocarbons, such as naphthalene and anthracene, which are capable of adding alkali metal in liquid ammonia or in other solvents, a special kind of metallo-organic synthesis is possible. According to Hugel and Lerer,[45] the resulting metallo-organic compounds, which can be considered as complex substitution products of sodium methyl, react with aliphatic halides, especially

[39] Schramm, *Ann.*, **218**, 388 (1883).
[40] Gilman and Heck, *J. Am. Chem. Soc.*, **50**, 2223 (1928). A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 47.
[41] F. Whitmore, J. Stehman, and J. Herndon, *J. Am. Chem. Soc.*, **55**, 3807 (1933).
[42] F. Whitmore and Badertscher, *J. Am. Chem. Soc.*, **55**, 1561 (1933).
[43] J. Gardner and P. Borgstrom, *J. Am. Chem. Soc.*, **51**, 3377 (1929).
[44] D. Flood and G. Calingaert, *J. Am. Chem. Soc.*, **56**, 1211 (1934).
[45] G. Hugel and M. Lerer, *Compt. rend.*, **195**, 249 (1932).

with isoamyl and isobutyl chlorides. Their findings are contrary to earlier claims. Sodium chloride is split off in this reaction and disubstituted hydrocarbons are formed. Because of the peculiarity of the reaction, the experimental details are described briefly.

45 g. of sodium powder, 30 g. of naphthalene, and 160 g. of isobutyl chloride are dissolved in 1 liter of liquid ammonia. The ammonia is evaporated and the residue extracted exhaustively with benzene. Fractional distillation yields a little tetralin, 10 g. of unchanged naphthalene, and 1,4-diisobutylnaphthalene which boils at 170° to 175°C. at 16 mm.

The preparation of 9,10-diisoamyl-9,10-dihydroanthracene is given in more detail.

2 liters of dry ether, 60 g. of sodium powder, and 200 g. of anthracene (10% less than the theoretical amount) are placed in a 5 liter flask. The air is displaced by nitrogen and the tightly stoppered flask shaken mechanically for 48 hours. Then 239 g. of isoamyl chloride are added dropwise to the purple solution while a continuous stream of nitrogen is admitted. If the reaction tends to become too violent, the flask is cooled in ice water. When the mixture becomes colorless, a little water is added to convert the excess sodium to sodium hydroxide. The ethereal solution is concentrated by distillation and the oily residue diluted with a little petroleum ether to promote the crystallization of the unchanged anthracene. After several days the solution is filtered, the petroleum ether evaporated, and the residue fractionated in a cathodic vacuum. A little anthracene distils first, and then the dihydrodiisoamylanthracene as a viscous liquid at 134° to 138°C. The yield is 75% of the theoretical amount. Some diisoamylanthracene crystallizes from the last portion.

(b) Acetylene Ketones

The synthesis of acetylene ketones from sodium acetylides and acid chlorides follows a simple and clear course in accordance with the following scheme: $R \cdot C : CNa + X \cdot CO \cdot R' \rightarrow NaX + R \cdot C : C \cdot CO \cdot R'$. It may be varied at will within the limits of the availability of the sodium acetylides. The synthesis is especially useful in the aromatic series and gives the same products which are obtained by means of the Friedel-Crafts reaction from propiolic acid chlorides and aromatic compounds. The aromatic acetylenes and the corresponding propiolic acids are obtained from the same starting material; namely, from the corresponding cinnamic acid. However, phenylacetylene may be prepared much more easily and cheaply than phenylpropiolic acid (see page 327). Therefore, benzoylphenylacetylene is prepared more conveniently from sodium phenylacetylene and benzoyl chloride than from phenylpropiolyl chloride and benzene.

According to Nef,[46] phenylacetylene is dissolved in 5 to 10 parts of dry ether, and the solution is treated with the calculated amount of sodium wire in ether. Hydrogen is evolved at once, and a granular crust of phenylacetylene sodium forms at the surface of the sodium. The reaction is allowed to proceed with occasional shaking. The ether may be removed cautiously with exclusion of air, but this is not necessary for most acetylene ketone syntheses.

Hurd and Cohen [47] have reported a 74% yield of benzoylphenyl-acetylene from sodium phenylacetylene and benzoyl chloride.

Different melting points have been reported for benzoylphenyl-acetylene. Nef obtained crystals from the distillate which, after re-crystallization from petroleum ether (boiling at 40° to 60°C.), melted at 49° to 50°C. Hurd and Cohen observed a melting point of 53° to 55°C. which increased to 65° to 66°C. after several recrystallizations of the product from alcohol. A case of polymorphism apparently exists. Similar observations have been recorded several times in the acetylene ketone series. For example, Stockhausen and Gattermann,[48] as well as Staudinger and Kon,[49] obtained anisoylphenylacetylene by the action of aluminum chloride on a solution of phenylpropiolyl chloride and anisole in carbon disulfide. Stockhausen and Gattermann reported a melting point of 100°C. for the anisoylphenylacetylene, while Staudinger and Kon reported 90° to 91°C. Weygand and Bauer,[50] obtaining the same compound from sodium phenylacetylene and anisoyl chloride, found its melting point to be 91°C.

(c) Malonic and Acetoacetic Ester Syntheses

The reactions of alkali enolates with halides, known as the malonic ester and acetoacetic ester syntheses, are similar in course to the acetylene ketone syntheses. In a strict sense, however, the enolates cannot be designated as metallo-organic compounds. Several factors determine whether the group —C(ONa):C= reacts with alkyl halides and with acyl halides to form enol ethers and esters or hydrocarbon derivatives. Among the determining factors are the nature of the keto-enol, the solvent, and the nature of the acid substituent. In general, it is easier to obtain derivatives of the type —CO·C·R= than it is to obtain derivatives of the type —C(OR):C=.

There is an essential difference between the method used for alkylation and that used for acylation. This difference is based upon the comparative acidity of the keto-enol intermediates. Compounds formed by alkylation of keto-enols are usually less enolized and weaker acids than

[46] U. Nef, *Ann.*, **308**, 275 (1899).
[47] C. Hurd and F. Cohen, *J. Am. Chem. Soc.*, **53**, 1071 (1931).
[48] F. Stockhausen and L. Gattermann, *Ber.*, **25**, 3538 (1892).
[49] H. Staudinger and N. Kon, *Ann.*, **384**, 126 (1911).
[50] C. Weygand and E. Bauer, *Ann.*, **459**, 141 (1927).

the starting materials.   On the other hand, compounds formed by acylation of keto-enols are more acid than the starting materials.   This difference was first observed by Claisen.[51]   For instance, by starting with sodium benzoylacetone and benzoyl chloride, acetyldibenzoylmethane is formed; but being a stronger acid, it reacts with unchanged sodium benzoylacetone to liberate benzoylacetone and to change to its own sodium enolate.   The latter, in turn, reacts with benzoyl chloride, thus forming as the main reaction product the O-benzoyl derivative of the acetyldibenzoylmethane-enol.

To improve the yield as much as possible, Claisen added portions of measured amounts of sodium ethylate to the alcoholic solution of the keto-enol which was being acetylated.   He allowed the reaction to proceed with a portion of the acid chloride and continued in this fashion until the calculated amount was used up.   In this case, chosen as an example, the yield of acetyldibenzoylmethane was increased 5-fold.

Frequently, these conditions are complicated by changing acidity and tendency towards enolization.   During acylation of keto-enols the acidity always increases, but the tendency towards enolization does not necessarily do so.   If the tendency towards enolization does increase, the acylation becomes especially difficult; if it decreases, as in the case of the acetyldibenzoylmethane which is stable in the triketo form, the acylation takes place more easily.   In some instances, the somewhat tedious method described above can be replaced by simpler ones.   More will be said about these later.

The alkylation of keto-enols is usually carried out by mixing the alcoholic alkaline solution of keto-enol with the halide at a suitable temperature, without the previous isolation of the alkali compound.   The method is presumably well known; therefore, only a few samples are given.

Ethylmalonic ester is prepared according to Michael (see also Conrad and Bischoff [52]) in the following manner.

100 g. of diethyl malonate are added, with shaking or stirring, to 14.4 g. of sodium wire and 300 cc. of dry ether, and the mixture is heated under a reflux on a water bath until the last traces of sodium metal have disappeared.   To the cooled solution are added 100 g. of ethyl iodide.   After the reaction (which starts at once) has subsided, the mixture is heated on a water bath until it shows a neutral reaction.   It is cooled again, and shaken with water, then with dilute sodium carbonate solution, and finally dried.   On fractional distillation, 80 g. of a distillate are obtained between 209° and 213°C.; then 23 g. of a colorless oil distil at 213° to 215°C.   The product which is still impure is converted to the free acid, precipitated as the calcium salt, and reesterified.   Pure diethyl ethyl malonate boils at 92°C. at 10 mm., as has been found by Schey.[53]

[51] L. Claisen, *Ann.*, **277**, 196 (1893); **291**, 53 (1896).
[52] A. Michael, *J. prakt. Chem.*, **72**, 548 (1905); M. Conrad and C. Bischoff, *Ann.*, **204**, 134 (1880).
[53] C. Schey, *Rec. trav. chim.*, **16**, 357 (1897).

Conrad's method gives a mixture of mono- and diethylmalonic ester which can scarcely be separated by fractional distillation.   E. Fischer and Dilthey [54] stated that the dialkylmalonic esters obtained by Conrad's method are always contaminated by monoalkylmalonic esters.   The subsequent reaction determines whether this difficulty which is usually overlooked will cause trouble.   For example, in the preparation of pure n-caproic acid from n-butylmalonic ester a contamination of di-n-butylmalonic ester is of no particular consequence.   The pure acid is obtained readily by fractional distillation and saponification of the malonic esters. For the preparation of ethyl n-butyl malonate, directions can be found in *Organic Syntheses;* see also Adams and Marvel, and Bischoff.[55]

Levene and coworkers [56] give directions for the preparation of n-undecylmalonic acid which is the best starting material for the preparation of pure n-tridecanoic acid.

To a solution of 2.05 g. of sodium in 50 cc. of absolute alcohol are added 14.2 g. of diethyl malonate and 25 g. of undecyl iodide.   The mixture is heated under a reflux on a water bath for 3 hours.   The reaction mixture is poured into water, the aqueous solution extracted with ether, and the ether extract washed with water and dried.   On distillation *in vacuo* the undecylmalonic ester is obtained as a colorless oil boiling at 208° to 209°C. at 21 mm. (corrected).

The crude product which remains after the ether has been removed is used for the preparation of undecylmalonic acid.   It is saponified by heating with excess 50% sodium hydroxide solution.   The soap is washed twice with acetone, then decomposed with concentrated hydrochloric acid, and the free acid is filtered with suction.   After the filter cake has been washed with water, it is dissolved in acetone and the solution filtered.   The acetone is removed by distillation on a water bath and the residue is recrystallized first from benzene and then from a mixture of acetone and petroleum ether.   The melting point of pure undecylmalonic acid is 108.5°C.   The yield of pure ester is usually about 90% of the theoretical.

Undecylmalonic acid is converted smoothly into tridecanoic acid by distillation at ordinary pressure.   After recrystallization, the tridecanoic acid melts at 42°C.

Although diethylmalonic ester is of considerable practical importance as a starting material for the manufacture of veronal, scarcely any directions for its preparation or suggestions for its purification have been offered since Conrad and Bischoff's [57] directions.   Only Michael [58] states that his method for the preparation of ethylmalonic ester may also be used for diethylmalonic ester.   Conrad's directions follow.

[54] E. Fischer and A. Dilthey, *Ber.*, 35, 851 (1902).
[55] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*, Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 250.   R. Adams and C. S. Marvel, *J. Am. Chem. Soc.*, 42, 316 (1920).   Bischoff, *Ber.*, 28, 2622 (1895).
[56] P. A. Levene *et al.*, *J. Biol. Chem.*, 23, 73 (1915).
[57] M. Conrad and C. Bischoff, *Ann.*, 204, 134 (1880).
[58] A. Michael, *J. prakt. Chem.*, 72, 548 (1905).

A solution of 9.2 g. of sodium in 150 g. of alcohol is mixed with 32 g. of diethyl malonate and immediately afterwards with 80 g. of ethyl iodide. After the vigorous reaction has subsided, the alcohol is distilled on a water bath, and the residue cooled and diluted with water. The aqueous solution is extracted with ether, and the extract dried and fractionally distilled. 30 g. of diethylmalonic ester boiling at 222° to 224°C. are obtained.

Instead of both ethyl groups being introduced into the malonic ester in one operation, this may be accomplished in successive reactions. The possibility of introducing two alkyl radicals of the same kind in one operation is apparently limited to the malonic ester. Apparently acetoacetic ester and β-diketones can be substituted only in steps. The method became historically important, because Kiliani [59] synthesized methyl-n-butylacetic acid by successive introduction of the ethyl and butyl groups into acetoacetic ester and by cleavage of the product thus obtained. The synthetic compound proved identical with the homologous acetic acid obtained from fructose cyanohydrin. No new methods are involved in the introduction of two alkyl groups by two steps.

Alkylations which in general proceed very readily in the aliphatic series often necessitate changes when applied to the aromatic diketones. Dibenzoylmethane, for instance, can be methylated quite readily, whereas Bradley and Robinson [60] were not able to convert p-methoxydibenzoyl-methane to the methyl derivative. Weygand and Bischoff [61] found that potassium compounds of such aromatic diketones react readily with methyl iodide, whereas sodium compounds do not. They employed a modified methylation method which was first suggested by Weygand and Forkel [62] for benzoylacetone. In this method acetone instead of alcohol is used as solvent. The method resembles that first suggested by Michael for preparing alkyl malonic esters. The sodium and potassium enolates can be prepared readily from the ethereal solutions of the keto-enols by use of alkali metals.

According to E. Fischer and Bülow (see also Weygand),[63] benzoylacetone is dissolved in 6 times its weight of dry ether and the calculated amount of sodium wire is added. Sodium benzoylacetone is obtained as a fluffy, sulfur-yellow powder.

According to Weygand and Forkel,[64] methylbenzoylacetone is prepared by dissolving 3 g. of sodium benzoylacetone, which has been dried over phosphorus pentoxide, in 50 cc. of warm, dry acetone and boiling the solution under a reflux with 1.9 g. of methyl iodide for 4 hours. After removal of the acetone by distillation the residue is dissolved in ether, and the ethereal solution is washed with water, dried, and distilled fractionally. An 88% yield of methylbenzoylacetone, boiling at 130° to 134°C. at 11 mm., is obtained.

[59] H. Kiliani, Ber., 19, 221 (1886).
[60] W. Bradley and R. Robinson, J. Chem. Soc., 1926, 2356.
[61] C. Weygand and C. Bischoff, Ber., 61, 689 (1928).
[62] C. Weygand and H. Forkel, Ber., 61, 688 (1928).
[63] E. Fischer and C. Bülow, Ber., 18, 2133 (1885); C. Weygand, J. prakt. Chem., 116, 297 (1927).
[64] C. Weygand and H. Forkel, Ber., 61, 688 (1928).

Dieckmann [65] found that methylbenzoylacetone when prepared in alcoholic solution is always contaminated with unchanged benzoylacetone which is difficult to separate.

A variety of radicals can be introduced into the reactive methylene groups of the keto-enols. Halogenated ketones and carboxylic acid esters and other similar compounds usually react as readily as the alkyl halides.

That the introduction of alkyl groups causes complications has already been mentioned briefly above. As an example of Claisen's method, directions are given below for the preparation of benzoylacetoacetic ester. The latter may be saponified to give acetophenone. The reaction sequence, benzoyl chloride → benzoylacetoacetic ester → benzoylacetic ester → acetophenone, typifies in its end effect the exchange of the halogen in an acid chloride for the methyl group. The method is tedious and not very productive but it represents a ketone synthesis which never fails.

According to Claisen,[66] 35.4 g. of sodium are dissolved in alcohol to make a total volume of 600 cc. 300 cc. of this solution are mixed in the cold with 100 g. of acetoacetic ester. To the cooled (5°C.) mixture are added, dropwise with continuous stirring, 45 cc. of benzoyl chloride, the temperature not being allowed to exceed 10°C. The mixture is allowed to stand for 30 minutes and then half of the remaining ethylate solution (150 cc.) is added in one portion and then, slowly, 22.5 cc. of benzoyl chloride. After a short interval the alternate addition of the ethylate solution and of the benzoyl chloride is repeated with half the amount added previously. This method of addition is continued until both solutions have been added. Meanwhile, a mixture of sodium chloride and sodium benzoylacetoacetic ester separates from the alcoholic solution. Having stood in the cold for 12 hours longer, the mixture is filtered, and the filter cake washed with ether. An additional small quantity of sodium enolate is precipitated from the filtrate by the ether washing and is added to the main portion. The crude sodium enolate is dried for a short time and dissolved in 3 times its weight of water. This solution is treated with acetic acid and cooled with ice until the precipitation of the oily compound is complete. The oil is dissolved in ether, and the solution dried over calcium chloride, filtered, and distilled fractionally *in vacuo* at 175° to 176°C. at 12 mm.

For conversion into ethylbenzoyl acetate, the oil which remains after the removal of the ether by distillation is used directly; see page 465. The yield of sodium salt is about 90% of the theoretical amount.

As has been mentioned above briefly, the benzoylation of the benzoylacetone can be carried out in a similar manner. The acetyldibenzoylmethane thus obtained can be prepared more conveniently by another method also proposed by Claisen. This method may be used for the benzoylation of the malonic and acetoacetic esters also, but the yields in the last two instances are poor. According to this method, a mixture of benzoyl chloride and benzoylacetophenone is treated with dry sodium carbonate in boiling ether.

[65] W. Dieckmann, *Ber.*, **55**, 2470 (1922).
[66] L. Claisen, *Ann.*, **291**, 67 (1896).

For example, 16.2 g. of benzoylacetone and 14 g. of benzoyl chloride are dissolved in 100 cc. of dry ether. After the addition of 32 g. of finely powdered dry sodium carbonate the mixture is allowed to stand, with the exclusion of moisture, in a flask equipped with a reflux condenser. The ether starts to boil after a short time, and the reaction mixture is allowed to stand for 16 hours at room temperature. The mixture of sodium chloride, sodium carbonate, and enolate is filtered off and washed with a little ether. The cake, still moist with ether, is dissolved in water, the ether blown out with air, and the acetyl-dibenzoylmethane precipitated with acetic acid. 10 g. of a pure product are obtained. An additional amount of the enolate may be extracted from the ethereal mother liquor and washings with a 10% solution of sodium carbonate. The total yield can be increased to 14 g. (87% of the theoretical amount).

The melting point of the pure acetyldibenzoylmethane (110°C.) depends on several conditions, such as alkalinity of the glass, keto-enol tautomerism, and polymorphism; see Dieckmann and Weygand.[67]

Weygand's method, described above, may also be used for acylation. Tribenzoylmethane can readily be obtained in a 45% yield from sodium dibenzoylmethane and benzoyl chloride in acetone. Claisen's [68] method which gives a similar yield is much more elaborate; see also Weygand.[69]

The principle of the acetoacetic ester synthesis is not confined to the keto-enols proper. Alkyl groups can be introduced into all ketones if they can be forced to form enols. According to Nef,[70] acetophenone can be methylated very readily once, twice, or even three times by heating with methyl iodide and potassium hydroxide in a sealed tube.

20 g. of acetophenone are heated with 30 g. of methyl iodide and 36 g. of pulverized potassium hydroxide in a sealed tube to 100°C. On distillation, 18.9 g. of a fraction which consists essentially of ethyl phenyl ketone boils at 95° to 107°C. and 15 mm. By repeated similar treatment isopropyl phenyl ketone is obtained, boiling at 215° to 218°C., and finally trimethylacetophenone, boiling at 219° to 221°C.

Haller and Bauer [71] converted fatty aromatic ketones to enolates as follows: In a flask equipped with a reflux condenser and with a mercury seal to exclude the air the ketone is dissolved in dry benzene and the calculated amount of finely powdered sodium amide is added. The mixture is heated to boiling on a water bath; ammonia is evolved and an almost clear brown, very hygroscopic solution is formed. The reaction requires 30 minutes to 3 hours, depending on the conditions. At the end of this reaction an alkali bromide or iodide is added; sodium halide separates and the alkylation product can be isolated in the usual manner.

Mixtures of alkylation products are generally obtained by Nef's simple method which is particularly good for the complete alkylation of

[67] W. Dieckmann, *Ber.*, 49, 2203 (1916); C. Weygand. *Z. anorg. allgem. Chem.*, 205, 414 (1932).
[68] L. Claisen, *Ann.*, 291, 67 (1896).
[69] C. Weygand, *Ber.*, 61, 688 (1928).
[70] U. Nef, *Ann.*, 310, 316 (1900).
[71] A. Haller and E. Bauer, *Compt. rend.*, 148, 70 (1909).

all hydrogen atoms that can be substituted. Haller and Bauer's method is preferable if single radicals, or different ones, in succession are to be introduced.

The methylene group is activated not only by adjacent carbonyl groups, but also by double bonds. Thus, cyclopentadiene treated with alkali metals quite readily yields substitution products of the formula

$$\begin{array}{c} CH=CH \\ \diagdown \\ \diagup \quad CHNa \\ CH=CH \end{array}$$
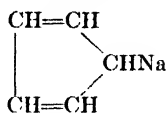
Henrich [72] found that a CH_2 group between a double bond and a carbethoxy group shows no essentially different behavior from the active methylene group in acetoacetic ester. An ordinary CH_2 group adjacent to two double bonds, however, is inactive if the ring tension is not present as a further activating factor.

Diethyl glutaconate, $C_2H_5OOC \cdot CH:CH \cdot CH_2 \cdot COOC_2H_5$, reacts quite vigorously, even in the cold, with methyl iodide and sodium alcoholate. In principle, therefore, this is the same reaction as that shown by malonic ester. For an important feature of this observation made by Henrich, see page 413.

(d) Ketone Syntheses with Grignard Compounds

One reaction in which the Grignard method generally fails is that of organo-magnesium compounds with acid halides. Gilman and Mayhue [73] point out that the yields of ketones by this reaction are usually unsatisfactory except in cases (possibly because of steric hindrance) in which the subsequent reaction which causes the formation of tertiary alcohols is avoided.

Until recently the synthesis of ketones from acid chlorides was therefore reserved for pure organo-metallic compounds. Gilman and Mayhue, however, discovered that by a simple change in the usual procedure satisfactory results can be obtained. If the second reaction component is not added to the Grignard solution as is the usual practice, but, instead, if the Grignard solution is added to the acid chloride, an excess of the organo-magnesium compound is never present. The subsequent reaction is eliminated because the Grignard compound reacts more readily with the unchanged acid chloride than with the ketone formed.

The solution of 14 g. of benzoyl chloride (0.1 mole) in 15 cc. of ether is placed in a 3-necked flask equipped with a stirrer, reflux condenser, and a valve to prevent the entrance of air. An ethereal solution of 0.1 mole of phenylmagnesium bromide is added with stirring, but without cooling, as fast as the boiling ether permits. The reaction

[72] F. Henrich, *Ber.*, 31, 2103 (1898).
[73] H. Gilman and M. Mayhue, *Rec. trav. chim.*, 51, 47 (1932).

mixture is treated with ice and hydrochloric acid and then distilled with steam until all benzoic acid has been removed. Benzophenone remains as an oil which is dissolved in petroleum ether. The solution is dried over sodium sulfate and distilled fractionally. The yield of benzophenone is 55% of the theoretical. When phenylmagnesium iodide is used, the yield is 68.5% and with phenylmagnesium chloride it is 48%. Triphenyl-carbinol is the chief by-product.

It is remarkable that the yields do not depend on whether the components are added rapidly or slowly, and whether cooling is applied or not. With a 5-fold amount the method is just as successful.

An interesting application of this method is the synthesis of aliphatic carboxylic acid with branched chains by Fordyce and Johnson.[74] They accomplished this by the reaction of dicarboxylic acid monoester chlorides with isoalkyl magnesium bromides; esters of acids with branched chains are formed. They can be converted into the saturated carboxylic acids by reduction with zinc and hydrochloric acid according to the method of Clemmensen. The ester chlorides may be replaced by the acid dichlorides.

A solution of 0.11 mole of isohexylmagnesium bromide is added dropwise with stirring to an ethereal solution of 31 g. of sebacyl chloride. The temperature is kept between 25° and 26°C. and the addition is completed in 1 hour. Thus, 7.4 g. of 10-ketoisopalmitic acid are obtained. This is a yield of 24% of the theoretical. The small yield is fairly satisfactory inasmuch as a lengthening of the chain by 10 carbon atoms takes place during the reaction with sebacyl chloride. 4 g. of the keto acid yield 3 g. of palmitic acid in the customary manner; that is, about 79% of the theoretical amount. For details the original paper must be consulted.

Komppa and Rohrmann [75] have reported investigations on the reaction of anhydrides of dibasic acids with organo-magnesium compounds. Glutaric anhydride and methylmagnesium iodide supposedly give the following four compounds:

$$CH_2 \cdot CO \cdot CH_3 \qquad CH_2 \cdot C(OH) : (CH_3)_2 \qquad CH : C(CH_3)_2 \qquad CH_2 \cdot C : (CH_3)_2$$
$$| \qquad\qquad\qquad | \qquad\qquad\qquad\qquad | \qquad\qquad\qquad | \;\;O$$
$$CH_2 \qquad\qquad\quad CH_2 \qquad\qquad\qquad\quad CH_2 \qquad\qquad\; CH_2 \;|$$
$$| \qquad\qquad\qquad | \qquad\qquad\qquad\qquad | \qquad\qquad\qquad |$$
$$CH_2 \cdot COOH \qquad\; CH_2 \cdot COOH \qquad\qquad CH_2 \cdot COOH \qquad CH_2 \cdot CO$$
$$\text{(I)} \qquad\qquad\qquad \text{(II)} \qquad\qquad\qquad\qquad \text{(III)} \qquad\qquad\quad \text{(IV)}$$
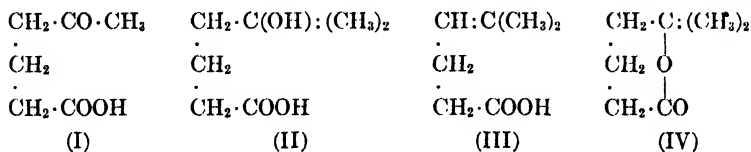
By the reaction of 1 mole of methylmagnesium iodide (I) is the chief product formed if conditions are suitable; with 2 moles of methylmagnesium iodide (IV) is obtained for the most part. Still larger amounts of the magnesium compound yield (III). Details may be found in the original paper.

[74] C. R. Fordyce and J. Johnson, *J. Am. Chem. Soc.*, **55**, 3368 (1933).
[75] G. Komppa and W. Rohrmann, *Ann.*, **509**, 259 (1934).

(e) Nitrile Syntheses

Only aliphatic compounds with halogen attached to saturated carbon atoms can undergo this reaction directly. This simple method usually consists of heating a combined solution of potassium cyanide and halide. Side reactions seldom occur.

Since the reaction is especially important in securing higher members of the aliphatic series, the preparation of tridecanonitrile from dodecyl bromide and potassium cyanide may be cited as an example. Details for the method are given in *Organic Syntheses*.[76] The method describes the conversion of the nitrile to the acid without isolation.

Margaronitrile is obtained, according to Braun and Sobecki,[77] by boiling under a reflux for 6 hours, a mixture of 23.4 g. of cetyl bromide, 15 g. of potassium cyanide, and 120 cc. of 70% alcohol. After the alcohol has been removed by distillation, the residue is dissolved in ether, and the solution is washed with water, dried with potassium carbonate, and distilled fractionally. 13 g. of margaronitrile, boiling at 199° to 200.5°C. at 13 mm., are obtained. This corresponds to a yield of 68% of the theoretical amount.

According to *Organic Syntheses*, potassium cyanide is distinctly superior to sodium cyanide in such cases. Otherwise the cheaper sodium cyanide may be used with the same result. For the preparation of trimethylene cyanide, according to *Organic Syntheses*,[78] sodium cyanide is used.

Alkali cyanide is sometimes replaced advantageously by cuprous cyanide. Although allyl cyanide may be prepared with potassium cyanide, according to Pomeranz,[79] the yields are much better when the directions as given in *Organic Syntheses* are followed. These directions are based on the method of Bruylants.[80] Instead of the allyl bromide given in these directions, Breckpot [81] used allyl chloride and obtained excellent results.

In other cases, the difference in reactivity of chlorine and bromine is so great that, according to Gabriel,[82] γ-chlorobutyronitrile, $CN \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot Cl$, can be obtained almost exclusively from 1-chloro-3-bromo-propane, $Cl \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot Br$, by using a little less than the calculated amount of potassium cyanide in alcoholic aqueous solution.

[76] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 292.
[77] v. Braun and Sobecki, *Ber.*, 44, 1472 (1911).
[78] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 536.
[79] Pomeranz, *Ann.*, 351, 357 (1907).
[80] Bruylants, *Bull. soc. chim. Belg.*, 31, 175 (1922).
[81] Breckpot, *Bull. soc. chim. Belg.*, 39, 465 (1930).
[82] Gabriel, *Ber.*, 23, 1771 (1890); 42, 1252, foot-note (1909).

(f) Grignard Syntheses with Oxygen- and Nitrogen-Containing Components

General Remarks on Preparation of Grignard Solutions. Most Grignard reactions are carried out with diethyl ether. In a few cases dibutyl or diisoamyl ether is used as solvent.

The rôle of the ethers in the Grignard reactions is not one of a solvent alone. The ether also acts as a specific reaction promoter. In other media such as benzene or ligroin, the reaction takes place with much greater difficulty, if at all. But the reaction can be forced by the addition of small amounts of tertiary amines. They act as the nitrogen analogues of the ethers.

Although the handling of small amounts of magnesium-organic compounds in ethereal solution presents no difficulties, one must remember that larger proportions may be a great source of danger if treated carelessly. In a Grignard synthesis the addition of water to a batch of material which may have reacted partially is as serious as pouring water into concentrated sulfuric acid.

In the preparation of a Grignard solution metallic magnesium is always used, ether almost always, and then an organic halide.

1. Magnesium—The chemical trade of today is able to furnish magnesium metal suitable for Grignard reactions more cheaply and of better quality than can be prepared in the laboratory from magnesium ribbon. In almost all cases it is unnecessary to purify the commercial product. It is stored dry and may be, if necessary, washed by decantation with pure dry ether in the reaction flask itself. The other metals present in the magnesium remain as a dark powder after the reaction and do not disturb the reaction. In general, magnesium turnings which can be obtained in different sizes are preferred. In some cases, however, magnesium powder of definite grain size may offer advantages.

The amount of magnesium is usually equivalent to that of the halide. Occasionally the metal is used in excess.

Magnesium is covered with a layer of hydroxide which, at first, prevents attack at the surface. If the reaction liquid is not absolutely anhydrous, this protective coating may be regenerated. To start the reaction several expedients are used; see page 370.

2. Ether—The ether used for Grignard reactions must be free from water and alcohol. To make certain of this, the ether is allowed to stand a rather long time over sodium wire.

Isoamyl ether is advantageously redistilled repeatedly over sodium.

3. Organic Halides—It is customary to use bromides for Grignard reactions. They have the advantage of reacting more readily than chlorides with magnesium, but in some cases chlorides give considerably better yields. The iodides which react still more vigorously are seldom used.

Because of its higher boiling point, methyl iodide is frequently more convenient to use than the methyl bromide. Heterocyclic iodides, such as 2-iodothiophene, are sometimes more easily available than other halides. For high molecular chains in which the additional cost of the iodine is of minor importance the iodides are to be preferred occasionally because of their higher reactivity.

Reagents of the highest possible degree of purity are absolutely essential. They must be especially free from acids, water, and alcohol.

Properties of Grignard Solutions. Ethereal solutions of magnesium-organic compounds are sensitive to moisture, carbon dioxide, and oxygen. This is readily understandable because often, according to W. Schlenk and W. Schlenk, Jr.,[83] not only the mixed compounds of the type RMgHI must be assumed to be present in the solutions, but also, in an equilibrium with them and with the magnesium halide, pure metallo-organic compounds of the type MgR_2.

A calcium chloride tube usually provides enough protection for simple operations of short duration. It is advisable to add a soda-lime tube as a device for absorbing carbon dioxide.

The entrance of atmospheric oxygen is seldom prevented. In certain experiments it is advantageous, at least at the beginning, to displace the air with nitrogen and to provide mercury seals. During prolonged reactions the ether boiling under a reflux cannot always be completely condensed. This difficulty becomes an advantage, because the ether vapor keeps the entrance of air within tolerable limits; see also page 373.

Because of the greater surface of metal the heterogeneous reaction with the metallic magnesium is more vigorous at the start than towards the end when the surface is reduced. Three phases can be noted in every operation of this kind:

1. The start of the reaction, when heat is applied under some conditions.

2. The main phase which proceeds with evolution of heat. The heat is dissipated partly by the walls of the flask, partly by the reflux condenser. In order to shorten the reaction time, that is to speed up the addition of the halide, the condenser is frequently assisted by external cooling of the reaction flask.

3. The end-reaction. Because of the low concentration of the halide in the solution and because of the small surface of the magnesium metal during this phase external heat must be applied frequently.

The real art in handling a Grignard reaction consists in carrying out the process with the maximum speed compatible with safety under the conditions required for the reaction.

[83] W. Schlenk and W. Schlenk, Jr., *Ber.*, 62, 920 (1929).

Start of Grignard Reaction. It is always practical to start the reaction artificially. To do this a certain minimum concentration of halide in the solution is necessary to avoid too long a waiting period. The concentration required varies from case to case. In small batches a relatively large portion of the halide may frequently be added at the start.

In larger batches, however, this practice may be very dangerous. The reaction velocity may increase rapidly and the ether may boil so violently that the evolution of heat can no longer be controlled. The general procedure in such cases is as follows:

The magnesium is just covered with ether; a small crystal of iodine is added and then a small amount of the halide. The start of the reaction is awaited patiently. The ether may be brought to a gentle boil by heating on a water bath. The start of the reaction can be recognized after a little experience by the spontaneous boiling of the ether and by the appearance of the metal splinters. Additional amounts of halide in ether are then added very gradually. If the boiling becomes too violent, the addition must be stopped at once. This is especially true at the beginning, because a further increase in the speed of reaction has to be expected from the exposure of new metal surfaces. At this point the reaction flask is frequently cooled in ice water or merely with cold water in order that the halide solution may be added faster than without this cooling. After a short time the cooling may be stopped temporarily, or even permanently. The end-reaction has to be speeded by heating on a water bath. The end of the reaction may be assumed to have been reached after the elapse of an average reaction time. In dubious cases this time can be ascertained by preliminary experiments. In most cases the amount of unchanged metal gives an approximate indication.

As an aid, the stirring of the reaction mixture may be considered. If this operation is to be successful, a suitable stirring device must be provided. Good results are obtained with a stirrer designed by Hershberg.[84]

Reaction with Grignard Solution. Generally the preparation of the Grignard solution is immediately followed by further reaction with a third compound. This subsequent reaction does not always proceed at once to the point shown in the general scheme. Ethylene oxide, for instance, apparently first yields an oxonium compound with aliphatic organomagnesium compounds; see *Organic Syntheses*.[85]

The Grignard solution has to be brought to a suitable temperature; in most cases cooling is necessary. An optimum temperature must also be maintained throughout the reaction. Therefore, it is advantageous to insert a thermometer at the beginning.

[84] Hershberg, *Ind. Eng. Chem., Anal. Ed.,* 8, 813 (1936).
[85] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 308.

Whereas the Grignard solution proper is usually homogeneous, solid precipitates may appear during the subsequent reaction.   This possibility must be taken into consideration if the new reagent (carbon dioxide, ethylene oxide, formaldehyde, and others) is admitted in gaseous form. To avoid plugging the tubes it is preferable to pass the gas directly onto the surface rather than into the solution.

Heating is frequently necessary to complete the reaction.   The end of the reaction can be recognized by the absence of organo-magnesium compounds in the solution, or by other means.   Gilman, Schulze, and Heck [86] have described a generally useful color reaction for Grignard compounds.

Decomposition of Reaction Products.   The last operation in a Grignard synthesis is the decomposition of the primary reaction product.   This phase of the reaction is always exothermic.   Careless technique not only imperils the success of the experiment, but may be dangerous.

Hydrochloric acid, sulfuric acid, and ammonium chloride may be considered as hydrolyzing agents.   Water yields magnesium hydroxide which increases the difficulty of working up the reaction mixture.

If the reaction mixture can be removed readily from the reaction flask, it is best poured onto ice.   The suitable acid is then added in proper concentration, more ice being added if necessary.   If polymerizations or óther undesirable reactions are expected because of the use of acid, ammonium chloride solution is employed.

The hydrolyzing agents must be added to the flask if the reaction mixture cannot be removed because of its consistency.   A quick dilution and cooling should always be provided by the addition of abundant ice and water lest local superheating cause evaporation of the ether, losses, and fires.

General directions cannot be given for the final isolation of the product.

Special Measures.   Some halides react with magnesium only after a long period.   Occasionally no reaction occurs without the assistance of special activators.

The activating effect of iodine has already been mentioned.   It is more advantageous to add one or more crystals of iodine than to add an ethereal solution.   Under such circumstances stirring should be avoided.

The replacement of iodine by bromine offers no advantages.   Grignard reactions which start very slowly, as with tertiary and certain aromatic halides, cannot be made to start even in this manner.

Baeyer [87] suggests starting such reactions by means of activated magnesium.   10 g. of magnesium filings are heated over a free flame in a

[86] Gilman, Schulze, and Heck, *J. Am. Chem. Soc.*, 47, 2002 (1925); 52, 4949 (1930).
[87] A. v. Baeyer, *Ber.*, 38, 2759 (1905).

long necked flask of 150 cc. capacity. Then one-half the amount of iodine is added while the flask is rotated. One portion must be used up before the next is added. The temperature is raised as high as possible without melting the magnesium. After 15 to 30 minutes there is obtained a dull gray powder which must be carefully protected from moisture.

Gilman, Peterson, and Schulze [88] recently activated a magnesium-copper alloy with iodine and found this product superior not only to Baeyer's but to all others as well.

The magnesium alloy (12.75% copper) is used as a powder passing through a 100 to 200 mesh screen. 5 g. of this powder are mixed with 1 g. of iodine in a mortar and the mixture is placed in a long necked 200 cc. Pyrex flask which is provided with a 2-hole rubber stopper holding a thermometer (360°C.) and an open glass tube. The flask is evacuated to 3 mm. pressure with an oil pump and then heated with shaking to 300°C. over a free flame. All of the iodine disappears within 8 to 10 minutes. A sublimate which might be deposited in the neck is dislodged back into the flask. The powder which must not be allowed to melt is a granular mass. After cooling, the powder is exposed to the air for 15 to 20 minutes to decrease its reactivity and then stored in sealed containers.

To use the activated material for starting a Grignard reaction, the necessary amount (usually 0.25 g.) is heated in a test-tube over a burner until the flame shows a yellow coloration from sodium, or in a Pyrex tube until fumes are no longer noticeable. The powder is then added, while still warm, to the previously prepared small amount of halide solution in ether. This solution must contain the halide in a 15 to 20% concentration. Lower or higher concentrations are unsuitable. As soon as the vigorous reaction which lasts about 1 minute has subsided, the reaction mixture is poured into the reaction flask which already contains all of the necessary amount of magnesium and some halide. From this point the usual procedure is observed.

Another method of activation consists of adding a small amount of a different simple Grignard solution to the mixture of ether, magnesium, and halide. The Grignard solution is prepared from a halide such as ethyl bromide which in the subsequent reaction yields only easily separable by-products. After the reaction of the simple Grignard solution has subsided, this solution is added to the main reaction mixture.

A homogeneous solution of the organo-magnesium compounds is not always obtained in ether. High molecular compounds separate as oils or even solids. In the first case, enough of a solvent like benzene is added to the warm mixture to give a homogeneous solution. Once Grignard

[88] Gilman, Peterson, and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

compounds have solidified, they can be redissolved only with difficulty and are troublesome to work up.

In every Grignard reaction the following metallo-organic synthesis is a possibility:

$$R \cdot HI + HIMgR \longrightarrow R \cdot R + MgHI_2$$
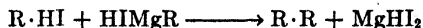
Experience shows that the more vigorously the reaction proceeds the more this undesirable side reaction occurs. This occurrence is not easily understandable at first glance. However, in experiments made with bromobenzene under such conditions, considerable amounts of biphenyl are found. Biphenyl is present even in very gentle reactions and can be detected in the end-product by its distinct odor.

Another difficulty which occurs occasionally requires similar precaution. Under some conditions the reaction stops at an intermediate stage (see above, page 370) and has to be completed by raising the temperature. To do this, a part of the ether is removed by distillation and the rise in temperature of the residue is noted. In practice the ether removed by distillation is replaced by a higher boiling, inert solvent and the desired reaction is brought to completion under a reflux at a suitable temperature. General directions cannot be given.

The same expedient is employed if the end-reaction takes place at a higher temperature.

Gilman and Hewlett [89] have described an apparatus for the performance of Grignard reactions with exclusion of atmospheric oxygen. This apparatus can be used for other types of reactions also (see Fig. 10).
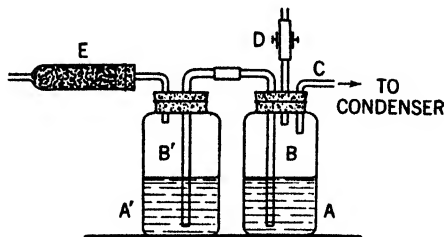
FIG. 10. —Liquid seal according to Gilman.

A and A' are two wide mouthed bottles in which tubes B and B' almost touch the bottom. The bent tube C is connected with the top opening of the reflux condenser by means of a rubber tubing. An ordinary glass cock or a piece of rubber tubing with a pinch clamp is provided at D. Tube E is filled with a mixture of calcium chloride and soda-lime and has a side tube to equalize any vacuum caused by a sudden cooling

[89] H. Gilman and P. Hewlett, *Rec. trav. chim.*, **48**, 1124 (1929).

of the reaction flask. Without this outlet mercury from the receptacle of the stirrer might be drawn in.

The apparatus is operated as follows: Bottle A is filled with an inert oil of low vapor pressure (paraffin oil). Flask A' is empty. After the connection with the reaction flask has been made, the cock at D is opened and the flask swept with an inert gas. After D has been closed, pressure of the gas displaces the oil from A to A'. By this means a small pressure is built up in the reaction flask. This pressure has to be taken into consideration when the liquids are added to the reaction mixture from dropping funnels. In such cases slight suction is applied at E. Since the sealing liquid is somewhat viscous, the tubes B and B' must have a diameter of at least 10 to 15 mm. The amount of ether absorbed by the oil after a short time is of no consequence. The capacity of each of the two bottles, A and A', ought to be at least twice that of the free reaction space; that is, twice the combined volume of the free flask and reflux condenser. The authors used two 1 liter bottles in connection with a 1 liter reaction flask half-full of reaction liquid. The height of the mercury column in the stirrer seal is best adapted to the length of the tubes B and B'. The bell of the seal is inserted into the mercury container to at least one-fifth of the maximum height of the oil column in the tubes B and B'. If the reaction flask contains much liquid, the sweeping of the reaction space with an inert gas may be omitted, because the Grignard solution uses up the oxygen and leaves an inert nitrogen atmosphere.

Once the apparatus has been put into operation no further attention is necessary. If heating under a reflux requires a long time, the boiling may be stopped overnight if necessary. The oil returns from A' to A at the same rate the flask is cooled but the sealing liquid can never reach the reaction mixture if the capacities of the bottles are sufficiently large.

Gilman [90] studied methods for determining the concentration of Grignard solutions. The following methods have been proposed: (1) titration with iodine, (2) gravimetric analysis, (3) gas analysis, (4) acid titration. The last is the most convenient for preparative purposes. The method of gas analysis resembles that of Zerevitinov. The acid titration method may be carried out in the following manner.

An aliquot part of the Grignard solution, about 20 cc., is measured accurately to within 0.1 cc. in a graduate cylinder and poured slowly into a 400 cc. Erlenmeyer beaker containing 50 cc. of distilled water. The graduate is washed first with a few cubic centimeters of standardized sulfuric acid, about 0.25 N, then repeatedly with distilled water; the wash liquids are all added to the Erlenmeyer beaker. After the addition of about 20 cc. of sulfuric acid, which must be an excess, the mixture is

[90] H. Gilman, *J. Am. Chem. Soc.*, **45**, 150 (1923).

heated on a hot-plate to complete the reaction.   The beaker is cooled and the excess sulfuric acid is back-titrated with sodium hydroxide, methyl orange being used as an indicator.   The calculation is made according to the basic equation, $2R \cdot MgX + H_2SO_4 \rightarrow 2R \cdot H + MgSO_4 + MgX_2$. The values obtained are usually a little too high, but for the most part the errors fall within the accuracy required for preparative purposes.

(g) Examples for Synthesis of Alcohols, Aldehydes, and Carboxylic Acids by the Grignard Method

1. Grignard Compounds and Carbonyl Compounds.   The basic reaction scheme for this group is

$$\begin{array}{c} R' \\ \diagdown \\ C{:}O + XMgR''' \longrightarrow R'R''R'''C \cdot OMgX \longrightarrow R'R''R'''C \cdot OH \\ \diagup \\ R'' \end{array}$$
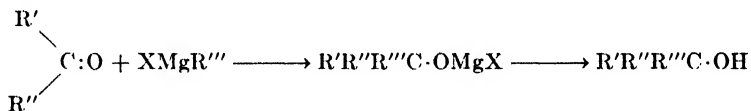
R' and R'' may both be hydrocarbon radicals, but one or even both of them may also be hydrogen atoms.   Ketones, aldehydes, and especially formaldehyde may be changed by Grignard compounds to yield tertiary, secondary, or primary alcohols.

Complications during these reactions are unusual and the yields are satisfactory.   Formaldehyde was frequently used formerly in the form of the solid polymerization products, trioxymethylene, or paraformaldehyde.   They dissolve partly in ether as the monomer and are gradually used up completely in this way.   Buelens [91] recommends facilitating the depolymerization by the addition of a little fused zinc chloride.   However, in many instances better yields are obtained by admitting gaseous formaldehyde obtained from paraformaldehyde by heating to about 200°C.   Under some circumstances excess formaldehyde may promote the formation of acetals.   In the event that they do form, these can be hydrolyzed easily by dilute acids.   Examples for the preparation of tertiary alcohols may be found in elementary textbooks.

The preparation of secondary alcohols from aldehydes is straightforward.   However, the preparation of primary alcohols by means of formaldehyde merits description.   According to the older method of Grignard and Tissier, [92] commercial trioxymethylene is used.   The reaction mixture is boiled for a rather long time, sometimes for several days. Yields are unsatisfactory.   Ziegler [93] describes a more rapid method of preparation in which gaseous formaldehyde generated by heating trioxymethylene is used.   About twice the theoretical amount of trioxymethyl-

[91] A. Buelens, *Rec. trav. chim.*, **28**, 119 (1909).
[92] Grignard and Tissier, *Compt. rend.*, **134**, 107 (1902).
[93] K. Ziegler, *Ber.*, **54**, 737 (1921); **55**, 3408 (1922).

ene is used to compensate for losses from the reverse polymerization. According to Ziegler and Tiemann,[94] the vapors are delivered through a glass tube of 2 to 3 cm. diameter, which is provided with an opening through which is inserted a glass rod in a rubber seal to remove solid, polymerized formaldehyde.

In the preparation of α-naphthylcarbinol, Ziegler [95] adds 3 g. of ethyl iodide to 8 g. of magnesium turnings suspended in 30 cc. of ether. While this mixture is still reacting, a solution of 64 g. of α-bromonaphthalene in 150 cc. of ether is added to it. After 30 minutes the main reaction is completed. The mixture is heated for 15 minutes longer, until the magnesium, except for small residues, has dissolved. Formaldehyde generated from 25 g. of trioxymethylene is admitted. After the usual isolation 28 g. of α-naphthylcarbinol boiling at 162° to 163°C. at 11 mm. are obtained. This corresponds to a yield of 58% of the theoretical amount. The melting point, after recrystallization from benzene-petroleum ether, is 59.5° to 60°C.

Observations have been made that the use of monomeric formaldehyde is to be recommended for the preparation of aliphatic alcohols by this method. On the other hand, Bourgom [96] has pointed out that the reaction time can be shortened and the yields increased by using methylal in the place of ether. The conversion of n-butylmagnesium bromide to n-amyl alcohol gives a yield of 70%. Diamyl acetal of formaldehyde is formed as an intermediate.

Paraformaldehyde cannot be used for Grignard syntheses in the same way as trioxymethylene. It is depolymerized by distillation with 5% sulfuric acid shortly before use.

