RECENT ADVANCES IN ORGANIC CHEMISTRY

VOLUME II

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ALFRED W. STEWART, D.Sc.

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RECENT ADVANCES IN ORGANIC CHEMISTRY

BY

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PREFACE

THE present volume contains an account of the developments in some of the newer fields of organic chemistry.

Fresh chapters have been written for this edition on the diterpenes and triterpenes, the problems presented by the decalins and other fused ring-sytems, and the peculiar isomerism of the diphenyl derivatives. Other sections have been revised or rewritten when this seemed necessary. These alterations and additions have added about fifty pages to the size of the volume.

As can be seen from the table of contents, an effort has been made to strike a fair balance in the space allotted respectively to problems of constitution and theoretical questions.

The references to the literature are indicated by figures, whilst footnotes are distinguished by asterisks, etc. In this way the reader will be saved unnecessary glances at the foot of the page.

The book will, it is hoped, serve to guide the reader in the fields with which it deals, and encourage him to go further in the study of the various subjects discussed, since this is the main function of a work of this kind.

In conclusion, I desire to acknowledge the great assistance which has been given to me by Professor D. N. M'Arthur, Dr. H. Graham, and Mr. N. S. Capper, to whom I am indebted for their help in proof reading, and also for suggestions which have led to improvements in the text of the volume.

ALFRED W. STEWART.

THE DONALD CURRIE LABORATORIES,
THE QUEEN'S UNIVERSITY OF BELFAST,
December, 1930.

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RECENT ADVANCES IN ORGANIC CHEMISTRY

CHAPTER I

ORGANIC CHEMISTRY IN THE TWENTIETH CENTURY

In the form in which it exists to-day, organic chemistry may be said to take its root in the work of Frankland [1] at the middle of last century. Once the doctrine of the constancy of valency was accepted, the way was open for Couper [2] and Kekulé [3] to bring order into the vast mass of material which had been accumulated in earlier times; while, later, van't Hoff [4] and Le Bel [5] carried the ideas of molecular arrangement out of two dimensions into three and laid the foundation of our present views. Following in the track of these pioneers, the chemists of the latter half of the nineteenth century rapidly developed the theoretical side of the subject; while, on the other hand, the modern formulæ lent to synthetical work a certainty which had previously been unknown.

Despite the Briarean efforts of the synthetic school, it is safe to say that the latter half of the nineteenth century will be regarded as a time when theoretical speculation played the main part in the development of the subject. Of the hundred thousand organic compounds prepared during that time, the majority were still-born and their epitaphs are inscribed in

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[1] Frankland, *Phil. Trans.*, 1852, **142**, 417.
[2] Couper, *Phil. Mag.*, 1858, iv., **16**, 104.
[3] Kekulé, *Annalen*, 1866, **137**, 129.
[4] van't Hoff, *Voorstell tot uitbreiding der structuur formules in de ruimte* (1874).
[5] Le Bel, *Bull. Soc. chim.*, 1874, ii., **22**, 377.

Beilstein's Handbook. Compared with the great clarifying process which laid the basis of our modern views, they weigh but little in the balance.

The new century opened under different auspices. At first it seemed as though the discoveries in electronic physics would have their reaction upon our structural views; but though several attempts [1] have been made in this region of the subject, organic chemists in general have not welcomed them with anything like whole-hearted encouragement. There is a feeling, apparently, that in abandoning the usual structural formulæ and replacing them by electronic symbols the subject is being complicated instead of simplified; and this feeling, whether it be due to scientific caution or to mere conservatism, has certainly carried the day for the present.

During the last fifty years the flood of synthetic material, principally from the German laboratories, has tended to obscure the genesis of what we still, out of respect for tradition, term organic chemistry. In its early days the science was devoted to the study of compounds produced by natural methods in plants and animals; and it is interesting to find that during the new century a return has been made to the older field.

The twentieth century was hardly begun, when in 1903 Komppa devised a synthesis of camphor, and thus cleared up a problem which had engaged the attention of many investigators. Later came the work of Perkin and his school in the terpene group, which gave a fresh impetus to study in this branch of the subject.