Kohler [97] has elucidated the reaction of Grignard compounds with unsaturated ketones. In the reaction of benzalacetophenone with phenylmagnesium bromide, diphenylstyrylcarbinol, $(C_6H_5)_2C:CH\cdot CHOH\cdot C_6H_5$, is not formed, as was supposed at first. Instead, the ω,ω-diphenylpropiophenone, $(C_6H_5)_2CH\cdot CH_2\cdot CO\cdot C_6H_5$, is formed by addition of the conjugated system in the 1,4 position. Therefore, benzalacetophenone always reacts with only 1 mole of phenylmagnesium bromide. Kohler [98] has described the preparation of diphenylpropiophenone.

54 g. of benzalacetophenone are added slowly to a Grignard solution prepared as usual from 12 g. of magnesium and 80 g. of bromobenzene in 750 cc. of ether. The mixture thus prepared is poured into cold dilute sulfuric acid. Diphenylpropiophenone separates in a 90% yield. The product can be purified by recrystallization from alcohol in colorless needles melting at 96°C.

Diphenylpropiophenone reacts further with a phenylmagnesium bromide solution in a normal way, according to Kohler,[99] forming $\alpha,\alpha,\gamma,\gamma$-

[94] K. Ziegler and P. Tiemann, *Ber.*, **55**, 3409 (1922).
[95] K. Ziegler, *Ber.*, **54**, 739 (1921).
[96] A. Bourgom, *Bull. soc. chim. Belg.*, **33**, 101 (1924); *Chem. Abstracts*, **18**, 1814 (1924).
[97] E. P. Kohler, *Am. Chem. J.*, **31**, 642 (1904).
[98] E. P. Kohler, *Am. Chem. J.*, **29**, 352 (1902).
[99] E. P. Kohler, *Am. Chem. J.*, **31**, 651 (1904).

tetraphenylpropyl alcohol, $(C_6H_5)_2CH \cdot CH_2 \cdot COH(C_6H_5)_2$, which after recrystallization from ligroin melts at 96°C. Although this melting point corresponds with that of the starting material, a mixed melting point depression of 20°C. occurs when the product of crystallization is combined with the starting material.

2. Grignard Compounds and Esters. The basic scheme of this group is

$$R' \cdot C \overset{OC_2H_5}{\underset{O}{\diagdown}} + 2XMg \cdot R'' \longrightarrow R'R''C \cdot OMgX \longrightarrow R'R_2''COH$$

or

$$HC \overset{OC_2H_5}{\underset{O}{\diagdown}} + MgXR \longrightarrow HRC{:}O + MgXOC_2H_5$$
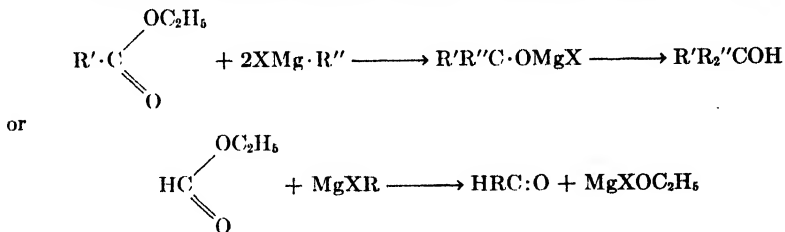
R' may be a hydrocarbon residue or hydrogen. Tertiary or secondary alcohols are obtained. Aldehydes, too, are obtained by this method under certain conditions with formic acid esters.

Possibilities of variation are limited in this reaction, because both radicals introduced by the Grignard reagent are the same. Nevertheless, the ester syntheses is to be preferred, because the esters are frequently cheaper and more conveniently available than ketones and aldehydes. Side reactions seldom occur, and the yields are usually excellent.

Only with formic acid esters can the reaction be stopped after the first step. Aldehydes are then obtained by hydrolysis of the corresponding addition products, $R \cdot CH \overset{OC_2H_5}{\underset{OMgX}{\diagdown}}$. The same result is realized better by the use of ortho esters. They usually react very smoothly with Grignard compounds according to the following scheme.

$$R \cdot C(OC_2H_5)_3 + R' \cdot MgX \longrightarrow R \cdot C(OC_2H_5)_2 \cdot R' + Mg(OC_2H_5)X \overset{H_2O}{\longrightarrow} R \cdot CO \cdot R'$$
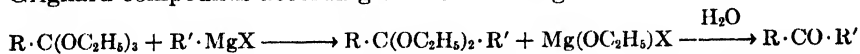
The use of carbonic acid esters is a special case. They yield tertiary alcohols with three identical groups in accordance with the following equation.

$$O{:}C(OC_2H_5)_2 + 3R \cdot MgX \longrightarrow R_3 \cdot C \cdot O \cdot MgX + 2Mg(OC_2H_5)X$$
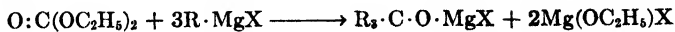
Triethylcarbinol may be prepared conveniently from ethyl propionate and ethylmagnesium bromide. However, pure ethyl propionate free from homologues is not cheap. The preparation through diethyl ketone is not cheap either. Therefore, triethylcarbinol is best prepared according to the directions given in *Organic Syntheses* [100] from ethyl carbonate and ethylmagnesium bromide.

[100] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 602.

Weygand prepared thiophene aldehyde diethyl acetal according to suggestions of Grishkevitch-Trokhimovskii [101] in the following manner.

A Grignard solution is prepared from 6.6 g. of magnesium and 53 g. of 2-iodothiophene in 65 cc. of absolute ether (see page 91).   To the solution are added, with cooling, 38 g. of ethyl orthoformate and the mixture is boiled under a reflux for 6 hours to complete the reaction.   After the reaction mixture has been cooled, it is added to ammonium chloride solution in a separatory funnel.   The mixture is well shaken and the ether layer washed with another portion of ammonium chloride solution.   The ethereal solution is then washed with water and dried over calcium chloride.   Upon distillation in a vacuum a forerun consisting of unchanged ortho ester is obtained.   Thiophene aldehyde acetal then distils as a colorless oil at 97° to 102°C. at 15 mm.   The yield of 24 g. is 51% of the theoretical.

The thiophene aldehyde is obtained from the acetal by boiling with dilute hydrochloric acid.   The reaction product is distilled with steam and the distillate is extracted with ether.   The ether solution is washed with water, dried, and distilled.   The thiophene aldehyde boils at 192°C.

3. Grignard Compounds with Alkylene Oxides.   The basic reaction of the group is as follows:

$$CH_2 \cdot CH_2 + XMgR \longrightarrow R \cdot CH_2 \cdot CH_2 \cdot OMgX \longrightarrow R \cdot CH_2 \cdot CH_2 \cdot OH$$
$$\diagdown O \diagup$$
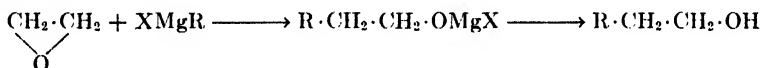
Alcohols are obtained with a carbon chain lengthened by two members. Since ethylene oxide is now available commercially at a reasonable price, the method is finding greater favor.

A good example of this method is the preparation of *n*-hexyl alcohol according to the directions in *Organic Syntheses.*[102]

In a similar way propylene oxide may be used for the synthesis of primary alcohols, according to the following scheme:

$$CH_2 \cdot CH_2 \cdot CH_2 + MgXR \longrightarrow R \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OMgX \longrightarrow$$
$$\diagdown O \diagup$$

$$R \cdot CH_2 \cdot CH_2 \cdot CH_2OH$$
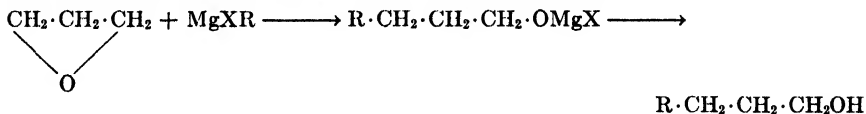
Primary alcohols are obtained with a lengthening of the carbon chain by three members.

An example furnished by Derick and Bissell [103] has little practical value, because the *n*-hexanol obtained with propylmagnesium bromide is better prepared according to the method described above or by other methods.   However, theirs is apparently the only method which has been described in detail.   Only a note by Bermejo and Gómez Aranda [104] is

[101] Grishkevitch-Trokhimovskii, *Chem. Abstracts*, 6, 223, 2406 (1912).
[102] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.*   Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 306.
[103] C. Derick and Bissell, *J. Am. Chem. Soc.*, 38, 2484 (1916).
[104] L. Bermejo and V. Gómez Aranda, *Chem. Abstracts*, 24, 828 (1930).

available on the analogous preparation of *n*-amyl alcohol from trimethylene oxide and ethylmagnesium bromide.

To the Grignard solution of 4.3 g. of magnesium and 24 g. of *n*-propyl bromide the mixture of 10 g. of trimethylene oxide and 25 cc. of ether is added slowly. After the reaction has subsided, the mixture is heated under a reflux for 1 hour, 200 cc. of dry benzene are added, and the ether removed by distillation until the temperature reaches 70°C. The heating under a reflux is continued for 4 hours longer. The mixture is then cooled and the viscous reaction product decomposed with water. No heating effect is observed. The magnesium hydroxide is dissolved in 30% sulfuric acid and the mixture distilled with steam. When the oily portion of the distillate is worked up, 10 cc. of *n*-hexanol boiling at 155°C. are obtained.

By the use of propylene oxide good yields apparently are obtained of carbon chains lengthened by three members.

Alkylene oxides of larger rings, such as tetrahydrofuran, are free from strain. Therefore, they would be expected to be inert in the presence of Grignard reagents for the synthesis of long aliphatic chains with an odd number of carbon atoms.

4. Grignard Compounds and Carbon Dioxide. The basic reaction is as follows:

$$R \cdot MgX + CO_2 \longrightarrow R \cdot COOMgX \longrightarrow R \cdot COOH$$
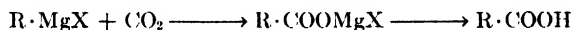
Organic Syntheses gives detailed directions for the preparation of methylacetic acid by this method; see also Gilman and Zoellner.[105] The method described there may be considered an example for similar preparations.

In an analogous manner the cyclohexylcarboxylic acid is obtained from cyclohexyl chloride in an 85% yield.

5. Grignard Compounds and Ketenes. Ketenes react with Grignard compounds according to the following scheme:

$$R_2C:C:O + XMgR' \longrightarrow R_2C:\overset{.}{C}(OH)R' \longrightarrow R_2CH \cdot CO \cdot R'$$
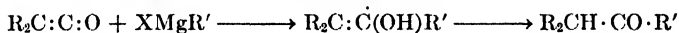
The carbon double bond does not participate in the reaction.

II. FORMATION OF SINGLE BONDS WITH CONDENSATION AGENTS

A. Removal of Halogen as Halide

1. Wurtz and Fittig Syntheses

The synthesis of Wurtz in its original form, namely the action of sodium upon aliphatic halides, is used only rarely. At any rate, it presents one of the few possibilities for the preparation of very long carbon chains of definite molecular weight. An example of this chain elongation

[105] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*, Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 361. Gilman and Zoellner, *J. Am. Chem. Soc.*, **53**, 1945 (1931).

is the preparation of hexacontane from myricyl iodide according to Hell and Hägele.[106]

Myricyl iodide reacts only slowly with sodium in petroleum ether or in benzene. The melt reacts a little better but only at such a high temperature that hydrogen iodide and iodine are easily split off. The reaction is most successful with finely divided potassium. 1 part of potassium is heated with 10 parts of myricyl iodide at 130° to 140°C. The reaction is apparently completed in 2 hours. In the tedious isolation the reaction product is boiled successively with water, alcohol, petroleum ether, and glacial acetic acid, then recrystallized from benzene, and again extracted with boiling petroleum ether. Hexacontane remains as a somewhat crystalline, colorless powder, melting at 101° to 102°C.

Morton and coworkers [107] have recently described noteworthy investigations on the Wurtz reaction. Their original papers must be consulted for the details.

More important is Fittig's synthesis concerning which a few general comments should first be made.

Only this much needs be said about the qualities of the reaction components: The sodium requires no special preparation. The halides and solvent must be rigorously dried.

Sodium in the form of wire or as thin slices is used. The slices may be prepared rapidly; they can be weighed readily under benzene and react with sufficient speed. If the reaction is too sluggish, it is best to use sodium or potassium powder.

Dry ether is particularly well suited as a solvent. Petroleum ether and benzene may also be used.

The reactivity of the halide increases, as usual, in the following order: chlorides, bromides, and iodides.

In general, the sodium, covered by the solvent, is placed in a flask equipped with a reflux condenser, calcium chloride tube, and a dropping funnel. The halide mixture, if necessary in solution, is added slowly dropwise. The reaction, which is occasionally much retarded, may start after several hours with such great violence that the condenser cannot accommodate the vapors. In dubious cases the reaction may be started with a little ethyl acetate which provides shiny sodium surfaces. The acetoacetic ester thus formed can be removed easily. Acetonitrile also has an accelerating effect.

Usually the solvent starts to boil after a short time. The halide mixture is added at such a rate that the reaction continues. In case the spontaneous boiling stops, the flask is warmed in a water bath for some time. A hot-plate or oil bath is better, because of the dangerous sodium metal. It is advantageous to allow the mixture to stand overnight in

---

[106] C. Hell and C. Hägele, *Ber.*, **22**, 502 (1889).
[107] Morton *et al.*, *J. Am. Chem. Soc.*, **54**, 1919 (1932); **58**, 1697 (1936).

order to determine whether the reaction has made further progress. At first the metal is covered with grayish blue spots. During subsequent reaction the pieces increase in size on being changed to the halide. Like blue rock salt the halide contains metallic sodium in the lattice and therefore appears colored. After a little experience one can judge from the appearance of the pieces how far the reaction has gone. A small piece of sodium may also be removed and examined for a metallic center. Some preparations require as long as 2 or 3 days for the reaction to reach completion. Nothing definite can be said about the ratio of the amounts used. A small excess (0.05 mole) is usually not harmful. Many conditions determine whether the halides are to be used in a strictly equimolecular ratio or whether an excess of one or the other may be used to advantage. It should be remembered that the smooth course of the Fittig reaction is based on the fact that aromatic halides react very much faster with the metal than do the aliphatic halides, and that aryl sodium in turn reacts faster with alkyl halides. If the reaction between aryl sodium and alkyl halide (as with secondary bromides) is slow, diaryl is formed as an undesirable by-product. It may prove advantageous in such cases to use an excess of both aryl halide and sodium. In most cases, however, an excess of alkyl halide is to be preferred because this excess reagent can be removed readily during the subsequent reactions.

Isolation of the reaction product is a simple procedure. As much of the liquid as possible is distilled directly from the reaction flask, first on a water bath and then with a free flame or in an oil bath, decomposition being avoided. Occasionally considerable overheating is necessary. The distillation is carried out under reduced pressure, a short necked flask being used.

The distillate may be extracted in doubtful cases, the unchanged sodium always being first destroyed cautiously with alcohol. When high boiling hydrocarbons are used, it is preferable, after the reaction has been completed, first to add alcohol until all the unchanged sodium has been dissolved. The mixture is then washed with water, dried, and fractionated. The additional work involved in washing is worth while. Without the washings the sodium salts remaining in the reaction flask necessitate overheating during the fractional distillation.

It is advantageous to collect several fractions on the first distillation. In subsequent fractionations a little sodium is always added to the distilling flask to remove unchanged halide.

It is important to learn whether one of the by-products, dialkyl or diaryl, which are almost invariably present, has a boiling point close to that of the desired product. In some cases mixtures are obtained which are difficult to separate. Tertiary aliphatic halides apparently are not

suitable for the Fittig reaction.   No details can be found in the literature on this matter.   Weygand was unable to prepare tertiary amylbenzene from tertiary amyl bromide and bromobenzene.   In this case the Friedel-Crafts reaction is used.   The preparation of tertiary amylbenzene by the Friedel-Crafts method fortunately proceeds without rearrangement of the aliphatic radical (see page 398).

As a practical example, the preparation of n-propylbenzene, according to Fittig,[108] may be described.

In a 500 cc. 2-necked flask equipped with a reflux condenser and a dropping funnel, 44 g. of sodium in the form of thin slices and 300 cc. of dry ether are cooled to 0°C.   To the mixture is added slowly a solution of 100 g. of freshly distilled bromobenzene (b.p. 156° to 157°C.) and 98 g. of n-propyl bromide (b.p. 70° to 71°C.).   The latter is first washed with a sodium carbonate solution, and then dried and distilled.   The solution of bromides is also precooled to 0°C. and added within 5 minutes.   The flask is removed from the freezing mixture.   The reaction starts after about 45 minutes and is completed in about 3 hours.   During this time the reaction is controlled by cooling the flask from time to time in ice water.   After the mixture has been allowed to stand overnight, the ether is removed by distillation, first on a water bath, then on an oil bath, until the residue in the flask has a dry appearance.   The residue is extracted repeatedly with several portions of distilled ether.   The main portion and the ether extracts yield a total of 60 g. of n-propylbenzene, boiling at 157° to 158°C. on fractionation through a Widmer column. This yield is 79% of the theoretical amount, when based on n-propyl bromide.   A distillation from sodium is unnecessary, because the distillate is entirely free of bromine. If alcohol is added after the reaction, and the mixture is worked up as suggested above, the yield is practically the same.

The Fittig synthesis is the most productive of all the possible methods for preparing n-propylbenzene and the higher normal homologues.   Complaints in the literature about unsatisfactory yields can always be traced back to errors of technique.

2. Removal of Halogen with Copper, Silver, Zinc, and Alkali Alcoholates

(a) Copper and Silver as Condensation Agents

In addition to the alkalies, copper and silver are especially suited for the removal of halogens.   Wislicenus[109] obtained adipic acid from β-iodopropionic acid with finely dispersed silver.

This finely dispersed silver, called "molecular silver" by Wislicenus, is prepared according to Gomberg and Cone[110] in the following manner.

250 g. of pure, well washed silver chloride are placed in a beaker with heavy walls. A porous beaker which contains several zinc bars is inserted.   Water is then poured in. The silver chloride is connected with the zinc through a platinum sheet welded with platinum wire.   The water in the porous cup is acidified slightly and the whole set-up allowed to stand undisturbed.   The reaction is usually complete after a few days. Care

---

[108] R. Fittig, *Ann.*, 149, 324 (1869).
[109] J. Wislicenus, *Ann.*, 149, 220 (1869).
[110] M. Gomberg and M. Cone, *Ber.*, 39, 3286 (1906).

must be taken that the liquid level in the porous cup is always a little below the outside level to keep diffusion of the zinc chloride at a minimum. The gray-silver powder is washed successively with water, ammonia, water, alcohol, and ether. The silver is finally dried in a vacuum over sulfuric acid and heated to 150°C. The directions of Gomberg and Cone are a modification of the method of Wislicenus. The latter brings the silver chloride into contact with zinc under water without a diaphragm and washes the silver off the zinc pieces. However, since the silver still contains zinc, it must be washed with hydrochloric acid.

The "molecular silver" of Wislicenus was formerly used rather often for similar reactions. Hell and Rothberg [111] prepared dimethylsuccinic acid ester from α-bromopropionic acid ester by heating with an equal weight of silver at 150° to 160°C. During the heating frequent shaking was necessary. The silver slime conglomerated in the flask and had to be stirred up. The supernatant oil was decanted readily from the silver bromide after the reaction was completed. The residual silver bromide was extracted with ether. Isolation of the reaction product by fractional distillation was difficult because both diastereomeric forms of 1,2-dimethyl succinate are formed. Details can be found in the original paper.

The method can be used rather generally. Very high molecular, substituted succinic acid esters have been obtained occasionally in this manner; see Jones.[112]

Silver is quite generally useful in the aliphatic series as a halogen-removing agent. Copper, on the other hand, is more efficient in the aromatic series. Zincke [113] obtained phenylacetic ester by this means from bromobenzene and chloroacetic ester. Later, Ullmann and co-workers [114] prepared biphenyl derivatives. They even consider this method a substitute for Fittig's synthesis. This is quite true as far as the preparation of diaryls is concerned. In most cases the expensive iodides are used unless the presence of substituents, such as the nitro group, has a loosening effect on the nuclear halogen.

According to Ullmann and Bielecki,[115] 2,2'-dinitrobiphenyl is prepared by mixing 30 g. of o-chloronitrobenzene with 50 g. of dry sand. The mixture is heated to 200° to 210°C. and 30 g. of copper powder are stirred in slowly with a thermometer. After each addition one must wait until the temperature has dropped to 220°C. The temperature must not exceed 250°C. When all the copper has been added, the mixture is kept at 240° to 245°C. for 30 minutes longer. The reaction product is allowed to cool and is then extracted with benzene. Upon concentration of the extracts 2,2'-dinitrobiphenyl, melting at 124°C., is obtained in a 60% yield.

Although the o-dinitrobiphenyl may be prepared with comparative ease in this manner from the readily available o-chloronitrobenzene,

[111] C. Hell and M. Rothberg, *Ber.*, **22**, 60 (1889).
[112] Jones, *J. Am. Chem. Soc.*, **37**, 586 (1915).
[113] Th. Zincke, *Ber.*, **2**, 738 (1869).
[114] F. Ullmann *et al.*, *Ann.*, **332**, 38 (1904).

p-nitrochloro- and p-nitrobromobenzenes do not react well with copper powder. m-Nitrochloro- and m-nitrobromobenzenes are unchanged after prolonged heating with copper powder.   In both cases the iodine derivatives must be used.   If, however, as in picryl chloride, 1 halogen atom is especially activated by multiple substitution, the reaction with copper powder may take place in an explosive manner.   Hexanitrobiphenyl is prepared according to Ullmann and Bielecki [115] as follows:

20 g. of picryl chloride are dissolved in 200 cc. of nitrobenzene, the solution is brought to a boil, and 15 g. of copper powder are added slowly.   As soon as no more metal particles are visible (about 5 to 10 minutes), the mixture is filtered; the residue is extracted with 20 cc. of nitrobenzene and the nitrobenzene solutions concentrated to 50 cc.   Upon addition of ether, hexanitrobiphenyl crystallizes.   A total yield of 9.6 g. can be obtained if the mother liquor is worked up.   This is a yield of 55% of the theoretical.   By recrystallization from toluene the compound containing 0.5 mole of crystal toluene can be obtained in a pure form.   Its melting point is 238°C.

(b) Zinc as Condensation Agent

Zinc plays a special part as a means of removing halogen in the preparation of radicals of the trivalent carbon.   The principle of the method is described in elementary textbooks.

The use of zinc in synthetic work, particularly in the Reformatski synthesis,[116] has become more important in recent times.   The following basic reaction shows that this synthesis is a precursor of the Grignard method:

$$R \cdot CO \cdot CH_3 + Zn + BrCH_2 \cdot COOC_2H_5 \longrightarrow CH_3 \cdot RC \underset{CH_2 \cdot COOC_2H_5}{\overset{OZnBr}{<}}$$

$$\longrightarrow R \cdot C(OH)CH_3 \cdot CH_2 \cdot COOC_2H_5$$
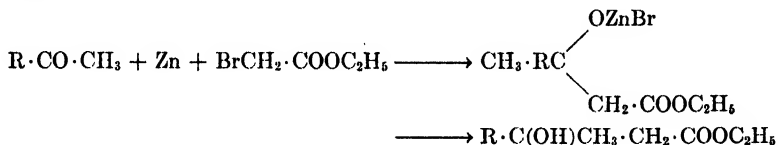
By splitting off water from the β-hydroxy esters (commonly called hydracrylic acid esters) which form as intermediates, unsaturated esters of the formula, $R \cdot C(CH_3) : CH \cdot COOC_2H_5$, are obtained.   They are frequently obtained as end-products of the synthesis.

The Reformatski synthesis gives acrylic acids if aldehydes are used as starting material.   Homologues of bromoacetic ester yield substituted acrylic acids, $R \cdot CH : C(R') \cdot COOH$ and $R \cdot C(R') : C(R'') \cdot COOH$, the former from aldehydes, the latter from ketones.

The original directions called only for common zinc.   Later experience showed that its activity might be increased in various ways.   Lewinsohn [117] recommends heating 1 kilo of zinc with about 1 g. of iodine, with

[115] Ullmann and Bielecki, *Ber.*, **34**, 2176 (1901).
[116] Reformatski, *Ber.*, **20**, 1210 (1887).
[117] A. Lewinsohn, *Perfumery Essent. Oil Record*, **15**, 45 (1924).

continuous shaking, in a large flask over a free flame. The mixture loses a metallic luster and acquires a gray-black appearance. Granulated zinc may also be covered with a warm solution of copper sulfate. After a red-brown film has formed, the metal is washed well with water.

Nieuwland and Daly [118] describe a variation of the method. They replace bromoacetic ester with the inexpensive chloroacetic ester and find that the reaction, which can be catalyzed with copper powder, takes place with zinc and ketones but not with aldehydes. For instance, 35 g. of acetophenone, 38 g. of chloroacetic ester, and 35 g. of benzene are carefully heated with 18 g. of zinc and 3 g. of copper powder until the violent reaction subsides. The end-product is isolated as usual. The yields vary considerably. Kon and Nargund [119] could not check the results of Nieuwland and Daly. They were unable to observe a condensation between acetophenone and chloroacetic ester. In other preparations they succeeded even without the use of copper powder.

The directions given by Lewinsohn [120] exemplify the method as applied on a semicommercial scale.

In a 30 to 40 liter enameled iron pot equipped with a reflux condenser, a stirrer, and a delivery tube for the zinc, 5.48 kilos of bromoacetic ester, 5 kilos of methyl hexyl ketone, and 7 kilos of dry benzene are heated to 100°C. At first, 200 g. of zinc are added. A violent reaction occurs and the whole mixture starts to boil. A total of 3 kilos of zinc is added gradually in 200 g. portions. The reaction should not be allowed to become too violent but not too slow either, because once stopped, the reaction is difficult to start. When all the zinc has disappeared after the last portion has been added, the reaction mixture is allowed to boil 30 minutes longer. The gelatinous mass, while still warm, is mixed with ice water and the mixture acidified with hydrochloric acid. The benzene layer is separated, washed first with water, then with a sodium carbonate solution, and again with water. The solution is dried over sodium sulfate and fractionated *in vacuo*. Benzene and unchanged methyl hexyl ketone distil up to 110°C. at 12 mm. A mixture of β-methyl-β-hexylacrylic acid ester and β-hydroxynonylic acid ester distils from 111° to 125°C. The unsaturated ester is formed as a by-product involving removal of water. The third fraction boiling from 126° to 145°C. contains the main portion of the hydroxy acid ester; the last fraction boiling at 146° to 160°C. contains higher condensation products. By redistillation of the second and third fractions 300 g. of the unsaturated ester and 4100 g. of the hydroxy acid ester are obtained.

Lindenbaum [121] describes the preparation of β-methyl-β-phenylhydracrylic acid ester, $C_6H_5 \cdot C(CH_3)(OH) \cdot CH_2CO \cdot OC_2H_5$, as follows:

12 g. of acetophenone and 20 g. of bromoacetic ester in 75 cc. of dry benzene are treated with 8 g. of zinc. After the vigorous reaction has subsided, the reaction mixture is boiled under a reflux for 45 minutes. The solution is shaken with dilute sulfuric acid, dried, and fractionated. Thus 19.2 g. of the ester are obtained as a colorless oil boiling at 146° to 147°C.

[118] J. A. Nieuwland and S. Daly, *J. Am. Chem. Soc.*, **53**, 1842 (1931).
[119] Kon and Nargund, *J. Chem. Soc.*, 1932, 2461.
[120] A. Lewinsohn, *Perfumery Essent. Oil Record*, **15**, 45 (1924).
[121] S. Lindenbaum, *Ber.*, **50**, 1270 (1917).

In most cases the purpose of the synthesis is not the preparation of the hydracrylic acid ester; rather, the unsaturated esters and the corresponding carboxylic acid esters are desired. Methods for preparing the unsaturated acids are described in the section on ethylene bonds on page 317.

The hydracrylic acid esters are heated with phosphorus oxychloride or distilled over phosphorus pentoxide. In such cases the esters described above do not have to be isolated first.

According to Stoermer, Grimm, and Laage,[122] the reaction mixture obtained by the method described above from 72 g. of acetophenone, 100 g. of bromoacetic ester, 250 g. of benzene, and 41 g. of zinc turnings is mixed with 20 drops of phosphorus oxychloride after the benzene has been removed by distillation. On fractional distillation 80 g. of β-methylcinnamic acid ester distil at 155° to 165°C. at 28 mm.

Phosphorus oxychloride is apparently preferable to other dehydrating agents formerly recommended; see Rupe and Busolt.[123] Lindenbaum [124] heats 19.2 g. of hydracrylic acid ester with 80 cc. of benzene and 6 cc. of phosphorus oxychloride at a boil for 25 minutes. After destroying the oxychloride with water he isolates the end-product.

The Reformatski synthesis offers no advantages in the simplest cases. But by combining benzaldehyde with α-bromopropionic ester, α-methylcinnamic acid ester is obtained by way of the ester of a hydroxy acid which contains 1 molecule more of water; see Dain.[125] By the reaction of ketones with homologues of bromoacetic acid ester, α,β-dialkylcinnamic acid esters are obtained; see Rupe and coworkers, and Braun.[126]

An important application of the Reformatski synthesis is described in the total synthesis of phytol, according to Fischer,[127] in which the synthesis of a saturated chain with definite branches is involved. The Reformatski synthesis was also valuable in the synthesis of the natural polyenes which contain the same, but unsaturated, chain. Kuhn and Hoffer [128] were the first to succeed in a synthesis of this kind. They prepared the natural dehydrogeranic acid, $(CH_3)_2C:CH \cdot CH:CH \cdot C(CH_3):-CH \cdot COOH$, by the following sequence of reactions:

$$(CH_3)_2C:CH \cdot CHO + CH_3 \cdot CO \cdot CH_3 \xrightarrow{\text{NaOH}} (CH_3)_2C:CH \cdot CH:CH \cdot CO \cdot CH_3$$
$$+ BrCH_2 \cdot COOCH_3 + Zn \longrightarrow (CH_3)_2C:CH \cdot CH:CH \cdot C(CH_3)OH \cdot CH_2 \cdot COOCH_3$$
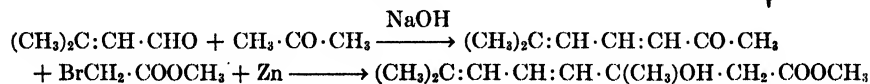
β-Methylcrotonaldehyde (see page 317) was condensed with acetone to give 6-methylheptadienone. This yields the hydracrylic acid ester

[122] R. Stoermer, F. Grimm, and E. Laage, *Ber.*, **50**, 959 (1917).
[123] Rupe and Busolt, *Ber.*, **40**, 4537 (1907); *Ann.*, **369**, 321 (1909).
[124] S. Lindenbaum, *Ber.*, **50**, 1270 (1917).
[125] Dain, *Chem. Zentr.*, **1898**, I, 668.
[126] J. v. Braun, *Ann.*, **451**, 47 (1927); H. Rupe *et al.*, *Ber.*, **47**, 68 (1914).
[127] G. Fischer, *Ann.*, **475**, 183 (1929).
[128] R. Kuhn and M. Hoffer, *Ber.*, **65**, 651 (1932).

with bromoacetic ester.   The natural dehydrogeranic acid is obtained by boiling the hydroxy acid ester first with phosphorus pentoxide in a benzene solution.   The unstable methyl ester is obtained.   Upon saponification of the ester with alcoholic potassium hydroxide a product identical with dehydrogeranic acid is obtained.   If barium hydroxide is used for simultaneous saponification and removal of water, the hydroxy acid is converted to a stereoisomer melting at 137°C.   The natural product melts at 186°C. (see Fischer and Löwenberg[129]).

Finally, the key substance for the synthesis of vitamin A (see page 435), the β-ionylideneacetaldehyde, was obtained by Karrer and co-workers [130] in the following manner.

100 g. of pure β-ionone (b.p. 126°C. at 7 mm.) are boiled on a sand bath with 110 g. of bromoacetic ester and 220 g. of pure benzene in a flask (1500 cc.) equipped with a reflux condenser and a calcium chloride tube.   Through the condenser is then slowly added, in portions, a total of 50 g. of pulverized zinc.   Generally a violent reaction occurs immediately after the addition of the first 10 g. portion.   The reaction is controlled by cooling, if necessary.   After all the zinc has been added, the mixture is boiled gently for 3 hours longer and the cooled brown reaction mixture is shaken for 1 hour with excess 10% acetic acid.   The liquid is then extracted in a separatory funnel with 1 liter of petroleum ether (boiling at 30° to 40°C.).   The benzene-petroleum ether mixture is shaken successively with 1% acetic acid, water, and with dilute sodium carbonate solution.   After the solution has been dried with sodium sulfate, the petroleum ether and benzene are removed by distillation.   The residue is heated for a short time to 170°C. to expel traces of bromoacetic ester, and is then distilled fractionally *in vacuo*.   After repeated distillations and alternate drying, 120 g. of ionylideneacetaldehyde, boiling at 165° to 168°C. at 7 mm., are obtained.   The hydracrylic acid ester was not observed in this case.   The unsaturated ester was obtained directly.

(c) *Sodium Ethylate as Condensation Agent*

Preparation of Glycidic Acids.   The reaction proceeds according to the following scheme:

$$R \cdot CHO + XCH_2 \cdot COOC_2H_5 + NaOC_2H_5 \longrightarrow R \cdot CH \cdot CH \cdot COOC_2H_5$$

with the oxygen bridge, and $+ NaX + C_2H_5OH$

or

$$R \cdot CO \cdot R' \longrightarrow RR' : C \cdot CH \cdot COOC_2H_5$$

with the oxygen bridge.
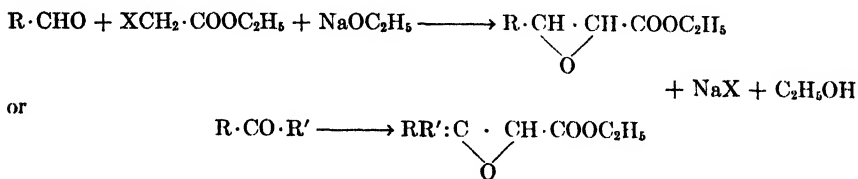
Although glycidic acid esters are commercially used for the preparation of aldehydes, only a few directions for a laboratory method can be found.   Erlenmeyer [131] gives only scant details on the reaction of benzaldehyde, monochloroacetic ester, sodium, and alcohol in ethereal solution.

[129] G. Fischer and K. Löwenberg, *Ann.*, 494, 263 (1932).
[130] P. Karrer *et al.*, *Helv. Chim. Acta*, 15, 883 (1932).
[131] Erlenmeyer, Jr., *Ann.*, 271, 161 (1892).

He adds chloroacetic ester dissolved in absolute ether to sodium and the molecular equivalent of benzaldehyde. Following the addition of a few drops of alcohol the temperature rises and all of the sodium disappears after several hours. On acidification with glacial acetic acid, sodium chloride and sodium phenyl glycidate are precipitated. The ether contains the phenylglycidic ester which can be isolated as usual. Inasmuch as the condensation proceeds under the influence of the alcoholate, it is preferable to start directly with them. Other directions suggest pulverizing sodium under xylene, converting the sodium with an excess of methanol to sodium methylate, and mixing the fine suspension of methylate at 5°C. with an equimolecular mixture of benzaldehyde and chloroacetic ester. Claisen [132] who investigated the condensation of ketones with chloroacetic ester and sodium amide prepared methylphenylglycidic ester from acetophenone in a very good yield. At almost the same time Darzens [133] published observations in the same field. Instead of using metallic sodium, as did Erlenmeyer, or sodium amide, as did Claisen, he used dry sodium ethylate. The directions given by Claisen and by Darzen for the preparation of β-phenylmethylglycidic acid ester are as follows:

1. Claisen's Method. 100 g. of acetophenone and 102 g. of chloroacetic ester are dissolved in 200 g. of dry ether and 38 g. of sodium amide are added gradually. Ammonia is evolved and sodium chloride separates while the mixture becomes moderately warm. The addition of the sodium amide requires 3 hours. The mixture is allowed to stand for 2.5 days and is then poured onto ice. The mixture is extracted repeatedly with ether, and the extracts dried over potassium carbonate and fractionated *in vacuo*. From nine combined batches of this size, a 73% yield of crude phenylmethylglycidic acid ester, boiling at 140° to 160°C. at 15 mm., is obtained. The acetophenone foreruns of the different batches are used for the succeeding runs. The yield of pure product, boiling at 147° to 149°C. at 17 mm., is not given.

2. Darzens' Method. Equimolecular amounts of a ketone and chloroacetic ester are cooled well and 1 mole of dry sodium ethylate is added slowly at a temperature below 5°C. After the mixture has been allowed to stand for 12 hours at room temperature, it is heated on a water bath for 5 to 6 hours. The cooled solution is acidified slightly with glacial acetic acid and diluted with water. The supernatant glycidic ester can be separated readily. The ester is dried over sodium sulfate and distilled *in vacuo*. The yields amount to 60 to 63% of the theoretical. If the amount of unchanged ketone which is recovered during the vacuum distillation is considered in the calculation, the yields are 90 to 100%. Darzens treated the following ketones according to this method: acetone, methyl isohexyl ketone, methyl heptyl ketone, methyl nonyl ketone, methylcyclohexanone, benzylacetone, acetophenone, p-ethylacetophenone, methyl cresyl ketone, isobutylacetophenone, and propyl phenyl ketone.

Still later Rosenmund and Dornsaft [134] studied the condensation of chloroacetic ester with aldehydes.

[132] L. Claisen, *Ber.*, **38**, 699 (1905).
[133] G. Darzens, *Compt. rend.*, **139**, 1214 (1904).
[134] K. Rosenmund and H. Dornsaft, *Ber.*, **52**, 1740 (1919).

4.9 g. of sodium wire are added with cooling to a solution of 20 g. of anisaldehyde and 18 g. of chloroacetic ester in absolute ether. The reaction which is started with a few drops of alcohol may become very violent if cooling is insufficient. After the reaction has subsided, the mixture is allowed to stand for ½ hour. The separated salt mixture is filtered by suction and washed or decanted several times with ether. The combined ether solutions are washed with water to remove dissolved salts. The p-methoxyphenylglycidic ester distilled at 187° to 191°C. at 18 mm. The product still contained traces of chlorine. Because of its instability, p-methoxyphenylglycidic acid could not be isolated from the salt mixture, but the p-methoxyphenylacetaldehyde formed from the glycidic acid was identified as the oxime.

B. Removal of Halogen as Hydrogen Halide

1. Friedel-Crafts Synthesis

(a) General Remarks

The medium in which a Friedel-Crafts synthesis is carried out is of considerable importance. The solvent most commonly used is carbon disulfide. Occasionally petroleum ether is preferable. In cases in which the condensation gives position isomers the ratio may be influenced by special solvents, such as nitrobenzene. But the choice of solvents is limited because many are changed under the conditions of the reaction. For syntheses with inexpensive aromatic hydrocarbons, such as benzene and toluene, an excess of these solvents is used for the sake of simplicity.

(b) Condensing Agents

1. Aluminum Chloride. Much has been written about the best quality of aluminum chloride for the Friedel-Crafts synthesis. It has been established that chemically pure aluminum chloride often produces reactions entirely different from those obtained with a chloride containing a certain percentage of basic chlorides. Greatly changed and thoroughly hydrolyzed aluminum chloride does not yield satisfactory results.

Dawson [135] describes a simple and practical apparatus for the laboratory preparation of aluminum chloride from aluminum and hydrogen chloride. One charge gives about 120 g. of chloride and the apparatus does not plug up. The preparation of aluminum chloride in the laboratory, however, is hardly worth while. If an especially pure product is desired, the commercial product is sublimed.

Aluminum chloride should be bought only in sealed ampules. They must be opened with care, because they usually have a little hydrogen chloride pressure. The ampule is wrapped in a towel, the neck scratched with a glass cutter, and the tip cracked off with a hot glass rod. The amount required for immediate use is removed and the balance resealed. For many purposes the sublimed technical aluminum chloride which con-

[135] G. A. Dawson, J. Am. Chem. Soc., 50, 133 (1928).

tains iron is sufficiently pure.   A purer product, for research purposes, is many times more expensive.

The commercial product consists of coarse pieces mixed with powder. The large size is no disadvantage, because the reaction is usually so violent that it must be moderated and the larger lumps react smoothly.   A finely powdered product like that obtained by sublimation is preferable if an addition compound is to be prepared, or if the reaction mixture must be stirred because of the slowness of some reactions.

Whether a given sample of aluminum chloride is suitable can be recognized by the absence of appreciable residue on sublimation.

Gattermann [136] studied the subject of the quality of aluminum chloride. He preferred the pure product obtained from aluminum and hydrogen chloride.   Gomberg,[137] however, recommended a product prepared from aluminum and chlorine.   Biltz and V. Meyer [138] draw attention to the fact that chloride which is no longer fresh can sometimes produce different results, and, according to Biltz, even better results than strictly fresh chloride.

By following the directions of Anschütz,[139] Biltz obtained tetraphenylethane from stilbene dibromide and benzene in varying yields, depending on the quality of the aluminum chloride.   Surprisingly enough a product which was partly hydrolyzed by being exposed to the air for 1 to 2 hours gave the best results.   Scholl [140] later confirmed this finding in other cases.   He suggested mixing the pure aluminum chloride with definite weighed amounts of crystallized hexahydrate.   Thus, the following reactions take place.

(1) $11AlCl_3 + AlCl_3 \cdot 6H_2O \longrightarrow 6Al_2OCl_4 + 12HCl$

(2) $5Al_2OCl_4 + AlCl_3 \cdot 6H_2O \longrightarrow 11AlOCl + 12HCl$
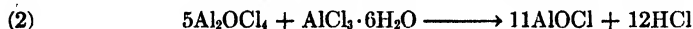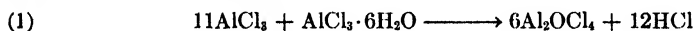
These equations give an idea of the amount of oxychloride present. Biltz [141] recently published a remarkable new observation concerning pure aluminum chloride.   Benzene and trichloroacetyl chloride in its presence yielded triphenylvinyl alcohol or triphenylethanone, respectively.

$Cl_3C \cdot CO \cdot Cl + 3C_6H_6 \longrightarrow (C_6H_5)_2C:C(OH) \cdot C_6H_5$,   or $(C_6H_5)_2:CH \cdot CO \cdot C_6H_5$
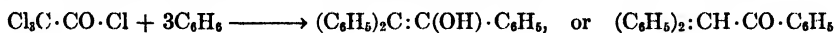
On the other hand, moist somewhat sticky chloride gave a fair yield of ω-trichloroacetophenone.   Biltz recalled the experience of Lippmann and Keppich [142] who were able to obtain anthraphenone from anthracene and

[136] Gattermann, *Ber.*, **25**, 3521 (1892).
[137] M. Gomberg, *Ber.*, **33**, 3146 (1900).
[138] H. Biltz, *Ber.*, **26**, 1960 (1893). V. Meyer, *Ber.*, **29**, 847 (1896).
[139] R. Anschütz, *Ann.*, **235**, 207 (1886).
[140] R. Scholl, *Ber.*, **32**, 3492 (1899).
[141] H. Biltz, *J. prakt. Chem.*, **142**, 196 (1935).
[142] P. Keppich, *Ber.*, **33**, 3087 (1900).

benzoyl chloride with moist aluminum chloride but never with the pure reagent.

A systematic check of all these questions might not only clear up many contradictions, but also might yield many useful and new results. Adam,[143] for instance, claims to have obtained fluorene from biphenyl and methylene chloride according to the following scheme:
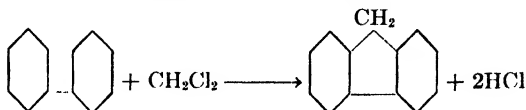
Meyer and Wesche [144] were unable to confirm the claims of Adam. A possible explanation of this discrepancy might lie in the use of chlorides of different reactivity.

Not much can be said here about the theory of the Friedel-Crafts reaction. Because aluminum chloride and its substitutes always react primarily as condensing agents rather than as catalysts, the reaction has been discussed at this point. More details on the rôle of the aluminum chloride in the course of the reaction can be found in a number of publications.[145]

2. Stannic Chloride. The milder acting stannic chloride is better suited than aluminum chloride for some reactions. In most cases, the commercial product may be used without further purification; if necessary, the product can be distilled.

3. Other Halides. These rarely offer any advantages. Beryllium chloride has recently been investigated, but the details are still lacking. According to Meerwein [146] boron fluoride can be used. It forms well defined molecular compounds in a mole ratio of 1:1 and 1:2 with simple aliphatic acids. Acid anhydrides also yield molecular compounds with boron fluoride. However, in the case of acetic anhydride the molecular compound proved to be a derivative of the diacetoacetic anhydride. This conclusion followed from acetylacetone occurring as the hydrolysis product. Meerwein stated that toluene, anisol, and phenol could be acetylated readily with acetic anhydride and boron fluoride. In a later paper Meerwein and Vossen [147] gave a few details. Their yields, however, were not very satisfactory.

[143] Adam, *Ann. chim. phys.*, 15, 233 (1888).
[144] R. Meyer and Wesche, *Ber.*, 50, 442 (1917).
[145] G. Perrier, *Ber.*, 33, 815 (1900); 26, 538 (Ref.) (1893); *Compt. rend.*, 116, 1298 (1893); J. Boeseken, *Rec. trav. chim.*, 19, 19 (1900); 20, 102 (1901); G. Gustavson, *Compt. rend.*, 136, 1065 (1903); *J. prakt. Chem.*, 68, 209 (1903); H. Wieland and L. Bettag, *Ber.*, 55, 2246 (1922); A. Schaarschmidt, *Angew. Chem.*, 37, 286 (1924); G. Schroeder, *Ber.*, 57, 1990 (1924); G. Kränzlein, *Aluminiumchlorid in der organischen Chemie*, Verlag Chemie, Berlin, 1932; C. A. Thomas *et al.*, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold, New York, 1942.
[146] H. Meerwein, *Ber.*, 66, 411 (1933).
[147] Meerwein and Vossen, *J. prakt. Chem.*, 141, 156 (1934).

A total of 26 g. of boron fluoride was admitted at 0°C. to a mixture of 9.2 g. of toluene and 20.4 g. of acetic anhydride. The reaction product was decomposed with an aqueous solution of sodium acetate, then distilled with steam, and the distillate worked up as usual. By this means, 9.5 g. of p-methylacetophenone were obtained. This yield is 71% of the theoretical amount. A few drops of acetylacetone and about 2 g. of methyl-benzoylacetone were also isolated. In a similar way, tetrahydroacetophenone was prepared from cyclohexene in a 27% yield. p-Methoxyacetophenone was obtained in a 95% yield, but details for its preparation were not given.

One of the few advantages of sublimed ferric chloride over aluminum chloride was shown by Nencki [148] to be the introduction of two acyl groups into polyphenols.

Ferric chloride has many disadvantages as a condensing agent. Oxidations and chlorinations accompany the removal of hydrogen halide.

In some cases metal chlorides can be replaced by other condensing agents. Grucarevic and Merz [149] condensed naphthalene and benzoyl chloride with phosphorus pentoxide at 180° to 200°C. and obtained a 90% yield of α- and β-naphthyl phenyl ketone. In contrast to aluminum chloride, very small amounts of phosphorus pentachloride can be used. Steinkopf [150] drew attention to the good results obtained by this method in the thiophene series.

(c) Details of Reaction

1. Preparation of Mixture. Various ways are possible to bring together the components involved in the reaction: aluminum chloride or stannic chloride, and the halide, or acid chloride, or anhydride, and the aromatic component.

(1) The components of the organic reaction are mixed with the solvent and the aluminum chloride is added in portions. This, the oldest method, is inconvenient because of the hygroscopic nature of the aluminum chloride and offers no advantages when compared with the other methods.

(2) The aluminum chloride is mixed with one of the organic components and with the diluent or solvent. The other compound is added slowly, pure or in solution. One has to determine whether the aluminum chloride forms a molecular compound.

(a) If the aluminum chloride is mixed with the halogen-containing component, the formation of a double compound must frequently be expected, especially with carboxylic acid chlorides. Formation of double compounds is an advantage under some circumstances, because they react less violently with the second component.

(b) A liquid such as benzene, which does not contain halogen and which acts as the diluent, may be conveniently mixed with aluminum chloride. The halogen-containing component is then added.

[148] M. Nencki, *Ber.*, **30**, 1766 (1897); **32**, 2418 (1899).
[149] S. Grucarevic and V. Merz, *Ber.*, **6**, 1240 (1873).
[150] W. Steinkopf, *Ann.*, **413**, 343 (1917); **424**, 1 (1921).

(*3*) In almost all cases in which the reaction is carried out in an inert diluent the following method is recommended.