In the alkaloid series great strides have been made, both in determining constitutions and in devising synthetic methods of preparing the natural substances; whilst the examination of plants and the extraction from them of new alkaloids is proceeding apace.

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[1] Nelson and Falk, *School of Mines Quarterly*, 1909, **30**, 179; *J. Amer. Chem. Soc.*, 1915, **37**, 274; Nelson, Beans, and Falk, *ibid.*, 1913, **35**, 1810; Falk and Nelson, *ibid.*, 1910, **32**, 1637; 1911, **33**, 1140; Falk, *ibid.*, 1912, **34**, 1041; Noyes, *ibid.*, 1912, **34**, 663; Fry, *ibid.*, 1912, **34**, 664; 1914, **36**, 248, 262, 1035; 1915, **37**, 885; 1916, **38**, 1323, 1327, 1333; *Zeitsch. physikal. Chem.*, 1911, **76**, 385, 398, 591; 1912, **80**, 29; 1913, **82**, 665; 1915, **90**, 458; Stark, *Jahrb. Radioaktiv Electronik*, 1908, **5**, 124; 1909, **6**, 12; 1912, **9**, 15; *Physikal. Zeitsch.*, 1912, **13**, 585; G. N. Lewis, *Valence* (1923).

In the carbohydrate group the problem which looms behind most of the modern investigations is the constitution of the celluloses. The celluloses have extremely complicated structures; and it was only by breaking up their molecules into simpler compounds and then identifying these that we could hope to determine the constitution of the parent substance. The first step in this direction was evidently to obtain and identify readily purifiable carbohydrate derivatives such as methyl ethers, acetyl derivatives, etc. Then by methylating or acetylating celluloses themselves previous to breaking them up, it is possible to recognize among the decomposition products certain well-defined fragments which permit of guesses being made at the structure of the original molecule. This method in the hands of Purdie, Irvine and their collaborators * has already given us the key to the constitution of cotton cellulose; and now that the road has been opened, it is not unreasonable to expect a rapid increase in our knowledge of this field.

Much more complicated is the riddle of the protein molecules. Although there is a surface similarity between proteins and celluloses owing to the fact that both molecular types are liable to fission under the action of hydrolysing agents, the decomposition products of the proteins are far more complex than those resulting from the break-down of celluloses. Fischer's work on the polypeptides has been a first step towards a more exact knowledge of the protein constitutions; but it is a very short step on a very long road.

The methods devised by Fischer in his investigation of the polypeptides served him later in his researches on the tannins.† In 1912, he put forward the view that the natural tannins were fully esterified glucoses in which digalloyl nuclei replaced the hydrogen atoms of hydroxyl groups; and this conception of the tannin structure was justified by his synthesis of penta-(*m*-digalloyl)-β-glucose, which closely resembles Chinese tannin in its properties. It must not be too hastily assumed, however, that Fischer's researches have furnished a key to the structure of all classes of tannins.

Turning to natural pigments, it will be found that the present century has seen a great advance in our knowledge. Kostanecki's researches on the flavone derivatives established the

---

* See Chapter II.

† See Chapter IX.

constitutions of many of the natural dyes. Willstätter's work on chlorophyll * has given us some insight into the nature of that mysterious substance, though it would be going too far to claim that even yet we know much about the chlorophyll structure ; whilst in the field of flower pigments the same investigator has established the general character of the anthocyanins † and has practically reduced future work to a stereotyped line.

The examination of the colouring matters of the blood and of the bile has opened up yet another branch of pure "organic chemistry" ; and the parallelism established between hæmin and chlorophyll suggests most interesting reflections as to the origin of these two natural substances which play so great a part in animal and vegetable economy.

So much for the effects of a return to the original aims of organic chemistry. When the purely synthetic side of the subject is examined, it must be admitted that, with some notable exceptions, the results are of much less general interest. Of new compounds there is no lack, certainly ; but there is a distinct dearth of interesting materials. One or two examples may be given here of substances which have an interest for chemists other than the mere specialist.