The condensing agent is either suspended or dissolved in the solvent and the mixture or solution of the organic reaction components is added slowly in a suitable manner. This method gives excellent results, especially when one of the components is readily changed. Weygand obtained acetylfuran from furan, acetyl chloride, tin tetrachloride, and petroleum ether in a much better yield than was obtained by Reichstein's [151] method. Reichstein suggested adding the acetyl chloride to a mixture of aluminum chloride, furan, and petroleum ether. During the reaction with aluminum chloride much of the furan which is present in excess resinifies. But if the furan and the acetyl chloride reach the condensing agent in equimolecular amounts, this fault is remedied. The acetylfuran, once formed, and its molecular compound with aluminum chloride are relatively stable.

The optimum amount of condensing agent cannot be stated generally. For ketone syntheses less than the equimolecular amount of aluminum chloride must never be used. A small excess is sometimes advantageous and is generally harmless.

2. Course of Reaction. The best results are obtained if the speed of the reaction and the addition of the reagents are so regulated that a large excess of unchanged material is never present. The progress is best followed by the evolution of hydrogen chloride. With unfamiliar reactions one starts by cooling with ice or, if necessary, even with a freezing mixture. One has to guard against failure of the reaction to occur at a low temperature. Cooling is stopped temporarily or moderated. At times the reaction is started at a little higher temperature and then the cooling is applied.

Occasionally some heat may be applied advantageously towards the end of the reaction. When carbon disulfide is used as a solvent, the heating has no harmful effect because of the low boiling point of the solvent. At times heating must be avoided.

Frequently an occasional shaking of the reaction mixture is sufficient, but stirring is often practical. If heating towards the end is to be avoided, a question arises as to how long the mixture must be allowed to stand after the components have been added. In doubtful cases this period should not be extended too long; never overnight. Directions are often found to wait, or to heat the mixture until the evolution of hydrogen chloride has ceased. It is not safe to follow such directions. The evolution of hydrogen chloride, especially at higher temperatures, rarely ceases completely. Calloway and Green [152] recently found that undesirable re-

[151] Reichstein, *Helv. Chim. Acta*, 13, 357 (1930).
[152] O. Calloway and L. Green, *J. Am. Chem. Soc.*, 59, 809 (1937).

actions can take place subsequently. They studied the conditions prevailing in ketone syntheses. In the synthesis of acetophenone they isolated dypnone as the principal product from higher boiling fractions which occurred when the reaction mixture was refluxed for a rather long time. They also observed that a mixture of acetophenone, benzaldehyde, carbon disulfide, and aluminum chloride yields more than 90% of the theoretical amount of benzalacetophenone.

A practical result of their investigations is a warning against the use of insufficient amounts of aluminum chloride in ketone syntheses, lest side reaction be especially favored. The side reaction described above cannot be blamed, of course, for poor yields with purely aromatic ketones, because in such cases this particular side reaction cannot occur.

3. Decomposition of Reaction Mixture. If a Friedel–Crafts synthesis is to be finished with a steam distillation, the mixture is added to crushed ice in the distilling flask and acidified with hydrochloric acid until all the aluminum hydroxide is gone. A mixture of concentrated hydrochloric acid and ice, placed in the flask at the very start, effects definite cooling. If the decomposition mixture is to be extracted with ether or other solvents, the most practical procedure is to place the ice in the separatory funnel.

The addition of ice and hydrochloric acid to the reaction mixture must be avoided until the safety of this method has been established. Occasionally definite local superheating may cause decompositions. If this method must be used because of the viscosity of the reaction product, the ice is added all at once instead of in small portions. The solution may also be precooled to decrease the violence of decomposition.

(d) Peculiarities of Friedel–Crafts Reaction

1. Replacement of Halides by Other Compounds. Aliphatic halides may be replaced by olefins, carboxylic acid chlorides, anhydrides, and occasionally by carboxylic acids.

Olefins, such as ethylene, propylene, and isobutylene, react as though addition of hydrogen chloride had occurred. Propylene reacts like isopropyl chloride, isobutylene like tertiary butyl chloride. An important commercial example of this variation is the synthesis of the so called xylene musk.
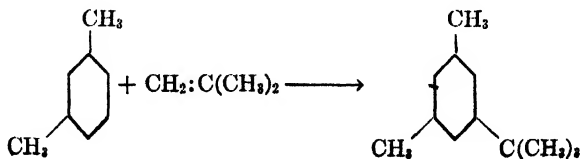
The perfume is obtained from the 1,3-dimethyl-5-*tert*-butylbenzene by the introduction of three nitro groups.

It is well known that acid chlorides may be replaced by acid anhydrides. The reaction takes the following course.

$$C_6H_5 + CH_3 \cdot CO \cdot O \cdot OC \cdot CH_3 \longrightarrow C_6H_5 \cdot CO \cdot CH_3 + CH_3 \cdot COOH$$
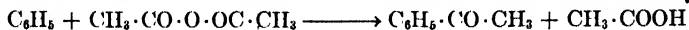
This procedure often gives better yields than the acid chlorides. An example is that of acetophenone. However, inasmuch as the anhydrides are usually available through the acid chlorides, no real advantage is gained. Exceptions are the inexpensive acetic and phthalic anhydrides.

The behavior of cyclic anhydrides of dibasic carboxylic acids is interesting and important. According to Gabriel and Colman,[153] β-benzoylpropionic acid, $C_6H_5 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOH$, is obtained from benzene and succinic anhydride.

Carbon dioxide reacts like a different acid anhydride with benzene and aluminum chloride, but it does not react uniformly. Benzoic acid and benzophenone are formed simultaneously.

Finally, under some conditions carboxylic acids themselves undergo the Friedel-Crafts reaction. Observations which suggested this possibility were made rather early. Nevertheless, the results obtained by Groggins, Nagel, and Stirton [154] are noteworthy. They started with the interesting observation that the reaction between toluene and acetic anhydride with aluminum chloride gives higher yields than are suggested by the following scheme, $C_7H_8 + C_4H_6O_3 \rightarrow C_7H_7 \cdot CO \cdot CH_3 + CH_3 \cdot COOH$. This is especially true if an excess of aluminum chloride is used. The large yield can be explained by the formation of an acetylating substance from aluminum chloride and acetic acid, presumably in the following manner.

$$CH_3 \cdot COOH + AlCl_3 \longrightarrow HCl + CH_3COOAlCl_2 \xrightarrow{AlCl_3} AlOCl + CH_3 \cdot COCl \cdot AlCl_3$$

Indeed, a 20% yield of acetyl chloride could be distilled from a mixture of acetic acid and aluminum chloride. As an example of their method, directions for the preparation of acetophenone are given.

390 g. of benzene (5 moles), 60 g. of glacial acetic acid (1 mole), and 400 g. of aluminum chloride (3 moles) react in boiling benzene at 86°C. for $5\frac{1}{2}$ hours. A yield of 77 g. of acetophenone is obtained. This corresponds to 64% of the theoretical amount. The method can be applied to aromatic carboxylic acids also. Whether this method is suitable for the laboratory depends a great deal on the conditions.

[153] Gabriel and Colman, *Ber.*, **32**, 398 (1899).
[154] P. H. Groggins, R. H. Nagel, and A. J. Stirton, *Ind. Eng. Chem.*, **26**, 1313, 1317 (1934).

The laboratory preparation of acetophenone, p-methylacetophenone, benzophenone, and other simple ketones is not worth while. In such cases, the costs of acetyl chloride, acetic anhydride, benzoyl chloride, or benzoic anhydride are high compared with the cost of the hydrocarbons. Therefore, the aim must be to use as much as possible of the acetyl group. Groggins and coworkers avoid the preparation of acid derivatives altogether, if possible.

On the other hand, if thiophene or higher benzene homologues are to be acetylated, quite different considerations must be taken into account. These aromatic components are so much more expensive than acetyl chloride, acetic anhydride, etc., that one must try to utilize the aromatic component to the fullest possible extent.

Another disadvantage of the acid method is the need for relatively high temperatures. An undesirable formation of binaphthyl takes place with naphthalene.

2. Halides of More Complicated Structure. (a) Phosgene can react with 1 or 2 chlorine atoms. Carboxylic acid chlorides or ketones are thus obtained.

(b) Oxalyl chloride yields 1,2-diketones, $Cl \cdot CO \cdot CO \cdot Cl + 2C_6H_6 \rightarrow C_6H_5 \cdot CO \cdot CO \cdot C_6H_5 + 2HCl$. Oxalyl chloride, however, is partly changed to phosgene under the conditions of the reaction. Accordingly, monoketones are also formed.

(c) Ethyloxalyl chloride is of considerable importance as a component for Friedel-Crafts syntheses. Roser [155] and later Bouveault [156] showed that glyoxylic acid ester can be prepared from it according to the equation, $C_6H_6 + Cl \cdot CO \cdot COOC_2H_5 \rightarrow C_6H_5 \cdot CO \cdot COOC_2H_5 + HCl$. This ester can be converted to the free keto acid, which in turn yields the aldehyde (see page 447). This aldehyde synthesis involves a series of steps, but is reliable and advantageous whenever the halides for Grignard syntheses are difficult to obtain.

(d) Cyanogen bromide, in simple reaction, forms nitriles. Cyanuric chloride reacts on all 3 chlorine atoms.

(e) Gattermann [157] found that carbamyl chloride yields amides readily according to the scheme, $C_6H_6 + Cl \cdot CO \cdot NH_2 \rightarrow C_6H_5 \cdot CO \cdot NH_2 + HCl$. These amides can be converted readily to acids.

In most cases additional substituents in the halide molecule do not have much influence. In each case one must consider whether groups which might themselves be attacked are present in the halogen-containing component. For example, while o-hydroxycarboxylic acid chlorides react smoothly, anthranilic acid chloride fails to react.

[155] Roser, *Ber.*, 14, 940, 1750 (1881).
[156] L. Bouveault, *Compt. rend.*, 122, 1062, 1207 (1896); *Bull. soc. chim.*, 15, 1014 (1896).
[157] L. Gattermann, *Ann.*, 244, 50 (1888).

3. Aromatic and Heterocyclic Components. All aromatic hydrocarbons and most heterocyclic compounds, especially thiophene, furan, and pyrrole, are suitable for the Friedel-Crafts synthesis with carboxylic acid chlorides and anhydrides. Furan is best treated with tin chloride. That pyridine is resistant is not surprising, considering its usual behavior during substitution; see, for instance, Jephcott.[158]

Substituted hydrocarbons react more or less readily. The larger their negative load the worse they react. Of the most important derivatives of the hydrocarbons the following react: phenols, phenol ethers, substituted amines, and halides. Nitro compounds are apparently resistant under the usual conditions of the synthesis. If the reaction is forced, reduction of the nitro group and chlorination occur; see Gilman and coworkers.[159]

Phenols and acid chlorides form carbonic acid phenyl esters without the use of condensing agents (see page 184). These esters can be rearranged to acyl phenols according to Fries (see page 484).

The aromatic character of the furan derivatives is so pronounced that they undergo many substitution reactions more rapidly than the corresponding benzene derivatives. Many substitutions which are not possible with benzene derivatives may be accomplished readily with furan derivatives. As mentioned above, substituted benzenes which contain substituents, such as the nitro or carboxyl groups, that direct to the *m* position, do not undergo the Friedel-Crafts reaction with acetyl chloride. For example, methyl benzoate cannot be acetylated. Gilman and Calloway [160] found that methyl pyromucate may be acetylated or acylated with aluminum chloride under the usual conditions. It is interesting that the influence of an ester group which hinders the reaction with methyl benzoate can be neutralized by another substituent. Anisic acid ester may be alkylated by the Friedel-Crafts reaction. α-Naphthoic acid ester, in which the second benzene nucleus plays the part of the reaction-promoting substituent, can also be alkylated.

4. Formation of Isomers. Concerning the position taken by the new group entering the aromatic nucleus in the Friedel-Crafts synthesis, the following may be said.

Since aromatic systems containing negative substituents do not react with aluminum chloride, only *o* or *p* substitution in the benzene nucleus may really be considered. The same is generally true for acylations. In alkylations *m* substitution is frequently encountered; see Baddeley and Kenner.[161]

[158] C. M. Jephcott, *J. Am. Chem. Soc.*, **50**, 1189 (1928).
[159] H. Gilman *et al.*, *J. Am. Chem. Soc.*, **57**, 907 (1935).
[160] H. Gilman and O. Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).
[161] G. Baddeley and J. Kenner, *J. Chem. Soc.*, **1935**, 303.

When the naphthalene nucleus is acylated in ligroin, α- and β-ketones are found together. The ratio of isomers can be shifted in favor of the β compound by using nitrobenzene as a diluent. In carbon disulfide only α-acetylnaphthalene is formed. As usual a lower temperature also favors the formation of α compounds; see Chopin.[162]

If the naphthalene nucleus is already substituted, several isomers are formed preferentially. For example, 2-bromonaphthalene forms the 1- and 6-acetyl derivatives. Anthracene forms 1-, 2-, or 9-acetylanthracene. Fluorene yields only 2-acetylfluorene.

The introduction of long side chains is difficult. Branched chains are always obtained even when normal halides are used. Isopropylbenzene is formed from n-propyl chloride, secondary butylbenzene from n-butyl chloride, and tertiary butylbenzene from isobutyl chloride. One cannot depend on the reaction products being completely uniform. Only compounds with the most highly branched side chains can be expected with certainty to be obtained pure. The synthesis of tertiary amylbenzene from tertiary amyl chloride is reliable.

Numerous other side reactions, such as the migration of side chains from 1 molecule to another, which are only of theoretical interest cannot be discussed here.

5. Formation of Ring Ketones in Friedel-Crafts Synthesis. Ring closure involving the position ortho to the aliphatic side chain takes place very easily if 5- or 6-membered rings can form. Whether the side chain consists only of carbon atoms or whether it also contains hetero atoms is not of consequence. The following reaction schemes give a summary.

Formation of 5-membered rings:

$$\text{C}_6\text{H}_4\text{—CH(CH}_2\text{COCl)}_2 \longrightarrow \begin{array}{c} \text{CH·CH}_2\text{·COOH} \\ \text{CH}_2 \\ \text{CO} \end{array} \qquad \text{Manske}\ [163]$$

$$\begin{array}{c} \text{CH}_2\text{·COCl} \end{array} \longrightarrow \begin{array}{c} \text{CH}_2\ \text{CO} \end{array} \qquad \text{Friedländer}\ [164]$$

$$\text{C}_6\text{H}_4\text{—S·CH}_2\text{·COCl} \longrightarrow \begin{array}{c} \text{S} \\ \text{CH}_2 \\ \text{CO} \end{array} \qquad \text{Friedländer}\ [165]$$
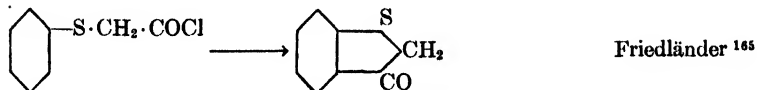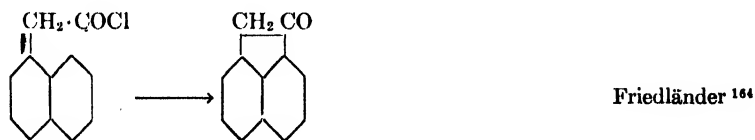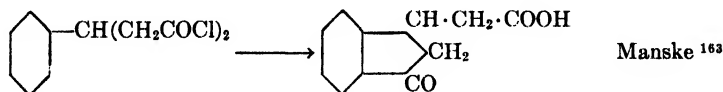
[162] Chopin, *Bull. soc. chim.*, **35**, 613 (1924).
[163] Manske, *J. Am. Chem. Soc.*, **53**, 1104 (1931).
[164] Friedländer, *Fortschr. Teerfarbenfabr.*, **10**, 199 (1910–12).
[165] Friedländer, *Fortschr. Teerfarbenfabr.*, **9**, 562 (1908–10).

Formation of 6-membered rings:

Manske [166]

Mayer and coworkers [167]

Weitzenböck [168]

Mayer and Fischbach [169]
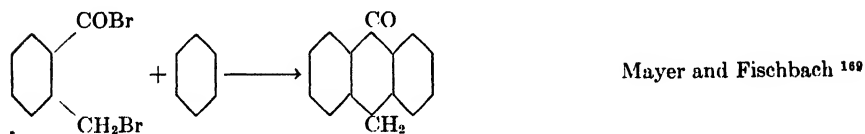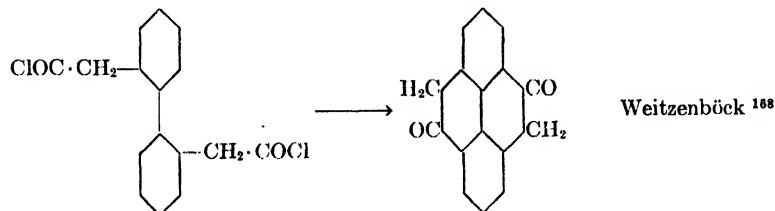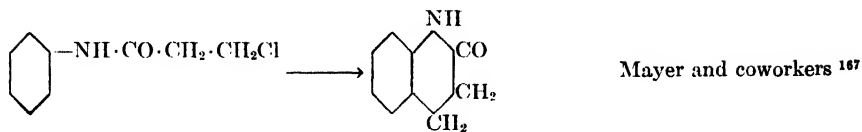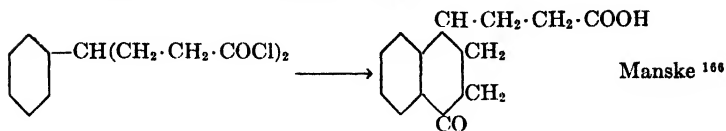
(e) Examples of Friedel-Crafts Synthesis

1. Aromatic Components. Since the Friedel-Crafts synthesis is discussed in elementary textbooks, this discussion will be limited to two examples of the ketone synthesis. According to the directions of Weygand *n*-amylacetophenone is obtained as follows:

In a flask equipped with a stirrer and a dropping funnel, 20 g. of aluminum chloride are covered with 100 cc. of carbon disulfide. The mixture of 15 g. of amylbenzene and 10.5 g. of acetyl chloride is added dropwise with stirring, the flask being cooled externally with ice. Immediately after the mixture has been added, notwithstanding a further evolution of hydrogen chloride, the clear, yellow solution is poured onto a mixture of ice and concentrated hydrochloric acid. The solution is extracted with ether until the ether extract is lighter than water. The extracts are then washed with water and dried over calcium chloride. After removal of the solvent the residue is fractionated. 16 g. of *n*-amylacetophenone boiling at 132° to 133°C. at 8 mm. are obtained. This corresponds to 83% of the theoretical amount. In previous runs which were allowed to stand after all reaction components had been added, considerably smaller yields were obtained.

Dibenzoylethylene, $C_6H_5 \cdot CO \cdot CH : CH \cdot CO \cdot C_6H_5$, is best prepared according to the method of Conant and Lutz.[170]

[166] Manske, *J. Am. Chem. Soc.*, **53**, 1109 (1931).
[167] Mayer *et al.*, *Ber.*, **60**, 858 (1927).
[168] Weitzenböck, *Monatsh.*, **34**, 193 (1913).
[169] Mayer and Fischbach, *Ber.*, **58**, 1251 (1925).
[170] J. B. Conant and R. C. Lutz, *J. Am. Chem. Soc.*, **45**, 1305 (1923).

Paal and Schulze [171] have discussed the *cis-trans* isomerism of the dibenzoylethylene.

2. Alicyclic Components. Zelinskii and Tarassoma [172] published extensive investigations on the Friedel-Crafts reaction of cycloparaffins with acetyl chloride. Depending on the conditions used, saturated or unsaturated ketones are formed. Rearrangements to methylcyclopentane derivatives occur if cyclohexane is used as the starting material. See the paper of Nenitzescu and coworkers.[173] Finally, Hopff [174] has published a few details of his experiences in this field. Formerly, details of his work could be found only in patents.

Nenitzescu and Cantuniari [175] have shown that the reaction may occasionally be used for preparative purposes.

1 liter of cyclohexane and 300 g. of freshly sublimed aluminum chloride are mixed with 150 g. of acetyl chloride with continuous stirring. On the following day, after the violent evolution of hydrogen chloride has subsided, the upper oil layer is fractionated. The oil gives 140 g. of hydrocarbons, consisting of condensation products of polycyclic nature which boil above 200°C. The lower layer is treated with ice and the ketone steam-distilled from the reaction product. On distillation, 88 g. of a fraction consisting chiefly of 1-methyl-2-acetylcyclopentane are obtained. This compound can be isolated as the semicarbazone. Unsaturated ketones, such as methylacetylcyclopentene, are formed if partly hydrated aluminum chloride is used in place of the freshly sublimed chemical. From an experiment similar to the one described above, only the semicarbazone of 1-methyl-2-acetyl-1,2-cyclopentene could be obtained when the aluminum chloride was pretreated with 20 g. of water.

Friedel-Crafts reactions between acid chlorides and hydroaromatic hydrocarbons have been recorded. Bergs, as well as Cook and Hewett,[176] recently studied the reaction of phenylacetyl chloride with cyclohexene in the presence of stannic chloride. The reaction proceeds according to the scheme,

$$C_6H_5 \cdot CH_2 \cdot COCl + \langle \hexagon \rangle \longrightarrow C_6H_5 \cdot CH_2 \cdot CO \cdot C \underset{CH_2-CH_2}{\overset{CH-CH_2}{<}} CH_2 + HCl$$
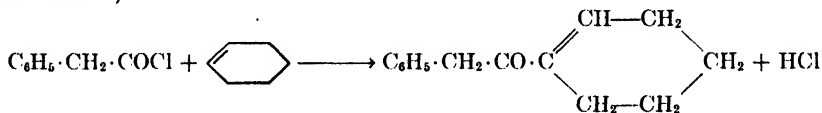
Thus, α,β-unsaturated ketones or tetrahydrodesoxybenzoins are formed. The above ketone is stable and shows no tendency to rearrange into a phenanthrene derivative. An example for the formation of such ketones is supplied by the directions of Bergs and Wittfeld [176] which follow.

[171] Paal and Schulze, *Ber.*, **33**, 3796 (1900); **35**, 168 (1902).
[172] Zelinskii and Tarassoma, *Ann.*, **508**, 115 (1934).
[173] Nenitzescu *et al.*, *Ann.*, **491**, 189 (1931); *Ber.*, **66**, 1097 (1933).
[174] H. Hopff, *Ber.*, **65**, 482 (1932).
[175] Nenitzescu and Cantuniari, *Ber.*, **65**, 1449 (1932).
[176] H. Bergs, *Ber.*, **67**, 238 (1934); W. Cook and Hewett, *J. Chem. Soc.*, 1933, 1098.

To a solution of 78 g. of stannic chloride and 180 g. of carbon disulfide, cooled to −10°C., is added a mixture of 25 g. of cyclohexene and 45 g. of phenylacetyl chloride at such a rate that the temperature does not exceed −5°C. Stirring is continuous. The reaction mixture is then treated as follows, according to an earlier method of Darzens.[177] After decomposition with ice and hydrochloric acid the primary product dissolved in carbon disulfide is treated with tertiary bases. Bergs first distils the carbon disulfide, heats the residue for 3 to 4 hours to 180°C. with 35 g. of dimethylaniline, and treats the mixture with aqueous hydrochloric acid. The solution is extracted with ether and the ethereal extract washed with water. The yield is 19 g. of ketone boiling at 171° to 176°C. at 12 mm.

Cook and Hewett treat the reaction mixture obtained from 250 g. of stannic chloride, 600 cc. of carbon disulfide, 154 g. of phenylacetyl chloride, and 82 g. of cyclohexene with ice and hydrochloric acid, wash the carbon disulfide solution with water, and dry it with sodium sulfate. After the addition of 130 g. of dimethylaniline they distil the carbon disulfide, heat the residue for 3 hours at 180°C., and proceed as described above. However, they shake the ethereal solution with a solution of sodium carbonate to remove the phenylacetic acid. By fractional distillation 48 g. of the ketone, boiling at 158° to 161°C. at 5 mm., are obtained. They report a melting point of 46° to 48°C.; Bergs reports 47°C.

2. Gattermann-Koch Synthesis

The aldehyde synthesis of Gattermann-Koch no longer has any very practical laboratory importance. However, the industrial importance of this method warrants its discussion.

Indications are that the halogen-containing component is formyl chloride, OCHCl, or formimide chloride, NHCHCl. A mixture of carbon monoxide and hydrogen chloride reacts according to the first formula in the presence of aluminum chloride and cuprous chloride, while a mixture of hydrogen cyanide and hydrogen chloride reacts according to the second formula. The cuprous chloride is not absolutely necessary. Most of the syntheses proceed under pressure in the presence of aluminum chloride alone. This variation of the Friedel-Crafts reaction is inconvenient in the laboratory, but very important industrially. The ability of cuprous chloride to bind carbon monoxide indicates its rôle.

The method consists of mixing the halogen-free component with the condensing agent and of admitting the gas mixture with stirring. The operation which requires a long time and is inconvenient gives variable results.

Benzene, which does not react directly with carbon monoxide and hydrogen chloride at atmospheric pressure, will react with hydrocyanic acid and hydrogen chloride. Toluene gives a fair yield of p-tolualdehyde with carbon monoxide and hydrogen chloride. This aldehyde is obtained more readily from p-xylene (see page 156). Ethylbenzene fails to react in the procedure in which carbon monoxide-hydrogen chloride is employed.

[177] G. Darzens, *Compt. rend.*, **150**, 707 (1910).

Braun [178] succeeded in obtaining a fair yield of *p*-ethylbenzaldehyde only once by this method. Many other authors have reported failures; see Cline and Reid.[179] Once Weygand obtained appreciable amounts of *o*-ethylbenzaldehyde. High boiling condensates were the main product.

Since the hydrogen cyanide-hydrogen chloride variation of this method gives better results, the hydrogen cyanide has been replaced by zinc cyanide in order to eliminate handling of the dangerous gas. The publications of Adams and coworkers [180] on this subject are of outstanding value. Hinkel and coworkers [181] have used the addition compound of hydrogen cyanide with aluminum chloride.

The method is apparently used commercially for the preparation of certain aldehydes which are obtained in the laboratory much more conveniently and safely by the Grignard synthesis or from the corresponding glyoxylic acid esters according to Bouveault (see page 396). Those cases in which the carbon skeleton is already present in the starting material are exceptions (see pages 134 and 156).

Most of the recent accounts of the Gattermann-Koch synthesis are to be found in patents. It is claimed that the aluminum chloride can be activated by titanium tetrachloride instead of cuprous chloride. Aldehydes of nitro compounds are obtained with carbon monoxide, hydrogen chloride, and aluminum chloride even in the absence of cuprous chloride and pressure. Phenols (*e.g.* β-naphthol with formamide) yield hydroxy aldehydes.

Wieland and Dorrer [182] studied the action of hydrogen cyanide and hydrogen chloride upon acetoacetic ester and acetylacetone. They found the reactive methylene group instead of the carbonyl group to be involved in the reaction,

$$CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3 + HNCHCl \longrightarrow (CH_3 \cdot CO)_2 : CH \cdot CH : NH \cdot HCl$$
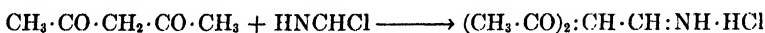
1,1-Diphenylethylene yields diphenylpropionitrile and polymers.

$$(C_6H_5)_2C : CH_2 + HNCHCl \longrightarrow (C_6H_5)_2C \cdot CH_2Cl \longrightarrow (C_6H_5)_2C \cdot (CN) \cdot CH_3$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad CH : NH$$
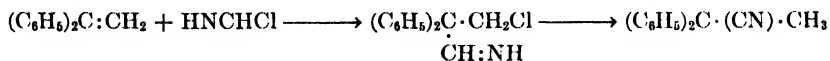
Wieland and Hasegawa [183] found that hydroaromatic compounds such as cyclohexane undergo a profound change of the carbon skeleton under the influence of carbon monoxide and aluminum chloride.

[178] J. v. Braun, *Ann.*, **436**, 304 (1924).
[179] E. Cline and E. Reid, *J. Am. Chem. Soc.*, **49**, 3150 (1927).
[180] R. Adams *et al.*, *J. Am. Chem. Soc.*, **45**, 2373 (1923); **46**, 1518 (1924).
[181] Hinkel *et al.*, *J. Chem. Soc.*, **1932**, 2793.
[182] H. Wieland and E. Dorrer, *Ber.*, **58**, 818 (1925); **63**, 404 (1930).
[183] H. Wieland and Ch. Hasegawa, *Ber.*, **64**, 2516 (1931).

3. Tiemann-Reimer Synthesis

The Tiemann-Reimer synthesis which has lost most of its former importance consists of the reaction between chloroform and phenols under the influence of concentrated alkalies. In the case of phenol, salicylaldehyde and a little *p*-hydroxybenzaldehyde are obtained, according to the following scheme:
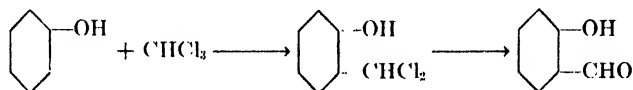
In principle, the reaction is analogous to the Gattermann-Koch synthesis if chloroform is regarded as the chloride of orthoformic acid. The yields obtained by this method vary widely even in the case of salicylaldehyde which may be found described in elementary textbooks. Salicylaldehyde is prepared commercially by the oxidation of *o*-cresol. Regardless of its shortcomings, the synthesis is so widely applicable that it might still prove to be advantageous in some special cases. Auwers and Keil [184] have studied the supposed course of the reaction.

An example of the adaptability of the synthesis is its application to pyrrole, of which the resemblance to phenol is known.

According to H. Fischer and Orth,[185] 210 g. of chloroform, 600 cc. of ethanol, 60 g. of freshly distilled pyrrole (b.p. 124°C.), and 200 cc. of water are placed in a 3 liter flask equipped with a stirrer and a reflux condenser. The mixture is heated to 40°C. and a cooled solution of 240 g. of potassium hydroxide in 480 cc. of water is added to it during 45 minutes, with continuous stirring. The temperature rises to 55° to 60°C. After the potassium hydroxide solution has been added dropwise, the stirring is continued for 1 hour longer. The mixture is then allowed to stand for 15 hours longer at 55° to 60°C. The alcohol is removed by distillation as fast as possible and as long as bumping allows. The residue is distilled with superheated steam of 200°C. until a small sticky residue remains in the flask, 5 to 8 liters of distillate being collected. The distillate is saturated with sodium chloride and the solution is extracted two or three times with 1 liter portions of ether. The extracts are dried over potassium carbonate and concentrated to about 100 cc. on a water bath. This residue is distilled *in vacuo*. Following a forerun of alcohol, chloroform, and unchanged pyrrole, the α-pyrrole aldehyde distils at 108° to 109°C. at 14 mm. as a colorless oil which solidifies immediately. The product may be purified by rapid recrystallization from petroleum ether. By this means, 16 to 18 g. of α-pyrrole aldehyde, melting at 50°C., are obtained.

C. Removal of Metal as Halide

The removal of metal with elementary halogen is the reversion of the Wurtz synthesis. This method is important for the preparation of 1,4-diketones of which acetonylacetone is an example. Acetonylacetone is

[184] K. Auwers and G. Keil, *Ber.*, **35**, 4207 (1902).
[185] H. Fischer and H. Orth, *Die Chemie des Pyrrols*. Akadem. Verlagsgesellschaft, Leipzig, 1934, p. 152.

obtained, according to Knorr and Haber,[186] by way of diacetylethyl succinate; see also E. Fischer.[187]

To a solution of 25 g. of acetoacetic ester in 150 g. of dry ether are added 5 g. of sodium wire. A violent evolution of hydrogen starts, but the sodium is soon covered by sodium acetoacetic ester. The reaction is best carried out in a bottle equipped with a reflux condenser and a calcium chloride tube. When the main reaction is finished, after 1 or 2 hours, the reflux condenser is removed, and the bottle is shaken well. When the sodium has disappeared after repeated shakings, an ethereal solution containing 20 g. of iodine is added in portions and with continuous shaking. The iodine is used up at once and sodium iodide separates. As soon as the iodine color persists, the solution is filtered and the ether removed by distillation. The residual oil which crystallizes soon is pressed on porous plates and recrystallized from 50% acetic acid. According to Knorr, the yields vary. If the mother liquors are worked up, a yield of 40% of the theoretical amount may be obtained. In larger preparations the oily portions are shaken with sodium carbonate solution. By this means an additional quantity of one of the desmotropic forms of diacetylethyl succinate can be recovered. The melting point which ranges from 85° to 90°C. is never sharp, because the ester rearranges somewhat during the melting. Additional details are given in the original paper.

For the conversion of diacetylethyl succinate to acetonylacetone see page 465.

According to Bischoff and Rach [188] ethylethane tetracarboxylate is obtained in a similar manner.

To a cooled solution of 2.3 g. of sodium in absolute alcohol are added 16 g. of diethyl malonate, followed by ether to the point of incipient cloudiness. An ethereal solution of 12.7 g. of iodine is then added. When the mixture is shaken, the color disappears. The sodium iodide which crystallizes is dissolved by the addition of water; the ether layer is separated, shaken with a dilute sodium thiosulfate solution, dried, and evaporated on a water bath. After recrystallization from ligroin an almost quantitative yield of product, melting at 76°C., is obtained.

D. Removal of Water

1. Formation of a Single New Bond

(a) Only Hydrogen at Point of Union

The removal of water from hydroxy compounds leads to the formation of a single new carbon bond; the method is restricted to relatively few cases.

In the aliphatic series it is possible to condense high molecular alcohols with each other; see Guerbet.[189] The reaction is as follows:

$$R \cdot ONa + H \cdot R' \cdot OH \longrightarrow R \cdot R' \cdot OH + NaOH$$
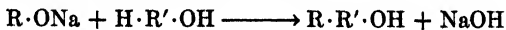
[186] L. Knorr and F. Haber, *Ber.*, 27, 1155 (1894).
[187] E. Fischer, *Anleitung zur Darstellung organischer Präparate*, Vieweg, Braunschweig, 1930, p. 53; *Ann.*, 306, 356, foot-note (1899).
[188] C. Bischoff and C. Rach, *Ber.*, 17, 2781 (1884).
[189] M. Guerbet, *Ann. chim. phys.*, 27, 67 (1902).

130 g. of sodium are dissolved in 1 kilo of amyl alcohol and the solution is boiled under a reflux for 24 hours. The boiling point rises from 132° to 250°C. soon after the sodium has dissolved. The mixture is cooled and diluted with water. Sulfuric acid is added to a slightly alkaline reaction, and the supernatant oil is separated, washed with water, and dried over potassium carbonate. Upon fractionation of the oil 125 g. of a neutral liquid boiling at 210° to 211°C. are obtained. A residue of 8 g. of a high boiling compound remains in the flask. Various fatty acids can be isolated from the aqueous alkaline liquid.

The reaction is quite complex and, therefore, the method has not gained any usefulness for syntheses.

The removal of water between alcohols and aromatic hydrocarbons proceeds more readily. According to V. Meyer and Wurster,[190] benzyl alcohol and benzene in a mixture of glacial acetic and sulfuric acids yield diphenylmethane even at room temperature. Hemilian [191] found that benzhydrol when boiled with toluene and phosphorus pentoxide gives an almost theoretical yield of diphenyltolylmethane. Other condensing agents such as stannic and zinc chlorides may be used instead of sulfuric acid.

Recently the method of alkylating the nucleus of aromatic compounds by means of alcohols has been variously applied commercially. Examples of this method are the preparation of cumene from benzene and isopropanol, of thymol and of others; see Verley.[192] Meyer and Bernhauer [193] thoroughly studied the method of condensation with sulfuric acid. They found, as was to be expected, that methanol does not condense, and that ethanol is not suitable. On the other hand, many compounds which are otherwise difficult to obtain can be prepared conveniently from high alcohols of the aliphatic series and benzyl alcohol. Normal carbon chains, however, cannot be introduced in this manner. All primary alcohols which happen to split off water yield the same product as the isomeric secondary or tertiary alcohols. This behavior is entirely analogous to that encountered in the alkylation of the benzene nucleus by means of the Friedel-Crafts reaction. A few examples will be given to illustrate the method. The yields of the products formed are occasionally good. Therefore, under some conditions the method should be preferable to the Friedel-Crafts reaction.

For the preparation of cumene 50 g. of benzene and 19 g. of isopropanol were heated, with stirring, for 3 to 4 hours with 400 cc. of 80% sulfuric acid at a bath temperature of 65°C. On isolation of the product in the usual way 65% of the theoretical yield of cumene was obtained.

[190] V. Meyer and C. Wurster, *Ber.*, 6, 964 (1873).
[191] W. Hemilian, *Ber.*, 7, 1209 (1874).
[192] A. Verley, *Chem. Abstracts*, 23, 395 (1929).
[193] H. Meyer and K. Bernhauer, *Monatsh.*, 53/54, 721 (1929).

In a corresponding manner, 40 g. of toluene and 25 g. of isopropanol with the same amount of 80% sulfuric acid gave a 35% yield of p-cymene.

In the same way, the three xylenes, phenol, o- and m-cresol, resorcinol, o-nitrotoluene, chlorobenzene, and naphthalene were treated with isopropanol, secondary butanol, isobutanol, and cyclohexanol.

Tchichibabin [194] later used phosphoric acid ($D = 1.83$ to 1.85) in place of sulfuric acid, especially for the alkylation of phenols and phenol ethers. Only branched chains could be introduced by this method. With few exceptions, Fittig's synthesis is still the best for the preparation of benzene homologues with normal chains. A further disadvantage of the dehydration method for the discussed alkylations is the occasional preponderance of higher alkylation products.

The formation of the condensation products according to this method proceeds without doubt through the alkyl sulfates. The same end-products are obtained by starting with the unsaturated hydrocarbons instead of the alcohols. The same behavior is true of the Friedel-Crafts reaction. When the olefins are readily available, they can be used equally well; see page 329.

In the same way that mixtures of alcohols and aromatic hydrocarbons lose water under the influence of sulfuric acid to yield benzene homologues, 1-phenyl-3-hydroxy compounds also lose water intramolecularly, giving indans according to the following scheme:
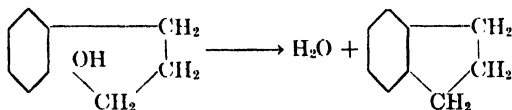
It is noteworthy that no isomerization occurs. Because of the stability of the 5-membered rings hydrindene but no methylbenzocyclobutane is formed.

Bogert and Davidson [195] recently studied the course of this reaction thoroughly and designated it cyclodehydration. The removal of water probably does not proceed directly according to the above scheme. Rather, unsaturated side chains form first and cyclization follows. But it is not impossible that in the case of γ-phenylbutanol the cyclization takes place directly. Thus, tetralin is obtained in good yield from the butanol, but not from 4-phenyl-1-butene. Not only primary but also secondary and tertiary alcohols of the above type undergo cyclization. Indans are obtained only from tertiary alcohols. With primary and secondary alcohols which contain the phenyl group in the position β to the hydroxyl group one must assume that the aryl olefins formed during

[194] Tchichibabin, *Bull. soc. chim.*, **2**, 497 (1935).
[195] M. Bogert and D. Davidson, *J. Am. Chem. Soc.*, **56**, 185 (1934).

the dehydration are polymerized faster than they are cyclized under the influence of sulfuric acid. Therefore, 1,1-dimethylindans and their homologues can be prepared but not the indans which still contain a hydrogen atom in the 1 position. On the other hand, tetralin as well as 1,1-dimethyltetralin may be obtained readily. In a later paper [196] 1,1,6-trimethyltetralin, the so called ionene, is described. Tiemann and Krüger [197] first obtained it by dehydration of α- and β-ionone. Bogert and coworkers verified the formula. The general procedure for the preparation of dimethylhydrindan is as follows:

1 volume of the tertiary alcohol is added dropwise slowly to 1.2 volumes of 85% sulfuric acid. The mixture is stirred well and its temperature kept at 10°C. The reaction apparently proceeds at once, but in order to make sure the mixture is stirred at room temperature for 1 hour longer. The mixture is then diluted with 10 to 15 volumes of water and distilled. The oily layer of the distillate is separated, the aqueous part being returned to the distilling flask and distilled again. The combined portions of oil are steam-distilled again from alkaline water, and the oil is dried and rectified. 1,1-Dimethylhydrindene, boiling at 191°C., was obtained in a 65% yield; 1,1,2-trimethylhydrindene, boiling at 208°C., in a 90% yield; tetralin in a 55% yield. Varying amounts of polymerization products remain as sticky oils or resin in the distilling flask during the steam distillation.

Numerous complex ring closures brought about by the removal of water are known. In this category belong the formation of α-naphthol from β-phenylcrotonic acid, according to Fittig and Erdmann,[198] as well as many heterocyclic syntheses including the quinoline synthesis of Scraup, the pyrrole synthesis of Knorr, and the anthraquinone synthesis of Heller.

(b) Hetero Atoms at Point of Union

The alkali condensation of aldehydes with ketones according to the scheme, $R \cdot CHO + CH_3 \cdot CO \cdot R' \rightarrow R \cdot CH : CH \cdot CO \cdot R' + H_2O$, succeeds readily in the case of methyl ketones (see page 426). The method fails, however, with the homologues of methyl ketones which are substituted in the methyl group. For example, benzalpropiophenone, $C_6H_5 \cdot CH : C(CH_3) \cdot CO \cdot C_6H_5$, cannot be obtained from benzaldehyde and propiophenone with alkali. The condensation is successful when gaseous hydrogen chloride is used. Hydrogen chloride which may also be used for the preparation of unsubstituted unsaturated ketones offers no advantages in these cases.

The hydrogen chloride method involves the initial formation of saturated chloro ketones of the following type:

$$R \cdot CHCl \cdot CH(CH_3) \cdot CO \cdot R \qquad \text{or} \qquad R \cdot CH_2 \cdot CCl(CH_3) \cdot CO \cdot R$$
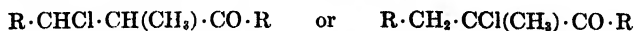
[196] M. Bogert and D. Davidson, *J. Am. Chem. Soc.*, **56**, 959 (1934).
[197] Tiemann and Krüger, *Ber.*, **31**, 808, 873 (1898).
[198] R. Fittig and H. Erdmann, *Ann.*, **227**, 245 (1885).

These chloro ketones lose hydrogen chloride readily when heated. Kohler [199] gives the following directions for the preparation of benzalpropiophenone.

An equimolecular mixture of benzaldehyde and propiophenone is saturated with hydrogen chloride and then allowed to stand for 2 days in ice water. The olive-colored solution is mixed with ether, washed with water and saturated bisulfite solution, and dried over calcium chloride. After the solvent has been removed by distillation, the residual oil solidifies almost completely in a freezing mixture. On recrystallization from petroleum ether the product melts at 83°C. On being heated the solid loses hydrogen chloride. Benzalpropiophenone, boiling at 190° to 192°C. at 28 mm., is obtained by vacuum distillation.

The course of the reaction is not clear. During the first 24 hours Weygand and Bischoff found no removal of water when they saturated a mixture of anisaldehyde and propiophenone. When microscopic water drops later become visible, the reaction mixture solidified quite suddenly, forming a red-brown mass of crystals which lost hydrogen chloride in air and turned almost colorless.

It is noteworthy that the unsaturated ketones formed by removal of the remaining molecule of hydrogen chloride occasionally appear in stereoisomeric forms; see Stobbe and Bremer.[200]

2. Removal of Water and Formation of Several New Carbon Bonds

Carbonyl groups of aromatic aldehydes as well as those of acid anhydrides of the phthalic anhydride type react with phenols and tertiary amines, forming triphenylmethane derivatives and phthaleins. The many dehydrating agents used for this reaction include zinc chloride and phosphorus oxychloride. This reaction which is of great importance in the chemistry of dyes and the reaction involving the formation of anthraquinone derivatives from phthalic anhydride and hydroquinone cannot be discussed here.

E. Removal of Alcohol, Carbonic Acids, etc.

1. Ester Condensations

The basic scheme of the reaction is as follows:

$$R' \cdot COOC_2H_5 + CH_2 \overset{CO \cdot R''}{\underset{R'''}{\diagup\diagdown}} \longrightarrow R' \cdot CO \cdot CH \overset{CO \cdot R''}{\underset{R'''}{\diagup\diagdown}} + C_2H_5OH$$
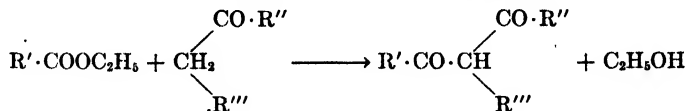
The radical R' may be hydrogen, an aliphatic, an aromatic, a heterocyclic, or a mixed residue. R''' may be hydrogen or any organic residue.

[199] P. Kohler, *Am. Chem. J.*, **31**, 655 (1904).
[200] H. Stobbe and K. Bremer, *J. prakt. Chem.*, **123**, 34 (1929).

R″ may also be any carbon-containing radical, as well as hydroxyaryl or hydroxyalkyl. The following subdivisions are formed.

1. Condensation of 2 ester molecules with each other:

$$CH_3 \cdot COOC_2H_5 + CH_3 \cdot COOC_2H_5 \longrightarrow CH_3 \cdot CO \cdot CH_2 \cdot COOC_2H_5 + C_2H_5OH$$
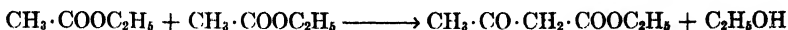
β-Keto esters are obtained.

2. Condensation of an ester molecule with an aliphatic, aromatic, or heterocyclic methyl ketone:

(a) $CH_3 \cdot COOC_2H_5 + CH_3 \cdot CO \cdot CH_3 \longrightarrow CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3 + C_2H_5OH$

(b) $C_6H_5 \cdot COOC_2H_5 + CH_3 \cdot CO \cdot C_6H_5 \longrightarrow C_6H_5 \cdot CO \cdot CH_2 \cdot CO \cdot C_6H_5 + C_2H_5OH$
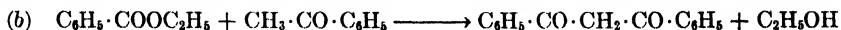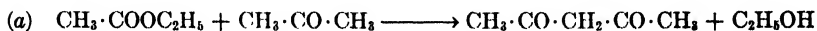
By this method 1,3-diketones with unsubstituted methylene groups are formed.

3. Condensations of an ester molecule with a ketone containing a methylene group adjacent to the carbonyl group:

$$CH_3 \cdot COOC_2H_5 + R \cdot CH_2 \cdot CO \cdot R \longrightarrow CH_3 \cdot CO \cdot CHR \cdot CO \cdot R + C_2H_5OH$$
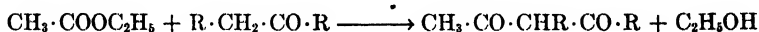
By this method, 1,3-keto aldehydes are obtained.

Some of the reactions listed are of little synthetic importance because the desired compounds can be obtained better and more conveniently in other ways. This lack of importance applies to *1*, *2b*, and *3* under the following conditions.

1. If aromatic substituted β-keto esters are to be prepared. Benzoylacetic ester, for example, is best obtained from benzoylation of acetoacetic ester, followed by removal of the acetyl residue; see page 464.

2b. 1,3-Diketones substituted on both sides by aromatic residues are best prepared from the corresponding, readily available chalcone derivatives; see page 202.

3. 1,3-Diketones substituted in the methylene group and β-keto esters can be obtained more readily from the corresponding unsubstituted ketones. For example, methylacetoacetic ester, $CH_3 \cdot CO \cdot CH(CH_3) \cdot COOC_2H_5$, is obtained by methylation of acetoacetic ester, as described on page 359.

Ester condensations frequently lead to important ring closures.

(a) General Remarks about Carrying Out Ester Condensations

The following condensing agents may be considered: alkali metals, usually sodium, sodium amide, and sodium alcoholate. Sodium amide, though used extensively in industry, is dangerous and must be treated with caution in the laboratory. Sometimes violent detonations occur

without apparent cause. Even fresh samples are not free of danger. Old and partially corroded products must be discarded.

There has been much controversy about the course of the reaction for some time and is not entirely explained even today. That the condensing agent proper is sodium alcoholate in all cases is clear; see McElvain.[201] As is known, the classical synthesis of acetoacetic ester from acetic ester and sodium always requires small traces of alcohol. These small amounts are normally present in ethyl acetate even after careful purification. According to Bouveault and Blanc, the first step is a reduction of the ester by nascent hydrogen. Thus, the condensing agent is really formed during the course of the reaction. Since more alcohol is formed as alcoholate during the subsequent condensation, it is good practice not to use large amounts of alcoholate at the start.

The poor results obtained by working with starting materials which have not been carefully purified cannot be blamed on the alcohol content of the ester. Rather, the facts, based on the methods of making esters, are that the contaminating alcohol can be taken out of a crude ester, especially ethyl acetate, only at the same time that water is removed. Ester which contains alcohol left in it during preparation always contains water. On the other hand, it is safe and in many cases advantageous to start the condensation of pure starting materials by means of measured additions of dry alcohol. Apparently the form in which the sodium is used is unimportant. Sodium wire and slices behave similarly.

For carrying out the reaction no general direction can be given. In most cases an initial period requiring heating or addition of materials, a main period and an end period can be observed. During the main reaction period it is advisable to moderate the reaction by cooling, so that the Bouveault-Blanc reductions in which sodium and ester are used for side reactions do not become prominent. The end-point cannot always be recognized if solid precipitations cover sodium mechanically and withhold it from the reaction.

For this reason caution must be exercised in further treatment of the reaction mixture which is usually first acidified. If possible, the contents of the flask should first be placed in a shallow porcelain dish, and large sodium lumps should be removed before the customary acidification.

In accordance with long established practice most ester condensations are still performed on a water bath. This method of heating is somewhat dangerous in the presence of large amounts of sodium.

Ester condensations belong to the small class of reactions which usually give better yields in larger preparations than in small ones. This

observation is in agreement with what has been said above on the alleged course of the reaction.

The following directions are given for the purification of ethyl acetate.

The ester is washed twice with an equal amount of water in a separatory funnel. Sodium carbonate solution is used if acid reaction can be detected. Washing with water is continued until the alkaline reaction disappears. The ester is dried first with a small amount of calcium chloride, and then with a rather large amount of calcium chloride for 24 hours. Losses sustained from the formation of a molecular compound are inevitable.

Inglis and Roberts [202] recommend using only water to wash the ethyl acetate for the acetoacetic ester synthesis. They dry the ester over molten potassium carbonate. The ester thus prepared still contains alcohol and boils within 2° to 3°C.

It is unnecessary to distil the ester which has been dried over calcium chloride or over potassium carbonate. The ester is very hygroscopic and, therefore, must not be filtered in air but is best siphoned off.

The use of metallic sodium is avoided whenever one of the reacting molecules contains groups which might be changed by nascent hydrogen. In such cases only sodium ethylate can be used.

(b) Examples

Since directions for simple cases of the ester condensation can be found in elementary textbooks, only a few of its applications in more complicated cases will be described below to show the importance of the method.

In the total synthesis of the cinchona alkaloids, hydroquinidine and hydroquinine, an acetoacetic condensation is used to join 2 molecules of the multinuclear heterocyclic systems.

Rabe and coworkers [203] treated 20 g. of the ethyl ester of benzoylhomocincholoipone (I) and 30 g. of the ethyl ester of quininic acid (II) with sodium ethylate, the latter being prepared from 3.5 g. of sodium and 7 g. of absolute ethanol. The components were heated without dilution to 80°C. Ice water was then added, and the alkaline solution was separated from the unchanged starting material and made acid to Congo paper. The separating oil was extracted with ether and dried over sodium sulfate. After evaporation of the ether the β-keto ester (III) remained. The benzoyl group was split from the ester by boiling for several hours with 17% hydrochloric acid. The ester was saponified and decarboxylated, thus yielding the hydroquinotoxine (IV). The yield of crude product was 12.9 g., corresponding to 62.5% of the theoretical amount. The toxine which did not crystallize was purified as the N-dibenzoyl-d-tartrate.

[202] H. Inglis and C. Roberts in H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 235.

[203] P. Rabe *et al.*, *Ber.*, 52, 1843 (1919); 64, 2497 (1931).

$$CH_2 \cdot CH_2 \cdot COOC_2H_5 + C_2H_5OOC$$

(I)   (II)

(III)

(IV)
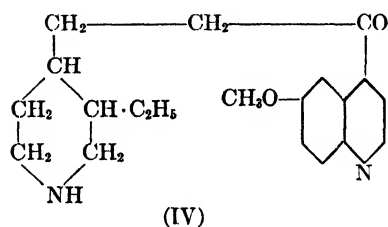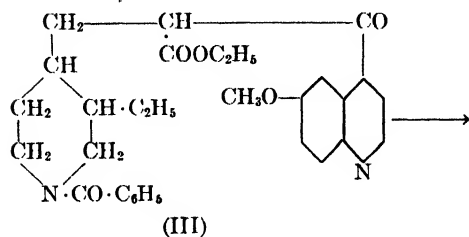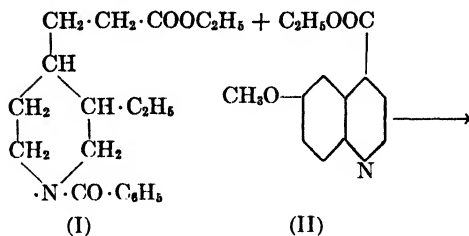
Dieckmann [204] reported an important amplification of the ester condensation. It consists of effecting a ring closure between the ester groups of the same chain. Thus, ethylcyclopentanone carboxylate is formed from diethyl adipate:
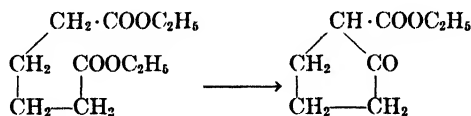
A few drops of alcohol and 4.6 g. of sodium wire are added to 20 g. of ethyl adipate. The mixture is heated on an oil bath. The reaction takes place at 100° to 110°C. with boiling and cleavage of alcohol. After a few minutes the mixture solidifies. It is heated for 30 minutes longer at 120° to 140°C., cooled, and the dry product pulverized. The powder is added to cold dilute sulfuric acid which is covered with an ether layer to prevent the sodium residues from catching fire. The ether layer is shaken with sodium carbonate solution to remove the more acidic by-products. The keto ester is extracted from the ether with 15% potassium hydroxide solution and the alkaline extract is acidified. Ethylcyclopentanone carboxylate, boiling at 103° to 104°C. at 11 mm., can be isolated in about 60% yield.

[204] W. Dieckmann, *Ann.*, **317**, 27 (1901).

Willstätter and Bommer [205] employed the above synthesis of Dieckmann for the total synthesis of cocaine. N-Methylpyrrolidinediethyl diacetate (V) is converted to tropinonecthyl carboxylate (VI); this intermediate was not isolated but was hydrolyzed to give tropinone.

$$CH_2—CH—CH_2·COOC_2H_5 \qquad CH_2—CH————CH·COOC_2H_5$$

(lines continue)

N·CH₃ → N·CH₃ CO

$$CH_2—CH—CH_2·COOC_2H_5 \qquad CH_2—CH————CH_2$$

(V) (VI)
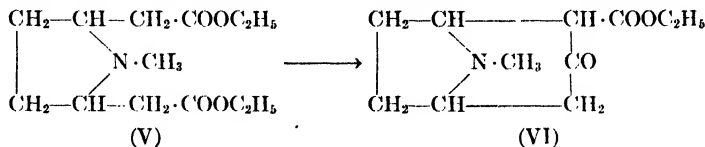
10 g. of pyrrolidinediethyl diacetate are heated with 10 g. of cymene and 2 g. of sodium powder, the reaction taking place at about 160°C. During the reaction which is complete in about 10 minutes, the temperature does not exceed 172°C. For conversion to tropinone the reaction product is dissolved in water, the solution saturated with potassium carbonate, and the oil which separates is boiled with dilute sulfuric acid. The tropinone thus formed yields 2.9 g. of tropinone picrate. Based on the amount of picrate, the yield is 25%.

The corresponding condensation does not take place with pyrrolediethyl diacetate.

(c) Special Ester Condensations

On the basis of Henrich's observation (see page 365) that the methylene group of ethyl glutaconate is greatly activated by the adjacent double bond, Lapworth [206] showed that methylene groups of unsaturated carboxylic acid esters, e.g. ethyl crotonate, $CH_3·CH:CH·COOC_2H_5$, also undergo ester condensations. Ethyl crotonate behaves like ethyl acetate in this respect. Condensed with diethyl oxalate and sodium ethylate it yields the oxaloethyl crotonate, $C_2H_5OOC·CO·CH_2·CH:CH·COOC_2H_5$. This behavior is like condensation of diethyl oxalate and ethyl acetate, which gives ethyl oxaloacetate.

Borsche and Manteuffel [207] reinvestigated this long forgotten reaction and applied it to other cases. It is noteworthy that potassium alcoholate must be substituted for sodium alcoholate.

In the preparation of ethyl oxalosorbate, $C_2H_5OOC·CO·CH_2·CH:CH·CH:CH··COOC_2H_5$, 13 g. of potassium are treated under 85 cc. of ether with 58 cc. of alcohol. To this mixture is added a solution of 24.3 g. of diethyl oxalate in 10 cc. of ether with external cooling in an ice bath and with shaking. 15 minutes later a solution of 23.3 g. of ethyl sorbate in 10 cc. of ether is added. The reaction mixture becomes dark red immediately. The mixture is allowed to stand for 24 hours. Then the yellow potassium enolate of the ethyl oxalosorbate is filtered as rapidly as possible by suction, washed with cold ether, and dried in a desiccator on a porous plate. The yield of enolate is 27 to 28 g. The enolate is dissolved in water, the solution acidified with 2 N acetic acid, and the

[205] R. Willstätter and M. Bommer, *Ann.*, 422, 17 (1921).
[206] A. Lapworth, *Proc. Chem. Soc.*, 16, 132 (1900).
[207] W. Borsche and R. Manteuffel, *Ber.*, 65, 868 (1932).

ester which solidifies rapidly is recrystallized from ligroin or ethyl acetate. The melting point is 100°C.

When 2.8 g. of the potassium compound are heated with a solution of 1.1 g. of acetic anhydride in 30 cc. of ether on a water bath for 30 minutes, the enol acetate of the oxalosorbic acid ester of the following formula is obtained: $C_2H_5OOC \cdot C(OCOCH_3):CH \cdot CH:CH \cdot CH:CH \cdot COOC_2H_5$. Potassium acetate separates. The enol acetate melts at 50° to 51°C. after recrystallization from petroleum ether.

2. Removal of Carboxylic Acids

Another interesting and different way of preparing β-diketones is the condensation of methyl ketones and acid anhydrides, by means of boron fluoride.

According to Meerwein and Vossen,[208] a mixture of 20 g. of acetophenone and 34 g. of acetic anhydride is cooled in an ice bath and saturated with boron fluoride. The reaction product which has formed a nearly solid mass of yellow crystals at the end of the reaction is added to a solution of 45 g. of sodium acetate in 100 cc. of water, and the mixture is steam-distilled. At first small amounts of an oil appear. The benzoylacetone which follows crystallizes in the condenser. The product is extracted with ether, washed with sodium bicarbonate, dried over sodium sulfate, and distilled *in vacuo*. By this means, 22.5 g. of benzoylacetone are obtained. The yield is 83.3% of the theoretical amount. In a similar way, 2-acetyltetralone was prepared in an 83.4% yield and 2-acetylcyclohexanone in a 56% yield. The equation for the reaction is as follows:

$$C_6H_5 \cdot CO \cdot CH_3 + O \underset{CO \cdot CH_3}{\overset{CO \cdot CH_3}{\diagdown}} \xrightarrow{BF_3} C_6H_5 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3 + CH_3 \cdot COOH$$
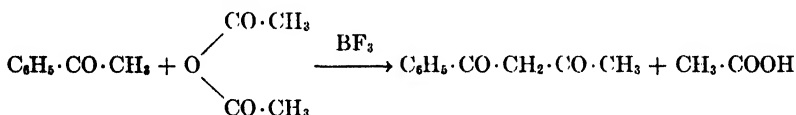
F. Removal of Nitrogen

The formation of new carbon to carbon bonds takes place with azo compounds by removal of nitrogen as a result of the action of diazo hydrocarbons on aldehydes, and with diazonium compounds.

Both aliphatic and fatty aromatic azo compounds, when heated, lose elementary nitrogen according to the general scheme, $R \cdot N:N \cdot R \rightarrow N_2 + R \cdot R$. This reaction is of theoretical interest only. Gomberg[209] succeeded in forcing the formation of tetraphenylmethane by heating a mixture of triphenylmethaneazobenzene and sand. Gomberg and Kamm[210] prepared tetraphenylmethane in a much more convenient way.

According to Schlotterbeck,[211] the action of diazomethane on aldehydes gives methyl ketones. The reaction is as follows:

$$R \cdot CHO + CH_2N_2 \longrightarrow N_2 + R \cdot CO \cdot CH_3.$$
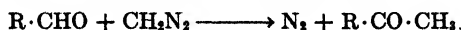
[208] H. Meerwein and D. Vossen, *J. prakt. Chem.*, 141, 157 (1934).
[209] Gomberg, *Ber.*, 36, 1090 (1903); 30, 2043 (1897).
[210] Gomberg and Kamm, *J. Am. Chem. Soc.*, 39, 2009 (1917).
[211] F. Schlotterbeck, *Ber.*, 40, 479 (1907).

This method, however, fails in those cases in which the preparation of the ketone by it would be desirable.   o-Tolualdehyde is an example.

The remarkable reaction of benzene and diazoacetic ester takes place in accordance with the following equation.

$$\text{(benzene)} + N_2CH \cdot COOC_2H_5 \longrightarrow N_2 + \text{(ring)} CH \cdot COOC_2H_5$$
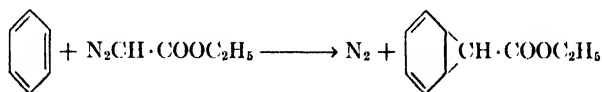
The so called pseudophenylacetic ester, or norcaradienecarboxylic acid ester, is formed.

According to Braren and Buchner,[212] 4 cc. of diazoacetic ester and 20 cc. of benzene are heated in a sealed tube for 8 hours at 130° to 135°C. The benzene from several combined preparations is removed by distillation in a water bath until the temperature of the solution reaches 97°C. The distillate also contains unchanged diazoacetic ester. The residue is distilled with steam for a rather long time. The distillate is extracted with ether, and the ethereal solution dried and distilled fractionally. About 12 to 15 g. of the pseudophenylacetic ester, boiling at 111°C. at 13 mm., are obtained from 50 g. of diazoacetic ester. The reaction takes place more readily with hydroaromatic compounds.[213]

According to Gattermann and Ehrhardt,[214] diazonium compounds are decomposed even in aqueous solution by the addition of copper powder and alcohol. They yield either diphenyl derivatives or condensed ring systems by the loss of nitrogen. The formation of diphenyl derivatives has only limited importance. However, according to Pschorr,[215] the formation of phenanthrene derivatives is frequently advantageous. The reaction is as follows:

$$\text{(structure)} \xrightarrow{} N_2 + HX + \text{(phenanthrene)}—COOH$$
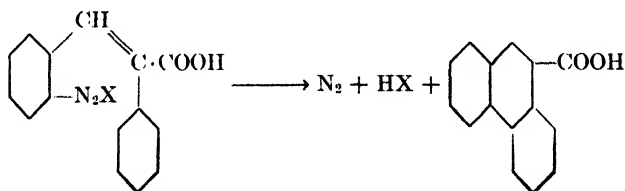
Numerous substituted phenanthrenecarboxylic acids have been obtained, starting with o-nitrophenylcinnamic acid. The nitro compounds are converted to the amino acids, diazotized, and the diazonium solution treated directly with copper powder. The acids are decarboxylated to yield phenanthrene derivatives.

[212] W. Braren and E. Buchner, *Ber.*, **34**, 989 (1901).
[213] Fr. Ebel, R. Brunner, and P. Mangel, *Helv. Chim. Acta*, **12**, 19 (1929).
[214] L. Gattermann and R. Ehrhardt, *Ber.*, **23**, 1226 (1890).
[215] R. Pschorr, *Ber.*, **29**, 496 (1896); **39**, 3106 (1906).

III. FORMATION OF ETHYLENE BONDS AND AROMATIC SYSTEMS

A. Removal of Water with Formation of New Ethylene Bond

The formation of an ethylene bond by removal of hydrogen to unite two reaction components is well known from the classical case of the indigo synthesis:

$$2 C_6H_4 \begin{array}{c} CO \\ \diagdown \\ NH \end{array} CH_2 + 2O \longrightarrow C_6H_4 \begin{array}{c} CO \\ \diagdown \\ NH \end{array} C:C \begin{array}{c} NH \\ \diagup \\ CO \end{array} C_6H_4$$
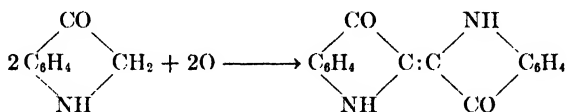
In this case atmospheric oxygen acts as the dehydrogenating agent. The reaction proceeds much more readily in the presence of oxidizing reagents.

A series of similar reactions is encountered in compounds having reactive methylene groups. According to Ziegler,[216] diphenylmethane is converted to tetraphenylethylene by heating with sulfur at 240° to 250°C. or higher. Benzyl cyanide gives a rather poor yield of dicyanostilbene when treated with bromine; see Reimer.[217]

$$2C_6H_5 \cdot CH_2 \cdot CN + 4Br = C_6H_5 \cdot C(CN):C(CN) \cdot C_6H_5 + 4HBr$$
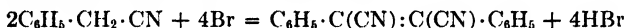
In most cases more convenient methods are available for the preparation of such condensation products; e.g., the preparation of diphenylmaleic acid which represents the saponification product of dicyanostilbene (page 418). The oxidation of several toluene derivatives to substituted stilbenes is of some importance; see Green.[218]

B. Removal of Halogen with Formation of New Ethylene Bond

1. Spontaneous Removal of Halogen as Hydrogen Halide

The spontaneous removal of halogen as was observed with iodomalonic ester (see page 353) does not occur here. Occasionally, however, the spontaneous loss of hydrogen halide between 2 molecules does occur. According to Kaufmann,[219] diphenyldiphenyleneethylene is formed in 5 to 10 minutes by melting a mixture of fluorene and benzophenone dichloride at 320° to 330°C. A 50 to 60% yield is obtained in accordance with the following equation:

$$\begin{array}{c} C_6H_4 \\ | \\ C_6H_4 \end{array} CH_2 + Cl_2C \begin{array}{c} C_6H_5 \\ \diagup \\ C_6H_5 \end{array} \longrightarrow \begin{array}{c} C_6H_4 \\ | \\ C_6H_4 \end{array} C:C \begin{array}{c} C_6H_5 \\ \diagup \\ C_6H_5 \end{array} + 2HCl$$
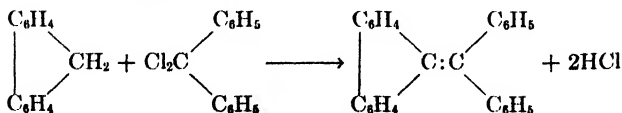
[216] H. Ziegler, Ber., 21, 779 (1888).
[217] Reimer, Ber., 14, 1797 (1881).
[218] Green, J. Chem. Soc., 93, 1724 (1908).
[219] Kaufmann, Ber., 29, 75 (1896).

The cooled melt is dissolved in a small amount of hot benzene. The compound which separates is recrystallized repeatedly from benzene. Colorless leaflets or needles containing crystal benzene which effloresce rapidly are obtained. The melting point is 229.5°C. The reaction is successful only in preparations of about 5 g.

2. Removal with Metals

A synthesis of ethylene hydrocarbons by a modified Wurtz synthesis can be carried out according to the scheme, $2R_2CX_2 + 4Me \rightarrow 4MeX + R_2:C:C:R_2$. Gill [220] was able to obtain di-o-dichlorostilbene dichloride, $C_6H_4Cl \cdot CHCl \cdot CHCl \cdot C_6H_4Cl$, from o-chlorobenzal chloride and molecular silver (see page 382). This dichloride on treatment with copper powder gave di-o-dichlorostilbene, $C_6H_4Cl \cdot CH:CH \cdot C_6H_4Cl$. If o-chlorobenzal chloride is treated with copper powder, di-o-dichlorostilbene is formed directly. The reaction proceeds in two stages and the method offers nothing new. Limpricht [221] replaced the silver by sodium and converted benzal chloride into stilbene.

3. Removal with Alkalies

A number of synthetic methods in the stilbene series proceed according to the following scheme:

$$2R \cdot CH_2X + 2NaOH \longrightarrow R \cdot CH:CH \cdot R + 2NaX + 2H_2O$$

Nitro- and cyanobenzyl chlorides are converted readily to the corresponding stilbenes when treated with alkalies in alcoholic solution.

According to Walden and Kernbaum,[222] 50 g. of p-nitrobenzyl chloride, melting at 74°C., are dissolved in 150 g. of warm alcohol and then cooled. A solution of 17.5 g. of potassium hydroxide in 15 cc. of water and 60 g. of alcohol is added. On addition of the first drop of alkali the color of the solution turns green, then through magenta to yellow. If the potassium hydroxide solution is added slowly, the evolution of heat is negligible. During the reaction yellow crystals separate. They are filtered by suction from the cooled solution. The crystals are washed with hot water, then with warm, dilute alcohol until they are free from chlorine. The yield is 36 g. or about 90% of the theoretical. The crude product is a mixture of the stereoisomeric 4,4-dinitrostilbenes melting in a wide range. The lower melting isomer can be extracted with acetone. The high melting compound, melting at 280° to 285°C., can be purified by recrystallization from glacial acetic acid, acetone, or nitrobenzene.

The same reaction can be applied to other groups of compounds. Ethyl bromomalonate yields ethylethylene tetracarboxylate; see *Organic Syntheses*.[223]

[220] Gill, *Ber.*, 26, 649 (1893).
[221] Limpricht, *Ann.*, 139, 318 (1866).
[222] P. Walden and A. Kernbaum, *Ber.*, 23, 1959 (1890).
[223] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 273.

C. Formation of New Ethylene Bonds by Removal of Metal with Halogen

The formation of a double bond by condensation involving the removal of inorganic salts has been realized only in one single case. This was done by the action of iodine upon sodium malonic ester. According to Bischoff and Rach [224] ethylethylene tetracarboxylate is obtained in the following manner.

To a solution of 4.6 g. of sodium in ethanol are added 16 g. of diethyl malonate. To the jell which forms an ethereal solution of 25.4 g. of iodine is added slowly with shaking. The shaking is continued for a short time and the sodium iodide which separates is then dissolved in water. The ether solution is shaken with a dilute sodium thiosulfate solution to remove the iodine, dried over calcium chloride, and the ether is removed by distillation. The residue which consists of a mixture of ethane- and ethylenedicarboxylic acid esters is dissolved in boiling ether. When it is cooled, spears of ethanetetracarboxylic acid ester crystallize first. As soon as the characteristic prisms of the ethylenetetracarboxylic acid ester appear, the solution is filtered again. 12 g. of ethylenetetracarboxylic acid ester, melting at 56° to 58°C., are obtained.

D. Formation of Double Bond by Removal of Water

The formation of new ethylene bonds by removal of water can be effected by the two following reactions.

(I) $\qquad$ $2R_2CHOH \longrightarrow R_2{:}C{:}C{:}R_2 + 2H_2O$

(II) $\qquad$ $R_2CO + H_2CR_2' \longrightarrow R_2{:}C{:}C{:}R_2 + H_2O$

Reaction II is the more important. An example of Reaction I is the preparation of diphenylmaleic anhydride from mandelic acid.

According to Bischoff and Walden,[225] mandelic acid is heated under 500 mm. pressure at 100° to 190°C. for a rather long time. Carbon dioxide, water, and benzaldehyde which are formed by decomposition of a part of the mandelic acid are split off. When the evolution of gas stops, the pressure drops. On further heating a yellow oil distils, part of it solidifying in the receiver. On distillation a fraction is obtained at 180° to 230°C. at 19 mm. The distillate solidifies soon and on recrystallization yields the diphenylmaleic anhydride melting at 154° to 155°C.

The reaction proceeds as follows:

$$C_6H_5{\cdot}CHOH{\cdot}COOH$$
$$+ \qquad \longrightarrow 3H_2O +$$
$$C_6H_5{\cdot}CHOH{\cdot}COOH$$
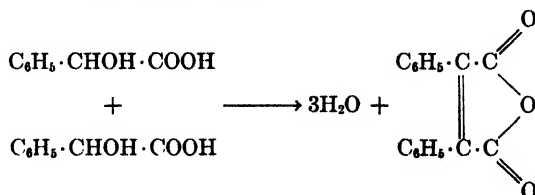
[224] Bischoff and Rach, *Ber.*, 17, 2781 (1884).
[225] C. Bischoff and P. Walden, *Ann.*, 279, 102 (1894).

This behavior is surprising inasmuch as α-hydroxy acids usually form lactides.

Numerous important condensations proceed according to Reaction II.

General Remarks on Perkin-Claisen-Knoevenagel Synthesis

The general expression for this widely applied reaction is

$$\begin{matrix} R' \\ \diagdown \\ \diagup \\ R'' \end{matrix} CO + H_2C \begin{matrix} R''' \\ \diagup \\ \diagdown \\ R'''' \end{matrix} \longrightarrow H_2O + \begin{matrix} R' \\ \diagdown \\ \diagup \\ R'' \end{matrix} C{:}C \begin{matrix} R''' \\ \diagup \\ \diagdown \\ R'''' \end{matrix}$$
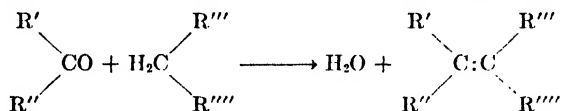
The carbonyl compound can be an aldehyde or a ketone. Almost without exception aldehydes can undergo this reaction but with ketones it is not always successful. The second reaction component requires a substituent to activate the methylene group. The nature of this substituent may vary. It is not even necessary that the activating group be immediately adjacent to the methylene if the side chain is attached to an aromatic or heterocyclic system. One of the two residues R''' and R'''' may be hydrogen.

The last case will be discussed first.

The methyl group can undergo the reaction in aliphatic systems (or in systems which have an aromatic or heterocyclic radical attached to a more distant point), if it is next to

1. A carbonyl group, methyl ketones

2. A carboxyl group, acetic acid (ethyl acetate)

3. A cyano group, acetonitrile

Furthermore, methyl groups attached to a nucleus are reactive under conditions as follows:

4. (*a*) if the aromatic nucleus carries the other substituents in definite positions; (*b*) in the case of certain heterocyclic compounds.

(*a*) Mononitrotoluenes are as incapable of reacting with benzaldehyde as is toluene itself. However, according to Thiele and Eskales,[226] 2,4-dinitrotoluene, benzaldehyde, and piperidine readily yield·dinitrostilbene.
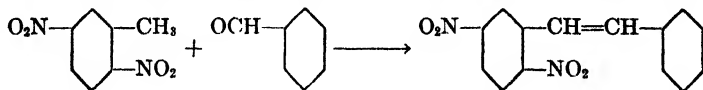
(*b*) According to Ladenburg,[227] α-picoline and benzaldehyde yield α-propenylpyridine at 250°C.
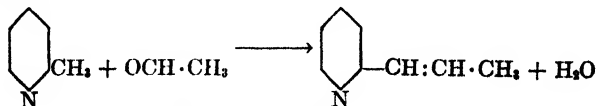
[226] Thiele and Eskales, *Ber.*, **34**, 2843 (1901).
[227] Ladenburg, *Ann.*, **247**, 26 (1888).

The acid and ketone syntheses will be discussed first.

1. Synthesis of α,β-Unsaturated Acids

The prototype of this reaction is the cinnamic acid synthesis of Perkin:

$$C_6H_5 \cdot CHO + CH_3CO \cdot O \cdot OCCH_3 \longrightarrow C_6H_5 \cdot CH:CH \cdot COOH + CH_3 \cdot COOH$$
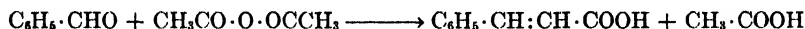
Many different views which cannot be discussed individually here have been held about the course of this reaction. The reaction is applicable to derivatives of benzaldehyde with different results. Hydroxy- and nitrobenzaldehydes undergo the reaction readily. Nuclear homologues of benzaldehyde give poor results. The unsaturated acids derived from them are better prepared according to Claisen's method by way of the esters (see page 425). Acids derived from alkoxybenzaldehydes are best prepared according to Knoevenagel's method.

Acrylic acid and its aliphatic homologues, *e.g.* crotonic acid, etc., can be prepared by oxidation of the corresponding unsaturated aldehydes (see page 152), or from low molecular aldehydes through the corresponding alkylidenemalonic acids (see page 424), or from halogenated saturated carboxylic acids by removal of hydrogen halide.

Most closely related to Perkin's synthesis is that suggested by Knoevenagel, which proceeds according to the following general scheme.

$$R \cdot CHO + CH_2(COOH)_2 \longrightarrow H_2O + R \cdot CH:C(COOH)_2$$
$$\longrightarrow R \cdot CH:CH \cdot COOH + CO_2$$
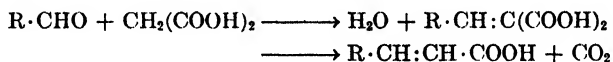
The aldehyde is made to react with acetic anhydride, or in alcoholic ammonia solution with malonic acid. Either the substituted malonic acid or its ammonium salt is obtained and a molecule of carbon dioxide is split off by heating.

A variation of this method also suggested by Knoevenagel is especially advantageous for the aliphatic series. Malonic ester is used instead of malonic acid.

The following combinations are possible:

(1) Aldehydes and malonic acid.
    (a) The condensing agent is ammonia or amines.
    (b) The condensing agent is glacial acetic acid or acetic anhydride.
(2) Aldehydes and malonic ester.
    (a) The condensing agent is hydrogen halide.
    (b) The condensing agent is acetic anhydride.
    (c) The condensing agent is ammonia or amines.

(*1, a*) Ammonia or amines, when used as condensing agents, apparently form addition compounds with the aldehydes in the first phase of the reaction. According to Rodionov and Malewinskaja,[235] amino acids occasionally appear as the end-products.

$$R \cdot CHO + NH_3 + CH_2(COOH)_2 \longrightarrow R \cdot CH(NH_2) \cdot CH_2 \cdot COOH + CO_2 + H_2O$$
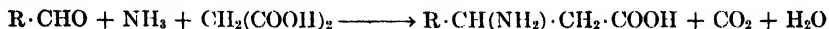
Benzaldehyde and primary amines yield Schiff bases, such as benzalaniline. With secondary amines, compounds of the type $C_6H_5 \cdot CH(NR_2)_2$ are formed. Occasionally these intermediate compounds are isolated first and then made to react with malonic acid.

The preparation of *p*-methoxycinnamic acid from anisaldehyde and malonic acid with alcoholic ammonia is given as an example.

According to Knoevenagel,[236] enough 8% alcoholic ammonia is added to a mixture of equimolecular amounts of anisaldehyde and malonic acid, so that it contains 1 mole of NH_3. The mixture is heated slowly, the alcohol is removed by distillation, and the residue heated for 1 hour on a water bath. The viscous mass becomes solid. The solid is dissolved in water and precipitated with sulfuric acid. A 91% yield of *p*-methoxycinnamic acid is obtained. Knoevenagel used 1.3 g. of anisaldehyde and 1.2 g. of malonic acid (a 20% excess). The reaction time would have to be changed in larger preparations.

Most of Knoevenagel's work is to be found in patents. As usual, few ·details can be learned from them. The following directions for preparing nonylenic acid are taken from a patent.[237]

Enanthaldehyde (114 parts) and 114 parts of malonic acid are heated with 2 g. of piperidine for 12 hours at 100°C. The reaction product is finally distilled *in vacuo*.

A small amount of piperidine is apparently the best reagent for condensing aliphatic aldehydes with malonic acid. Excess malonic acid is to be avoided in these syntheses, because aliphatic aldehydes react with 2 molecules of malonic acid according to the following scheme.

$$R \cdot CHO + 2CH_2(COOH)_2 \longrightarrow R \cdot CH \begin{matrix} CH(COOH)_2 \\ \\ CH(COOH)_2 \end{matrix} + H_2O$$
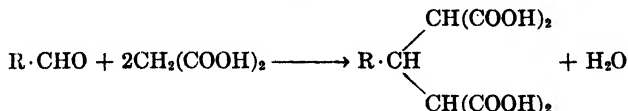
Directions for the preparation of crotonic acid, pyridine being used as the condensing agent, have been given by Scheibler.[238]

To a solution of 100 g. of malonic acid and 135 g. of absolute alcohol are added 86 g. of pyridine. The solution is cooled externally in a freezing mixture, and 85 g. of acetaldehyde are added in portions through the condenser during 30 minutes. The freezing mixture is removed and the flask heated on a water bath. Soon an evolution of gas

[235] Rodionov and Malewinskaja, *Ber.*, **59**, 2952 (1926).
[236] Knoevenagel, *Ber.*, **31**, 2606 (1898).
[237] German Patent, 156,560.
[238] Scheibler, *Ber.*, **48**, 1815 (1915).

starts. To avoid losses of aldehyde the heating bath is removed temporarily until the evolution of gas subsides. The heating is resumed cautiously. As soon as the reaction has become less violent, heating on the water bath is continued for 3 to 4 hours. By this method, 45 g. of crotonic acid, melting at 71°C., can be isolated. The yield is 55% of the theoretical amount.

The advantage of first isolating and then using the condensation products of aldehyde and base is shown by the experience of Knoevenagel [239] in preparing o-nitrocinnamic acid. Resinous products were always obtained from o-nitrobenzaldehyde, malonic acid, and aniline (1 mole each) in alcoholic solution. When, however, o-nitrobenzalaniline and malonic acid were heated with a little alcohol for 30 minutes on a water bath, a 50% yield of o-nitrocinnamic acid was obtained.

(1, b) The method is analogous to Perkin's. According to Komnenos [240] a 50% yield of crotonic acid is obtained by boiling a mixture of equimolecular amounts of malonic acid, glacial acetic acid, and excess paraldehyde for 3 days.

Malonic acid can be replaced by cyanoacetic acid in many cases.

$$R \cdot CHO + CN \cdot CH_2 \cdot COOH \longrightarrow R \cdot CH:CH \cdot CN + CO_2 + H_2O$$
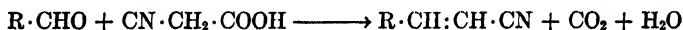
Nitriles of unsaturated acids can be prepared conveniently by this method. In the preparation of the free unsaturated acids use of the cyano acids is no better than the use of malonic acid.

(2) The preparation of unsaturated acids by the indirect alkylidene-malonic ester method is occasionally advantageous. The following examples illustrate the method.

(b) Condensation with acetic anhydride, improved by Thorpe. [241]

According to Komnenos, [242] 100 g. of malonic ester, 100 g. of acetic anhydride, and 57 g. of acetaldehyde are heated in an autoclave for 30 hours at 100°C. On distillation of the reaction mixture a 70% yield of ethylidenemalonic ester, boiling between 113° and 120°C. at 20 mm., is obtained.

(c) Condensations with ammonia or amines.

According to Knoevenagel, [243] piperonalmalonic ester is prepared as follows: 10 g. of piperonal are mixed with 10.7 g. of malonic ester and 6 drops of piperidine are added. The mixture is heated for 8 hours on a water bath, 5 drops of piperidine being added every 2 hours.

Better yields are obtained by the use of an additional mole of malonic ester according to the following directions of Knoevenagel. [243]

[239] Knoevenagel, *Ber.*, **31**, 2609 (1898).
[240] Komnenos, *Ann.*, **218**, 149 (1883).
[241] Thorpe, *J. Chem. Soc.*, **1923**, 3353.
[242] Komnenos, *Ann.*, **218**, 156 (1883).
[243] Knoevenagel, *Ber.*, **31**, 2594 (1898).

A mixture of 10 g. of piperonal, 21.6 g. of malonic ester, and 10 drops of piperidine is heated at 110° to 120°C. for 23 hours, 40 drops of piperidine being added during this interval. The yield, based on piperonal, is 65% of the theoretical.

A corresponding excess in the preparation of alkylidenemalonic esters, e.g. $CH_3 \cdot CH:C(COOH)_2$, is unsuccessful, because the alkylidenebismalonic esters are formed (see page 423).

Whereas the two methods described above are limited in their usefulness, the condensation according to Claisen's directions [244] almost never fails and in general gives excellent yields. The Claisen method proceeds through the corresponding ethyl esters with sodium ethylate as a condensing agent, according to the following equation:

$$R \cdot CHO + CH_3 \cdot COOC_2H_5 \longrightarrow R \cdot CH:CH \cdot COOC_2H_5 + H_2O$$
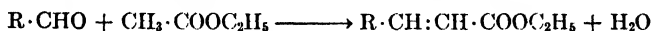
The reaction can be carried out in a simple manner. In most cases metallic sodium with the addition of a little alcohol, instead of ready made ethylate, is used.

The aldehyde is dissolved in ethyl acetate, pieces of sodium and a small amount of alcohol being added, and usually with good cooling and stirring. A simple equation for this reaction cannot be given. The good results can presumably be explained by the fact that the water formed during the reaction is bound as sodium hydroxide and thus removed from the reaction equilibrium. Such would not be the case if sodium ethylate were used. This is the reason why at least 1 mole of sodium is always used for 1 mole of aldehyde.

Claisen's method may be used with good results for the preparation of cinnamic acid esters substituted in the side chain.

$$C_6H_5 \cdot CHO + CH_3 \cdot CH_2 \cdot COOCH_3 \longrightarrow R \cdot CH:C(CH_3) \cdot COOCH_3 + H_2O$$
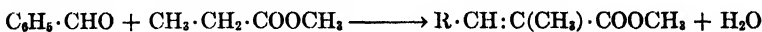
Methyl-α-methylcinnamate is obtained from methyl propionate and benzaldehyde. The methyl esters react especially well.

Directions of Weygand are given for the preparation of ethyl p-methylcinnamate by Claisen's method.

In a 3-necked flask (1000 cc.) equipped with a dropping funnel, a reflux condenser, and a stirrer with a mercury seal, 29 g. of sodium, free of oxide, in 400 cc. of dry xylene are heated on an oil bath above the melting point. The sodium-xylene mixture is then allowed to cool with vigorous stirring. The sodium solidifies in the form of small spheres. After the sodium has settled, the cooling bath is removed, as much xylene as possible is siphoned off, and the rest displaced with petroleum ether. The third neck is closed with a calcium chloride tube and the flask immersed in a freezing mixture. Cold (0°C.), pure ethyl acetate (445 cc.) and 4 cc. of dry alcohol are added and the mixture is cooled with stirring to −5°C. Through the dropping funnel, 106 g. of p-tolualdehyde are added during 2 to 2.5 hours; the temperature must not exceed −5°C. When all of

[244] L. Claisen, Ber., 23, 978 (1890).

the sodium is used up (about 1 hour), the solution is acidified carefully with 90 to 95 cc. of glacial acetic acid. The mixture is diluted with water and the ester layer separated. The aqueous portion is extracted with fresh ethyl acetate. The combined ester solutions are washed successively with 300 cc. of dilute hydrochloric acid, water, bicarbonate solution, and water. The ester solution is dried over sodium sulfate. On fractional distillation 100 g. of ethyl p-methylcinnamate, distilling at 143° to 148°C. at 15 mm., are obtained. This yield is 60% of the theoretical amount.

o- and m-methylcinnamic acid esters are obtained in a corresponding manner. The Perkin synthesis gives unsatisfactory yields with p-tolualdehyde, glacial acetic acid, and sodium acetate.

2. Synthesis of α,β-Unsaturated Aldehydes and Ketones

The formation of aldols is discussed on page 341.

At this point we need only to discuss how the removal of water can be promoted in cases in which it does not take place spontaneously under the reaction conditions.

The aldol formation is inconsequential if 1 mole of aldehyde and 1 mole of ketone and not 2 molecules of aldehyde participate in the reaction. Even when 2 molecules of ketone react with each other, the addition step is not always readily apparent.

For example, acetone yields the diacetone alcohol readily with sodium hydroxide at 0°C. according to the reaction, $2CH_3 \cdot O \cdot CH_3 \rightarrow (CH_3)_2$:-$COH \cdot CH_2 \cdot CO \cdot CH_3$; see page 342. But from acetophenone, dypnone, $C_6H_5(CH_3):C:CH \cdot CO \cdot C_6H_5$, is obtained directly. These ketone condensations undergo subsequent reactions readily. Acetone forms not only mesityl oxide, but phorone, $(CH_3)_2:C:CH \cdot CO \cdot CH:C:(CH_3)_2$, and mesitylene as well. Acetophenone is able to form only triphenylbenzene, which is analogous to mesitylene.

In general the condensation of aldehydes and ketones proceeds smoothly, because the aldehydes react under such mild conditions that the keto group remains intact and, if equimolecular amounts are used, no subsequent reactions occur.

On the other hand, aldehydes of the aromatic series frequently tend to react with 2 molecules of a methyl ketone, according to the following scheme:

$$R \cdot CHO + 2CH_3 \cdot CO \cdot R' \longrightarrow R' \cdot CO \cdot CH_2 \cdot CHR \cdot CH_2 \cdot COR'$$
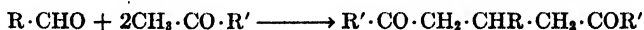
The 1,5-diketones thus formed frequently decompose at higher temperature, according to the following scheme:

$$R \cdot CH(CH_2 \cdot CO \cdot R')_2 \longrightarrow R \cdot CH:CH \cdot CO \cdot R' + CH_3 \cdot CO \cdot R'$$

Even more complex mole ratios can be found, such as the formation of triketones from 2 moles of aldehyde and 3 moles of ketone. The formation of these by-products can be avoided easily, or minimized greatly, by the choice of suitable condensation conditions.

Alkalies and acids can act as condensing agents. In the use of hydrogen halides addition products are formed first according to the following scheme:

$$R \cdot CHO + CH_3 \cdot CO \cdot R' + HX \longrightarrow R \cdot CHX \cdot CH_2 \cdot CO \cdot R' + H_2O$$
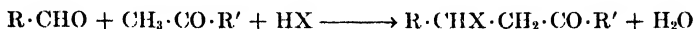
The addition compounds are converted readily to unsaturated ketones by heat (see page 408).

As might be expected, methyl ketones react the most readily. But even their homologues and ketones which contain especially active methylene groups, and which in their general behavior resemble the α-diketones, also react readily. An example of the last type is desoxybenzoin, $C_6H_5 \cdot CO \cdot CH_2 \cdot C_6H_5$.

The general method of condensation is quite simple if alkaline reagents are used. Molecular amounts of the components are mixed and diluted with ethanol or methanol, or dissolved in enough alcohol to make a clear solution at room temperature. The condensing agent is then added.

Depending on the conditions, concentrated aqueous or alcoholic alkalies as well as sodium methylate or ethylate solutions may be used.

In the aliphatic series the acid condensation is apt to be most successful. In the aromatic series the alkaline condensation is more advantageous.

The directions of Herold for the preparation of pseudoionone are given as an example of the alkaline condensation in the aliphatic series. Lemongrass oil which contains 70 to 75% of citral is used as starting material for citral. The isolation of citral cannot be described in detail here.

150 g. of citral are stirred with a mixture of 150 g. of acetone, 150 g. of water, and 24 g. of 35% sodium hydroxide solution (8.5 g. of sodium hydroxide in 15.5 g. of water) on a water bath at 35°C. for 20 hours, until the odor of citral can no longer be detected. The flask is closed with a cotton plug to avoid losses of acetone. The temperature during the stirring is kept at 35°C. The deep yellow solution is neutralized with sulfuric acid while being cooled externally with ice. The acetone is evaporated on a water bath, the residue is cooled, and the lower aqueous layer is separated in a separatory funnel while the oil is washed twice with water. After the oil has been dried over potassium carbonate, it is distilled *in vacuo*. The forerun up to 110°C. at 12 mm. is discarded or used in a new condensation. The fraction distilling at 110° to 165°C. is redistilled. By this means 115 to 120 g. of pseudoionone, boiling at 145° to 148°C. at 12 mm., are obtained. The yield is 60 to 63% of the theoretical amount. The product thus prepared contains contaminations which are difficult to separate, but it is sufficiently pure for conversion to α- or β-ionone; see page 473.

The preparation of benzalacetone is notable in that a considerable excess of acetone is used to avoid the formation of dibenzalacetone. For the sake of comparison an older method devised by Claisen, and improved

by Vorländer,[245] is given. The newer method is to be found in *Organic Syntheses*.[246]

The Claisen-Vorländer method is as follows: To 20 g. of benzaldehyde, 30 g. of acetone, and 20 g. of water are added 10 cc. of a 10% sodium hydroxide solution with cooling. The mixture is allowed to stand for 3 days at room temperature and is shaken frequently during this period. The solution is acidified with glacial acetic acid and the excess acetone is removed by distillation on a water bath. The residue is extracted with ether, and the ethereal solution is dried over calcium chloride and distilled *in vacuo*. Thus, 14 g. of benzalacetone, boiling at 151° to 153°C. at 25 mm., are obtained.

A comparison of the old and new directions is instructive. By the old method a yield of 7 parts of benzalacetone for 10 parts of benzaldehyde is obtained, while the lowest yield by the new method is between 9 and 11 parts. The time consumed by the old method is less and the product obtained is apparently purer even after the first distillation.

The directions in *Organic Syntheses* omit special drying of the reaction product, a measure which frequently is advantageous for preparations of the size described.

Benzalacetone attacks the skin and the mucous membranes even more strongly. Its odor is agreeable in great dilution; in higher concentrations, however, the odor is disagreeable and persistent. The compound must be handled with caution.

Two sets of directions for the preparation of benzalacetophenone are included as examples for the condensation of an aromatic aldehyde with aromatic methyl ketones.

1. The first method is that of Dilthey; see also Claisen.[247]

A mixture of 12 g. of acetophenone and 10.5 g. of benzaldehyde is cooled below 0°C. After the addition of 3 cc. of 20% sodium ethylate solution, the mixture is allowed to stand for several days. 17 g. of benzalacetophenone can be isolated from the solid. This yield is 90% of the theoretical.

If the mixture is diluted with an equal volume of methanol and the solution inoculated after several hours, less time is required for the preparation. The precipitate is washed on a Büchner funnel with cold (0°C.) methanol, then with dilute acetic acid, and finally with water to assure removal of the alkali.

2. The second method is described in detail in *Organic Syntheses*.[248]

The purification of benzalacetophenone is an interesting example of polymorphous forms which appear during recrystallization. Therefore it is discussed somewhat more thoroughly at this point.

[245] L. Claisen, *Ann.*, 223, 137 (1884). D. Vorländer, *Ann.*, 294, 275, foot-note (1897).
[246] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 77.
[247] Dilthey, *J. prakt. Chem.*, 101, 190 (1921); L. Claisen, *Ber.*, 20, 657 (1887).
[248] P. Kohler and M. Chadwell in H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 78.

Claisen and Claparède [249] who were the first to prepare benzalaceto-phenone observed that the transparent crystals obtained by recrystallization became cloudy on drying in a desiccator. They found no change in the melting point. Weygand [250] found that the clear crystals appearing spontaneously in solutions consist of a metastable form which melts at 57°C. Under certain conditions this product changes gradually even in the mother liquor to a form melting at 59°C.

The recrystallization can be so manipulated without difficulty that either form is obtained. The solution is brought to a boil again, while the neck of the Erlenmeyer flask is closed by a cotton plug, so that the solvent vapors penetrate the cotton. The flask is then allowed to stand for a short time. Only the metastable form which grows much faster than the stable one can be found. The metastable form may be isolated by filtration and washing.

If, however, the solution is inoculated with the stable form, con-glomerates are obtained which adhere to the glass and which are less agreeable to work with. But the stable form is rarely obtained if care is not taken by means of frequent stirring to produce many seeds. Since crystals of the stable form grow very slowly, seeds of the metastable form can take place.

. Benzalacetophenone is prone to separate as an oil from warm solu-tions. For the recrystallization, 4 to 5 times its weight of alcohol is used. The crystallization is started by inoculation while the solution is still lukewarm. The liquid is then cooled at the same rate as the mother liquor becomes more dilute, at first gradually in running water, then in ice, and finally in a freezing mixture. From 880 g. of crude product prepared according to the directions of *Organic Syntheses*, 770 g. of a product melting at 55° to 57°C. are obtained. On concentration of the mother liquor 40 to 50 g. of a less pure crop can be obtained.

It is surprising that the corresponding condensation is successful with α-keto aldehydes of the type of phenylglyoxal, $C_6H_5 \cdot CO \cdot CHO$. The aldehyde group reacts with the methyl ketone. This behavior made possible, for instance, a convenient preparation of dibenzoylethylene, $C_6H_5 \cdot CO \cdot CH : CH \cdot CO \cdot C_6H_5$, which was usually obtained only indirectly and inconveniently until Conant and Lutz (see page 399) prepared it from fumaroyl chloride and benzene. The condensation of phenylglyoxal and acetophenone according to Smedley [251] is obsolete, but monosubstituted dibenzoylethylenes can still be prepared best according to this method. The directions of Smedley require changes. Phenylglyoxal and aceto-

[249] Claisen and Claparède, *Ber.*, 14, 2464 (1881).
[250] C. Weygand, *Ann.*, 472, 168 (1929).
[251] Smedley, *J. Chem. Soc.*, 95, 226 (1909).

phenone do not react in acetic anhydride in the manner he thought.   The yields, too, are poor in glacial acetic acid.   Acetophenone and its homologues can be condensed readily with phenylglyoxal, according to the following directions of Weygand.