The discovery of the ketens by Staudinger brought to light a completely fresh class of substances of remarkable reactivity ; and the problem of the relative activities of the carbonyl and ethylenic bonds in these compounds promises eventually to throw light upon some aspects of chemical linkages. Work in the field of the ketens has also clarified our ideas with regard to the nature of the aliphatic diazene derivatives.

By far the most interesting set of compounds prepared in the last quarter of a century has been the derivatives of various elements in a state of abnormal valency. Gomberg's triphenylmethyl seemed at first likely to remain without a parallel ; but in recent times a perfect flood of abnormalities has been let loose by further investigation. The aryl derivatives of the alkali metals, the metal-ketyls,‡ the tri-aryl-methyl series, to name only a few, have forced upon the notice of chemists the fact that the old and apparently well-tried dogma of the permanent quadrivalence of carbon is in a very shaky condition. By the researches

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* See Chapter VIII.

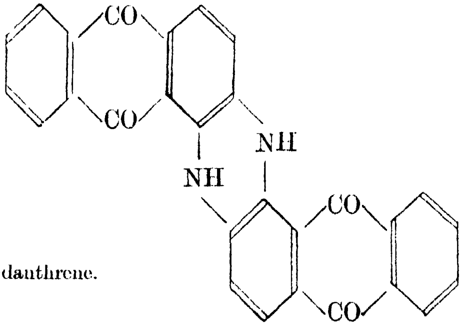
† See Chapter VII.

‡ See Chapter XIII.

in these and allied fields,* carbon has been definitely ranked among the ionogenic elements ; and the way was made open for the ready acceptance of G. N. Lewis's general theory of valency on the electronic basis.

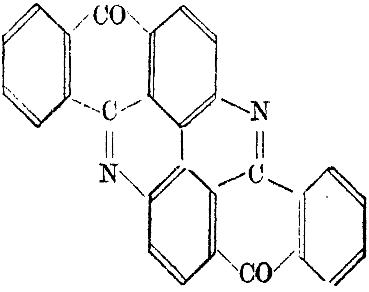
On the technical side organic chemists have not been idle. The great dye industry pours out its flood of colour ; and although as a general rule its products have a commercial rather than a scientific interest, two classes deserve notice here.

Vat dyes are those which, like indigo, are almost insoluble in water, but yield on reduction leuco-compounds soluble in alkali. The actual dyeing process is carried out by impregnating the fabric with the leuco-compound and then allowing or forcing oxidation to take place. The earliest example of the anthraquinone vat dyes, indanthrene, was produced in 1901. It is prepared by fusing 2-amino-anthraquinone with alkali, or by condensing 1-amino-anthraquinone with itself :—



Indanthrene.

To the same class belongs flavanthrene :—



Flavanthrene

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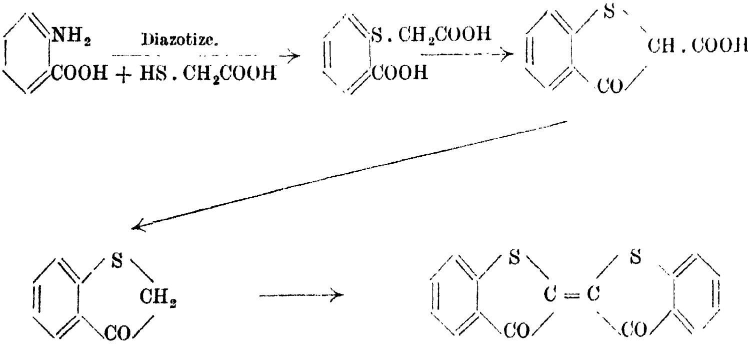
* See Chapter XIV.

which can be produced by heating 2-amino-anthraquinone with alkali to a temperature higher than that required to form indanthrene. Indanthrene is a valuable dye-stuff of greater stability than indigo; whilst flavanthrene, though giving a blue vat, dyes cotton yellow.

Another class of anthraquinone vat dyes are the acyl derivatives of amino-anthraquinones. For the most part these are yellow or orange in colour, whilst the anthraquinone-imines vary in tint from orange to red or claret colour according to their constitution.