For the preparation of p-methyldibenzoylethylene, $CH_3 \cdot C_6H_5 \cdot CO \cdot CH:CH \cdot CO \cdot C_6H_5$, 13.5 g. of freshly prepared, monomeric phenylglyoxal (see page 135) are boiled under a reflux with 23 g. of p-methylacetophenone, 80 cc. of glacial acetic acid, and a drop of concentrated sulfuric acid for 90 minutes.   The cooled reaction mixture is poured into water in a separatory funnel and extracted with ether.   The extract is washed neutral with water, dried over calcium chloride, and treated with decolorizing carbon.   After filtration the ether is removed by distillation.   The residue is dissolved in methanol and the solution cooled in a freezing mixture. 12 g. of slightly reddish crystals melting at 86.5°C. are obtained.   On recrystallization from methanol treated with decolorizing carbon the compound is obtained in light yellow needles, but the melting point is unchanged.

3. Special Cases

To the variations of the Perkin-Claisen synthesis belongs one recently published by Michael and Ross [252] which affords a very convenient preparation of tiglic acid (α-methylcrotonic acid).   The best of the former methods for its preparation was that given by Wislicenus and Pückert.[253] It consists in the reduction of methylacetoacetic ester with sodium amalgam to α-methyl-β-hydroxybutyric acid, from which the unsaturated acid is obtained by removal of water at about 200°C.   The method of Michael and Ross also leads through α-methyl-β-hydroxybutyric acid, but the latter is obtained by nuclear synthesis from acetaldehyde, or paraldehyde, and methylmalonic acid according to the following equation:

$$CH_3 \cdot CHO + HC(CH_3)(COOH)_2 \longrightarrow CH_3CHOH \cdot C(CH_3)(COOH)_2$$
$$\longrightarrow CO_2 + CH_3 \cdot CHOH \cdot CH(CH_3) \cdot COOH$$
$$\longrightarrow H_2O + CH_3 \cdot CH:C(CH_3) \cdot COOH$$
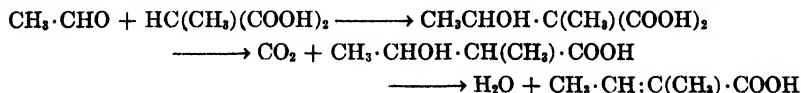
By this procedure part of the α-methyl-β-hydroxybutyric acid is obtained in the form of its acetate which on distillation under ordinary pressure is readily converted into tiglic and acetic acids.   The directions of Michael and Ross [254] for the preparation of tiglic acid follow.

A mixture of 50 g. of methylmalonic acid, 37 g. of paraldehyde, 43 g. of acetic anhydride, and 25 g. of glacial acetic acid is heated under a reflux on a water bath for 48 hours and then boiled gently for 4 hours on a sand bath.   The solution is distilled

[252] Michael and Ross, J. Am. Chem. Soc., 55, 3692 (1933).
[253] Wislicenus and Pückert, Ann., 250, 243 (1889).
[254] Michael and Ross, J. Am. Chem. Soc., 55, 3692 (1933).

through a 15 cm. column until the temperature of the distilling vapors reaches 140°C. Distillation at 15 mm. yields 19 g. of tiglic acid (b.p. 90° to 115°C.) which solidify in the receiver, and 13 g. of α-methyl-β-acetoxybutyric acid boiling at 147° to 150°C. at 10 mm. The latter, as mentioned above, upon distillation at ordinary pressure also yields tiglic acid; the total yield amounts to about 70% of the theoretical. If the acetoxymethylbutyric acid is not desired, the reaction mixture is distilled directly at ordinary pressure. The tiglic acid thus obtained is recrystallized from water. It melts at 65°C.

4. Synthesis of Polyenes

Polyenes is the name given to compounds which contain the typical group $R \cdot (CH:CH)_n \cdot R$. They are closely related to the natural carotenoids which also contain the continuous chain of conjugated double bonds; however, the latter carry methyl groups as side chains and can all be thought of as being built up from isoprene residues. R. Kuhn first published the syntheses of polyenes which do not occur in a natural state, and eventually succeeded in synthesizing vitamin A, a naturally occurring compound which has the characteristics of a polyene.

The naturally occurring polyenes are either hydrocarbons, as the carotenes proper, or oxygen-containing compounds; e.g., ketones or dicarboxylic acids such as bixin, or alcohols such as vitamin A.

The diphenylpolyenes of the type $C_6H_5 \cdot (CH:CH)_n \cdot C_6H_5$, were the first to be synthesized. The lowest members of the series, stilbene and diphenylbutadiene, were already well known; diphenylhexatriene was described by Smedley,[255] who obtained it according to an unpublished method of C. W. Knell. R. Kuhn,[256] after numerous failures, worked out the following method for the preparation of larger quantities of the compound. It involved, first, an improvement in the directions of Thiele [257] for the preparation of hydrocinnamoine, $C_6H_5 \cdot CH:CH \cdot CHOH \cdot CHOH \cdot CH:CH \cdot C_6H_5$.

500 g. of zinc dust and 30 cc. of glacial acetic acid are added rapidly, with stirring, to a solution of 400 g. of copper sulfate in 5 liters of water at 80°C. When all the copper has been precipitated (after about 1 minute) and the solution has become colorless, 500 g. of cinnamaldehyde heated to 80°C. are added rapidly with vigorous stirring. When the odor of cinnamaldehyde has disappeared (about 5 minutes), the reaction mixture is allowed to cool, and the zinc precipitate is filtered with suction and extracted with 700 cc. of boiling ethanol. The filtrate is cooled to −10°C. and hydrocinnamoine crystallizes. The mother liquor is used for another extraction of the zinc precipitate. By repeated extractions a total yield of 20% of the theoretical amount of hydrocinnamoine is obtained. After several recrystallizations from a little absolute ethanol it melts at 156°C.

The conversion of hydrocinnamoine to diphenylhexatriene is best accomplished by treatment of the former with P_2I_4 (phosphorus diiodide) to form the diiodide which loses iodine spontaneously. While a dibro-

[255] J. Smedley, J. Chem. Soc., 93, 372 (1908).
[256] R. Kuhn, Helv. Chim. Acta, 11, 89 (1928).
[257] R. Kuhn and A. Winterstein, Ber., 60, 433 (1927); J. Thiele, Ber., 32, 1296 (1899).

mide and a hexabromide can be formed with bromine, the elimination of the bromine offers some difficulty.

According to Kuhn,[258] 50 g. of finely pulverized hydrocinnamoine are suspended in 700 cc. of absolute ether. To this thoroughly agitated suspension is added, in six portions over a 30 minute period, a total of 60 g. of finely powdered P_2I_4. The dark brown-colored solution from which the triene has crystallized is shaken with a little aqueous sodium hydroxide and thiosulfate solutions until its color turns to light yellow. It is then filtered with suction and the residue is boiled with 200 cc. of 0.1 N sodium hydroxide in order to remove the phosphorus diiodide and some sulfur. Residual hydrocinnamoine is removed by boiling with 100 cc. of methanol. The remaining triene is practically pure. It is obtained in a yield of 90% of the theoretical.

The ether may be replaced by carbon disulfide as a solvent; in which case the P_2I_4, prepared according to Germann and Traxler,[259] need not be isolated. Diphenylhexatriene may be recrystallized from the usual organic solvents such as carbon tetrachloride, benzene, etc. Its melting point is 200°C., its color greenish yellow; the solutions show an intense blue fluorescence.

Diphenyloctatetraene was prepared by Fittig and Batt [260] from cinnamaldehyde, sodium succinate, and acetic anhydride; see page 421. R. Kuhn [261] improved the method by adding lead oxide to the batch, thus permitting the reaction to proceed in a homogeneous phase.

A mixture of 236 g. of succinic acid, 528 g. of cinnamaldehyde, 446 g. of lead oxide, and 610 g. of acetic anhydride is heated with shaking for 10 minutes at 140°C. The resulting clear, reddish brown solution is allowed to boil under a reflux for 5 hours. After 2 hours, partial crystallization of diphenyloctatetraene can be observed. The solution is cooled to 40°C. and the thick crystalline mush removed by filtration as rapidly as possible in order to avoid contamination with precipitated lead acetate. The mother liquor is boiled under a reflux with another portion of 100 g. of acetic anhydride for 3 hours, whereby a small additional amount of diphenyloctatetraene is obtained. The hydrocarbon is washed with a little acetic anhydride, then with glacial acetic acid to remove brown resins, and finally with alcohol and water. The yield amounts to 86 g., corresponding to 16% of the theoretical amount. The compound is recrystallized from chloroform. It melts at 232°C., is greenish yellow in color, and shows a green fluorescence

For the preparation of the higher diphenylpolyenes two variations may be used. By substituting dihydromucic acid, $HOOC \cdot CH_2 \cdot CH : CH \cdot - CH_2 \cdot COOH$ (which can be obtained from mucic acid), for succinic acid the condensation with cinnamaldehyde in the manner described yields diphenyldecapentaene in 7% of the theoretical amount. M.p., 253°C.; color, orange. If cinnamaldehyde is replaced by cinnamenylacrylic aldehyde (phenylpentadienal), $C_6H_5 \cdot (CH : CH)_2 \cdot CHO$, the condensation

[258] R. Kuhn, *Helv. Chim. Acta*, 11, 106 (1928).
[259] F. Germann and R. Traxler, *J. Am. Chem. Soc.*, 49, 307 (1927).
[260] R. Fittig and L. Batt, *Ann.*, 331, 160 (1904).
[261] R. Kuhn, *Helv. Chim. Acta*, 11, 106 (1928).

with succinic acid gives a 10% yield of diphenyldodecahexaene, melting at 267°C.; its color is brownish orange.

Dihydromucic acid and cinnamenylacrylic aldehyde condense to give a 4% yield of diphenyltetradecaheptaene which has a melting point of 279°C. and a bronze color. Finally, diphenylhexadecaoctaene (4% yield) was obtained from phenylheptatrienal and succinic acid. Its melting point is 285°C.; its color is bluish copper-red.

Still higher members of this series were obtained recently with hexadiene-3,5-dicarboxylic acid, the preparation of which is described below (page 435).

The unsaturated fatty acids of the type $CH_3 \cdot (CH:CH)_n \cdot COOH$ are more closely related to the natural polyenes. In the syntheses of these acids the preparation of unsaturated aldehydes like the formation of crotonaldehyde is combined with the preparation of unsaturated acids by the malonic ester condensation.

R. Kuhn and Hoffer [262] prepared the aldehyde of sorbic acid, hexadienal, $CH_3 \cdot (CH:CH)_2 \cdot CHO$, together with octatrienal, $CH_3 \cdot (CH:CH)_3 \cdot CHO$, from crotonaldehyde and acetaldehyde.

140 g. of crotonaldehyde (obtained by fractionation of a technical sample) are mixed with 172 g. of acetaldehyde, freshly prepared from paraldehyde, and 3 g. of piperidine, and allowed to stand for 1 to 2 hours. The mixture becomes deep red in color without noticeable evolution of heat. After 30 minutes a small flocculent precipitate appears and the liquid turns lighter in color. The flask is equipped with a bulb condenser which is cooled to 10° to 15°C. with a calcium chloride solution and a thermometer is immersed in the liquid. The air in the flask is replaced by carbon dioxide, and the flask is slowly heated on a water bath. The liquid commences to boil at 47°C.; after 3 to 4 hours, during which time the boiling point increases to 75° to 80°C., 1 g. of piperidine is added, and the mixture heated on the water bath until the boiling ceases (3 to 4 hours). After the mixture has cooled, 20 to 30 cc. of water are removed with the aid of a separatory funnel, and the dark orange-red solution is diluted with a little ether and dried over sodium sulfate. Upon fractionation through a Widmer column in a current of carbon dioxide, there are obtained about 25 g. of sorbic aldehyde, boiling at 65° to 73°C. at 12 mm., and about 15 g. of octatrienal, boiling at 97° to 115°C.

These aldehydes, according to Kuhn and Hoffer,[263] may be purified through the bisulfite compound, or by treatment with ammonia. The sorbic aldehyde fraction (see above) is dissolved in twice its volume of ether, and dry ammonia is passed into the solution which is cooled in ice at first, and then allowed to come to room temperature. The liquid becomes cloudy and a resin, amounting to 5 to 10% of the sorbic aldehyde used, is deposited on the walls of the flask. After standing for 10 minutes, the solution is rapidly washed several times with water and dried with

[262] R. Kuhn and M. Hoffer, *Ber.*, **63**, 2164 (1930).
[263] R. Kuhn and M. Hoffer, *Ber.*, **64**, 1978 (1931).

sodium sulfate. A milky cloudiness appearing in the aqueous layer is disregarded. Upon repeated fractionation, 50 to 60% of the starting material is recovered as pure sorbic aldehyde. It boils at 64° to 66°C. at 11 mm. (or at 173° to 174°C. at 754 mm., corrected).

Octatrienal is very unstable; its bisulfite compound forms in colorless leaflets when the aldehyde is shaken with a 100% excess of 30% cold sodium bisulfite solution. This compound can be recrystallized from water containing a little bisulfite, the solution being effected originally by warming very gently. If a small amount of the bisulfite compound is dissolved in water and a 10% sodium carbonate solution is added, the free aldehyde separates as an oil. The oil solidifies on scratching and cooling, and by recrystallization from petroleum ether the aldehyde is obtained as yellowish needles, melting at 55°C. The yield is 40 to 50% of the theoretical.

Kuhn and Hoffer [264] used the fractions described above for the preparation of unsaturated fatty acids.

A mixture of 36 g. each of the sorbic aldehyde fraction, malonic acid, and pyridine is heated under a reflux with a small flame so that carbon dioxide is evolved in a regular stream. After 2 hours the reaction is completed by heating to the boiling point for a short time. The mixture is then allowed to stand overnight at room temperature. A part of the octatrienecarboxylic acid formed crystallizes. The mother liquor is chilled and acidified, Congo red being used as an indicator. The crystals that separate are washed with ice-cold ether, which renders them almost colorless. Upon recrystallization from aqueous alcohol, or from dilute acetic acid, 18 g. of crude product which still contains some sorbic acid are obtained. After recrystallization from 50 parts of ether the product melts at 189° to 189.5°C. (corrected), with partial decomposition. Pure octatrienecarboxylic acid, in a thick layer, has a very pale lemon-yellow color.

Decatetraenecarboxylic acid (2 to 2.5 g.) was obtained in a similar manner from 12 g. each of octatrienal, malonic acid, and piperidine. After repeated recrystallization from glacial acetic acid decatetraenecarboxylic acid melts at 210° to 211°C. with partial decomposition. Its color is brownish yellow.

Kuhn, Badstübner, and Grundmann [265] obtained higher members of the series by use of the same method. Finally, still higher members, such as 1,30-diphenyltriacontadecapentaene, were prepared by new, unpublished procedures; see Kuhn.[266]

Kuhn and Grundmann [267] succeeded in approaching more closely to the structure of the polyenes by changing from the above unsaturated fatty acids to the dicarboxylic acids of the type, $HOOC \cdot (CH:CH)_n \cdot COOH$. Some previous experiments were useful here; see page 413.

[264] R. Kuhn and M. Hoffer, *Ber.*, 63, 2169 (1930).
[265] R. Kuhn, W. Badstübner, and C. Grundmann, *Ber.*, 69, 98 (1936).
[266] R. Kuhn, *Angew. Chem.*, 50, 703 (1937).
[267] R. Kuhn and C. Grundmann, *Ber.*, 69, 1757 (1936).

Diethyl oxalosorbate, $C_2H_5OOC \cdot CO \cdot CH_2 \cdot (CH:CH)_2 \cdot COOC_2H_5$, prepared as described by Borsche and Manteuffel [268] gives a potassium compound which can be converted into the enol acetate of the formula, $C_2H_5OOC \cdot C(OCOCH_3):CH \cdot (CH:CH)_2 \cdot COOC_2H_5$, by treatment with acetic anhydride. Starting with this compound Kuhn and Grundmann prepared hexatrienedicarboxylic acid in the following manner.

The enol acetate, on treatment with nascent hydrogen from aluminum amalgam, or zinc dust in pyridine-acetic acid, takes up 1 mole of hydrogen and changes to the 1,6-dihydro compound, $C_2H_5OOC \cdot CH(OCOCH_3) \cdot \cdot (CH:CH)_2 \cdot CH_2COOC_2H_5$. This yields diethyl hexatriene dicarboxylate by the removal of a molecule of acetic acid with a solution of potassium hydroxide in ethanol. Potassium hydroxide in methanol gives the dimethyl ester. Aqueous potassium hydroxide gives an 83% yield of the potassium salt of the free hexatriene-1,6-dicarboxylic acid. The free acid can be recrystallized from a large quantity of 50% alcohol. It is then snow-white and melts in a preheated bath at 316° to 318°C. with effervescence.

Octatetraene-1,8-dicarboxylic acid is obtained from methyl octatriene dicarboxylate in a similar manner.

By the reduction of hexatriene-1,6-dicarboxylic acid with sodium amalgam a hexadienedicarboxylic acid is obtained which can be rearranged with potassium hydroxide to hexadiene-(3,5)-dicarboxylic acid of the formula, $HOOC \cdot CH_2 \cdot CH_2 \cdot (CH:CH)_2 \cdot COOH$. This, on reaction with cinnamaldehyde according to the procedure described on page 431, yields 1,12-diphenyldodecahexaene.

The first naturally occurring polyene prepared was dehydrogeranic acid; see page 386.

Later, Kuhn and Morris [269] synthesized vitamin A. Its formula is:

$$R \cdot CH:CH \cdot C:CH \cdot CH:CH \cdot C:CH \cdot CH_2OH,$$
$$\underset{CH_3}{|} \qquad\qquad \underset{CH_3}{|}$$

where R =
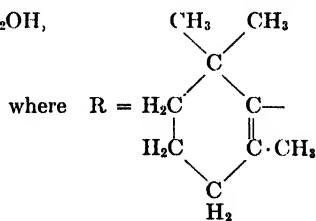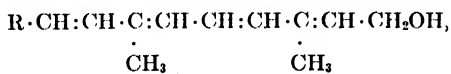
The synthesis starts from β-ionone, $R \cdot CH:CH \cdot CO \cdot CH_3$. Karrer and coworkers [270] had already prepared ethyl β-ionylidene acetate, $R \cdot CH:CH \cdot C(CH_3):CH \cdot COOC_2H_5$, by means of the Reformatski reaction; see page 386.

[268] W. Borsche and R. Manteuffel, *Ber.*, 65, 868 (1932).
[269] R. Kuhn and C. Morris, *Ber.*, 70, 853 (1937).
[270] P. Karrer et al., *Helv. Chim. Acta*, 15, 878 (1932).

The problem was to convert this ester into the aldehyde with the same number of carbon atoms; namely, β-ionylideneacetaldehyde, $R \cdot CH:CH \cdot C(CH_3):CH \cdot CHO$. A Bouveault-Blanc hydrogenation of the ester could, of course, not be considered. However, Braun and Rudolph [271] had worked out a method for the conversion of esters to aldehydes based on the following well known reaction sequence:

$$R' \cdot COOC_2H_5 + H_2N \cdot C_6H_4 \cdot CH_3 \longrightarrow R' \cdot CO \cdot NH \cdot C_6H_4 \cdot CH_3 \longrightarrow$$
$$R' \cdot CCl:N \cdot C_6H_4 \cdot CH_3 \longrightarrow R' \cdot CH:N \cdot C_6H_4 \cdot CH_3 \longrightarrow R' \cdot CHO + C_7H_7 \cdot NH_2$$
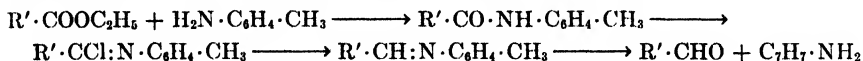
A carboxylic acid ester is converted to the substituted acid amide by means of an aromatic amine. The acid amide reacts in its tautomeric form with phosphorus pentachloride to give an imide chloride which can be converted in a number of ways into a Schiff base by replacement of the chlorine atom by hydrogen. Braun and Rudolph accomplished this with the chromous chloride method described on page 45. The Schiff base, upon hydrolysis, yields the desired aldehyde. Thus Kuhn and Morris were able to prepare the toluide of β-ionylideneacetic acid in 80% yield by the reaction with o-toluidenemagnesium iodide, $CH_3 \cdot C_6H_4 \cdot NHMgI$ (see page 273). From the toluide a 30% yield of β-ionylidene-acetaldehyde is obtained. Upon condensation of this aldehyde with β-methylcrotonaldehyde, $(CH_3)_2 : C : CH \cdot CHO$, according to the piperidine method described above, an unsaturated aldehyde containing 20 carbon atoms and five conjugated double bonds is prepared, though not in a pure state.

$$\underset{\qquad CH_3 \qquad\qquad CH_3}{R \cdot CH:CH \cdot C:CH \cdot CH:CH \cdot C:CH \cdot CHO}$$
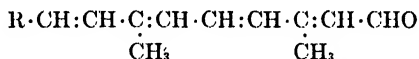
However, upon reduction with aluminum isopropylate in isopropanol (see page 36), 2.6 g. of an oil which by chromatographic analysis and spectrographic examination proved to be identical with the natural vitamin A were obtained. The degree of purity corresponded to a vitamin A content of 7.5%. This was determined by feeding experiments with rats. This degree of purity is equal to the natural vitamin standard.

5. Synthesis of Unsaturated Nitro Compounds

Thiele and Haeckel (see also Bouveault and Wahl [272]) gave a method which can be used generally for the preparation of nitroethylenes. It consists of the condensation of aldehydes with nitromethane:

$$R \cdot CHO + CH_2:NOOK \longrightarrow R \cdot CHOH \cdot CH:NOOK \longrightarrow$$
$$R \cdot CHOH \cdot CH:NOOH \longrightarrow R \cdot CHOH \cdot CH_2 \cdot NO_2 \longrightarrow R \cdot CH:CH \cdot NO_2$$
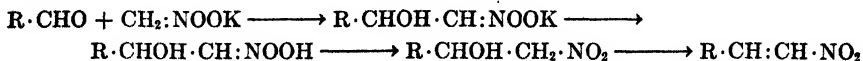
[271] J. v. Braun and W. Rudolph, *Ber.*, 67, 269, 1735 (1934).
[272] Thiele and Haeckel, *Ann.*, 325, 7 (1902). Bouveault and Wahl, *Compt. rend.*, 135, 41 (1902).

The alkali salt of the aci form of a nitroethyl alcohol is formed first. In some cases the free acinitro compound splits off water spontaneously and changes to the nitroethylene derivative; in other cases the removal of water must be forced.

The method described in *Organic Syntheses* [273] for the preparation of ω-nitrostyrene from nitromethane and benzaldehyde is a good example.

The lower membered nitroethylenes of the aliphatic series are very unstable; they polymerize very readily. Nitrobutylene and higher members of the series are more stable. As an example, directions of Schmidt and coworkers [274] for the preparation of 1-nitroamylene follow.

1-Nitropentanol, $CH_3 \cdot (CH_2)_2 \cdot CHOH \cdot CH_2 \cdot NO_2$, is first prepared as follows: A mixture of 14.4 g. of butyraldehyde, freshly distilled in a current of hydrogen, 12.2 g. of nitromethane, and 60 g. of water is cooled in ice water and treated, while shaken vigorously, with 25.8 cc. of 33% potassium hydroxide solution in small portions. The clear yellow solution formed is extracted with ether to remove unchanged starting materials. The ether is separated from the aqueous layer and the latter cooled by addition of ice and acidified with very dilute sulfuric acid. Nitropentanol separates as a yellowish oil; it is extracted with ether, washed with sodium chloride solution, and dried over sodium sulfate. Upon distillation *in vacuo* at 2 mm. the compound, which is still yellowish in color (19 g. = 71% of the theoretical yield), is obtained as a colorless liquid boiling at 87° to 88°C. when redistilled at 3 mm.

For the conversion of the nitro alcohols to the nitroölefins the acetates of the former are prepared first; see Schmidt and coworkers. [275]

8 g. of nitropentanol are dissolved in 15 cc. of chloroform and 4 g. of acetyl chloride are added. After the spontaneous reaction has subsided, the mixture is heated on a water bath for several hours until hydrogen chloride is no longer evolved. The reaction mixture is extracted with ether and the extract is washed with saturated sodium chloride solution. From the washings an additional amount of the acetyl derivative can be extracted with ether but these extracts must be washed again with saturated sodium chloride solution. The combined ether extracts are dried with sodium sulfate and distilled *in vacuo*. Acetyl-1-nitropentanol, $CH_3 \cdot (CH_2)_2 \cdot CH(OCOCH_3) \cdot CH_2NO_2$, distils at 111° to 113°C. at 10 mm.; the yield (8.4 g.) is 80% of the theoretical amount.

Acetic acid is readily removed by boiling the ethereal solution with potassium bicarbonate.

7 g. of the above acetyl derivative are dissolved in 35 cc. of ether and the solution is boiled with 6 g. of potassium bicarbonate for 7 hours. Upon distillation *in vacuo* 3.5 g. (76% of the theoretical) of 1-nitroamylene boiling at 69° to 70°C. at 12 mm. are obtained.

6. Synthesis of Aromatic Nuclei

Hexamethylbenzene is obtained in a very convenient manner according to the directions of Reckleben and Scheiber. [276]

[273] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 413.
[274] E. Schmidt *et al., Ber.,* **58**, 2431 (1925); **61**, 2142 (1928).
[275] E. Schmidt *et al., Ber.,* **61**, 474, 2142 (1928).
[276] Reckleben and J. Scheiber, *Ber.,* **46**, 2363 (1913).

A combusion tube 30 cm. long is filled with commercial aluminum oxide and heated electrically or in a combustion furnace to about 400°C. One end of the combustion tube is fitted with a small distilling flask which is set into a vigorously boiling water bath. The other end is connected with a well cooled receiver. An equimolecular mixture of acetone and methanol (100 g. of acetone and 55 g. of methanol) is added through a dropping funnel into the distilling flask at such a rate that the added mixture evaporates at once.

The product collected in the receiver consists of an aqueous and a lighter, brown oil layer together with an abundant quantity of crystalline hexamethylbenzene. The crystals are separated, and from the oily layer the low boiling contaminants are removed by distillation. The residue is cooled in a freezing mixture and the hexamethylbenzene is thus recovered from it. The foreruns are again distilled over the heated aluminum oxide. A total yield of 20% of the theoretical amount of hexamethylbenzene is obtained. After recrystallization from boiling alcohol it melts at 164°C.

E. Removal of Carbon Dioxide and Water from Carboxylic Acids

The fundamental reaction, $2R \cdot COOH \rightarrow R \cdot CO \cdot R + H_2O + CO_2$, has been known for a long time and has long been in practical use for nuclear syntheses. The common technical example is the manufacture of acetone by dry distillation of calcium acetate. Symmetrical ketones are obtained by heating the calcium or barium salts of a single acid, while a mixture of salts of two different acids produces three different ketones, two of them symmetrical, the other unsymmetrical. The greater the difference in the molecular weights of the two carboxylic acids, the more favorable are the conditions for the separation of the three ketones. If one wishes to prepare the higher methyl ketones, the ratio of the two carboxylic acids used has a marked influence on the yield. If an excess of the cheap calcium or barium acetates is used, more acetone will be formed than with equimolecular amounts, but, on the other hand, less of the symmetrical high molecular ketone will also be obtained.

If calcium acetate is replaced by calcium formate, aldehydes are obtained (Piria) according to the scheme,

$$R \cdot COOH + H \cdot COOH \longrightarrow R:CHO + CO_2 + H_2$$
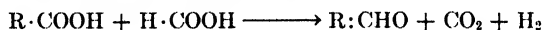
The reaction may be used, as already mentioned, for all carboxylic acids which are not otherwise changed under the conditions of the condensation. The procedure is very simple. In many cases it suffices to mix the acid thoroughly with calcium or barium hydroxide and to heat the mixture in a retort. In some cases it is better to prepare dry alkaline earth salts beforehand. The method is of current importance. It can be used whenever the Friedel-Crafts synthesis fails and the suitable carboxylic acid is readily available. For example, of the three methyl-acetophenones only the p compound can be obtained directly from toluene by the Friedel-Crafts synthesis. Other methods by which this compound,

as well as the *o* and *m* isomers, may be obtained are as follows: (*1*) from the corresponding toluides by conversion to the nitriles followed by treatment with methylmagnesium iodide; (*2*) by treatment of the toluic acid chlorides with methyl zinc; (*3*) by the reaction of the toluic acid chlorides with the sodium derivative of acetoacetic ester, followed by hydrolysis.

Of these methods the first gives poor yields, the second is expensive and inconvenient, and the third gives poor yields and is tedious (see page 363).

The distillation of a mixture of barium toluate and barium acetate, though giving only a 25% yield of the theoretical amount of the corresponding acetyltoluene, is very simple and, therefore, most economical in the last analysis; see Weygand and Schächer.[277]

Especially good results are obtained in a special case; namely, the preparation of cyclopentanone from adipic acid and barium hydroxide (see page 441). For the preparation of suberone, the 7-membered cyclic ketone, the only method known is through suberic acid. Cyclohexanone, of course, is more conveniently obtained from cyclohexanol. For the preparation of the higher membered ring ketones see page 442.

Special conditions prevail if the reacting carboxyl groups are secondary ones. Thus, upon distillation of barium diphenyl acetate, diphenylmethane and tetraphenylallene are obtained simultaneously; see page 329. The formation of diphenylmethane is caused by more thorough decompositions. The tetraphenylallene is not formed according to the equation, $(C_6H_5)_2 : CH \cdot CO \cdot CH : (C_6H_5)_2 \rightarrow (C_6H_5)_2 : C : C : C : (C_6H_5)_2 + H_2O$, from tetraphenylacetone which might be the primary reaction product; see page 329. With respect to this diphenylmethane formation, a behavior similar to that of diphenylacetic acid is exhibited by all acids which can readily be decarboxylated; no ketones are formed.

Squibb [278] converted the calcium-barium salt method into a catalytic one. The acid vapors are passed over certain carbonates or oxides so that the reaction takes place at a suitable temperature on the surface of the catalyst. Thorium oxide proved exceptionally useful for laboratory purposes.

The catalytic method, it is strange to say, has a somewhat limited usefulness. While the dry distillation method gives satisfactory yields of diaryl ketones from aromatic acids with a carboxyl group attached to the nucleus, the catalytic method fails for preparative purposes in these cases because decarboxylation proceeds too rapidly.

If, however, fatty aromatic carboxylic acids of the type of phenyl-

[277] C. Weygand and F. Schächer, *Ber.*, **68**, 230 (1935).
[278] Squibb, *J. Soc. Chem. Ind.*, **14**, 506 (1895); **15**, 612 (1896); *Chem. Zentr.*, **1895**, I, 775; *ibid.*, **1896**, I, 898; *J. Am. Chem. Soc.*, **17**, 187 (1895).

acetic acid are used, catalytic ketone formation again proceeds normally, and good yields of ketones can be obtained from mixtures of aromatic acids with fatty acids, or fatty aromatic acids. Thus, the ability of one of the acids involved to form a ketone is the only prerequisite to the success of the catalytic method.

In ketone syntheses thorium oxide is the preferred catalyst in every case. For aldehyde syntheses which can be performed, according to Sabatier and Mailhe,[279] by passing the mixture of formic acid vapors together with the carboxylic acid involved over catalysts, manganese oxide sometimes gives better results.

Organic Syntheses [280] gives details for the preparation of the thorium oxide catalyst as well as for the preparation of phenylacetone.

The thorium oxide-catalyzed formation of ketones from carboxylic acids is less useful with high molecular weight compounds because of their high boiling points. However, by substituting esters for the free acids Swann, Appel, and Kistler [281] obtained ketones in excellent yields. Ethyllaurate, for example, at a temperature of 360°C., and a distillation rate of 3 to 4 g. per minute, gave 92.5% of the theoretical yield of laurone.

The preparation of the catalyst and a description of the apparatus used by Swann and coworkers are given in an earlier paper.[282] The usual thorium oxide-pumice catalyst is replaced by a thorium oxide-aerogel the preparation of which is rather tedious and cannot be described here. The catalyst furnace is electrically heated, and the temperature measured with a thermocouple. The reaction chamber consists of two concentric tubes of Pyrex glass sealed together as in a Dewar flask. For details the original paper should be consulted.

The dry distillation of the alkaline earth salts of the carboxylic acids has been used for a long time for the preparation of ketones, and in many cases gives such excellent results that it may under certain conditions prove to be very suitable as a laboratory method. Thus, cyclopentanone is prepared according to a patent [283] as follows:

An intimate mixture of 500 parts of adipic acid and 20 parts of finely pulverized barium hydroxide hydrate is heated slowly in a retort to 290° to 295°C. as long as a distillate forms. The cyclopentanone is salted out with solid sodium carbonate, dried, and rectified. A yield of 70% or more of the theoretical amount of cyclopentanone, boiling at 130° to 130.5°C., is obtained.

[279] Sabatier and Mailhe, *Compt. rend.*, 154, 561 (1912).
[280] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 389.
[281] Swann, Appel, and Kistler, *Ind. Eng. Chem.*, 26, 1014 (1934).
[282] Swann, Appel, and Kistler, *Ind. Eng. Chem.*, 26, 388 (1934).
[283] Bayer and Co., German Patent, 256,622.

The preparation of cyclopentanone from adipic acid by the catalytic method is said to be most favorably carried out at a reaction temperature of 35°C. and with manganese oxide as the catalyst.[284] The yield amounts to 80% of the theoretical. In this case, therefore, the simpler dry distillation method is almost as good as the catalytic method. In the last analysis, however, the distillation method is essentially a catalytic reaction also. *Organic Syntheses* [285] gives a method which is similar to the one described above.

The removal of carbon dioxide from dicarboxylic acids gives good yields of ring ketones only in a few cases. Ruzicka and coworkers [286] have shown that they are best (80%) for the 5 atom ring, decreasing to 70% for the 6 atom ring, 50% for the 7 atom ring, 20% for the 8 atom ring, and to only a few tenths of 1% for the 9 to 12 atom rings; and then increasing again to 5% for the 15- to 16-membered rings.

Ziegler [287] pointed out that the conditions used by Ruzicka for ketone formation, involving the thermal removal of carbon dioxide from two reactive groups, one of each end of a long chain, are very unfavorable because the reaction takes place in a condensed phase; that is, at maximum density. The ease of formation of 5-, 6-, and 7-membered rings explains why good yields are obtained from acids of the requisite chain length, but as the number of atoms in the dibasic acid increases there is more probability for the carbon dioxide to be eliminated between neighboring molecules than between two ends of the same molecule.

Reasoning thus, Ziegler indicated that better yields could be expected if the cyclization could be carried out at a very low concentration, and that it would of necessity have to be done in solution. The *inter*molecular reaction between a nitrile molecule of the formula, $R \cdot CH_2 \cdot CN$, and a molecule of the sodium compound, $R \cdot CHNa \cdot CN$, derived from the nitrile yields the sodium compound of a cyanoketimide according to the equation,

$$R \cdot CHNa \cdot C \vdots N + N \vdots C \cdot CH_2 \cdot R \longrightarrow R \cdot CH - \underset{\substack{\Vert \\ C \vdots N \quad NNa}}{C} \cdot CH_2 \cdot R$$
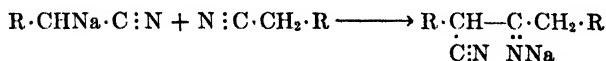
The ketimide on hydrolysis gives first a cyano ketone and then a 1,3-ketocarboxylic acid, which on decarboxylation forms a ketone. *Intra*molecularly, the reaction should proceed as follows:

[284] Sabatier and Mailhe, *Compt. rend.*, **158**, 987 (1914).
[285] H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 192.
[286] L. Ruzicka, *Helv. Chim. Acta*, **9**, 230, 715, 1008 (1926); **11**, 686 (1928).
[287] K. Ziegler, *Ber.*, **A67**, 139 (1934).

$$
\begin{array}{ccc}
\begin{array}{l}
\text{CH}_2\text{——CH}_2 \\
\quad|\qquad\quad| \\
\qquad\quad \text{C}:\text{N} \\
(\text{CH}_2)_n \quad + \\
\qquad\quad \text{CHNa}\cdot\text{CN} \\
\quad|\qquad\quad| \\
\text{CH}_2\text{——CH}_2
\end{array}
& \longrightarrow &
\begin{array}{l}
\text{CH}_2\text{——CH}_2 \\
\quad|\qquad\quad| \\
\qquad\quad \text{C}:\text{NNa} \\
(\text{CH}_2)_n \\
\qquad\quad \text{CH}\cdot\text{CN} \\
\quad|\qquad\quad| \\
\text{CH}_2\text{——CH}_2
\end{array}
\longrightarrow
\begin{array}{l}
\text{CH}_2\text{——CH}_2 \\
\quad|\qquad\quad| \\
\qquad\quad \text{CO} \\
(\text{CH}_2)_n \\
\qquad\quad \text{CH}\cdot\text{COOH} \\
\quad|\qquad\quad| \\
\text{CH}_2\text{——CH}_2
\end{array}
\end{array}
$$
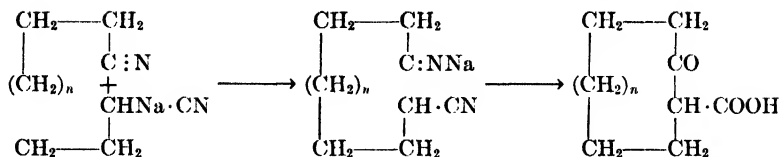
The reaction is carried out by adding the solution of a dinitrile to the ethereal solution of an alkali-organic compound such as diethyl sodium amide, or better yet to a solution of a fatty aromatic sodium amide. Thus hydrogen is exchanged for sodium (or lithium) and the sodium compound of the dinitrile is formed; this undergoes the cyclization under suitable conditions.

A few remarks on the details of the method may be added here. See Ziegler.[288] The principle of the above reaction is derived from some work by Thorpe[289] who obtained cyanocyclopentanone from adipic acid nitrile, using sodium ethylate as the condensing agent. However, the reaction is incomplete and apparently results in an equilibrium. Lithium or sodium ethylaniline are more suitable condensing agents.[290]

A clear solution of lithium butylaniline is prepared from 40 cc. of ethereal 10 N lithium butyl solution, 500 cc. of ether, and 93 cc. of ethylaniline. The mixture is stirred and heated to the boiling point and a solution of 27.2 g. of suberic dinitrile in ether is added through the reflux condenser in such a manner that no drops are formed. The addition takes 13 to 14 hours. The reaction mixture which is only slightly brown in color if air is carefully excluded is poured quickly into 600 cc. of 2 N hydrochloric acid. The ether solution is shaken for 5 minutes with a mixture of 40 cc. each of water and concentrated hydrochloric acid in order to saponify the imide group. By shaking with hydrochloric acid the ethylaniline is completely extracted. From the ether solution cyanosuberone is isolated in a yield of 24 to 25 g., 90% of the theoretical amount.

For the preparation of the higher membered ring ketones Ziegler developed an elaborate apparatus which cannot be described here. The duration of the runs was extended to 240 to 340 hours, the condensing agent was used in greater dilution (3 liters), and each 0.2 mole of dinitrile was dissolved in 500 to 700 cc. of benzene. The rate of addition was 2 to 2.5 cc. per hour. The steady addition without the formation of drops was effected by displacing the nitrile solution continuously with mercury. Even a single drop would cause much too high a concentration.

In summarizing, Ziegler[291] makes the following comments: Each 0.1 g. of dinitrile is brought into reaction with 1500 cc. of 0.67% sodium alkyl aniline solution which contains 25% excess alkyl aniline. The highest possible concentration of the dinitrile in ether is added while

[288] K. Ziegler, *Ann.*, **504**, 94 (1933); **513**, 43 (1934).
[289] Thorpe, *J. Chem. Soc.*, **95**, 1903 (1909).
[290] K. Ziegler and R. Aurnhammer, *Ann.*, **513**, 55 (1934).
[291] K. Ziegler, H. Eberle, and H. Ohlinger, *Ann.*, **504**, 120 (1933),

the mixture is stirred and boiled vigorously. If changes are made, care must be taken that the ratio (amount of nitrile)/(amount of reagent × time) remains constant.

With this method the yield of higher membered ring ketones is increased to 15% for the 13-membered ring, and to about 60% for 14- and 15-membered rings. With larger rings a distinct, alternating effect appears; compounds with an odd number of members in the ring, *e.g.* 17 and 19, are obtained in noticeably lower yields. The maximum yield (over 80%) is obtained with the 18-membered ring. It is remarkable that with this method also the tendency to form 9-, 10-, and 11-membered rings is slight. The yields are not much better than with the dicarboxylic acids; the increase in yield begins with the 12-membered ring; it amounts to about 7% of the theoretical.

Ziegler's method may, of course, be used successfully for other cyclizations.

An outline of the method used for the synthesis of the natural musk ketone, muscone, β-methylcyclopentanone,[292] follows.

ω-Bromo-n-decylmalonic ester, $Br(CH_2)_{10} \cdot CH(COOC_2H_5)_2$, is prepared in the usual manner from 1,10-dibromo-n-decane and ethyl malonate. The ester is then converted to the ω-bromo-n-decylmethylmalonic ester, $Br \cdot (CH_2)_{10} \cdot C(CH_3)(COOC_2H_5)_2$. The second bromine atom is also replaced by a malonic ester residue and the tetracarboxylic acid obtained by saponification is decarboxylated to give the dicarboxylic acid, $HOOC \cdot (CH_2)_{11} \cdot CH(CH_3) \cdot COOH$. The ester of this dicarboxylic acid when treated according to the Bouveault-Blanc method gives a 30% yield of the glycol, $OHCH_2 \cdot (CH_2)_{11} \cdot CH(CH_3) \cdot CH_2 \cdot OH$, which is converted through the dibromide to the dinitrile, $CN(CH_2)_{12} \cdot CH(CH_3) \cdot CH_2 \cdot CN$. From 5 g. of this dinitrile, 2.5 g. of racemic muscone are obtained by cyclization.

[292] K. Ziegler, *Ann.*, 512, 164 (1934).

Fission of Carbon-Carbon Bonds

The division of this chapter has been made according to the following considerations.

The thermal decomposition of carbon compounds can take place at any temperature. However, only those reactions which take place at artificially produced, elevated temperatures will be treated here. Oxidative degradation is effected with oxidizing agents. Hence, the Hofmann degradation of acid amides by means of hypobromite might be considered as an oxidative degradation. However, on studying the equation, $R \cdot CONH_2 + O \rightarrow R \cdot NH_2 + CO_2$, one finds that the desired primary amine belongs to a lower oxidation stage than the acid amide. Accordingly, the reaction could be called a reductive degradation. More important, however, than these considerations of the mere formula is the fact that the same preparational purpose, namely the substitution of a carboxyl group by a primary amino group, is achieved with other degradation reactions, such as the Curtius and Braun degradations, which proceed without actual oxidation. The common characteristic of all these reactions which a chemist would regard as belonging together is the hydrolysis of isocyanates or of urethanes. Therefore these reactions are treated under the heading, "Hydrolytic Degradation." It is true that they are associated with rearrangements and, therefore, they are discussed in the chapter on rearrangements, as far as the rearrangement products are of preparative value.

There is a further consideration in regard to the opening of carbon rings. In so far as the opening of the ring takes place by oxidation and *without loss of carbon* it might have been discussed in previous chapters where ring closures were treated. However, because the methods of ring opening are completely similar to the degradation methods proper, only such reactions are treated here (and the ring opening will therefore be treated in the present chapter, although it proceeds without the loss of carbon atoms) which are accompanied by loss of carbon; e.g., the degradation of long side chains, but not the conversion of terminal methyl groups into carboxyl groups.

1. THERMAL DECOMPOSITION

A. Removal of Carbon Dioxide

Numerous carboxylic acids lose carbon dioxide according to the equation, $R \cdot COOH \rightarrow R \cdot H + CO_2$. The degradation takes place most readily with carboxylic acids carrying, adjacent to the carboxyl group, certain radicals designated as negative which may be of the most varied nature.

In the simplest case, that of acetic acid, the progressive substitution of the hydrogen atoms of the methyl group by halogens increases the acidity, but has a loosening effect upon the carboxyl group. The higher the atomic weight of the substituent the more pronounced is the effect. Trichloroacetic acid, for instance, can be distilled without decomposition and decomposes only slowly at temperatures above 200°C. Triiodoacetic acid, however, decomposes when warmed gently. The salts decompose more easily. Trichloroacetic acid, on being heated with aniline, is converted to chloroform and carbon dioxide, potassium tribromoacetate is decomposed to bromoform and bicarbonate even when covered with acetone, while salts of triiodoacetic acid apparently are altogether unstable. This reaction is of no preparative importance.

Similarly, α-nitrocarboxylic acids decompose readily to give nitro hydrocarbons; see page 293.

The preparation of styrene from cinnamic acid [1] is a reaction of this type.

Further, the best method for the preparation of furane involved the removal of carbon dioxide from pyromucic acid. Formerly, this reaction was carried out in a sealed tube, or by heating pyromucic acid with sodalime, but a much more convenient modification which gives excellent yields is now available.[2]

In general, the derivatives of malonic acid split off 1 mole of carbon dioxide when heated above their melting points to give monobasic carboxylic acids. A few examples were described on page 424, and below are given the directions of Adams and Marvel [3] for the preparation of n-caproic acid from n-butylmalonic acid (see page 361). These authors thoroughly studied the conditions of the carbon dioxide removal. Before they developed the method described below, they tried by means of distillation to remove the ether from an ethereal solution of butylmalonic acid obtained in the regular course of preparation and then to decompose

[1] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 440.

[2] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 274.

[3] R. Adams and C. S. Marvel, *J. Am. Chem. Soc.*, **42**, 317 (1920).

the residue thermally, but caproic acid volatilized easily together with carbon dioxide. The saponification of the ester together with the decarboxylation is best carried out as follows:

To a solution of 500 g. of potassium hydroxide in an equal amount of water in a 5 liter flask equipped with a condenser and a dropping funnel, 500 g. of butylmalonic ester are slowly added with frequent shaking. The ester is rapidly hydrolyzed and by the time the butylmalonic ester has been added the reaction is practically complete and the solution is clear. To complete the hydrolysis and to distil the main portion of the alcohol formed the condenser and dropping funnel are removed and the flask is heated on a steam bath for 1 to 2 hours. Then the reflux condenser and the dropping funnel are replaced and the solution acidified with 1500 cc. of concentrated hydrochloric acid, the acid being added slowly enough to prevent excessive foaming. After boiling for 4 to 5 hours almost all of the oily n-caproic acid is distilled through a downward condenser. The oil is separated from the aqueous distillate and 400 cc. of the water returned to the distilling flask (5 liters). After another distillation the caproic acid is separated and the combined aqueous layers are salted out with calcium chloride. The caproic acid is dried with calcium chloride and distilled. It boils at 200° to 205°C. The yield is 200 g. (74% of the theoretical amount).

In the case of carboxylic acids which do not split off carbon dioxide or do so only at such high temperatures that complete decomposition of the molecule results, advantage is taken of the fact that the salts of the acids may also be thermally decomposed. In such a case two concurrent reactions take place, according to the equations,

$$(R \cdot COO)_2Me + H_2O \longrightarrow 2RH + MeCO_3 + CO_2$$
$$(R \cdot COO)_2Me \longrightarrow R \cdot CO \cdot R + MeCO_3$$
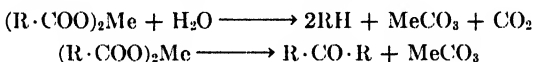
Both reactions give a metal carbonate but one leads to the production of a hydrocarbon, while the other gives a ketone. It is obvious from the equations that the presence of water favors the production of the hydrocarbon, so that if the ketone is required, it is desirable to start with a dry salt and calcium hydroxide.

The purely preparative importance of the method is slight, but it is useful as a means of establishing the constitution of aromatic or heterocyclic nuclei. If small amounts are to be treated, the reaction mixture, sometimes diluted with quartz sand or iron filings, is put into a combustion tube, and carbon dioxide is passed through while the tube is heated. For larger quantities iron retorts with flat bottoms in which the substance can be spread out in a thin layer are advantageous.

In certain special cases the use of other salts proved to be advantageous; thus, Straus [4] prepared phenylacetylene from the copper salt of phenylpropiolic acid. Even though better methods are known for the preparation of phenylacetylene itself, the method may serve well in other cases.

[4] F. Straus, Ann., **342**, 222 (1905).

Side reactions occur in many cases, especially with alicyclic compounds. Thus, cyclohexanecarboxylic acid does not yield cyclohexane but a mixture of dihydro- and tetrahydrobenzene.

The thermal decomposition of α-ketocarboxylic acids, the isomeric glycidic and α-hydroxy acids, takes place under certain conditions.