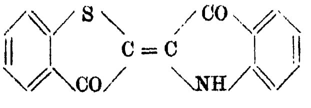
In 1906 Friedländer[1] discovered the thio-analogue of indigo in which the two imino groups are replaced by sulphur atoms; and this substance has become the foundation of a very extensive group of dyes. The following scheme shows one method of synthesis :—



Thio-indoxyl.

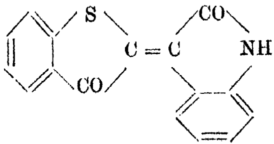
Thio-indigo.

Thio-indigo imparts a reddish-violet colour to the fabric, and modified tints can be produced by using the amino or halogen derivatives. Further changes in colour are obtained by condensing together one isatin and one thio-indoxyl group, producing mixed structures :—



Violet A.

and



Scarlet.

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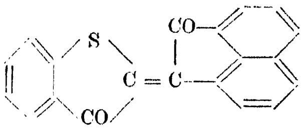
[1] Friedländer, *Ber.*, 1906, **39**, 1060.

whilst by uniting thio-indoxyl with diketo-acenaphthenequinone the valuable dye thio-indigo scarlet is obtained :—

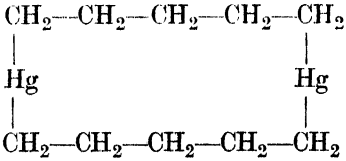


Synthetic drugs have been produced in large numbers in recent years. Of these one of the most important is salvarsan or 606 which is dihydroxy-diamino-arsenobenzene dihydrochloride. It has been used with success to kill the spirochæte which produces syphilis, though, of course, it has no effect in repairing the ravages already caused by the disease if treatment has been delayed. Another organic arsenic derivative employed is atoxyl (also known as arsamin or soamin) which is the mono-sodium salt of *p*-aminophenyl-arsenic acid. It is chiefly utilized in cases of sleeping sickness. Both drugs, if used incautiously, may produce blindness.

Numerous new local anæsthetics are now known, such as stovaine, novocaine, and β-eucaine. Adrenaline has been synthesized; and the constituents of ergot are now manufactured for pharmaceutical purposes.

In the field of simple mono-heterocyclic compounds, a considerable extension of our knowledge has been made; and at the present time the catalogue of elements which can play their part as members of ring-compounds is large compared with the list of three—oxygen, sulphur, and nitrogen—which originally represented the limit of our knowledge in this branch.

Mercury yields a remarkable twelve-membered ring [1]



$$\begin{array}{ccccccccc} CH_2 & - & CH_2 & - & CH_2 & - & CH_2 & - & CH_2 \\ | & & & & & & & & | \\ Hg & & & & & & & & Hg \\ | & & & & & & & & | \\ CH_2 & - & CH_2 & - & CH_2 & - & CH_2 & - & CH_2 \end{array}$$

by the action of 1, 5-dibromopentane on sodium amalgam. Curiously enough, the six-membered compound containing one mercury atom in the ring was not obtained in this reaction. By acting on silicon chloride with a Grignard reagent prepared from 1, 5-dibromopentane and subjecting the dichloro-derivative thus

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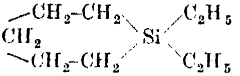
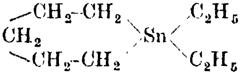
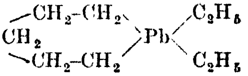
[1] Hilpert and Grüttner, *Ber.*, 1914, **47**, 186.

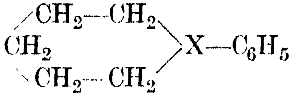
formed to the action of methyl-magnesium bromide, it is possible to obtain the six-membered ring (I.). The analogous tin and lead compounds (II.) and (III.) are obtained by the direct action of the Grignard reagent on diethyl-tin dichloride [1] and diethyl-lead dibromide.[2]


(I.)

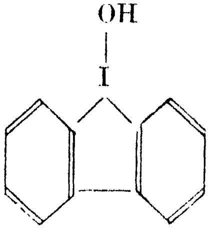

(II.)