1. The α-keto acids which can be prepared by various methods are decomposed to aldehydes and carbon dioxide as indicated by the equation, $R \cdot CO \cdot COOH \rightarrow R \cdot CHO + CO_2$. According to Bouveault [5] the decarboxylation proceeds more smoothly through the arylimino derivatives, $R \cdot C(:N \cdot R') \cdot COOH$, which are formed with primary aromatic amines, than it does in the direct manner. The arylimino derivatives are converted to Schiff bases, $R \cdot CH:N \cdot R'$. The procedure is simple: the keto acid is boiled with excess aniline until the removal of water is complete, the water and aniline are removed by distillation, the residue is mixed with mineral acid to hydrolyze the Schiff base, and the aldehyde is extracted with ether. As an example directions for the preparation of *p-n*-propylbenzaldehyde according to Weygand follow.

50 g. of aluminum chloride are suspended in a mixture of 40 g. of *n*-propylbenzene, 60 g. of nitrobenzene, and 150 cc. of carbon disulfide in a 3-necked flask (500 cc.) equipped with a stirrer, a dropping funnel, and a reflux condenser. The stirrer is started and 53 g. of oxalic ester chloride are added from the dropping funnel at such a rate that the reaction does not become too violent. After the vigorous evolution of hydrogen chloride has subsided, the reaction mixture is poured onto ice and excess hydrochloric acid ($D = 1.19$) is added whereby the color of the solution changes from reddish brown to yellow. It is extracted with ether, and the ethereal extract washed twice with dilute sodium carbonate solution and twice with water. The sodium carbonate extracts are saved. After the material is dried, the ether solution yields upon vacuum distillation 52 g. (71% of the theoretical amount) of ethyl *p-n*-propylphenyl glyoxylate boiling at 172° to 175°C. at 12 mm.

The sodium carbonate extracts contain a considerable amount of free glyoxylic acid in the form of the sodium salt. 11 g. of crude product can be recovered from the carbonate solution by acidification, followed by extraction with ether. This represents a total yield of 88% of the theoretical, based on *n*-propylbenzene.

11 g. of the pure ester are saponified by boiling for several minutes with 25 cc. of 10% aqueous sodium hydroxide until the mixture becomes homogeneous. The solution is then acidified with hydrochloric acid, extracted with ether, dried with sodium sulfate, and the ether removed by distillation. The residue consists of 9 g. of *p-n*-propylphenyl-glyoxylic acid in the form of a yellowish syrup. The acid solidifies in a freezing mixture and can be recrystallized from petroleum ether but with considerable loss. It forms colorless, very hygroscopic needles melting at 37° to 38°C. The crude product can be used for the preparation of *n*-propylbenzaldehyde.

The crude acid obtained from 44 g. of the ester in the manner described above is mixed with a small excess of freshly distilled aniline (about 20 g.) in a Claisen flask. The solid aniline salt is thus formed. When the product is heated, water and carbon dioxide are split off with a little foaming, leaving a yellowish liquid which is distilled immediately

[5] L. Bouveault, *Bull. soc. chim.*, 15, 1020 (1896); 17, 363 (1897).

in vacuo. After a forerun, the Schiff base distils at 205°C. at 12 mm. The yield is 32 g., 72% of the theoretical amount. Finally, 150 cc. of 25% sulfuric acid are added to 32 g. of the base and the mixture is heated for 15 minutes on a steam bath. The cooled reaction mixture is extracted three times with ether, and the ether solution is washed with sodium carbonate solution and with water, dried with sodium sulfate, and distilled. 14 g. (65% of the theoretical amount) of *p-n*-propylbenzaldehyde, boiling at 112° to 114°C. at 13 mm., are obtained. The higher boiling fraction (5 g.) contains more of the aldehyde.

Another method of decarboxylation of α-keto acids leads through the bisulfite compounds. This method is mentioned on page 464 in connection with the preparation of phthalaldehydic acid from phthalonic acid.

2. The glycidic acids (see page 387) decompose spontaneously on heating, as indicated by the equation,

$$R \cdot CH \underset{O}{\overset{\diagdown \diagup}{\cdot} CH \cdot COOH} \longrightarrow R \cdot CH : CHOH + CO_2 \longrightarrow R \cdot CH_2 : CHO$$
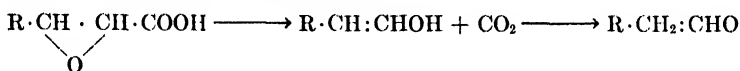
They can be prepared, according to Darzens, by hydrolysis of the esters obtained by treating aldehydes with sodium alcoholate and chloroacetic ester. They can also be prepared readily from acrylic acids directly by treatment with peracids, or indirectly through the chlorohydrins; see below. The lower members of the series are distilled at ordinary pressure, the higher ones *in vacuo.*

Claisen [6] has shown that if about four-fifths of the calculated amount of dilute hydrochloric acid is added to an aqueous solution of sodium methylphenylglycidate and the mixture distilled with steam after the evolution of carbon dioxide has ceased, a 70 to 80% yield of 1-methyl-1-phenylacetaldehyde is obtained.

Sometimes it is not necessary to isolate the glycidic acid. For example, Erlenmeyer and Lipp [7] have shown that the reaction product of hypochlorous acid and cinnamic acid which consists of a mixture of the two phenylchlorolactic acids, $C_6H_5 \cdot CHCl \cdot CHOH \cdot CHOH$ and $C_6H_5 \cdot CHOH \cdot CHCl \cdot COOH$, may be used directly.

1 mole of phenylchlorolactic acid (see page 70) is mixed with 5 times its weight of water and 2 moles of 25% sodium hydroxide solution. Some sodium phenyl glycidate which separates is redissolved by heating and 0.75 mole of 25% sulfuric acid is added. After the evolution of carbon dioxide ceases, the mixture is distilled with steam. 30 g. of phenylacetaldehyde, boiling at 85° to 86°C. at 10 mm., can be isolated in the usual manner from 100 g. of phenylchlorolactic acid. The aldehyde is unstable; it polymerizes readily. Darzens [8] merely states that the lower members of the glycidic acid series are converted to aldehydes even at ordinary temperature with removal of carbon dioxide, while the higher ones have to be distilled *in vacuo.*

[6] L. Claisen, *Ber.*, **38**, 704 (1905).
[7] Erlenmeyer and Lipp, *Ann.*, **219**, 182 (1883).
[8] G. Darzens, *Compt. rend.*, **139**, 1216 (1904).

3. α-Hydroxy acids split off formic acid or its decomposition products, carbon monoxide and water. In some cases heat alone effects the cleavage; in others concentrated sulfuric acid is necessary. The reaction proceeds as follows:

$$R \cdot CHOH \cdot COOH \longrightarrow R \cdot CHO + CO + H_2O$$

or $$R_2{:}COH \cdot COOH \longrightarrow R \cdot CO \cdot R + CO + H_2O$$
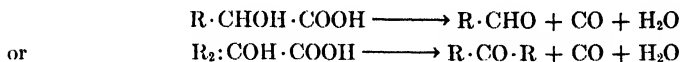
The decomposition of oxalic acid ($HOOC \cdot COOH \rightarrow HCOOH + CO_2$) may be considered as a special case in which carbon dioxide takes the place of the aldehyde. The degradation of citric acid to acetonedicarboxylic acid, as described by Pechmann, is also a reaction of this type. Details of the procedure may be found in *Organic Syntheses.*[9]

Simpler directions by Henle [10] follow.

To 250 g. of pulverized citric acid are added 500 g. of 15% oleum. After the foaming caused by the heat has subsided (about 15 minutes), the mixture is heated on a steam bath. (The reaction is carried out under a hood, or the carbon monoxide is burned at the end of a glass tube 8 mm. in diameter.) The foaming is controlled by shaking the flask. When the carbon monoxide flame goes out, the flask is cooled in water, in ice, and finally in a freezing mixture, despite the presence of unchanged starting material. The mixture is then poured, with stirring, on 300 g. of crushed ice in a thick walled beaker which is well cooled. After 1 to 2 hours standing the crystals are filtered with suction and dried on porous plates.' A crude yield of 150 g. of acetonedicarboxylic acid, which still contains sulfuric acid, is obtained, but it may be used directly in this form for other preparations. To purify it, it is extracted with acetic ester and then yields 100 g. of a product melting at 138°C.

Blaise [11] has investigated the degradation of many other α-hydroxy-carboxylic acids to the aldehydes through the lactides, but finds the method is frequently unsatisfactory. Darzens and Lévy [12] have modified the method so that good yields of aldehydes can be obtained. The reaction proceeds from esters brominated in the α position through the α-methoxycarboxylic acids according to the reaction sequence,

$$R \cdot CH_2 \cdot COOH \longrightarrow R \cdot CHBr \cdot COOCH_3 \longrightarrow R \cdot CH(OCH_3) \cdot COOCH_3 \longrightarrow$$
$$R \cdot CH(OCH_3) \cdot COOH \longrightarrow R \cdot CHO + CO + CH_3OH$$
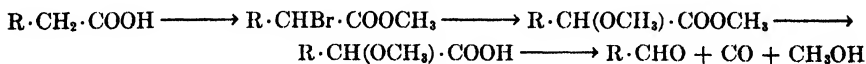
The α-methoxy esters are obtained from the α-bromo esters by treatment with sodium methylate; thus, α-bromostearic acid ester yields α-methoxy-stearic acid ester and this, on saponification, gives α-methoxystearic acid melting at 62.5°C. and boiling at 190°C. at 5 mm. The methoxy acid

[9] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*, Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 10. v. Pechmann, *Ann.*, **261**, 155 (1891).
[10] F. W. Henle, *Anleitung für das organisch-chemisches Praktikum.* Akadem. Verlagsgesellschaft, Leipzig, 1927, p. 223.
[11] Blaise, *Compt. rend.*, **138**, 679 (1904); *Bull. soc. chim.*, **31**, 354, 483 (1904).
[12] G. Darzens and A. Lévy, *Compt. rend.*, **196**, 348 (1933).

is decomposed smoothly by heating for 1 hour to 300°C. to give an almost theoretical yield of margaric aldehyde.

4. The decarboxylation of α-nitrocarboxylic acids to nitro hydrocarbons has already been described. A generally useful method due to Wislicenus and Endres [13] for the preparation of primary nitro compounds from acid nitriles proceeds as follows:

$$R \cdot CH_2 \cdot CN + C_2H_5O \cdot NO_2 + C_2H_5ONa \longrightarrow R \cdot C \cdot CN \longrightarrow$$
$$\overset{\cdot\cdot}{N}OONa$$

$$R \cdot CH(NO_2) \cdot COOH \longrightarrow R \cdot CH_2 \cdot NO_2$$
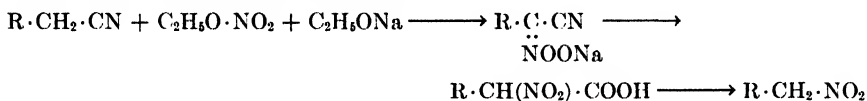
The sodium compound of an acinitronitrile yields on saponification an α-nitrocarboxylic acid from which a nitro hydrocarbon is obtained by decarboxylation.

The preparation of phenylnitromethane from benzyl cyanide as described in *Organic Syntheses* [14] serves as a good example.

5. The decarboxylation of α-amino acids can be carried out advantageously, according to Wada,[15] through the hydantoins formed by reaction with urea. The hydantoins are hydrolyzed by concentrated alkalies or acids to form carbon dioxide and ammonia; thus, the basic primary amines are obtained in good yields according to the reaction,

$$R \cdot CH(NH_2) \cdot COOH + H_2N \cdot CO \cdot NH_2 \longrightarrow H_2N \cdot CO \cdot NH \cdot CHR \cdot COOH \longrightarrow$$

$$\begin{array}{c} R \cdot CH\text{---}NH \\ | \qquad\quad \diagdown CO \xrightarrow{\;H_2O\;} R \cdot CH_2 \cdot NH_2 + 2CO_2 + NH_3 \\ | \qquad\quad \diagup \\ CO\text{---}NH \end{array}$$
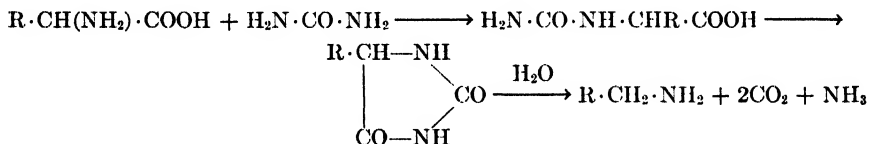
For example, 10 g. of phenylalanine are boiled under a reflux for 35 minutes with an excess of urea (5 g.) in 150 cc. of water. The uramido acid thus formed is converted to the hydantoin by evaporation to dryness with hydrochloric acid and the dry residue is dissolved in ether. The hydantoin crystallizes from the ether upon concentration. The product (4.9 g.) is refluxed for 10 hours with 70 cc. of water and 20 cc. of concentrated sulfuric acid. The solution is then made alkaline and extracted with ether. There are thus obtained 2.5 g. of phenylethylamine (80% of the theoretical amount) boiling at 189°C.

In place of urea urethane, potassium cyanate, or phenyl isocyanate in neutral or alkaline solution may be used. Uramido acids or their salts are formed and these with dilute acids yield the hydantoins. Wada [15] describes the decarboxylation of glycine, leucine, lysine, tyrosine, proline, tryptophan, arginine, cystine, aspartic acid, and glutamic acid.

According to Wohl [16] the following is the best method for the removal

[13] W. Wislicenus and A. Endres, *Ber.*, 35, 1757 (1902).
[14] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 512.
[15] M. Wada, *Biochem. Z.*, 260, 47 (1933).
[16] A. Wohl, *Ber.*, 26, 734 (1893).

of hydrogen cyanide from acetylated aldonic acid nitriles. The nitrile (0.5 g.) is dissolved in 4 cc. of ethanol and 0.25 g. of silver nitrate and excess ammonia are added at once and the solution acidified after several hours standing.

B. Removal of Other Fragments

Thermal Decomposition in Gaseous Phase

In recent times pyrolysis brought about by passing definite compounds in the gaseous phase over red-hot metal wires has found a number of uses. It was first used as a laboratory method for the preparation of isoprene (see below). Ott and Schmidt [17] applied the method to the preparation of carbon suboxide from diacetyltartaric anhydride.

The round part of the decomposition flask (see Fig. 11) has a capacity of 500 cc.; the two parts of the reaction cylinder are connected by a rubber gasket. Today this gasket would be replaced by a ground joint as described below in the apparatus for the preparation of butadiene. The suggested use of the inner part of an incandescent lamp as support for the heating element is outdated because of the simplified construction of the modern incandescent lamps. Furthermore, the length of the platinum wire (2 meters) used by Ott and Schmidt as a heating element was extended to 4 meters by Diels, Beckmann, and Tönnies [18]; see Fig. 12. Ott brought the wire to red heat with a current of 4 to 4.5 amperes. The receiver (Fig. 11) is cooled in a freezing mixture; this is followed by a receiver cooled to −70°C. with a mixture of alcohol and liquid air. The gases (carbon monoxide and carbon suboxide) formed by the reaction are finally condensed in a third receiver cooled with liquid air.

FIG. 11.—Apparatus for the preparation of carbon suboxide.

FIG. 12.—Arrangement of the glass rods for the heating wire according to Diels.

The reaction is performed by placing 250 g. of diacetyltartaric anhydride (see page 181) in the reaction flask which is heated in a suitable bath to about 200°C. The apparatus is evacuated with an efficient pump, thus causing the diacetyltartaric anhydride to boil vigorously. As a safety measure the exit gases from the pump are burned in the flame of a gas burner, since some carbon monoxide may escape condensation. The pressure in the apparatus should be about 11 mm. During 6 to 8

[17] E. Ott and K. Schmidt, *Ber.*, **55**, 2126 (1922).
[18] O. Diels, R. Beckmann, and G. Tönnies, *Ann.*, **439**, 84 (1924).

hours about 189 g. of diacetyltartaric anhydride are decomposed. 15 g. condense in the top of the cylinder and 46 g. remain in the flask as a black residue. In the receiver cooled with liquid air, 31.5 g. of crude product are condensed; this is 41% of the theoretical amount. Some of the carbon suboxide entrained with the carbon monoxide and is therefore lost. Diels and coworkers obtained 55 to 60% with the lengthened heating wire. The crude product can be purified by fractionation. Pure carbon suboxide boils at 5° to 7°C. at ordinary pressure; see Stock and Stoltzenberg.[19]

For the preparation of carbon suboxide solutions see page 330.

In recent times several methods have been developed for the preparation of butadiene. Of these, the one based on a German patent,[20] and which consists in the thermal decomposition of various hydroaromatic compounds, appears to be the best for laboratory purposes. The principle of the method is the same as that used by Harries and Gottlob [21] for the preparation of isoprene from dipentene.

All details for the preparation of butadiene based on Harries' suggestions can be found in *Organic Syntheses*.[22] The product obtained according to the method described there has a butadiene content of about 82 to 88%. It can be purified through the tetrabromide which, according to Thiele (see page 315), yields butadiene when treated with zinc and alcohol.

The preparation of ketene is also described in detail in *Organic Syntheses*.[23]

II. OXIDATIVE DEGRADATION

It is of advantage to distinguish between two kinds of degradation: one, where the degradation of a carbon compound takes place with oxidizing agents according to plan and step by step; and the other, where the possibilities present in the molecule are used to obtain definite degradation products. Both methods are important for establishing the constitution of compounds as well as for preparative purposes. Frequently the molecule must be altered prior to the degradation. These transformations consist, for the most part, of introducing groups containing oxygen or double bonds.

1. Degradation of Aliphatic Chains Starting from the End

The oxidative degradation of carbon chains as carried out by Krafft with the natural fatty acids possesses only historical interest. It consists in the conversion of a carboxylic acid to the methyl ketone which

[19] A. Stock and H. Stoltzenberg, *Ber.*, **50**, 498 (1917).
[20] German Patent, 252,499.
[21] Harries and Gottlob, *Ann.*, **383**, 228 (1911).
[22] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 102.
[23] H. Gilman and A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 330.

upon oxidation with chromic acid yields acetic acid and a carboxylic acid containing 1 less carbon atom. This procedure can be repeated and, if the chain is not branched, only one member is split off each time. Stearic acid was thus degraded to *n*-capric acid and, since the latter was obtained by synthesis, the constitution of the former was established. The procedure is outdated, and methods are available today to solve such problems more exactly and more conveniently. These methods, however, are not of an oxidative nature.

Wieland, nevertheless, used the method for the degradation of the side chain in the bile acids. The ester of the carboxylic acid was converted, by means of a Grignard reaction, to a tertiary alcohol which was then oxidized to the carboxylic acid, $R \cdot CH_2 \cdot COOR' \rightarrow R \cdot CH_2 \cdot C(OH)(CH_3)_2$. For a suggestion by Karrer [24] the original literature should be consulted.

The degradation of long side chains on aromatic and heterocyclic nuclei to the carboxyl group attached to the nucleus is usually simpler. The most essential facts were discussed previously (see page 137). Nothing further need be said at this point. Changes of method are only necessary with side chains containing halogen. Silver nitrate is then added in order to bind the halogen which would make the oxidation difficult.

The degradation of aliphatic chains with methyl groups as side chains possesses analytical importance because the methyl groups can be determined as acetic acid; see Kuhn and Roth, and Pregl-Roth.[25]

These methods of degrading side chains are rather violent, and if sensitive places in the molecule must be preserved other methods are required. Frequently, the degradation of aromatic methyl ketones to the carboxylic acid with a carboxyl group at the nucleus is desired. The use of hypochlorite or hypobromite is recommended for this purpose, since the other side chains then remain intact. The method is rather inconvenient because one must work with aqueous suspensions. Fuson, Bertetti, and Ross [26] investigated the course of this reaction and succeeded in isolating α,α,α-tribromo-2,4,6-trichloroacetophenone as an intermediate in the hypobromite oxidation of 2,4,6-trichloroacetophenone.

5 g. of 2,4,6-trichloroacetophenone (from 2,4,6-trichlorobenzoyl chloride and methyl-magnesium chloride in a 50% yield) are stirred with 500 cc. of sodium hypobromite solution for 30 hours at about 50°C., and then for 50 hours at 70°C. The sodium hypobromite solution is prepared by dissolving 50 g. of bromine in 500 cc. of 10% sodium hydroxide solution at 0°C. 8 g. (80%) of the tribromo ketone melting at 126° to 127°C. separate. The compound on prolonged heating with 50% sodium hydroxide solution is hydrolyzed almost quantitatively to trichlorobenzoic acid.

[24] P. Karrer, *Helv. Chim. Acta*, **15**, 1218, 1399 (1932).
[25] R. Kuhn and H. Roth, *Ber.*, **66**, 1274 (1933). F. Pregl, *Die quantitative organische Mikroanalyse*, 4th rev. ed. by Hubert Roth, Springer, Berlin, 1935. p. 246.
[26] Fuson, Bertetti, and Ross, *J. Am. Chem. Soc.*, **54**, 4380 (1932).

The trihalogen ketone formed during the reaction is stabilized by the o-substituted chlorine atoms.   Otherwise it could not be isolated.

The same reaction can be successfully carried out with other methyl ketones.   Benzalacetone, for example, yields cinnamic acid, $C_6H_5 \cdot CH:-CH \cdot CO \cdot CH_3 \rightarrow C_6H_5 \cdot CH:CH \cdot COOH$; pinonic acid is converted to pinic acid, see page 459, while isogeronic acid gives dimethyladipic acid.[27]

Kröhnke [28] described a very ingenious method for the degradation of methyl ketones to the carboxylic acids containing 1 less carbon atom. Monobromo ketones made by the action of bromine upon the methyl ketones are treated with pyridine.   The crystalline pyridinium bromides thus formed are hydrolyzed with sodium hydroxide in aqueous alcoholic solution to form carboxylic acids and methylpyridinium bromide.

$$R \cdot CO \cdot CH_3 \longrightarrow R \cdot CO \cdot CH_2Br \longrightarrow R \cdot CO \cdot CH_2 \cdot N(C_5H_5)Br \longrightarrow$$
$$R \cdot COOH + CH_3 \cdot N(C_5H_5)Br$$
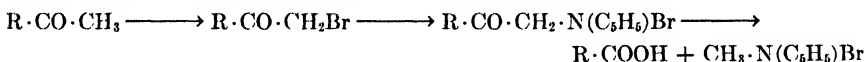
The whole reaction sequence may be carried out without special purification of the intermediates and good yields of the desired carboxylic acids are obtained.   The preparation of α-naphthoic acid serves as a good example.

α-Acetylnaphthalene is dissolved in 5 to 10 parts of glacial acetic acid, the calculated amount of bromine added in the cold, and the mixture gently heated on a water bath. The reaction mixture is poured into water containing a little sulfur dioxide, and the α-naphthacyl bromide that separates is collected on a filter, dried on a porous plate, and then mixed with pyridine.   After the reaction has subsided, the mixture is heated for a short time on a water bath and then dissolved in alcohol.   The α-naphthacylpyridinium bromide, which is precipitated from the alcohol solution with ether, can be recrystallized from 10 parts of water; it melts at 170°C.   The bromide (0.5 g.) is dissolved in 40 cc. of water and 12 cc. of methanol and decomposed by heating on a water bath for 12 minutes with 2 cc. of 10% sodium hydroxide solution.   Upon acidification α-naphthoic acid is precipitated.

In a similar manner, 0.5 g. of β-naphthacylpyridinium bromide gives 0.25 g. of β-naphthoic acid.

In addition to the degradation of ketones the degradation of tertiary alcohols must be considered, for under certain conditions the latter are formed as intermediates, which cannot be isolated, by oxidation of compounds containing a tertiary hydrogen atom.

2. Degradation of Aliphatic Chains from Within

(a) *Starting with Oxygen-Containing Groups*

Special conditions arise if more than 1 single carbon atom is substituted.   The conditions are most favorable if two adjacent hydroxyl groups are present, or can be prepared, as in the case of 1,2-diols or 1,2-

[27] Tiemann and Schmidt, *Ber.*, **31**, 883 (1898).
[28] F. Kröhnke, *Ber.*, **66**, 604 (1933).

glycols. The group $=\text{C(OH)}\!-\!\text{C(OH)}=$ may be readily dehydrogenated with suitable oxidizing agents. The 1,4-diradicals thus formed tend to rearrange to a more stable configuration (see Criegee [29]) according to the scheme,

$$
\begin{array}{c}
-\!\!-\text{C}\!-\!\text{O}\cdot\cdot \\
| \\
-\!\!-\text{C}\!-\!\text{O}\cdot\cdot
\end{array}
\longrightarrow \;\; -\!\!-\text{C}\!=\!\text{O} + \text{O}\!=\!\text{C}\!\!-\!\!-
$$
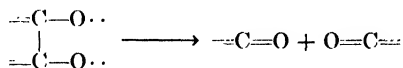
Thus, carbonyl compounds are obtained as products of the cleavage. The reaction is of preparative importance when the molecule is symmetrical and gives rise to only one cleavage product, or when the molecule is unsymmetrical but yields cleavage products that are easily separated.

The oxidizing agents to be considered for this type of reaction are periodic acid (see Malaprade [30]), lead tetraacetate (see Criegee [31]), and osmium tetroxide (see Criegee [32]). Lead tetraacetate is most useful because of its solubility in organic solvents. Periodic acid can be used in aqueous solutions. A need for osmium tetroxide will hardly ever arise.

It is not always necessary to start with 1,2-diols for the cleavage with lead tetraacetate. One or both hydroxyl groups may be replaced by amino groups so that 1,2-diols, 1-hydroxy-2-amines, and 1,2-diamines may be used. The reaction may also be adapted to α-hydroxy acids, α-amino acids, and oxalic acids.

Oeda [33] has, for example, prepared phenylacetaldehyde by the cleavage · of phenyllactic acid.

A mixture of 10 g. of phenyllactic acid (from phenylalanine) and 150 cc. of benzene is boiled until most of the phenyllactic acid has passed into solution. The solution is stirred continuously during the gradual addition of 26 g. of lead tetraacetate. The lead acetate that separates is filtered and washed with benzene. The solvent is removed from the filtrate and washings, and the residue upon distillation *in vacuo* yields 4.2 g. (58% of the theoretical amount) of phenylacetaldehyde, boiling at 84° to 86°C. at 17 mm.

Weygand recommends the following method for the preparation of glyoxylic acid ester from tartaric acid ester.

A solution of 232 g. of diethyl tartrate in 1200 cc. of dry benzene is cooled with ice and 500 g. of lead tetraacetate are added, with stirring, during 1 hour. The temperature is kept below 10°C. The reaction is completed by stirring for an additional 12 hours. The precipitate is filtered with suction, the cake washed with benzene, and the benzene removed by distillation with the aid of a water pump. After the first 500 cc. have been distilled, the receiver is changed and the distillate is tested for glyoxylic acid ester. For this purpose a portion of the new distillate is heated with an equal volume of 2 N ammonia. If glyoxylic acid is present, a yellow color changing to blood-red develops. In the above case the solution was concentrated to a volume of 300 cc. This residue is

[29] R. Criegee, *Angew. Chem.*, **50**, 153 (1937).
[30] Malaprade, *Compt. rend.*, **186**, 382 (1928).
[31] R. Criegee, *Ann.*, **481**, 268 (1930); *Ber.*, **64**, 260 (1931).
[32] R. Criegee, *Ann.*, **522**, 75 (1936).
[33] H. Oeda, *Bull. Chem. Soc. Japan*, **9**, 13 (1934).

mixed with 900 g. of absolute ethanol and the solution is fractionated under reduced pressure. After removal of the alcohol, the residual benzene distils at 40° to 48°C. at 17 mm., followed by 146 g. (43% of the theoretical) of the alcoholate of the glyoxylic acid ester boiling at 54° to 55°C. at 16 mm.

(b) Starting with Double Bonds

Cleavage of Ethylene Bond—The cleavage of the ethylene bond with various oxidizing agents can be represented by the following scheme:

$$=\!\!C\!=\!\!C\!= \;+\; O_2 \longrightarrow =\!\!CO + OC\!=$$
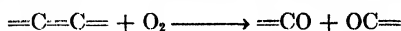
A study of the course of oxidation shows that without exception the cleavage is preceded by an addition. With permanganate, the most important oxidizing agent, the intermediate products are glycols, the cleavage of which has already been discussed on page 455.

Hardly less important is the cleavage with ozone; see page 120. The addition product, an ozonide of heterocyclic structure, which first forms can be decomposed with water to give aldehydes and hydrogen peroxide according to the equation,

$$\underset{\underset{O\text{------}O}{|}}{R\cdot CH}-O\text{---}\underset{}{HC}\cdot R + H_2O \longrightarrow 2R\cdot CHO + H_2O_2$$
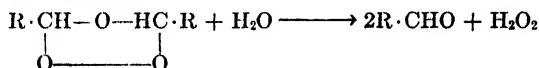
Since the hydrogen peroxide is an oxidizing agent, carboxylic acids may be expected among the cleavage products. If it is desirable to isolate the aldehydes, the ozonide should be treated with zinc dust and glacial acetic acid.

$$\underset{\underset{O\text{------}O}{|}}{R\cdot CH}-O\text{---}\underset{}{CH}\cdot R + 2H \longrightarrow 2R\cdot CHO + H_2O$$
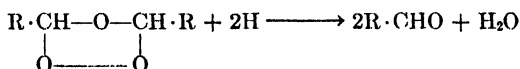
Not only aliphatic but also aromatic double bonds react with ozone; benzene, for instance, yields a triozonide.

Of the other oxidizing agents, hydrogen peroxide and the peracids have already been discussed (see page 122). They are suitable under certain conditions for the preparation of ethylene oxides and oxido compounds. Their cleavage offers nothing new, because they are supposedly first converted to glycols.

With chromic acid the cleavage takes place so readily that no intermediates can be isolated.

The oxidizability of the double bond depends to a very large extent on the substituents involved. In most cases aliphatic compounds containing double bonds are stable towards the oxygen of the air; however, see cyclohexene, page 120. The stability towards oxygen is considerably diminished in conjugated systems such as are present in the drying oils. However, there appears to be no cleavage of molecules, the drying effect being due to an enlargement of the molecule (polymerization).

A ready cleavage by the oxygen of the air results with compounds in which a double bond connects two rings; Graebe's hydrocarbon, dibiphenyleneethylene, for instance, yields in alcoholic or ethereal solutions, when exposed to air, 2 moles of fluorenone, according to the equation,
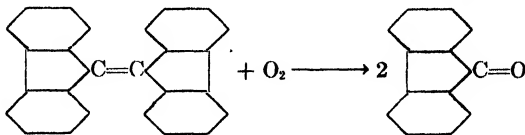
This equation represents the ideal case of oxidative degradation; see Hantzsch and Glover and also Graebe.[34]

In most cases, however, stronger oxidizing agents are necessary. Their number is large and they differ greatly from each other in the effect they produce. As far as methods are concerned, two groups must be distinguished. One includes the oxidizing agents which attack the double bond directly at the point where it is present in the molecule; the other yields cleavage products which can be regarded as having been formed by a rearrangement during the reaction. The latter reagents are not suitable for the determination of constitution, but they have preparative importance if the rearrangement proceeds in one direction only. This is the case with unsaturated carboxylic acids of the aliphatic series with normal chains. Thus, oleic acid gives a good yield of palmitic acid in a smooth reaction when melted with sodium hydroxide. It is true that the preparation of palmitic acid in this manner has no point, but an analogous reaction for the preparation of n-nonylic acid is quite useful. It consists in the cleavage of undecylenic acid, which can be obtained in any desired amount by cracking castor oil. The double bond of undecylenic acid which is at the end of the chain is supposedly moved under the influence of melted alkalies towards the carboxyl group, so that the compound which actually undergoes the oxidation is octylacrylic acid. Krafft's directions [35] for the preparation of n-nonylic acid according to this procedure follow; see also pages 458 and 472.

1 part by weight of undecylenic acid is mixed with 3 to 4 parts of potassium hydroxide and a little water, and the mixture is heated with continuous stirring in an iron pot. As soon as no more steam is evolved, the temperature rises and the molten mass evolves a considerable amount of hydrogen for 2 to 3 hours. The cooled melt is dissolved in water and the solution is filtered and decomposed by heating with hydrochloric acid. The oil that separates is washed with water and distilled under reduced pressure. The main fraction solidifies when cooled in ice, and a pure sample is obtained by pressing the product on cold porous plates. The first low melting fraction can be redistilled.

[34] A. Hantzsch and W. H. Glover, *Ber.*, **39**, 4156 (1906). Graebe, *Ber.*, **25**, 3146 (1892).
[35] F. Krafft, *Ber.*, **15**, 1691 (1882).

n-Nonylic acid melts at 12.5°C. and boils at 186°C. at 100 mm., 253° to 254°C. (corr.) at 760 mm. Heating to the boiling point at ordinary pressure is harmful to the purity of the product.

A good example of the permanganate oxidation of a double bond is the preparation of azelaic acid from ricinoleic acid as described by Hill and McEwen in *Organic Syntheses*.[36]

Many attempts have been made to split ozonides by catalytic hydrogenation instead of with glacial acetic acid and zinc dust. Fischer, Düll, and Ertel [37] determined the conditions under which the cleavage, which proceeds according to the equation on page 456, gives the best yield of products. It proved necessary to work carefully even during the ozonization itself. Dilute solutions and low temperatures must be used and an excess of ozone must painstakingly be avoided. During the hydrogenation, which is a strongly exothermic reaction, any kind of heating must be avoided lest the so called acid rearrangement of the ozonide which simultaneously yields equal moles of carboxylic acid and carbonyl compound become predominant. A palladium-calcium carbonate catalyst containing 5% palladium [38] is used.

3. Degradation of Alicyclic Ring Systems

The degradation of alicyclic ring systems is not only important for establishing constitution (*e.g.*, the polycyclic terpenes and sterols) but it occasionally offers a possibility of readily preparing derivatives of cyclopropane and cyclobutane which are difficult to prepare otherwise.

Norcaradienecarboxylic acid (see page 415) is converted, according to Braren and Buchner,[39] by oxidation with permanganate in sulfuric acid solution into 1,2,3-cyclopropanetricarboxylic acid. However, the yield is very poor, and the acid can be prepared more conveniently by the addition of diazoacetic ester to fumaric ester.[40]

From a number of natural terpenes, including sabinene and thujone, Kondakov and Skvorzov [41] have obtained tanacetonedicarboxylic acid, cyclopropane-1-isopropyl-1-acetic-2-carboxylic acid (see also Semmler [42]).

Baeyer [43] has obtained the so called α-pinonic acid by oxidation of pinene with permanganate as follows:

100 g. of α-pinene (boiling at 155° to 160°C.) are emulsified by stirring vigorously with 600 cc. of water. A lukewarm solution of 233 g. of potassium permanganate in 2

[36] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 53.
[37] F. G. Fischer, H. Düll, and L. Ertel, *Ber.*, 65, 1467 (1932).
[38] M. Busch and H. Stöve, *Ber.*, 49, 1064 (1916).
[39] W. Braren and E. Buchner, *Ber.*, 34, 995 (1901).
[40] E. Buchner and H. Witter, *Ber.*, 23, 2583 (1890).
[41] Kondakov and Skvorzov, *J. prakt. Chem.*, 69, 181 (1904).
[42] Semmler, *Ber.*, 33, 1455 (1900); 36, 4367 (1903).
[43] A. Baeyer, *Ber.*, 29, 22 (1896).

liters of water is added dropwise to the externally cooled emulsion until the permanganate is not longer decolorized. After standing for 12 hours the solution is decolorized with a little methanol, the manganese oxide is removed by filtration, and the filtrate is concentrated in a current of carbon dioxide. 2 liters of concentrate from three batches are extracted thoroughly with ether (ten times), acidified with sulfuric acid, and after saturation with ammonium sulfate again extracted ten times with ether. The ether extract of the acid solution is neutralized with a little bicarbonate solution. A slightly soluble sodium salt that separates is removed by filtration and the aqueous portion of the filtrate is extracted twenty times with ether (a continuous extraction apparatus would be more suitable). The aqueous solution is again acidified, saturated with ammonium sulfate, and extracted completely with ether. Upon removal of the ether by distillation from the last ether extract, 150 g. of crude product remain. From it, 10 g. of crystals separate on standing overnight. The non-crystalline portion is fractionated *in vacuo* at 14 mm. The forerun consists of 5.8 g. (up to 180°C.). A second fraction, 17.5 g., distils from 180° to 187°C., then follows 9.4 g. at 187° to 200°C., and finally 7.8 g. at 200° to 230°C. The fraction boiling at 180° to 187°C. solidifies immediately; the first and third yield crystals slowly, while the last one remains amorphous. The total yield of crystalline pinonic acid from 300 g. of pinene amounts to 30 to 40 g. After recrystallization from water it melts at 103° to 105°C.

For conversion to pinic acid 5 g. of pinonic acid dissolved in aqueous sodium hydroxide are added in one portion to a sodium hypobromite solution made by adding 20 g. of bromine slowly to a cold solution of 15 g. of sodium hydroxide in 150 cc. of water. Bromoform separates after a short time. A little more sodium hydroxide is added and the mixture is allowed to stand for 1 hour. The reaction mixture is then poured into a cool solution of bisulfite and dilute sulfuric acid. The bromoform is separated and the aqueous solution is saturated with ammonium sulfate and thoroughly extracted with ether. Removal of the ether leaves 5.5 g. of a thick oil which soon solidifies. The yield is quantitative. Upon concentration of its aqueous solution pinic acid crystallizes in long prisms melting at 101° to 102.5°C. Pinonic acid can also be oxidized with dilute nitric acid; see Baeyer and Deussen.[44] Further information on pinic acid, especially the active form,[45] and the steric chemistry of the compound,[46] can be found in the original literature.

The following formulas illustrate the degradation:

α-Pinene   α-Pinonic acid   Pinic acid
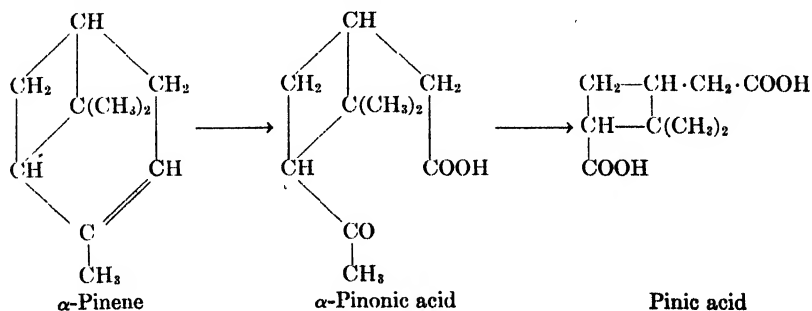
The ring system of the sterols and the bile acids is similar to that of the terpenes in many respects. Therefore, the methods of degradation

[44] E. Deussen, *J. prakt. Chem.*, 145, 36 (1936).
[45] Barbier and Grignard, *Compt. rend.*, 147, 599 (1908).
[46] M. Grandperrin, *Ann. chim.*, 6, 5 (1936); *Chem. Abstracts*, 30, 8190 (1936).

used for establishing their constitution are closely related to those used in the terpene series. The side chain is most easily degraded. From the chromic acid oxidation products of cholesterol Windaus and Resau [47] isolated, by steam distillation, a ketone with 8 carbon atoms which was converted to the semicarbazone and proved to be methyl isohexyl ketone, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH \cdot (CH_3)_2$. It is obvious that methyl isohexyl ketone in this case is the most readily isolated product of many formed by the action of chromic acid upon cholesterol.

It is apparent from the formula that the secondary hydroxyl at carbon atom 3 should be converted to a keto group by very mild oxidation. This can indeed be accomplished in different ways; see page 146. The further oxidation of the cholestenone formed was carried out by Diels and Abderhalden.[48] However, it is not necessary to isolate the cholestenone. Cholesterol may be used directly as starting material.

To a hypobromite solution, prepared by adding 75 g. of bromine to a well cooled mixture of 250 cc. of 33% aqueous potassium hydroxide solution and 500 cc. of water, 50 g. of finely pulverized cholesterol are added, and the mixture is shaken mechanically. After 6 hours the greater part of the cholesterol has disappeared; the greenish alkaline solution is filtered to remove a small amount of tarry material, most of which adheres to the walls of the container. The filtrate is cooled with ice and acidified with dilute sulfuric acid; whereupon a semisolid mass precipitates. After 15 hours the solid is collected on a filter, washed with water, and pressed as dry as possible. The cake is boiled with 200 cc. of absolute ethanol until the product has become granular. After several hours standing in ice the precipitate, consisting of potassium sulfate and an acid of the formula, $C_{27}H_{44}O_4$ (this correct formula was established later), is filtered with suction, washed with a little alcohol, and boiled for 30 minutes with 800 cc. of methyl ethyl ketone. The filtrate is concentrated to incipient crystallization. After about 15 hours, 6 g. of the so called Diels acid are obtained. The mother liquor yields an additional 2 g. After recrystallization from methyl ethyl ketone the product melts (with decomposition) at 290°C. (297°C. corrected).

The fact that the Diels acid contains the same number of carbon atoms as does cholesterol is evidence that the hydroxyl group is attached to a carbon contained in a ring. The double bond, also, must have been present in a ring, as can be deduced from the following transformation.

Cholesterol, according to Windaus and to Lettré and Inhoffen,[49] is converted, by the use of fuming nitric acid, into a compound of the formula, $C_{27}H_{44}NO_2(ONO_2)$. In the formation of this compound the hydrogen atom at the ethylene bond (C atom 6) is replaced by a nitro group and the hydroxyl group is esterified with nitric acid. By reduction with glacial acetic acid and zinc dust (Windaus [49]) a saturated keto alcohol is obtained.

[47] Windaus and Resau, *Ber.*, 46, 1246 (1913).
[48] Diels and Abderhalden, *Ber.*, 36, 3179 (1903); 37, 3092 (1904).
[49] Windaus, *Ber.*, 36, 3752 (1903); Lettré and Inhoffen, *Über Sterine, Gallensäuren und verwandte Naturstoffe*, Enke, Stuttgart, 1936, p. 22.

40 g. of zinc dust are added gradually, in the cold, to a mixture of 20 g. of the nitro compound and 300 cc. of glacial acetic acid. When the vigorous reaction which proceeds with evolution of nitrous gases has subsided, 40 cc. of water are added and the solution is boiled under a reflux for 12 hours. The reaction mixture is cooled, 300 cc. more water are added, and the solution is extracted with ether. The extract is shaken several times with a dilute potassium hydroxide solution and the ether removed by distillation. In order to saponify the acetyl derivative formed the residue is boiled with a mixture of 200 cc. of alcohol and 60 cc. of concentrated hydrochloric acid. The keto alcohol (cholestanolone) crystallizes as fine needles. After cooling, the crystals are filtered with suction, washed with dilute alcohol, and recrystallized from 75% alcohol. 14 g. of pure cholestanolone, melting at 142° to 143°C., are obtained.

The value of this transformation rests in the fact that the point of the molecule where the double bond was originally attached has now been rendered more reactive for oxidation than the hydroxyl group. According to Windaus and Stein [50] the hydroxyl group can be replaced by chlorine when treated with phosphorus pentachloride in the cold, while the keto group does not react and β-chlorocholestanone is formed. This, however, can be converted to a dicarboxylic acid, $C_{27}H_{45}O_4Cl$, with fuming nitric acid and glacial acetic acid. Since this dicarboxylic acid still contains all the carbon atoms of cholesterol, it is apparent that the double bond must be contained in a ring.

Windaus and coworkers [50, 51] were able to show that the hydroxyl group and the double bond belong to two different rings. The chloro-dicarboxylic acid described above can be saponified to give a hydroxydi-carboxylic acid, $C_{27}H_{46}O_5$, which can be converted to a ketodicarboxylic acid, $C_{27}H_{44}O_5$, and by further oxidation into a tetracarboxylic acid, $C_{27}H_{44}O_8$. It was pointed out that, if the hydroxyl group and the double bond were present in the same ring, a tetracarboxylic acid could not be obtained and all the carbon atoms of cholesterol could not be retained.

Windaus and Dalmer [52] applied Blanc's rule (see page 191) to several dicarboxylic acids obtained by oxidation of cholesterol derivatives. The double bond in cholesterol may be hydrogenated, the cholestanol formed dehydrogenated to cholestanone, and the latter oxidized to a dicarboxylic acid, $C_{27}H_{46}O_4$.

5 g. of this dicarboxylic acid are mixed with acetic anhydride and heated until all of the anhydride is removed by distillation. The residue is distilled at 15 to 20 mm. and yields at 250°C. a light yellow oil which soon solidifies. The distillate is dissolved in ether and the solution shaken with dilute sodium hydroxide solution. The ether is removed by distillation and the solid residue after recrystallization from dilute alcohol melts at 100° to 100.5°C.

This compound proved to be a ketone, $C_{26}H_{44}O$, which, according to Blanc's rule, could only be formed from a dicarboxylic acid, the carboxyl

[50] Windaus and Stein, *Ber.*, **37**, 3702 (1904).
[51] Windaus and Deppe, *Ber.*, **66**, 1563 (1933).
[52] Windaus and Dalmer, *Ber.*, **52**, 162 (1919).

groups of which are separated by at least 4 carbon atoms. In order to prove whether a 1,6- or a 1,7-dicarboxylic acid was involved the ketone was oxidized to a new dicarboxylic acid, $C_{26}H_{44}O_4$. This, when treated with acetic anhydride, did not yield a new ketone but an acid anhydride. Therefore, a 1,5-dicarboxylic acid must have been formed through oxidation of the ketone, $C_{26}H_{44}O$, obtained from the dicarboxylic acid, $C_{27}H_{46}O_4$. The latter is thus shown to be a 1,6-dicarboxylic acid. At the same time it shows that the hydroxyl group of cholesterol is in a 6-membered ring, the A ring.

For a long time the B ring of the cholesterol molecule was considered to be a 5-membered ring, but it was eventually shown that it is also a 6-membered ring. The constitution was established in a manner similar to that employed for the A ring. The following results were obtained in one of the methods employed.

In order to render ring B suitable for oxidation the cholesterol molecule was first modified as follows:[53] Cholesteryl chloride, formed from cholesterol by replacing the hydroxyl group with chlorine in the usual manner, was converted by means of amyl alcohol and sodium to cholestene in which the double bond remains intact. Cholestene, on treatment with nitric acid and sodium nitrite, gave nitrocholestene in a reaction analogous to that described above for cholesterol. From the nitro compound, by the use of zinc dust and acetic acid, Windaus and Dalmer [54] obtained a saturated ketone which they called heterocholestanone, but which is known today as 6-cholestanone. The oxidation of heterocholestanone is best effected with fuming nitric acid in glacial acetic acid. Chromium trioxide gives inferior results. The dicarboxylic acid, $C_{27}H_{46}O_4$, was formed by opening ring B in exactly the same manner that the isomeric dicarboxylic acid was obtained from cholestanone by opening ring A.

However, while a ketone was formed from the last mentioned dicarboxylic acid with acetic anhydride, in the manner described, the other dicarboxylic acid gave an acid anhydride by the same treatment. According to Blanc's rule as applied hereto, the dicarboxylic acid formed from heterocholestanone can in no case be a 1,6-, but must be either a 1,5- or a 1,4-dicarboxylic acid. Thus ring B ought to consist of five members. But Windaus, Rosenbach, and Riemann [55] have already pointed out some discrepancies as a result of the application of this rule, and Stange [56] finally succeeded in converting the acid into a 5-membered ring ketone by the dry distillation of the barium salt of the dicarboxylic acid.

[53] J. Mauthner and W. Suida., *Monatsh.*, 15, 87 (1894).
[54] Windaus and Dalmer, *Ber.*, 52, 162 (1919).
[55] A. Windaus, A. Rosenbach, and Th. Riemann, *Z. physiol. Chem.*, 130, 114 (1923).
[56] O. Stange, *Z. physiol. Chem.*, 218, 75 (1933).

In this manner the number of members in the A and B rings of cholesterol was finally established.   The investigation of rings C and D in cholesterol was very much more difficult.   The bile acids, however, which were known to contain the same ring system, yielded suitable starting materials.   Most important of these is desoxycholic acid the two hydroxyl groups of which are attached to carbon atoms 3 and 12, respectively. This acid offered the possibility of rendering the C ring of the system suitable for oxidation.   When desoxycholic acid was dehydrogenated with chromium trioxide,[57] diketocholanic acid was obtained.   This in turn was converted to 12-α-ketocholanic acid by a moderate Clemmensen reduction.[58]   Starting from this acid, Wieland and Dane [59] split the D ring from the system and thus obtained a tricarboxylic acid, $C_{13}H_{20}O_6$, the nature of which is that of a cyclopentane derivative and as such proved the number of carbon atoms in ring D.

Wieland, Schlichting, and Jacobi [60] carried out a systematic degradation of the side chain of the bile acids but only the principle will be described here.   The tricarboxylic acid, $C_{13}H_{20}O_6$, could be obtained only in such small amounts that the investigations were carried out with the saturated cholanic acid.   This was esterified and converted to the tertiary carbinol with methylmagnesium iodide.   The carbinol when oxidized gave, besides other products, the next lower carboxylic acid, norcholanic acid, according to the scheme,

$$R \cdot CH_2 \cdot COOH \longrightarrow R \cdot CH_2 \cdot C(OH)(CH_3)_2 \longrightarrow R \cdot COOH$$
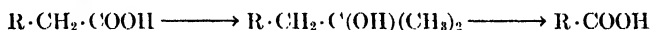
The same degradation principle was continued.   Since another acid with 1 carbon atom less was obtained (although with great difficulty), the original carboxyl group must have been next to two methyl groups.   Thus the formula of cholanic acid can be written $R' \cdot CH_2 \cdot CH_2 \cdot COOH$.   From there the degradation does not proceed in the same manner, because the next carbon atom towards the ring system carries a methyl group, $R'' \cdot CH(CH_3) \cdot CH_2 \cdot CH_2 \cdot COOH$.   The ketone corresponding to this formula, $R'' \cdot CO \cdot CH_3$, was isolated in crystalline form from the by-products.

4. Degradation of Aromatic and Heterocyclic Ring Systems

It is frequently possible to obtain important products from condensed ring systems by oxidative degradation of one of the rings.   When naphthalene, for instance, is degraded, phthalonic acid (I) may be isolated as an intermediate.

[57] Wieland and Sorge, Z. *physiol. Chem.*, 97, 18 (1916).
[58] Wieland and Boersch, Z. *physiol. Chem.*, 106, 198 (1919).
[59] Wieland and Dane, Z. *physiol. Chem.*, 216, 91 (1933).
[60] H. Wieland, O. Schlichting, and R. Jacobi, Z. *physiol. Chem.*, 161, 79 (1926).

$$\text{(I)} \qquad\qquad \text{(II)}$$
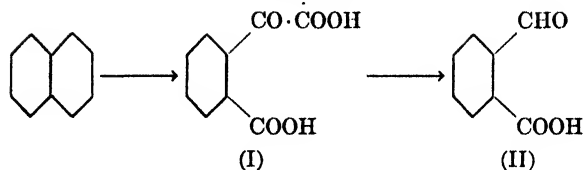
This can be decarboxylated to give phthalaldehydic acid (II).[61]   The preparation of fumaric acid from furfural [62] may be cited as an example of the oxidative degradation of a heterocyclic system.

III. REDUCTIVE DEGRADATION

The preparation of n-pimelic acid by reduction of salicylic acid with nascent hydrogen was formerly considered an operation which could be performed successfully only with very small batches.   Recently, however, directions for preparing it in larger amounts have appeared.[63]

IV. HYDROLYTIC DEGRADATION

The hydrolytic cleavage of carbon to carbon bonds takes place most readily when oxygen is attached to certain points in the molecule.   The preparative value of this reaction is limited to a few fields, the most important of which is the cleavage of 1,3-diketones and 1,3-keto acid esters.

The starting materials for the cleavage reactions are usually synthesized.   Since the relevant facts have already been outlined on pages 359 and 408 et seq., it is necessary at this point to add only a discussion of the reaction.

A. Cleavage of β-Keto Acid Esters and of 1,3-Diketones

The cleavage of 1,3-keto esters proceeds, as is well known, in two directions:

1. Acid cleavage,

$$R \cdot CO \cdot CHR' \cdot COOC_2H_5 \longrightarrow R \cdot COOH + R' \cdot CH_2 \cdot COOH + C_2H_5OH$$

2. Ketone cleavage,

$$R \cdot CO \cdot CHR' \cdot COOC_2H_5 \longrightarrow R \cdot CO \cdot CH_2 \cdot R' + CO_2 + C_2H_5OH$$
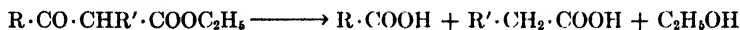
Acid and ketone cleavage always takes place simultaneously.   The acid cleavage proceeds most smoothly with very concentrated alkalies, the ketone cleavage with dilute alkalies, ammonia, or moderately dilute acids.

[61] A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. II, Wiley, New York, 1943, p. 523.   German Patents, 79,693 and 86,914.
[62] A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. II, Wiley, New York, 1943, p. 302.   Milas, *J. Am. Chem. Soc.*, 49, 2007 (1927).
[63] A. H. Blatt, ed., *Organic Syntheses*.   Collective Vol. II, Wiley, New York, 1943, p. 535.   A. Müller, *Monatsh.*, 65, 18 (1935).

For the synthesis of substituted carboxylic acids it is frequently better to use malonic esters, as these are converted readily to the malonic acids which can be decarboxylated just as readily; see page 445. If the reaction is performed with alcoholic rather than with aqueous alkalies, or with alkali-alcoholate solutions, the so called ester cleavage takes place as follows:

$$R \cdot CO \cdot C(R_2') \cdot COOR + R'' \cdot OH \longrightarrow R \cdot COOR'' + R_2' \cdot CH \cdot COOR$$
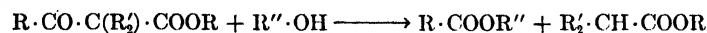
The cleavage of 1,3-diketones gives only monoketones, but diketones of the general formula, $R' \cdot CO \cdot CH_2 \cdot CO \cdot R''$, yield mixtures, because the cleavage can take place in two directions as follows:

$$R' \cdot CO \cdot CH_3 \longleftarrow R' \cdot CO \cdot CH_2 \cdot CO \cdot R'' \longrightarrow CH_3 \cdot CO \cdot R''$$

However, if R' is an aromatic residue while R'' is aliphatic, the fatty aromatic ketone is obtained almost exclusively upon acid hydrolysis. Thus, from benzoylacetone, $C_6H_5 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$, acetophenone is obtained, and from substituted benzoylacetones, substituted acetophenones; see page 363.

A practical example, the preparation of acetonylacetone as described by Knorr,[64] best illustrates the method.

A mixture of 10 g. of diethyldiacetosuccinate and 100 cc. of an exactly 3% sodium hydroxide solution (titrated) is placed in a flask protected with a soda-lime tube and heated on a water bath for 2 to 3 hours until acidification of a sample no longer results in the separation of diethyldiacetosuccinate. The reaction mixture is allowed to cool and saturated with potassium carbonate and the oil that separates is extracted with ether. The ether extract is dried and distilled. A considerable amount of acetonylacetone is carried over with the ether vapors, but if the foreruns are worked up a total yield of 4 g. (90% of the theoretical amount) boiling at 194°C. can be obtained.

B. Degradation of Carboxylic Acids through Acid Amides and Hydrazides

Only the degradation proper is discussed at this point, because the preliminary reactions have been described previously.

According to Hofmann,[65] the acid amide is treated with 1 mole of bromine, the reaction product mixed with 5% alkaline bromine solution, and the amine formed distilled with steam. In many cases the preliminary treatment with bromine is unnecessary. It suffices to treat the amide directly with an alkaline solution of bromine. The preparation of anthranilic acid from phthalimide, as described in Henle,[66] may serve as an example.

To a cold solution of 20 g. of sodium hydroxide (0.5 mole) in 100 cc. of water, 16 g. of bromine (0.1 mole) are added. The solution is cooled to −10°C. and a suspension of

[64] L. Knorr, *Ber.*, **22**, 2100 (1889).

[65] Hofmann, *Ber.*, **14**, 2725 (1881); **18**, 2738 (1885).

[66] F. W. Henle, *Anleitung für das organisch-chemisches Praktikum*, Akadem. Verlagsgesellschaft, Leipzig, 1927, p. 91. Hoogewerff and van Dorp, *Rec. trav. chim.*, **10**, 6 (1891).

14.8 g. of phthalimide (0.1 mole) in 20 cc. of water is added with mechanical stirring. If necessary the last of the suspension is washed into the flask with 10 cc. of water. The freezing mixture is then removed and the mixture allowed to warm up slowly while the stirring is continued. At 10°C. a clear solution should result. Upon addition of 12 g. of pulverized sodium hydroxide (0.3 mole) the temperature rises to about 40°C. It is then increased to 80°C. The solution is then cooled, neutralized with 32 cc. of concentrated hydrochloric acid ($D = 1.18$), and finally acidified with 15 cc. of glacial acetic acid. After standing for several hours in the cold the anthranilic acid is collected on a filter, washed with a little water, and dried over sulfuric acid. A yield of 12 g. of anthranilic acid, 87% of the theoretical amount, melting at 144° to 145°C., is obtained. The crude product can be purified by recrystallization from water or from ligroin. The anthranilic acid retained in the mother liquor can be precipitated with cupric acetate solution as copper anthranilate.

In a similar manner Hoogewerff and van Dorp [67] obtained benzylamine from phenylacetamide.

1 mole of phenylacetamide is added to a solution of 1 mole of bromine in 4 moles of 20% sodium hydroxide solution. The mixture is heated for a time on a water bath and the benzylamine is distilled with steam. The yield amounts to 80 to 85% of the theoretical.

A variation of the Hofmann degradation proposed by Jeffreys (see also Gutt) [68] gives considerably better yields especially with aliphatic amides of high molecular weight. The improvement consists in the use of alkali-alcoholate in alcoholic solution and urethanes appear as intermediates.

$$R \cdot CONH_2 + Br_2 \longrightarrow R \cdot CONHBr + NaOCH_3 \longrightarrow R \cdot NH \cdot COOCH_3$$
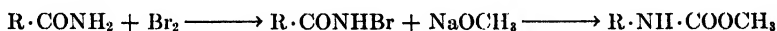
The mechanism of the reaction need not be discussed here. Jeffrey's procedure [68] for the preparation of pentadecylamine from palmitamide serves as a good example.

To a solution of 25.5 g. of palmitamide in 65 g. of warm methanol is added a solution of 4.6 g. of sodium in 115 g. of methanol. To this mixture 16 g. of bromine are added dropwise. The sequence is not important; bromine may be added first and then the methylate solution. The mixture is heated for 10 minutes on a water bath, neutralized with acetic acid, and the alcohol removed by distillation. The residue is extracted with water, the undissolved urethane (methylpentadecyl carbamate) collected on a filter, washed with water, and dried. Upon treatment with warm ligroin (b.p. 70° to 80°C.) any unchanged acid amide remains undissolved. From the ligroin a yield of 83 to 94% of the theoretical amount of urethane melting at 60° to 62°C. is obtained. This is mixed carefully with 4 times its weight of calcium hydroxide and the mixture distilled. The pentadecylamine formed distils almost quantitatively. It is dissolved in ligroin, dried with potassium carbonate, and distilled from sodium. It melts at 36.5°C. and boils at 298° to 301°C.

[67] Hoogewerff and van Dorp, *Rec. trav. chim.*, 5, 252 (1886).
[68] Jeffreys, *Ber.*, 30, 898 (1897); *Am. Chem. J.*, 22, 14 (1899). J. Gutt, *Ber.*, 40, 2063 (1907).

Organic Syntheses [69] describes a method for the preparation of 3,4-dimethoxyaniline from 3,4-dimethoxybenzamide. Here the expensive sodium hypobromite is replaced by sodium hypochlorite.

Another example is the preparation of α-aminopyridine from picolinamide.[70]

A solution of 10 g. of bromine in 1 liter of 3.5% potassium hydroxide is added gradually to finely powdered picolinic acid amide until complete solution results. About 800 cc. of the solution are necessary to dissolve the amide. The mixture is then heated on the water bath and with continuous shaking portions of hypobromite are added until a red color appears. At this point the solution is heated until the color has disappeared and then filtered to remove any by-products formed in the reaction. The filtrate is rendered slightly acid with acetic acid and extracted thoroughly with ether in order to remove a by-product. It is then made strongly alkaline with potassium carbonate and again extracted with ether. α-Aminopyridine, boiling at 199° to 200°C. and melting at 56°C., is isolated from the ether extract in the usual manner.

The so called Curtius degradation of acid hydrazides and azides accomplishes the same preparational purpose, but in certain respects it is more advantageous. It leads through the following intermediates, all of which, except the isocyanic esters, can be isolated.

$$R \cdot COOC_2H_5 + H_4N_2 \longrightarrow R \cdot CO \cdot NH \cdot NH_2 \xrightarrow{HNO_2} R \cdot CO \cdot N_3 \longrightarrow$$

$$O:C:N \cdot R \xrightarrow{C_2H_5OH} C_2H_5O \cdot CO \cdot NH \cdot R \longrightarrow R \cdot NH_2$$
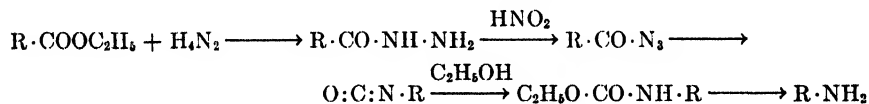
With an ester at the start, the hydrazide is obtained in a very smooth reaction without the formation of by-products. This is readily converted to the azide by treatment with nitrous acid. The azide is supposedly rearranged, with elimination of nitrogen, into an isocyanic acid ester which cannot be isolated. At the same time alcohol is added and the urethane results. The latter is hydrolyzed with strong hydrochloric acid to yield the hydrochloride of a primary amine. At first glance, the intermediates appear very numerous, but in most cases they are well defined crystalline compounds. Furthermore, valuable diamines, the preparation of which is very difficult otherwise, are frequently obtained from dicarboxylic acids.

C. Other Degradation Methods

According to a patent granted to Schmidt,[71] primary amines can be obtained directly from hydrazoic acid and carboxylic acids as indicated by the equation,

$$R \cdot COOH + N_3H \longrightarrow N_2 + CO_2 + R \cdot NH_2$$
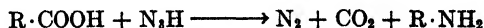
[69] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 45.
[70] H. Meyer, *Monatsh.*, 15, 173 (1894).
[71] K. F. Schmidt, German Patent, 500,435.

This is completely analogous to the Curtius' degradation, but is much simpler. Results obtained with Schmidt's method varied. Oesterlin [72] recently published conditions under which good yields of several primary amines can be obtained more conveniently even than by a method given by Braun.[73]

Concentrated sulfuric acid is covered with a layer of the carboxylic acid dissolved in chloroform and small portions of sodium azide are added. Thus the preparation of a chloroform solution of hydrazoic acid as recommended by Braun can be avoided. The reaction proceeds with generation of heat and with evolution of gas while the mixture is stirred. A 20% excess of sodium azide is used. From 5 g. of hydrocinnamic acid and 2.4 g. of sodium azide, for instance, at a reaction temperature of 45°C., phenylethylamine is obtained in a yield of 70% isolated as 3.6 g. of the hydrochloride.

Diamines can be obtained from dicarboxylic acids in the same manner. For example, putrescine is obtained from adipic acid and sodium azide in a yield of 80%.

As a result of a thorough study of the degradation of primary and secondary carboxylic acids, Braun [74] succeeded in developing a useful method for the preparation of aldehydes and ketones, respectively.

$$R \cdot CH_2 \cdot COOH \longrightarrow R \cdot CHO \quad \text{or} \quad R_2CH \cdot COOH \longrightarrow R \cdot CO \cdot R$$
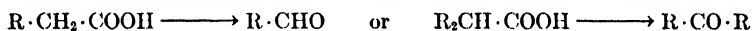
The method consists of the following steps: a hydrogen atom in the position α to the carboxyl group is replaced by bromine; the acid chloride is prepared (the order may also be reversed), and treated with sodium azide; the brominated acid azide is converted, with evolution of nitrogen, to a brominated isocyanic ester; the latter is hydrolyzed to a brominated amine which cannot be isolated, but changes at once into the desired carbonyl compound. Thus, the degradation proceeds as follows, if an acid with a secondary carboxyl group serves as starting material:

$$R_2:CHCOOH \longrightarrow R_2:CBr \cdot COOH \longrightarrow R_2:CBr \cdot COCl \longrightarrow$$
$$R_2:CBr \cdot CON_3 \longrightarrow R_2:CBr \cdot N:C:\acute{O} \longrightarrow R_2:CBr \cdot NH_2 \longrightarrow R \cdot CO \cdot R$$
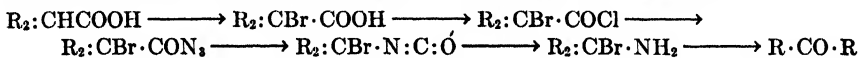
If one of the radicals (R) is replaced by hydrogen, the final product is an aldehyde. The yields amount to about 60% of the theoretical. The conversion of the α-bromo acid chloride to the final carbonyl compound may be carried out without isolating the intermediates. As an example, the degradation of hexahydrobenzoic acid to cyclohexanone follows.[75]

Hexahydrobenzoic acid is treated with phosphorus pentachloride and heated with bromine for 5 hours at 125°C. The resulting bromo acid chloride is hydrolyzed by shaking with water and the α-bromohexahydrobenzoic acid is distilled in a high vacuum. By treatment with thionyl chloride it is again converted to its acid chloride. This is converted to the azide with 1.5 moles of sodium azide in benzene, toluene, or pyridine.

[72] M. Oesterlin, *Angew. Chem.*, **45**, 536 (1932).
[73] J. v. Braun, *Ber.*, **64**, 2866 (1931); *Ann.*, **490**, 126 (1931).
[74] J. v. Braun, *Ber.*, **67**, 218 (1934).
[75] Aschan, *Ann.*, **271**, 265 (1892).

Technical sodium azide, even if carefully dried, reacts only slowly or not at all, but it can be activated by mixing with a trace of hydrazine hydrate. Upon heating the reaction starts at about 80°C. If 0.05 mole of acid chloride is used, the reaction is complete within 10 minutes of the time the evolution of nitrogen is first observed. However, the heating is continued for a short time, and the mixture is then cooled and saponified with 2.5 moles of cold alcoholic potassium hydroxide. The alkaline solution is acidified with hydrochloric acid and distilled with steam. The cyclohexanone can be isolated from the condensate as the bisulfite compound. In a similar manner the following compounds were prepared: dibutyl ketone from dibutylacetic acid; dicyclopentyl ketone from dicyclopentylacetic acid; enanthol (heptaldehyde) from caprylic acid; cyclopentylformaldehyde from cyclopentylacetic acid; and γ-phenylbutyraldehyde from δ-phenylvaleric acid.

As can be seen, the reaction is by no means simple and in a true sense hardly suitable for preparative work, but it proved to be invaluable for establishing the constitution of the naphthenic acids.

Rearrangements of Carbon Compounds

with the Exception of Steric Rearrangements

A great many phenomena are brought together under the term molecular rearrangements. They differ greatly from one another in respect to their real nature. From the standpoint of method, however, the manner in which these rearrangements take place is less interesting than their starting materials and end-products.

Optically active compounds and ethylene derivatives undergo steric rearrangements. In these cases there is no change in constitution nor in the connection of the atoms with one another. Rearrangements which involve a change in constitution and which are the only ones treated here can be divided into three classes: first, those in which the carbon structure remains unchanged; second, those in which the carbon structure is changed but retains its connection in a new set-up; and, finally, the ones in which the rearrangement of the skeleton is accompanied by a separation of carbon bonds, without the formation of new linkages.

However, not all reactions by which new carbon bonds are formed are considered molecular rearrangements as, for instance, the formation of o-toluidine from methylaniline. Many of them are considered condensation reactions and have, therefore, been treated previously.

The three types of molecular rearrangements mentioned above correspond entirely to the three groups:

1. Changes at the molecule.

2. Formation of carbon bonds.

3. Degradation of carbon skeletons.

To the first group belong many tautomeric rearrangements, the shifting of multiple bonds, and the place exchange of substituents which do not contain carbon: acinitro compounds → real nitro compounds; eugenol →̇ isoeugenol; α-naphthalenesulfonic acid → β-naphthalenesulfonic acid.

The rearrangements of the second group are nearly always accompanied by a change in the chemical function of the molecule and do not necessarily lead to isomers as do most of those previously mentioned. The rearrangement of neopentyl bromide to amyl bromide and of camphene

hydrochloride to isobornyl chloride belong in this group despite the fact that they both proceed without change of their functional group. The benzidine rearrangement, on the other hand, is accompanied by change in function. The pinacol rearrangement takes place with change in function as well as with removal of water. Finally, the benzilic acid rearrangement takes place with addition of water.

To the third group belongs the Beckmann rearrangement. In this case the acetanilide formed from acetophenone oxime is isomeric with the starting material, it is true, but the phenyl group is not bound to a carbon atom as previously. Therefore, from the point of view of method the reaction is similar to a degradation.

How strictly one adheres to a classification based on the foregoing observations depends on practical considerations. The Fries rearrangement, for instance, consists in the conversion of phenol esters into phenol ketones; thus, if it is only a question of preparing the ketones, the preparational purpose is accomplished in almost the same manner in which aromatic ketones are usually formed, except that the Fries rearrangement proceeds through an intermediate, which in most cases is not stable. The Fries rearrangement, thus, appears to be a variation of the aromatic ketone synthesis; however, it is treated with the other rearrangements.

Other groupings are suggested, of course, if these reactions are considered from a theoretical standpoint. Whitmore and several coworkers recently undertook the task of finding the common base of intramolecular rearrangements by means of the electron theory. Details of their theories can be found in the original papers.[1]

I. SHIFTING OF MULTIPLE BONDS

All multiple bonds (double and triple bonds) can be shifted by the action of suitable reagents. If this can be accomplished without changing the structure of the molecule, the reactions belong to this chapter. All reactions in which the shifting of a multiple bond takes place with a change in the structure are considered later.

In general it may be stated that the direction in which the bonds shift is determined by the following rules.

1. The molecule tends to assume a symmetrical arrangement; for instance, ethylacetylene changes to dimethylacetylene, $CH_3 \cdot CH_2 \cdot C : CH \rightarrow CH_3 \cdot C : C \cdot CH_3$. Whether the tendency to become symmetrical is really the active factor, or whether the multiple bond breaks away from the hydrogen, as other observations seem to indicate, remains to be decided.

2. The multiple bond tends to approach certain groups or substituents; for instance, methylchavicol is converted to anethole, $CH_3O \cdot C_6H_4 \cdot$ -

[1] C. Whitmore *et al.*, *J. Am. Chem. Soc.*, **54**, 3274 (1932); **56**, 1129 (1934).

$CH_2 \cdot CH:CH_2 \rightarrow CH_3O \cdot C_6H_4 \cdot CH:CH \cdot CH_3$, or methyl allyl ketone to methyl propenyl ketone, $CH_3 \cdot CO \cdot CH_2 \cdot CH:CH_2 \rightarrow CH_3 \cdot CO \cdot CH:CH \cdot - CH_3$. Thus, the so called negative substituents, such as phenyl or acetyl, apparently attract the double bond. This holds true also for unsaturated acids. The preparation of *n*-nonylic acid from *n*-undecylenic acid (see page 457) serves as a good example. However, discrepancies occur if these very simple rules are applied to more complicated systems. The tendency of the multiple bond to approach certain substituents and the tendency to escape from the hydrogen can concur or compete with one another. In the same manner, different negative substituents can vie with one another, and finally the presence of additional multiple bonds can further complicate the case. A certain tendency towards formation of conjugated systems may be assumed in such cases.

The rearrangement takes place in the presence of alkalies or acids. The action of an acid can frequently be explained by a temporary ester formation with subsequent removal of the acid in a different manner.

A. Shifting of Ethylene Bond

Probably the most important rearrangement of an ethylene bond is the conversion of eugenol to isoeugenol. It proceeds readily only at an elevated temperature presumably because of the free hydroxyl group of the eugenol.

According to Tiemann,[2] 12.5 parts of potassium hydroxide are dissolved in 18 parts of boiling amyl alcohol. .The solution is decanted from undissolved carbonate and heated with 5 parts of eugenol for 16 to 20 hours at 140°C. The amyl alcohol is removed by distillation with steam, the solution is acidified with sulfuric acid, and the oil that separates is washed with a solution of sodium carbonate and distilled with steam. A colorless, viscous oil, boiling at 261°C., is thus obtained. It solidifies to a crystalline mass in a freezing mixture.

Gockhale, Sudborough, and Watson [3] have reduced the reaction time from 16 to 20 hours to 5 minutes by heating the eugenol with 11 moles of a potassium hydroxide melt for 5 minutes at 220°C.

The conversion of methylchavicol to anethole can be successfully accomplished by boiling it with alcoholic potassium hydroxide.[4] The reaction is quite common as far as the allyl derivatives of benzene are concerned. Allylbenzene itself can be converted to propenylbenzene by heating it with alcoholic potassium hydroxide in a sealed tube at 130°C.; see Klages.[5]

[2] F. Tiemann, *Ber.*, 24, 2870 (1891).
[3] Gockhale, Sudborough, and Watson, *Chem. Abstracts*, 18, 1995 (1924).
[4] J. Eykman, *Ber.*, 23, 859 (1890).
[5] Klages, *Ber.*, 39, 2591 (1906).

The rearrangement of a double bond is very common in the terpene series where it frequently takes place in the cold under the influence of strong acids. The general tendency here consists of a shift of a double bond from a side chain towards the nucleus, or into the nucleus. The numerous papers of Wallach [6] present a discussion of this problem.

An important example of ring formation with simultaneous shifting of the double bonds is the rearrangement of pseudoionone (I) to α- or β-ionone (II, III); this can be so directed that one of the two isomers is formed in the preponderant amount.

β-Ionone (III)   Pseudoionone (I)
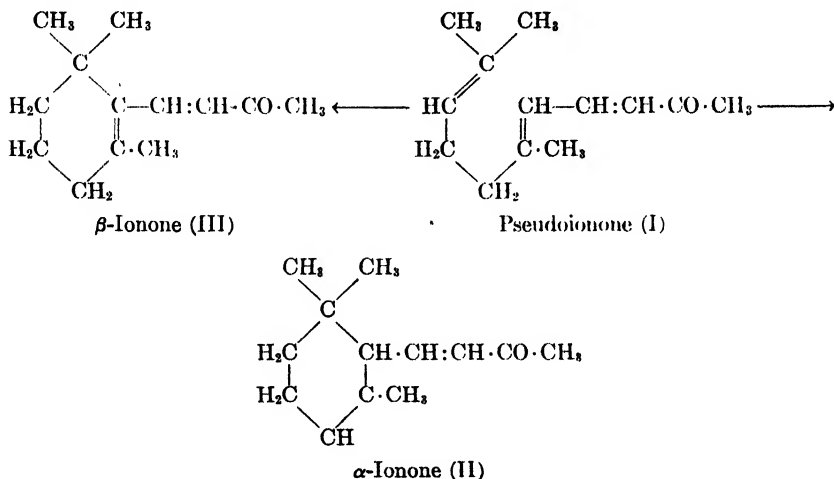
α-Ionone (II)

β-Ionone is obtained with sulfuric acid as the main product.

Sulfuric acid (70%) is cooled to −10°C. and pseudoionone is added with stirring. The mixture is removed from the cooling bath and the stirring continued. The temperature rises to 34°C and the color of the mixture changes for a short time from a brownish red to a light yellowish brown. As soon as this change occurs the solution is poured onto crushed ice and the mixture stirred well until the ice melts. The oily layer is separated, washed with sodium carbonate solution to remove the acid, and dried with potassium carbonate. The mixture of the isomers is fractionated *in vacuo* and the fraction boiling at 130° to 145°C. at 20 mm. collected.

α-Ionone is prepared as follows:

20 g. of pseudoionone are added dropwise without cooling and with stirring to 150 g. of 85% phosphoric acid. The temperature is held at 30° to 35°C. for 25 minutes. After dilution with 500 cc. of cold water, the solution is extracted with ether. This extract is treated as described above.

In both cases the mixture can be steam-distilled before the fractionation.

[6] Wallach *et al.*, *Ann.*, **239**, 24, 33 (1887); **286**, 130 (1895); **360**, 26 (1908).

For the separation of α- and β-ionone, 100 g. of the mixture are boiled under a reflux for 12 to 16 hours with 300 g. of 40% sodium bisulfite solution, 25 g. of 30% sodium hydroxide solution, and 30 g. of ammonium chloride. The reaction mixture is allowed to cool, the lower clear aqueous layer is separated, the oil washed thoroughly with 50 cc. of water, and the combined aqueous parts extracted with ether. The aqueous solution is diluted with an equal volume of water, saturated with sodium chloride, and cooled in ice. The bisulfite compound of α-ionone crystallizes. The crystals are filtered with suction, washed with a little ice-cold water, and boiled with a solution of sodium carbonate. The α-ionone is recovered by distillation with steam or extraction directly with ether. After the extract has been washed and dried (see above), it is fractionated *in vacuo*. α-Ionone boils under 12 mm. pressure at 127°C. The mother liquor contains the readily soluble bisulfite compound of β-ionone. It is boiled with excess sodium carbonate solution and treated as described above. The boiling point of β-ionone is 130°C. at 12 mm.

The yield varies; 100 g. of pseudoionone, by rearrangement with sulfuric acid, give about 12 g. of α- and 20 g. of β-ionone.

B. Shifting of Acetylene Bond

Generally the same holds true for the acetylene bond as for the ethylene bond. For a summary of the subject see Faworski.[7] However, a reversal of the direction occurs here in the rearrangements; ethylacetylene, for example, changes to dimethylacetylene when treated with alcoholic potassium hydroxide at 170°C., but, if ethylmethylacetylene is treated with sodium metal at a high temperature, the sodium compound of *n*-propylacetylene is formed, $C_2H_5 \cdot C \vdots C \cdot CH_3 \rightarrow C_2H_5 \cdot CH_2 \cdot C \vdots CNa$. Bourguel[8] found that under the influence of sodium amide the triple bond shifts from even more remote points to the end of the chain. A similar difference in behavior appears in the conversion of the acetylene bond to the allene bond. Faworski found that isopropylacetylene is converted, by means of alcoholic potassium hydroxide, to dimethylallene, $(CH_3)_2 \vdots CH \cdot C \vdots CH \rightarrow (CH_3)_2 \vdots C \vdots C \vdots CH_2$. The latter can be reconverted into isopropylacetylene under the influence of sodium.

Marvel and coworkers[9] recently studied new cases of these rearrangements which lead to variously substituted allene derivatives.

Similar conditions can be observed whenever several acetylene bonds are present in the same chain. Dipropargyl changes to dimethyldiacetylene, $CH \vdots C \cdot CH_2 \cdot CH_2 \cdot C \vdots CH \rightarrow CH_3 \cdot C \vdots C \cdot C \vdots C \cdot CH_3$.

[7] A. Faworski, *J. prakt. Chem.*, 44, 208 (1891).
[8] Bourguel, *Compt. rend.*, 178, 1984 (1924).
[9] C. S. Marvel *et al.*, *J. Am. Chem. Soc.*, 57, 2619 (1935); 58, 29, 865 (1936).

II. SHIFTING OF HALOGEN

Lucas and Jameson [10] found that *n*-butyl bromide, 1-bromobutane, changes slowly but completely to 2-bromobutane at 248°C. Hückel and Ackermann [11] studied the rearrangements of the butyl bromides and concluded, on the basis of vapor pressure measurements which were performed with the isomeric butanes obtained by rearrangement, that isobutyl bromide, on being heated, is partially converted into 2-bromo-*n*-butane. Thus, a reliable example was found for the isomerization of branched chains to normal ones.

It is to be noted that molecular rearrangements also take place with Grignard compounds; these rearrangements become apparent during subsequent reactions. Gilman and Kirby [12] studied the anomalous behavior of benzylmagnesium chloride, which has been known for a long time. When benzylmagnesium chloride reacts with formaldehyde, *o*-tolylcarbinol and not the expected β-phenylethyl alcohol is obtained. Similar anomalous reactions occur with benzylmagnesium chloride more frequently than had formerly appeared to be the case. For the details the original literature should be consulted; see Johnson. [13]

A special case of isomerization of halogen occurs in the rearrangement of the ordinary into the so called asymmetric phthalyl chloride. This conversion has been studied particularly by Ott whose directions can be found in *Organic Syntheses*. [14]

Some observations made by Plant and Tomlinson [15] indicate that glutaric acid chloride, too, exists in isomeric forms.

A rearrangement which might be of preparative importance under certain conditions takes place if olefin dibromides which contain a tertiary bromine atom are saponified. Thus, isobutyraldehyde is obtained from isobutylene dibromide according to the equation $(CH_3)_2:CBr \cdot CH_2Br + H_2O \rightarrow (CH_3)_2:CH \cdot CHO + 2HBr$. Whitmore and coworkers [16] recently studied this reaction. The dibromides to be rearranged can be obtained by treating tertiary alcohols with bromine; the olefins need not be isolated. As an example the directions for the preparation of isobutyraldehyde from tertiary amyl alcohol are given.

Tertiary amyl alcohol is heated to 60° to 70°C. and 1 mole of bromine is added at such a rate that no bromine accumulates and the temperature does not rise. Two layers

[10] H. Lucas and A. Jameson, *J. Am. Chem. Soc.*, 46, 2476 (1924).
[11] W. Hückel and P. Ackermann, *J. prakt. Chem.*, 136, 15 (1933).
[12] H. Gilman and J. Kirby, *J. Am. Chem. Soc.*, 54, 345 (1932).
[13] J. Johnson, *J. Am. Chem. Soc.*, 55, 3029 (1933).
[14] A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 528. E. Ott, *Ann.*, 392, 245 (1912).
[15] S. Plant and M. Tomlinson, *J. Chem. Soc.*, 1935, 856.
[16] C. Whitmore *et al.* ,*J. Am. Chem. Soc.*, 55, 1136 (1933).

are formed, the lower consisting of isobutylene dibromide, the upper of aqueous hydrobromic acid. The yield of isobutylene dibromide boiling at 143° to 150°C. amounts to 68 to 75% of the theoretical. About 15% of the bromine used is obtained as hydrobromic acid through side reactions, while considerable amounts of higher brominated compounds and a small amount of tertiary butyl bromide are formed.

2 moles of isobutylene dibromide are heated with 2 liters of water in a flask equipped with a fractionation column 90 cm. high. At first only enough heat is supplied so that the column acts as a reflux condenser; later on the temperature is raised. At a temperature of 59° to 64°C. isobutyraldehyde appears at the head of the column. After 50 hours the dibromide layer in the flask has disappeared and 185 g. of distillate have collected. This is treated with hydroquinone and rectified through a 45 cm. column. There are thus obtained 108 g. (75% of the theoretical amount) of isobutyraldehyde, boiling at 58° to 65°C. The rate of hydrolysis may be increased considerably by stirring. The crude product obtained from amyl alcohol and bromine may be hydrolyzed directly.

The so called allylic rearrangement, $R \cdot CH{:}CH \cdot CHX \cdot R' \leftrightharpoons R \cdot \cdot CHX \cdot CH{:}CH \cdot R'$, should also be considered here. The lability of the system can be seen most distinctly when the hydroxyl group of the isomeric alcohols, $R \cdot CH{:}CH \cdot CH_2OH$ and $R \cdot CHOH \cdot CH{:}CH_2$, is exchanged for bromine. According to Prévost,[17] this exchange gives one and the same bromide if $R = C_2H_5$ (see below), but the bromide on saponification yields both alcohols. The alcohols are stable up to 225°C.; at about 360°C., however, the secondary is partially converted to the primary. The corresponding chlorides, in contrast to the bromides, can be isolated. They can even be distilled without decomposition. At 175°C., however, they form an equilibrium in which there is a slight excess of the primary chloride. Isomeric esters and ethers can also be obtained from the alcohols. The radicals R and R' have been varied considerably. Kirrmann and Rambaud,[18] for instance, studied the vinylglycolic ester of the formula, $CH_2{:}CH \cdot CHOH \cdot COOC_2H_5$. Rambaud[19] extended these investigations to other substituents and gave a theoretical explanation. At the beginning of his bibliography mention is made of Klages' statement (page 472), that allylbenzene changes to propenylbenzene. Actually the shift of the double bond in the chain is nothing but an allylic rearrangement for the case $X = H$.

Winstein and Young[20] recently prepared, in a pure state, the two isomeric bromides which correspond to crotyl alcohol and methylvinylcarbinol; that is, the lower homologues of the halides first studied by Prévost. These two bromides, crotyl and methylvinylcarbinyl bromides, rearrange to an equilibrium rapidly at 100°C. and at a measurable rate even at room temperature. Therefore, corresponding halides formerly

[17] Ch. Prévost, *Compt. rend.*, **187**, 1052 (1928).
[18] A. Kirrmann and R. Rambaud, *Compt. rend.*, **194**, 1168 (1932).
[19] R. Rambaud, *Bull. soc. chim.*, **1**, 1206 (1934).
[20] S. Winstein and W. Young, *J. Am. Chem. Soc.*, **58**, 104 (1936).

considered uniform compounds might well have been mixtures. Thus, it is apparently necessary to check a large part of the material accumulated about the allylic rearrangement. The theoretical conclusions, too, might need a partial revision.

III. REARRANGEMENTS OF OXYGEN COMPOUNDS

1. Keto-Enol Tautomerism and Related Phenomena

The rearrangement of keto-enol tautomers into one another plays an important rôle even in methods of preparation. It renders difficult the preparation of pure compounds and the determination of the physical constants. The rearrangement,

$$-CH_2\cdot CO- \rightleftharpoons -CH{=}C(OH)- \quad \text{and} \quad =CH\cdot CO- \rightleftharpoons =C{=}C(OH)-$$
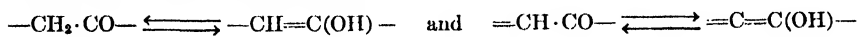
can be forced only in the direction of enol formation. The ketonization of the enol forms can be accelerated catalytically, but no real chemical means is available for shifting the equilibrium in this direction. Therefore, one must always depend on physical separations for the preparation of pure keto forms. Even the shifting of the equilibrium by the solvent plays an important rôle.

The media for the rearrangement of keto into enol forms are first, solvents which under certain conditions can entirely shift a previously established equilibrium; secondly, alkalies which force the enolization by the formation of salts. Furthermore, it is sometimes possible to separate the pure enol form from melts which represent mixtures by inoculation with particles of the solid enol form, if the formation of nuclei of the keto form does not take place, or if it can be hindered.

(a) Enolization by Solvents

Claisen [21] found that the triketo form of acetyldibenzoylmethane can be converted to the enol form as follows:

5 g. of the pure triketone (see below) are dissolved in 15 cc. of alcohol. After 10 minutes boiling a clear solution results. Upon cooling, a mixture consisting of 65% of the enol form and 35% of the triketo form is obtained. It reacts at once with ferric chloride in cold ethanol. By recrystallization from acetone a little more of the enol form is obtained. For a complete conversion of the triketo form or of keto-enol mixtures, the compound is dissolved in alcoholic potassium hydroxide solution and poured, with stirring, into ice-cold 5 N sulfuric acid. The solid enol that separates can be recrystallized from a large volume of petroleum ether without change; it melts at 80°C.

The conversion of the enol form to the triketo form can be performed, according to Claisen, as follows:

10 g. of the enol form (see above) or of any keto-enol mixture of the compound are dissolved in 300 cc. of 50% alcohol, and the solution is boiled for 30 seconds. Upon cooling, the solution at first becomes cloudy and soon sets to a mush of colorless needles.

[21] L. Claisen, *Ann.*, 291, 87 (1896).

After 3 hours the product is collected on a suction filter and washed with a little ether. There are thus obtained 9 g. of the pure triketone, a sample of which, when dissolved in cold alcohol, gives no color reaction with ferric chloride. The compound melts at about 110°C., but if the melting point determination is carried out in a capillary tube of ordinary glass a partial reconversion occurs during heating.

Subsequently, Michael [22] found that the melting point is constant at 146° to 149°C., if every trace of alkali is excluded and if the melting point determination is made in capillaries boiled in hydrochloric acid, or in capillaries made from glass free of alkali.

From this and numerous other observations of Claisen and Michael it is evident that keto-enol mixtures are always present in alcoholic solutions. Two conditions determine which of the two forms will crystallize from a homogeneous phase. Of course, the crystallization of the form which is predominant in the equilibrium is favored, but it must be added that the formation of crystal nuclei of one or the other form has a decided influence upon the nature of the end-product. From solutions in pure alcohol a predominant amount of the enol form crystallizes, but from dilute alcohol the triketo form of acetyldibenzoylmethane separates. The two reactions differ, however, in that the pure alcoholic solution does not become cloudy before crystallization, while small oil drops separate from the aqueous alcoholic solution prior to crystallization. Weygand [23] has been able to explain this difference by showing that melts of acetyl-dibenzoylmethane as well as the oil drops formed from aqueous alcoholic solutions consist of neither the triketo nor the enol form, but a much lower melting, polymorphous form of the enol, which, when once formed in the solid state, changes very readily and directly into the triketo form. The unstable form is, in this case, the precursor of the triketo form. The formation of nuclei of this unstable modification is especially favored under empirically discovered conditions. In conjunction with the foregoing another experiment by Claisen illustrates the importance of the nature of the product that is first formed.

If acetyldibenzoylmethane is dissolved, as described above, in 50% alcohol for conversion to the keto form and if this solution is not allowed to cool slowly but is poured into ice water, not the expected triketo form but a keto-enol mixture containing 90% of the enol is obtained. Even if the solution is prepared from the pure triketo form, the same mixture results. Thus, it follows that at least in this case the nature of the product that separates from solution is determined by the type of crystal nuclei which form first.

[22] A. Michael, *Ann.*, **390**, 59 (1912).
[23] C. Weygand, *Z. anorg. allgem. Chem.*, **205**, 414 (1932).

(b) Enolization through the Enolates

The standard method for the conversion of keto forms into keto-enols through alkali enolates was already touched upon briefly in the foregoing discussions. The preparation of the enolate solution need not be described in detail. In order to avoid cleavages it must always be carried out under mild conditions; that is, at low temperatures (see page 464). Consideration will be given, however, to the isolation of the free keto-enol forms from their salts. Alkali may be used in molecular amounts as well as in excess to favor the enol formation. Alkali also acts as an equilibrium catalyst even in traces. Weygand and Koch were able to obtain a pure and quite stable enol of methylbenzoylacetone, $C_6H_5 \cdot C(OH):C(CH_3) \cdot CO \cdot CH_3$, or $C_6H_5 \cdot CO \cdot C(CH_3):C(OH) \cdot CH_3$, which Dieckmann [24] obtained only in an impure state.

1 g. of oily methylbenzoylacetone (see page 362) is added to a solution of 0.15 g. of sodium in 3 cc. of methanol. The dark yellow solution is filtered at once and added to 30 cc. of 5 N sulfuric acid which is cooled with a freezing mixture. The emulsion which forms at first is stirred vigorously in order to precipitate the product in a finely divided form. If large oil drops form, the compound crystallizes with difficulty and is not very stable. The precipitate is filtered immediately, and washed with acidulated water, with a little alcohol, and then with petroleum ether. The compound is recrystallized at once from low boiling petroleum ether with a quartz apparatus. It melts at 51°C., the yield being almost quantitative.

Enol forms of diketones, being unsaturated hydroxy ketones, are very much inclined to form polymorphous compounds. The many discrepancies in the melting points recorded by different authors are probably due to this fact.

The enolization of monoketones does not take place in the same manner; that is, with alkalies. The enolates, *e.g.* of acetophenone (see page 364), are formed by the action of alkali metals with evolution of hydrogen, but free enol forms cannot be isolated in this way.

A method for the enolization of monoketones, based on a new principle, was discovered by Grignard and Savard.[25] It consists of the action of Grignard compounds on ketones of the type of pulegone or menthone which apparently act as hydroxy compounds because hydrocarbons are generated in the same way as in the Zerewitinov determination of active hydrogen. From the magnesium halide enolates the benzoates of the enols are obtained with benzoyl chloride. With acetyl chloride, by hydrolysis, the free enol forms result. The enol form of pulegone boils at 79° to 81°C. at 3 mm. It is obtained in a yield of 24%, is rather stable in a pure state, but reverts to the keto form in the presence of alkali or on steam distillation. It is not changed by carbonates.

[24] C. Weygand and P. Koch, *Ber.*, 68, 237 (1935). Dieckmann, *Ber.*, 55, 2480 (1922).
[25] V. Grignard and J. Savard, *Compt. rend.*, 179, 1573 (1924); 182, 422 (1926).

The enol of menthone [26] is obtained in an analogous manner, but it is much less stable than the enol of pulegone. The enol of cyclohexanone was obtained by Grignard and Blanchon [27] only as a mixture with ordinary cyclohexanone. Acetophenone-enol is still less stable. The enol forms of aliphatic ketones are not very stable either; butyrone, for example, rearranges completely 30 minutes after it is prepared. The preparation of the acetate of menthone also proves that the compound enolizes; see Gordon.[28]

(c) Other Rearrangements

Auwers, Ludewig, and Müller [29] recently reported on tautomeric rearrangements of α-ketols which proceed according to the scheme,

$$R \cdot CO \cdot CHOH \cdot R' \rightleftharpoons R \cdot CHOH \cdot CO \cdot R'$$
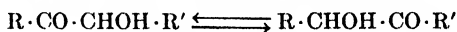
These are not keto-enol rearrangements but they belong to the same group of reactions, because they are completely analogous to the keto-enol tautomerism of asymmetrical 1,3-diketones. However, while the tautomeric keto-enols (see above, the two formulas of the enol of methylbenzoylacetone) can be isolated only in the solid state,[30] they form an equilibrium mixture in solution; or, if melted, methylbenzoylcarbinol, $C_6H_5 \cdot CO \cdot CHOH \cdot CH_3$ (β-ketol), and phenylacetylcarbinol, $C_6H_5 \cdot CHOH \cdot CO \cdot CH_3$ (α-ketol), which cannot only be isolated in the pure state, but are characterized as chemically different compounds.

For details of the preparation the original papers should be consulted. The β-ketol rearranges almost completely into the α-ketol on boiling with water and barium carbonate for 20 hours. The β-ketol may be distilled in vacuo without change but at its boiling point at atmospheric pressure it changes in part to the isomer. The reverse rearrangement proceeds only through the ester.

In reactions with tautomeric compounds it is a difficult matter to decide upon conditions under which derivatives of the one or the other form can be expected. Even though the alkali compounds, as well as other enolates, may be considered oxygen derivatives, they yield, nevertheless, in many reactions, carbon-substituted derivatives rather than the expected ethers or esters. The practical importance of the acetoacetic ester synthesis is based on this reaction. In alkylation reactions of keto-enols the formation of carbon derivatives can be avoided completely if diazomethane or its homologues are used. But this presupposes that the enol forms are present in the necessary concentration. It is

[26] V. Grignard and J. Savard, *Chem. Abstracts*, 21, 2678 (1927).
[27] V. Grignard and H. Blanchon, *Chem. Abstracts*, 24, 1342 (1930).
[28] S. M. Gordon, *Chem. Abstracts*, 22, 584 (1928).
[29] K. v. Auwers, H. Ludewig, and A. Müller, *Ann.*, 526, 143 (1936).
[30] C. Weygand, *Ber.*, 68, 234 (1935).

for this reason that the enolization must be artificially brought about in certain instances.

Oxygen-alkylated products can be obtained if dialkyl sulfates are used in place of alkyl halides. Thus, according to Auwers,[31] a satisfactory yield of a benzoylacetone-enol ether is obtained when an alkaline benzoylacetone solution is treated in the cold with dimethyl sulfate. On the other hand, sodium benzoylacetone, when heated with methyl iodide in acetone, gives a quantitative yield of C-methylbenzoylacetone (see page 362).

It is easier to obtain acetates and other O esters of the enols. While C derivatives are formed almost exclusively when alkaline solutions are used (an example of this was given above in the preparation of acetyldibenzoylmethane, page 363), the treatment with acid chlorides in pyridine generally leads to O-acyl compounds. These, however, frequently rearrange under the influence of alkalies into C derivatives. This exchange sometimes takes place, to a smaller extent, even on mere heating; see Wislicenus.[32] This rearrangement, which corresponds in principle to the so called Fries rearrangement, is of no special preparative importance.

Just as the tautomerism of the α-ketols belongs systematically in the same class as the tautomerism of keto-enols, so does the enol-ester rearrangement, a phenomenon which is of special importance in connection with the shifting of an acyl group in sugar chemistry. It is encountered not only with sugars but also with simple polyhydric compounds; see the difficulties in preparing the isomeric mono- and diglycerides, page 181.

Theoretically, α-ketols of the type of benzoin should also enolize, and as a result compounds of the formula, $R \cdot C(OH):C(OH) \cdot R$, the so called stilbenediols, should be obtained. Their alkali compounds are familiar. Staudinger and Pinkert [33] obtained the potassium salt of stilbenediol from benzil and potassium powder in benzene in an atmosphere of nitrogen. This salt when treated with water changes at once into benzoin; with acetic anhydride, however, it yields stilbenediol diacetate. In a similar manner, Bachmann [34] obtained the sodium salt of stilbenediol. The alkali compounds of stilbenediol are colored, both in solution and in the solid state; the benzene solution of the potassium salt of stilbenediol is reddish brown; the solid sodium salt of stilbenediol is orange.

While the rearrangements discussed so far involve a functional carbonyl group on the one hand and a functional hydroxyl group on the other, the conversion of ethylene oxides to carbonyl compounds is ac-

[31] K. v. Auwers, *Ber.*, **45**, 996 (1912).
[32] W. Wislicenus, *Ber.*, **38**, 546 (1905).
[33] H. Staudinger and A. Pinkert, *Helv. Chim. Acta*, **5**, 708 (1922).
[34] W. Bachmann, *J. Am. Chem. Soc.*, **56**, 964 (1934).

companied by the change of an ether oxygen to a functional carbonyl group. This change, however, proceeds only in one direction. The preparation of phenylacetaldehyde through phenylglycidic acid (see page 448), which proceeds with removal of carbon dioxide, is an example of this type of reaction. Rearrangements without simultaneous cleavages have been studied by Darmon.[35] Phenylglycidic ethers of the type,

$$C_6H_5 \cdot CH \underset{O}{\diagdown\diagup} CH \cdot CH_2 \cdot OR$$
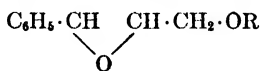
theoretically can yield two different ketones, $C_6H_5 \cdot CH_2 \cdot CO \cdot CH_2 \cdot OR$ and $C_6H_5 \cdot CO \cdot CH_2 \cdot CH_2 \cdot OR$, upon isomerization with zinc chloride. However, ketones of the first type are always obtained; thus, here, too, the opening of the ethylene oxide ring takes place in the neighborhood of the phenyl group. Favorsky, Tchitchonkin, and Ivanov [36] extended the knowledge of this reaction by subjecting methylethyl and ethyl-*n*-propylethylene oxides to the rearrangement. The oxides were passed over zinc chloride heated to 315° to 320°C., and that ring opened in such a manner that the ketone formed always carried the carbonyl group as close as possible to the end of the chain.

2. Cannizzaro Rearrangement of Keto Aldehydes and Related Reactions

α-Keto aldehydes are converted quite generally to α-hydroxy acids under the influence of alkalies: $R \cdot CO \cdot CHO \xrightarrow{H_2O} R \cdot CHOH \cdot COOH$. This fact is of decisive importance for the biological degradation of the carbohydrates. Details cannot be given here; the subject has been treated in two articles by Meyerhoff.[37]

Glyoxal changes, even in the cold, to sodium glyoxylate when treated with alkalies; see Debus.[38] In a similar manner mandelic acid is formed quantitatively from phenylglyoxal; see Pechmann.[39] However, this rearrangement can hardly be considered a method for preparation.

A certain similarity to the intramolecular Cannizzaro reaction is shown by the saccharinic acid rearrangement of sugars which, however, proceeds in most cases with a rearrangement of the carbon skeleton. By allowing galactose to stand for several weeks with calcium hydroxide, however, Kiliani and Sanda [40] obtained metasaccharinic acid, $CH_2OH \cdot CHOH \cdot CHOH \cdot CH_2 \cdot CHOH \cdot COOH$, in which the carbon skeleton of galactose

[35] M. Darmon, *Compt. rend.*, **197**, 1649 (1933).
[36] Favorsky, Tchitchonkin, and Ivanov, *Compt. rend.*, **199**, 1229 (1934).
[37] Meyerhoff, *Naturwissenschaften*, **24**, 689 (1936); **25**, 443 (1937).
[38] H. Debus, *Ann.*, **100**, 116 (1856).
[39] H. v. Pechmann, *Ber.*, **20**, 2904 (1887); **22**, 2558 (1889).
[40] Kiliani and Sanda, *Ber.*, **26**, 1649 (1893).

is retained. An oxidation of the aldehyde group takes place while an alcoholic group is reduced.

Rupe and Werdenberg [41] have shown that acetylene alcohols rearrange in two directions according to the scheme,

$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{C}\!-\!\!-\!\!-\text{C:CH}_2 \\
\diagdown\diagup \\
\text{O}
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\cdot\text{CH}_2\text{CH}_2\cdot\text{C}\cdot\text{C}:\text{CH} \\
| \\
\text{OH}
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{C}:\text{CH}\cdot\text{CO}\cdot\text{CH}_3
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{C}\!-\!\text{CH:CH} \\
|| \\
\!-\!\text{O}\!-\!
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_3 \\
| \\
\text{C}_6\text{H}_5\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{C}:\text{CH}\cdot\text{CHO}
\end{array}
$$
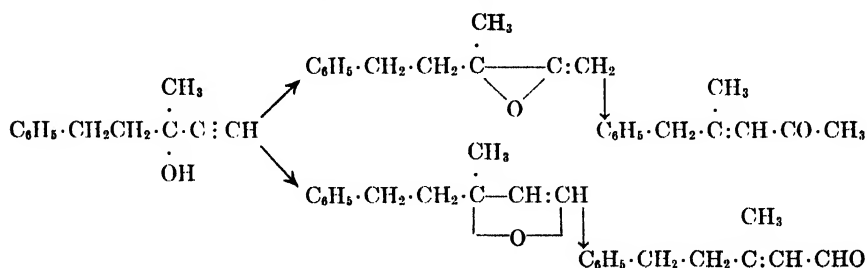
It is assumed that ethylene and propylene oxide derivatives appear as intermediates. The first, in which a rearrangement of the carbon skeleton occurs, proceeds in the same manner as the pinacol rearrangement; the second is similar to the isomerization of ethylene oxides. Both products of the rearrangement are formed simultaneously with formic acid.

According to Paul,[42] tetrahydrofurfuryl alcohol, when passed over aluminum at 370° to 380°C., changes to dihydropyran. This involves dehydration and a simultaneous enlargement of the ring.

$$
\begin{array}{ccc}
\text{H}_2\text{C}\!-\!\!-\!\!-\!\text{CH}_2 & & \text{CH}_2 \\
| | & \longrightarrow & \text{H}_2\text{C} \diagup \diagdown \text{CH} \\
\text{H}_2\text{C} \text{CH}\cdot\text{CH}_2\text{OH} & & \text{H}_2\text{C} \| \text{CH} \\
\diagdown \diagup & & \diagdown \diagup \\
\text{O} & & \text{O}
\end{array} + \text{H}_2\text{O}
$$
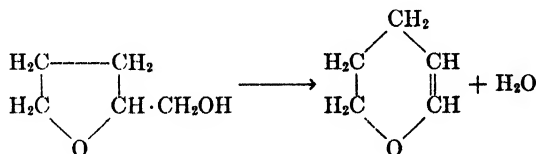
Whitmore and Rothrock [43] obtained tertiary butylmethyl chloride in the following manner from pinacolyl alcohol.

Concentrated hydrochloric acid is saturated with hydrogen chloride at −10°C. To 100 g. of this acid in a tube are added 20 g. of pinacolyl alcohol. The tube is sealed and allowed to stand with occasional shaking at room temperature. The solution is at first red and homogeneous. After a few hours a violet upper layer separates. This gradually increases for 5 days. It is separated, washed with concentrated hydrochloric acid, and twice with water. During the latter treatment the color disappears. The chloride on treatment with moist silver oxide changes in a few days, even at room temperature, to dimethylisopropylcarbinol.

[41] H. Rupe and H. Werdenberg, *Helv. Chim. Acta*, **18**, 542 (1935).
[42] R. Paul, *Compt. rend.*, **196**, 1409 (1933).
[43] C. Whitmore and S. Rothrock, *J. Am. Chem. Soc.*, **55**, 1106 (1933).

3. Fries Rearrangement

The rearrangement of phenol ethers or esters into phenols or phenol ketones, as indicated below, has been designated as a Fries rearrangement.

$$\text{C}_6\text{H}_4(\text{OH})(\text{CH}_3) \longleftarrow \text{C}_6\text{H}_5\cdot\text{O}\cdot\text{CH}_3 \longrightarrow \text{CH}_3\text{-C}_6\text{H}_4\text{-OH}$$

or

$$\text{C}_6\text{H}_4(\text{OH})(\text{CO}\cdot\text{CH}_3) \longleftarrow \text{C}_6\text{H}_5\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3 \longrightarrow \text{CH}_3\cdot\text{CO-C}_6\text{H}_4\text{-OH}$$
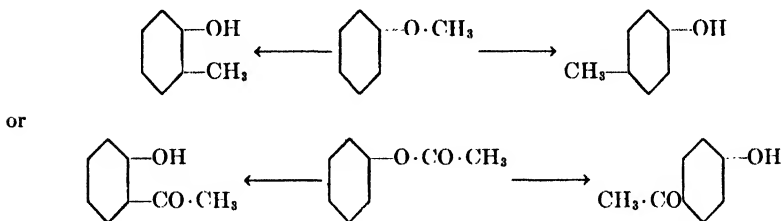
It was first noted by Fries and Fink [44] in the rearrangement of cresol acetates into cresyl ketones. Somewhat later Claisen [45] pointed out that the rearrangements of the phenol allyl ethers of the type, $\text{Ar}\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}:\text{CH}_2$, which he had discovered, were quite analogous to the rearrangements of the enol ethers. At first the allyl group was considered especially suited for rearrangement, but J. Niederl and Natelson [46] recently showed that o-cresyldiisobutyl ether changes to diisobutyl-o-cresol when boiled with a mixture of zinc chloride and hydrochloric acid. Natelson [47] later showed that the rearrangements involved take place even without catalysts at 250°C. Both rearrangements have much in common and therefore are best discussed together. The Fries rearrangement possesses great experimental importance, and is the basis of many syntheses of important phenol ketones. The reason for this, as Fries has pointed out, is that the direct introduction of the acetyl group, especially if it is substituted, does not proceed nearly as readily as it does indirectly, because phenols under the influence of aluminum chloride sometimes yield very disappointing products. As with similar syntheses, a certain limitation arises because of the relative positions of the hydroxyl and the acyl groups. In simple cases, contrary to the usual experience, the acyl group prefers the o position. Therefore, as Freudenberg has shown,[48] it is relatively easy to obtain o-hydroxyacetophenone in a fair yield from phenyl acetate.

To 100 g. of phenyl acetate 200 g. of aluminum chloride are added in small portions. The mixture is cooled at first, but after the violent reaction has subsided it is heated for 5 hours at 120°C. It is then decomposed with ice and distilled with steam superheated to 150°C. 37 g. of o-hydroxyacetophenone boiling at 91° to 92°C. at 13 mm. are obtained.

[44] K. Fries and G. Fink, *Ber.*, 41, 4271 (1908).
[45] L. Claisen, *Ber.*, 45, 3157 (1912); *Ann.*, 401, 21 (1913); 418, 69 (1919).
[46] J. Niederl and S. Natelson, *J. Am. Chem. Soc.*, 53, 274 (1931).
[47] S. Natelson, *J. Am. Chem. Soc.*, 56, 1583 (1934).
[48] K. Freudenberg and L. Orthner, *Ber.*, 55, 1748 (1922).

Fries and Fink [49] and Wittig [50] proceeded in practically the same manner, while Skraup and Poller [51] used zinc chloride for the rearrangement and found that o- and p-hydroxyacetophenone were formed simultaneously, although in a very poor yield. Huber and Brunner [52] studied the effect of ferric chloride and obtained, on heating for 4 to 5 hours at 65°C., a yield of 25% of the theoretical amount of p-hydroxyacetophenone.

These results indicate that the method is of little value for the preparation of p-hydroxyacetophenone. Meerwein [53] states that phenyl acetate can be rearranged into p-hydroxyacetophenone with boron fluoride but no experimental details have appeared as yet. Thus, it seems that in this case the indirect method should be avoided. Irvine and Robinson improved the older directions of Nencki and Stoeber [54] in the following manner.

81 g. of anhydrous ferric chloride are added to a solution of 63 g. of phenol in 48 cc. of carbon disulfide. To this mixture 95 cc. of acetyl chloride are added dropwise with shaking. The shaking is continued for 5 minutes after the addition is complete and then the carbon disulfide and excess acetyl chloride are carefully removed by distillation. The residue is decomposed with water; the solution is rendered alkaline by the addition of sodium hydroxide, decanted from the ferric hydroxide, and the latter washed by decantation. The solution is acidified and the p-hydroxyacetophenone which separates is recrystallized from water. The yield of product, melting at 110°C., is 30 g., 33% of the theoretical amount.

In any case, this method is preferable to the older one which consisted of splitting p-methoxyacetophenone with hydrobromic acid.

Even small variations change the picture considerably; thus, a yield of 32 to 35% of o-hydroxypropiophenone and 45 to 50% of the p compound is obtained from phenyl propionate with aluminum chloride in carbon disulfide; see *Organic Syntheses*.[55]

In connection with the Fries rearrangement, Rosenmund and Schnurr [56] have pointed out that the use of nitrobenzene favors the formation of the p isomer.

The phenol ester is dissolved in 5 times its weight of nitrobenzene and a little more than the theoretical amount of aluminum chloride (1.2 to 1.3 moles) is added in portions. Heat is generated, the mixture becomes dark in color, and the aluminum chloride passes into solution. Depend-

[49] K. Fries and G. Fink, *Ber.*, **41**, 4271 (1908).
[50] G. Wittig, *Ber.*, **57**, 89 (1924).
[51] S. Skraup and K. Poller, *Ber.*, **57**, 2033 (1924).
[52] H. Huber and K. Brunner, *Monatsh.*, **56**, 324 (1930).
[53] H. Meerwein, *Ber.*, **66**, 414 (1933).
[54] Nencki and Stoeber, *Ber.*, **30**, 1769 (1897). F. Irvine and R. Robinson, *J. Chem. Soc.*, **1927**, 2091.
[55] Hartung *et al.*, *J. Am. Chem. Soc.*, **53**, 4149 (1931). A. H. Blatt, ed., *Organic Syntheses*. Collective Vol. II, Wiley, New York, 1943, p. 543.
[56] K. Rosenmund and W. Schnurr, *Ann.*, **460**, 77 (1928).

ing on the circumstances, the mixture is allowed to stand overnight, or is heated to 60°C. for 1 hour, but never higher than 75°C. In the case of phenols with long side chains the temperature must be kept below 20°C. in order to avoid further rearrangements. The reaction mixture is poured slowly into cold water, 10% hydrochloric acid is added, and the mixture is heated on a water bath until it is clear. The solution is extracted with ether, and the extract is washed and extracted with 7.5% aqueous potassium hydroxide solution. From the alkaline solution the hydroxy ketone is precipitated with 25% hydrochloric acid.

This method yields p-hydroxy ketones mainly; see Auwers and Mauss.[57] Nitrobenzene, therefore, encourages a rearrangement to the p position and proves to be the same specific solvent as it is for the Friedel-Crafts synthesis; see page 397. Furthermore, the formation of p compounds is favored by low temperature. Rosenmund and Schnurr [58] even succeeded in rearranging p-hydroxy ketones into the o isomers.

5 g. of p-aceto-m-cresol are heated with 6 g. of aluminum chloride for 30 minutes at 170°C.; 4.4 g. of o-aceto-m-cresol are obtained.

In fact, the shift of an acetyl group from the nucleus into the side chain has been observed.[58]

5 g. of p-aceto-m-cresol are heated with 0.01 g. of camphorsulfonic acid for 30 minutes at 150°C.; m-cresol acetate is formed quantitatively.

One of the important technical uses of the Fries rearrangement involves the preparation of chloroacetylpyrocatechol, a product
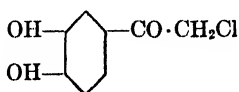
that serves as starting material for the adrenaline synthesis of Stolz.[59] Pyrocatechol monochloroacetate (see page 307) is rearranged as follows:

The chloroacetate is heated on a water bath with an equal volume of benzene and about 10% phosphorus oxychloride for 1 to 2 days. The mixture is cooled and filtered and the chloroacetylpyrocatechol obtained is recrystallized from water, the hot solution first being decolorized by the use of charcoal and sulfur dioxide. The yield amounts to 90% of the theoretical.

A more convenient method, which does not necessitate the isolation of the monochloroacetate, has been described by Hoberman.[60]

[57] K. v. Auwers and W. Mauss, *Ann.*, 464, 293 (1928).
[58] K. Rosenmund and W. Schnurr, *Ann.*, 460, 77 (1928).
[59] Stolz, *Ber.*, 37, 4149 (1904).
[60] H. Hoberman, *J. Am. Chem. Soc.*, 57, 1382 (1935).

A mixture of 50 g. each of monochloroacetic acid, pyrocatechol, and freshly distilled phosphorus oxychloride is placed in a flask equipped with a reflux condenser and a gas delivery tube and heated on the water bath for 1 hour in a current of sulfur dioxide. The reaction mixture is allowed to cool and the purple-colored crude chloroacetate is filtered and crystallized from water. The product is redissolved in aqueous acid solution, decolorized with carbon in the presence of sodium bisulfite, and again allowed to crystallize. The light violet-colored crystals are collected on a filter and washed with absolute alcohol and then with ether. A yield of 53.6 g. of chloroacetylcatechol, melting at 173°C., is obtained. Without due precautions only 8.3 g. are obtained.

A very interesting Fries rearrangement has been described by Blicke and Weinkauff.[61]

10 g. of diphenyl phthalate (see page 184) are heated with 10 g. of aluminum chloride and 25 cc. of tetrachloroethane for 6 hours at 100°C. Hydrochloric acid is then added, and the mixture is distilled with steam. After all the tetrachloroethane has distilled (a yellowish crystalline material which separates in the condenser is 1-hydroxyanthraquinone), the residue is treated with 120 cc. of 10% aqueous sodium hydroxide, filtered from an insoluble product (3 g. of α-hydroxyanthraquinone), and then acidified. A small amount (3 g.) of phenolphthalein crystallizes. The yield of phenolphthalein increases to 6.3 g. if the reaction mixture is heated for 30 minutes at 150°C.

Blicke and Weinkauff explain the formation of phenolphthalein by a temporary removal of phenol according to the following scheme:
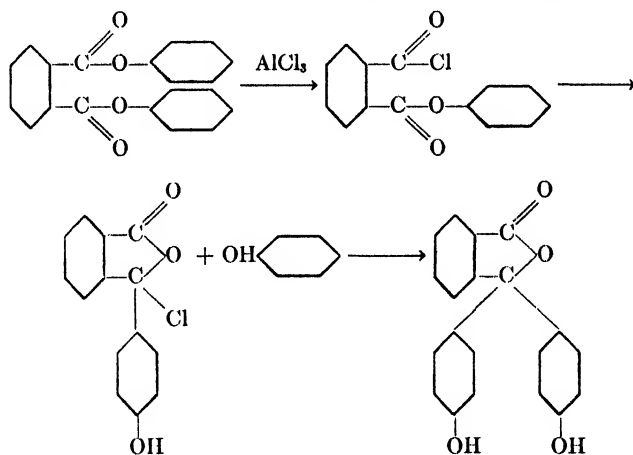
The rearrangement of α-naphthol esters by Rosenmund and Schnurr's method [62] yields the technically important 4-hydroxy ketones.

For example, a mixture of 6.1 g. of α-naphthyl acetate, 6.2 g. of aluminum chloride, and 30.5 g. of nitrobenzene is stirred for 2 to 3 hours at 0°C. and then allowed to stand for 15 hours. By the usual treatment followed by recrystallization from benzene, there is obtained a 42% yield of the 1,5-hydroxy ketone. The isomeric 1,3-hydroxy ketone (16%) can be obtained from the mother liquor.

[61] F. Blicke and O. Weinkauff, *J. Am. Chem. Soc.*, **54**, 330 (1932).
[62] H. Ledere, *J. prakt. Chem.*, **135**, 49 (1932).

Stoughton [63] prepared the o-hydroxy ketones of the naphthalene series and, as was to be expected, obtained the best yields at high temperatures (100° to 120°C.) and without a solvent. α-Naphthol acetate, for example, gave 60% of 2-acetyl-, 5% of 4-acetyl-, and 4% of 2,4-diacetyl-1-naphthol.

It is obvious that phenol esters can be prepared from the hydroxy ketones formed by the Fries rearrangement. The former can be re-arranged again and thus polyketones, which occasionally appear as by-products during the first rearrangement, can be obtained.

The rearrangement of the phenol ethers [64] which is analogous to the Fries rearrangement proceeds extraordinarily readily with allyl compounds.

Phenol allyl ether (see page 484) is boiled in a carbon dioxide atmos-phere until an immersed thermometer shows a rise in temperature from 190° to 220°C.; this takes about 6 hours. If the temperature does not rise to 220°C., further heating is of no avail, because a little more than usual of the by-product (methylcoumaran) has been formed, and this depresses the boiling point of the o-allylphenol. In order to remove the 4 to 6% of methylcoumaran which is always formed, the reaction product is dissolved in twice its volume of 20% aqueous sodium hydroxide and extracted twice with petroleum ether. The solution is then acidified and extracted with ether. The extract is dried over calcium chloride and distilled. A yield of more than 80% of the theoretical amount of allylphenol, boiling at 99°C. at 12 mm., is obtained. The rearrangement cannot be accelerated by catalysts. Pyridine hydrochloride causes an increase in the yield of methylcoumaran up to 60%.

The tendency of the allyl group to shift into the nucleus is so marked that a repetition of the above method, namely esterification of allyl-phenol with allyl bromide, rearrangement, etc., gives first o,o-diallylphenol and finally 2,4,6-triallylphenol. The allyl group eventually displaces even the carboxyl group of salicylic acid if the latter is used as starting material in place of phenol. In the rearrangement of the allyl ether of 2,5-diallylsalicylic acid carbon dioxide and triallylphenol are formed.

$$\underset{C_3H_5}{\overset{OC_3H_5}{\bigcirc}}\!\!-COOH \longrightarrow \underset{C_3H_5}{\overset{OH}{\bigcirc}}\!\!-C_3H_5$$
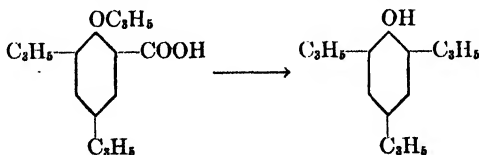
The allyl ethers of α- and β-naphthol show a completely analogous behavior; see Claisen.[65]

[63] R. Stoughton, J. Am. Chem. Soc., 57, 202 (1935).
[64] L. Claisen, Ann., 418, 79 (1919).
[65] L. Claisen, Ber., 45, 3158 (1912); Ann., 401, 61 (1913).

It is much more difficult to rearrange the saturated phenol ethers than the allyl ethers. Niederl and Natelson [66] attempted to synthesize thymol from m-cresol by rearranging the isopropyl ether of m-cresol with glacial acetic acid and concentrated sulfuric acid. They obtained a mixture of thymol and m-methyl-p-isopropylphenol. For the details the original paper should be consulted.

The Fries rearrangement may also be applied to compounds with an acid imino group such as carbazole. Plant and Williams [67] obtained 3-acetylcarbazole by heating N-acetylcarbazole with aluminum chloride at 100°C., while Meitzner,[68] using nitrobenzene as a solvent and a temperature of 125°C., obtained 3-acetylcarbazole as well as the 1-acetyl compound.

IV. TAUTOMERISM OF NITROGEN COMPOUNDS

(a) Nitro Compounds

The simplest case of tautomerism in the nitrogen-containing compounds is that of the nitro group. All points of preparative importance have been discussed previously; see page 292. While it is possible to obtain derivatives of both forms of the keto-enols, the aci-nitro forms of the nitro compounds which correspond to the enols cannot be converted into oxygen derivatives.

. The action of acid chlorides upon the salts of aci-nitro compounds yields, with rearrangement, acylated hydroxamic acids; see van Raalte.[69]

(b) Acid Amides

The tautomerism of the acid amides offers a further possibility of differentiation which does not exist for the keto-enols. In the latter case, alkali and heavy metal compounds of the enolate exhibit the same behavior when treated with either acylating or alkylating agents, producing in all cases acylated or alkylated carbon derivatives. In the acid amides, however, where the tautomerism is based on the system, —CO—NH— ⇌ —C(OH)=N—, oxygen derivatives are usually obtained from alkali salts or from alkaline solutions, while mercury and silver salts yield nitrogen derivatives.

The tautomerism of the acid amides is of preparative importance in that it makes possible the preparation of imide chlorides; see page 45. With acetanilide as an example the preparation of the isomeric O and C compounds may be treated briefly.

According to Hepp [70] monoalkyl acetanilides result when sodium acet-

[66] J. Niederl and B. Natelson, J. Am. Chem. Soc., 54, 1063 (1932).
[67] S. Plant and C. Williams, J. Chem. Soc., 1934, 1142.
[68] Meitzner, J. Am. Chem. Soc., 57, 2327 (1935).
[69] van Raalte, Rec. trav. chim., 18, 378 (1899).
[70] P. Hepp, Ber., 10, 328 (1877).

anilide. is treated with alkyl halides, and, despite the fact that the sodium is considered to be attached to oxygen in sodium acetanilide, a nitrogen derivative is formed. This is analogous to the results obtained with alkali enolates. On the other hand, as Bühner [71] has shown, if sodium acetanilide is treated with dimethyl sulfate, or if acetanilide reacts with silver oxide and methyl iodide, imidomethyl ethers are formed.

$$CH_3 \cdot CO \cdot NH \cdot C_6H_5 \longrightarrow CH_3 \cdot C{=}N \cdot C_6H_5$$

with ONa below, and branching:

$$\xrightarrow{RX} \quad CH_3 \cdot CO \cdot N \diagup^{R}_{\diagdown C_6H_5}$$

$$\xrightarrow{R_2O_2SO_2} \quad CH_3 \cdot C{=}N \cdot C_6H_5 \ (OR)$$

$$CH_3 \cdot CO \cdot N \cdot Ag \, (C_6H_5) \xrightarrow{RX} CH_3 \cdot C{=}N \cdot C_6H_5 \ (OR)$$
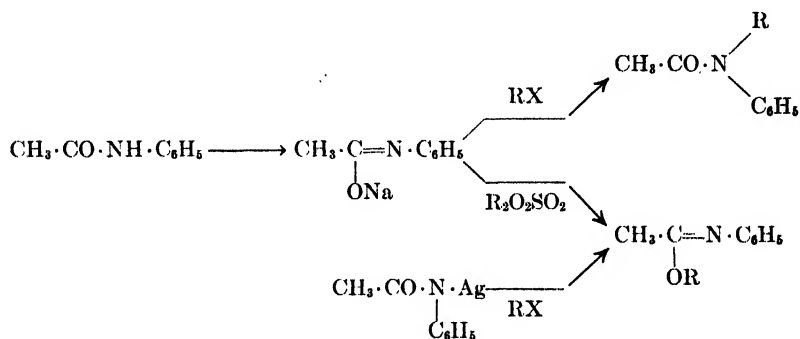
(c) Oximes

The tautomerism of the oximes with the nitro compounds has already been mentioned at several points (see page 267) because of its preparative importance. There is still another tautomerism of the oximes, that is of the unsaturated ones; namely, with the hydroxylamino compounds.

V. REARRANGEMENT OF CARBON SKELETONS

1. Rearrangement of Hydrocarbons

The rearrangement of hydrocarbons leads, almost without exception, to branched chain molecules. Thus far the preparative importance of such reactions has proved to be slight for the laboratory.

A very remarkable rearrangement of simple aliphatic nuclei was discovered by Whitmore and Rothrock.[72] In an attempt to convert the so called neopentyl alcohol, trimethylethanol, into the bromide there was obtained, contrary to Tissier's statement,[73] an addition product which was considered an oxonium salt, and which is stable up to 40°C. At 65°C. it slowly decomposes into a mixture of 72% of tertiary, 20% of primary, and 8% of secondary amyl bromides. Similarly, the chloride of neopentyl alcohol could not be obtained in this manner. However, it is readily formed, according to Fleming and Whitmore,[74] together with 6% of tertiary amyl chloride, by chlorination of tetramethylmethane.

[71] A. Bühner, Ann., 333, 293 (1904).
[72] F. Whitmore and S. Rothrock, J. Am. Chem. Soc., 54, 3431 (1932).
[73] Tissier, Ann. chim. phys., 29, 357 (1893).
[74] G. Fleming and F. Whitmore, J. Am. Chem. Soc., 54, 3460 (1932).

Here, too, apparently under the influence of the hydrogen chloride formed, a partial rearrangement takes place.

Many earlier observations concerning such rearrangements have been recorded. Eltekoff [75] obtained 2-bromo-n-pentane from isoamyl bromide. Rosanov [76] prepared 3-bromo-n-pentane from ethylcyclopropane with fuming hydrobromic acid.

Nenitzescu and Dragan,[77] starting with uniform materials, recently studied the effect of aluminum chloride upon aliphatic hydrocarbons. They found that n-hexane is isomerized for the most part even at its boiling point into a mixture of methylpentanes. At the same time, however, it is partly dehydrogenated to cyclohexane which could be definitely detected.

2 liters of hexane (b.p. 68° to 69°C.) are boiled on a water bath with 500 g. of aluminum chloride and 20 cc. of water for 7.5 hours. Upon distillation the following fractions are obtained: I, 25° to 45°C. (15 cc.); II, 45° to 59°C. (315 cc.); III, 59° to 66°C. (600 cc.); IV, 66° to 68°C. (340 cc.); V, 68° to 70°C. (210 cc.); VI, 70° to 76°C. (135 cc.); residue (60 cc.). Fractionation of the residue yields a liquid boiling at 78° to 80°C. (29 cc.) which, when treated with fuming nitric acid, gives a good yield of adipic acid. This fraction, therefore, consists of cyclohexane. The hydrogen liberated in the formation of cyclohexane from hexane is apparently used for the formation of pentane by reductive cleavage of hexane. Nenitzescu and Dragan furthermore studied the action of aluminum chloride on aliphatic hydrocarbons in the presence of acetyl chloride where a more complicated behavior was encountered.

Petrov and coworkers [78] treated n-heptane, n-octane, and α-hexene under pressure with catalysts such as zinc chloride and aluminum chloride; they discuss the different methods of cracking.

An investigation by Nenitzescu and Cantuniari [79] rounds out the numerous studies on the influence of catalysts such as aluminum chloride on the rearrangement of ring hydrocarbons. They showed that pure, anhydrous aluminum chloride is practically without effect on cyclohexane, but that with chloride-containing water the isomerization can be effected.

Cyclohexane (1500 cc.) is boiled for 3 hours with 500 g. of freshly distilled aluminum chloride and 13.6 cc. of water. The top layer is washed and dried. Upon fractionation 330 g. of practically pure methylcyclopentane boiling at 71.3° to 72.3°C. are obtained. In a reverse reaction, 150 cc. of methylcyclopentane, 50 g. of aluminum chloride, and 1.3 cc. of water give a mixture of cyclohexane and methylcyclopentane after boiling for 30 hours.

Thus, by treatment with aluminum chloride the two ring systems form an equilibrium mixture which was shown by refractive index de-

[75] A. Eltekoff, *Ber.*, **8**, 1244 (1875).
[76] Rosanov, *Chem. Zentr.*, 1923, I, 1940.
[77] C. Nenitzescu and A. Dragan, *Ber.*, **66**, 1892 (1933).
[78] D. Petrov *et al.*, *Ber.*, **68**, 1 (1935).
[79] D. Nenitzescu and P. Cantuniari, *Ber.*, **66**, 1097 (1933).

terminations to consist of about 22.8% of methylcyclopentane. However, hexane also exists in the mixture and, consequently, the reaction is still more complicated.

F. Mayer and Schiffner [80] reported a remarkable observation on the shifting of a phenyl group during the dehydrogenation of a ring system. 1-Phenyldihydronaphthalene-$\Delta^{1,2}$ (I) prepared from α-tetralone and phenylmagnesium chloride, with subsequent removal of water, gave, when

$$\text{(I)} \qquad\qquad \text{(II)}$$
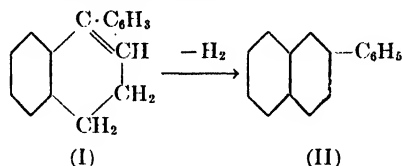
passed over silica gel under 16 mm. pressure at 350°C., only β-phenylnaphthalene (II). In a similar manner naphthalene homologues, such as α-ethylnaphthalene, were converted into β compounds.

2. Rearrangement of Oxygen-Containing Compounds

(a) Hydroxyl Compounds

The most important of all rearrangements of hydroxy compounds is that of the pinacols,

$$R_2:C(OH)\cdot C(OH):R_2 \longrightarrow R\cdot CO\cdot CR_3 + H_2O$$
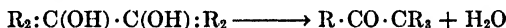
Its preparative importance is not slight. It leads to ketones which are not easily available otherwise, and from these to trisubstituted acetic acids. The rearrangement is effected by the use of moderately strong organic acids as well as by mineral acids. Fittig used dilute sulfuric acid for the conversion of pinacol into pinacolone. Directions for this rearrangement can be found in *Organic Syntheses*.[81]

With a little more difficulty, but in exactly the same manner, aromatic pinacolones are obtained from aromatic ketones of the type of benzopinacol; benzopinacolone can be prepared from benzopinacol by heating with acids to 200°C. A procedure for its preparation, worked out by Gomberg and Bachmann,[82] can be found in *Organic Syntheses*.[83]

The method is of slight preparative importance in the aromatic series. With regard to the nature of the rearrangement it should be pointed out that intermediates which appear to be ethylene oxides are formed. Such an intermediate appears even during the preparation of pinacolone.

[80] F. Mayer and R. Schiffner, *Ber.*, 67, 67 (1934).

[81] R. Fittig, *Ann.*, 114, 56 (1860). H. Gilman and A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 462.

[82] Gomberg and Bachmann, *J. Am. Chem. Soc.*, 49, 246 (1927).

[83] A. H. Blatt, ed., *Organic Syntheses.* Collective Vol. II, Wiley, New York, 1943, p. 71.

They are occasionally called α-pinacolones, and are easily converted into the real, so called β-pinacolones with which they are isomeric.

Thus, α-benzopinacolone,

$$(C_6H_5)_2:C\text{———}C:(C_6H_5)_2$$
$$\diagdown O \diagup$$
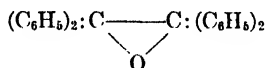
is obtained, according to Thörner and Zincke,[84] if a 5% solution of benzophenone in alcohol is added to a mixture of zinc turnings and hot concentrated hydrochloric acid, and the mixture boiled under a reflux for 1 to 2 hours, during which time more concentrated hydrochloric acid is added in order to insure a continuous vigorous evolution of hydrogen. The solution is filtered while hot and on cooling yields mainly α-benzopinacolone which, when pure, melts at 203°C.; see Schmidlin and Escher.[85]

The rearrangement of α- into β-pinacolones, which is probably the pinacol rearrangement proper, takes place in the same manner as does the rearrangement of ethylene oxides into aldehydes or ketones. It could be said that the establishing of the carbonyl function causes, or forces, the shifting of a carbon residue; see Meerwein.[86]

The β-pinacolones, on reduction, normally yield secondary alcohols, the so called pinacolone alcohols. These show an anomalous behavior in that the removal of water regenerates the carbon skeleton of the pinacol from which the pinacol alcohol was formed, $R\cdot CHOH\cdot CR_3 \rightarrow R_2:C:-C:R_2$. Such a reaction is called a retropinacol rearrangement. Thus, ordinary pinacolone alcohol yields tetramethylethylene together with other isomers when heated with acids; see Whitmore and Meunier.[87] A more complicated case has been described by Nasarov.[88] Tetramethylethylene, according to Haines and Adkins,[89] is most easily prepared by Thiele's method; that is, by conversion of pinacol to the dibromide, followed by removal of the bromine with zinc.[90]

Benzopinacolone alcohol, tetraphenyl ethyl alcohol, is converted readily to tetraphenylethylene.[91] 2 g. of the alcohol are boiled with 25 g. of acetyl chloride on a water bath for 5 hours. The hydrocarbon is precipitated with water.

[84] W. Thörner and Th. Zincke, *Ber.*, 11, 68 (1878).
[85] Schmidlin and v. Escher, *Ber.*, 43, 1153 (1910).
[86] H. Meerwein, *Ann.*, 405, 129 (1914).
[87] C. Whitmore and L. Meunier, *J. Am. Chem. Soc.*, 55, 3721 (1933).
[88] N. Nasarov, *Ber.*, 69, 18 (1936).
[89] B. Haines and H. Adkins, *J. Am. Chem. Soc.*, 47, 1424 (1925).
[90] J. Thiele, *Ber.*, 27, 455 (1894).
[91] Orékhoff, *Bull. soc. chim.*, 25, 189 (1919).

(b) Carbonyl Compounds

The most important rearrangement of this group, the benzilic acid rearrangement, involves the addition of a molecule of water to α-diketones to produce glycolic acids.

$$R \cdot CO \cdot CO \cdot R + H_2O \longrightarrow R_2 : C(OH) \cdot COOH$$
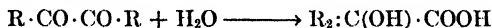
The reaction which is limited to the aromatic series is carried out in the presence of alkali. In the aliphatic series, as shown by Pechmann and Wedekind,[92] a very different reaction occurs; biacetyl, for example, proceeds through an aldol formation, removal of water, and ring closure, to *p*-xyloquinone. The benzilic acid rearrangement is described in elementary textbooks; see Gattermann-Wieland.[93] It consists of heating the benzils with aqueous alcoholic alkalies. Sometimes the results are unsatisfactory, a fact which was left unexplained for many years. According to Dilthey and Scheidt,[94] it is caused by the action of cyanide ions in the presence of which benzil is hydrolyzed to benzaldehyde and benzoic acid. Therefore, the reaction may fail if the benzil, obtained by the benzoin condensation, still contains traces of hydrocyanic acid.

(c) Expansion and Contraction of Rings

The subjects, "contraction of rings" and "expansion of rings," were formerly treated separately despite the fact that the splitting and reconnection of carbon bonds are not at all different in character. If it is not a question of the complicated and slightly uniform isomerizations of pure ring hydrocarbons, it is almost always possible to classify together ring isomerizations of quite definite types just as it is readily possible with other groups of rearrangements also, as for instance, the allyl rearrangement. A fine example for this is offered by the rearrangement of ethylene oxides into carbonyl compounds. If the formation of a functional carbonyl group is considered the motivating force (of course not in an energetic sense), then, in the case of an ethylene oxide ring having a secondary and a tertiary carbon atom,

$$R_2 : C \underset{\displaystyle O}{\underbrace{\qquad\qquad}} CH \cdot R'$$
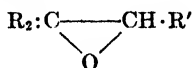
the rearrangement that results will depend upon the manner in which the ring opens. As can be seen, this rearrangement closely resembles the pinacol rearrangement. Tiffeneau and coworkers[95] succeeded, as illus-

[92] H. v. Pechmann and E. Wedekind, *Ber.*, **28**, 1845 (1895).

[93] Gattermann-Wieland, *Die Praxis des organischen Chemikers.* de Gruyter, Berlin, 1936, p. 225.

[94] W. Dilthey and P. Scheidt, *J. prakt. Chem.*, **142**, 125 (1935).

[95] M. Tiffeneau *et al.*, *Compt. rend.*, **201**, 277 (1935); **195**, 1284 (1932).

trated below, in expanding and contracting rings. The method is not new in principle but very clear and instructive.

$$CH_2 \cdot CH_2 \cdot C:CHR \qquad CH_2 \cdot CH_2 \cdot C\text{---}CHR \qquad CH_2 \cdot CH_2 \cdot CO$$
$$| \qquad\qquad\qquad\qquad |\quad\diagdown_O\diagup \qquad\qquad\qquad |\quad\diagdown CH \cdot R$$
$$CH_2 \cdot CH_2 \cdot CH_2 \qquad CH_2 \cdot CH_2 \cdot CH_2 \qquad CH_2 \cdot CH_2 \cdot CH_2$$
$$\text{(I)} \qquad\qquad\qquad\qquad \text{(II)} \qquad\qquad\qquad\qquad \text{(III)}$$

$$CH_2 \cdot CH_2 \cdot CH_2 \qquad CH_2 \cdot CH_2 \cdot CH_2 \qquad CH_2 \cdot CH_2 \cdot CH_2$$
$$| \qquad\diagdown CH \qquad\quad | \qquad\diagdown CH \qquad\quad |$$
$$CH_2 \cdot CH_2 \cdot CH \cdot R \qquad CH_2 \cdot CH_2 \cdot C\text{---}O \qquad CH_2 \cdot CH_2 \cdot C \cdot CHO$$
$$\qquad\qquad\qquad\qquad\qquad R \qquad\qquad\qquad\qquad\qquad R$$
$$\text{(IV)} \qquad\qquad\qquad\qquad \text{(V)} \qquad\qquad\qquad\qquad \text{(VI)}$$
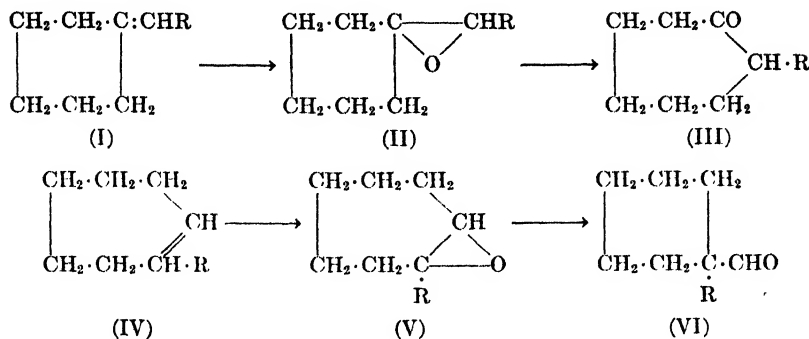
With anisalcyclohexane (I) as the starting material the ethylene oxide (II) can be obtained with perbenzoic acid. This rearranges with expansion of the ring into anisylcycloheptanone (III). The principle of this isomerization is entirely analogous to the one discussed above (see page 459). Benzalcyclohexane (R = phenyl) suffers no expansion of the ring, but forms phenylcyclohexylformaldehyde. In this case, the formation of the carbonyl group is effected by the shifting of the aromatic residue. Conversely, with phenylcycloheptene (IV) as the starting material, an ethylene oxide (V) is obtained, which rearranges partly with ring contraction to phenylcyclohexylformaldehyde (VI), partly, with a shift of the phenyl group, into phenylcycloheptanone. If R = anisil, the last rearrangement is still more pronounced.

A rearrangement, observed by Dey,[96] results when dimethylcyclohexanedione (menthone) is subjected to a Clemmensen reaction. A trimethylcyclopentanone, the structure of which was established, was obtained by contraction of the ring.

3. Nitrogen-Containing Compounds

(a) Hydrazine Derivatives and Diazoamino Compounds

The rearrangement of hydrazobenzene to benzidine by treatment of the former with strong acids is described in the elementary textbooks. It is the prototype of numerous reactions which follow a similar course, all of which have, therefore, been designated as "benzidine rearrangements."

The theoretical aspects of the mechanism may be discussed in so far as it is of preparative importance. Ingold and Kidd [97] have contributed an interesting discussion. If the benzidine rearrangement were to be considered a purely intramolecular rearrangement, then only a mix-

[96] A. Dey and R. Linstead, *J. Chem. Soc.*, 1935, 1063.
[97] K. Ingold and V. Kidd, *J. Chem. Soc.*, 1933, 984.

ture of two benzidines would be formed if a mixture of hydrazones, $\langle\!\!\!\!\begin{array}{c}A\end{array}\!\!\!\!\rangle$NH·NH$\langle\!\!\!\!\begin{array}{c}A\end{array}\!\!\!\!\rangle$ and $\langle\!\!\!\!\begin{array}{c}B\end{array}\!\!\!\!\rangle$·NH·NH·$\langle\!\!\!\!\begin{array}{c}B\end{array}\!\!\!\!\rangle$, was subjected to the rearrangement. If, on the other hand, the rearrangement should take an intermolecular course, a mixed benzidine of the formula $H_2N·\langle\!\!\!\!\begin{array}{c}A\end{array}\!\!\!\!\rangle\!\!-\!\!\langle\!\!\!\!\begin{array}{c}B\end{array}\!\!\!\!\rangle·NH_2$ could also form. However, it is not possible to obtain mixed benzidines in this manner.

In principle, the rearrangements of diazoamino to aminoazo compounds take a course very similar to that of the benzidine rearrangement. The similarity lies, above all, in the fact that in both cases, under the influence of acids, rearrangement products, which are more basic than the starting materials, are formed. Thus, it is said that the neutralization tendency of the acid forces the formation of the stronger base by a molecular rearrangement.

(b) Phenylhydrazones

One of the most remarkable of all molecular rearrangements is the formation of indoles from phenylhydrazones of the type of acetone phenylhydrazone. The reaction, which was discovered by E. Fischer, proceeds in the presence of zinc chloride with the loss of ammonia according to the following equation.
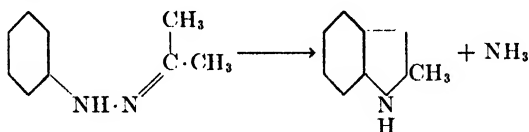
Many variations are possible. Acetone phenylhydrazone, as above, yields α-methylindole; propionaldehyde phenylhydrazone yields skatole, β-methylindole; finally, ethyl pyruvate phenylhydrazone yields ethylindole-α-carboxylate.

Various explanations have been given for the reaction mechanism; see Neber and coworkers, and Campbell and Cooper.[98]

VI. REARRANGEMENT ACCOMPANIED BY DEGRADATION OF CARBON SKELETON

1. Oximes

The Beckmann rearrangement of oximes is of special theoretical importance for stereochemical problems; see the numerous papers of Meisenheimer.[99]

[98] Neber *et al.*, *Ann.*, **471**, 113 (1929). Campbell and Cooper, *J. Chem. Soc.*, **1935**, 1208.

[99] J. Meisenheimer, *Ann.*, **468**, 202 (1929); **495**, 249 (1932).

Its preparative importance, however, is limited to a few special cases; see page 230. The ketoximes which undergo the Beckmann rearrangement must be prepared in most cases by nuclear synthesis. However, the end-products of the rearrangement are substituted acid amides and these are almost always more conveniently prepared by other methods. Only if a ring ketone such as the cyclohexanone in the above example is readily available does the rearrangement cause an opening of the ring which leads to valuable products.

2. Acid Amides

The Hofmann degradation (see page 445) leads through isocyanic acid esters of the formula, $R \cdot N : C : O$, which are obtained from acid amides, $R \cdot CONH_2$, by simultaneous rearrangement and dehydrogenation. However, as already mentioned above (see page 467) the isocyanic acid esters cannot be isolated as such but only as derivatives. Hence, the reaction has already been discussed in so far as its preparative importance is concerned. The same holds true for the Curtius and Lossen degradations.

SUBJECT INDEX

A

Acenaphthenol, preparation, 132

Acetaldehyde, formation, 125
preparation, 130, 142

Acetaldehyde diethyl acetal, preparation, 186

Acetaldol, preparation, 341

Acetaldoxime, preparation, 264

Acetals, formation, 185
preparation, 163, 186, 187, 188, 189
saponification, 200
sensitive, hydrolysis, 201

Acetamide, preparation and purification, 271

Acetanilide, preparation, 273, 471, 489

Acetic acid, glacial, and zinc dust, use in hydrogenation, 9
, use in bromination and chlorination, 76
preparation, 430, 453

Acetic anhydride, preparation, 128, 192

Acetoacetic ester, 359, 364, 410, 411

Aceto-*m*-cresol, *o*-, preparation, 486

Acetolysis, 194, 197

Acetone, chlorination, 83
halogenated, preparation, 84
halogen substitution products, preparation, 83
iodine derivatives, preparation, 84
preparation, 438

Acetonedicarboxylic acid, preparation, 449

Acetone hydrazone, preparation, 253

Acetonylacetone, preparation, 403, 404, 465

Acetophenone, methylation, 364
preparation, 125, 252, 363, 395, 396, 465

Acetophenone anil, preparation, 252

Acetoxyacetoacetic ester, *α*-, preparation, 132

Acetoxymalonic ester, preparation, 132

Acetylacetone, preparation, 392

Acetylaminobenzoic acid, *p*-, preparation, 141

Acetylanthracenes, preparation, 398

Acetylation, 185

Acetylbenzalacetophenone, preparation, 420

Acetyl bromide, preparation, 106

Acetylcarbazole, 1-, preparation, 489
3-, preparation, 489

Acetyl chloride, preparation, 102, 193, 395

Acetyl compounds, 1,2-diols, preparation, 123
preparation, 267

Acetylcyclohexanone, 2-, preparation, 414

Acetyldibenzoylmethane, preparation, 360, 363, 364, 481

Acetyldibenzoylmethane-enol, preparation, 360

Acetylene, polymerization, 340

Acetylene alcohols, rearrangement, 483

Acetylene bonds, addition of oxygen-containing compounds, 127
addition of water, 124
shifting, 474

Acetylene compounds, hydrogenation, 31

Acetylene dibromide, preparation, 65

Acetylenedicarboxylic acid, preparation, 326

Acetylenedicarboxylic acid esters, reaction with dienes, 337

Acetylene dichloride, preparation, 64

Acetylene diiodide, preparation, 65

Acetylene linkage, formation, 325

Acetylenes, aromatic, preparation, 358

Acetylenic bonds, addition of halogen, 64
addition of hydrogen halides, 65, 68

Acetylfluorene, preparation, 398

Acetyl groups, determination, quantitative, 199

Acetylisopropyl alcohol, preparation, 342

Acetylmandelyl chloride, preparation, 102

Acetylnaphthalene, *α*-, preparation, 398

Acetyl-1-naphthol, 2-, preparation, 488
4-, preparation, 488

Acetyl nitrate, preparation, 283