(III.)

In parallel with nitrogen, the elements phosphorus,[3] arsenic,[4] antimony [5] and bismuth [6] have now been found capable of yielding ring-compounds of the type :



wherein X represents the atom of the trivalent element. In each case the mode of preparation is by the action of the phenyl-dichloro-derivative of the element upon a Grignard reagent prepared from 1, 5-dibromopentane. The selenium analogue of thiophen has been obtained ; [7] and tellurium is now known as a ring-member.[10] Finally iodine has been found acting as a ring-member in diphenyl-iodonium hydroxide [8] ; and Collie and



Reilly [9] by the action of iodine on the barium salt of diacetyl-

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[1] Grüttner, Krause and Wiernik, *Ber.* 1917, **50,** 1549.

[2] Grüttner and Krause, *Ber.*, 1916, **49,** 2666.

[3] Grüttner and Wiernik, *Ber.*, 1915, **48,** 1473.

[4] *Ibid.*, 1915, **48,** 1479.

[5] *Ibid.*, 1915, **48,** 1484.

[6] *Ibid.*, 1915, **48,** 1475.

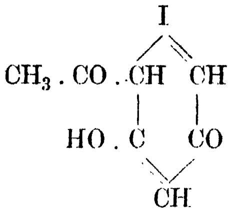
[7] Foa, *Gazzetta*, 1909, **39,** II., 527 ; compare Briscoe and Peel, *J.*, 1928, 1741.

[8] Mascarelli and others, *Gazzetta*, 1908, **38,** II, 619 ; 1911, **41,** I, 63, 68 ; 1912, **42,** I, 101 ; 1913, **43,** I, 26.

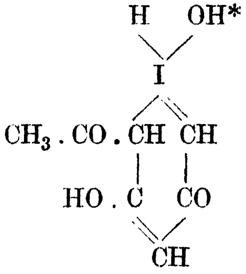
[9] Collie and Reilly, *J.*, 1921, **119,** 1550.

[10] Morgan and Drew, *J.*, 1920, **117,** 1456 ; 1924, **125,** 731, 1601 ; Morgan and Burgess, *J.*, 1928, 321 ; Drew, *J.*, 1926, 223 ; Drew and Thomason, *J.*, 1927, 116.

acetone, have obtained a compound which appears to have the following structure (I.):



(I.)



(II.)

It is interesting to note that this last substance in aqueous solution is strongly acidic, which differentiates it sharply from all previous alkyl derivatives of iodine. This is probably due to the formation of the hydrated form (II.) in which there is a double bond in the 3 : 4-position to the acidic hydrogen marked with the asterisk, as is required by the Vorländer Rule.

On the theoretical side of organic chemistry, to which we must now turn, Thiele's views on valency exerted a considerable influence during the century. It is very seldom that any theory is accepted immediately after being published; usually a considerable time is required during which the chemical world assimilates the author's views in a more or less unconscious manner, until some day they find their way into text-books. It is a remarkable tribute to the value of Thiele's partial valency theory that it became a classic almost as soon as it was published.

From the Thiele theory we may pass to the problem of benzene, since the two questions hinge upon one another at some points. During the last twenty years, the constitution of benzene has been discussed from almost every possible standpoint, and we are certainly not less wise than when the discussion began. Whether we are wiser is a more doubtful matter. Certainly much can be learned from the arguments adduced by the various writers who have dealt with the subject; and a perusal of the polemic is by no means a waste of time. The benzene problem in its present condition might well be described in the words used by some one to define Philosophy: "It is a subject in which the conclusion reached is of less importance than the means by which that conclusion is attained."

Linked with the problem of the constitution of benzene is another, which deals with the orientation of substituents in the benzene ring and the apparent directing influence which certain substituents exert upon the position taken up by a fresh incoming substituent.[1] This problem in turn has been brought into relationship with hypotheses with regard to the polarity of atoms in chains.

Passing to other subjects, intramolecular change must be mentioned, as in this region much work of first-class importance has been carried out since the beginning of the century. It would lead us too far were we to enter into any general discussion of the problem ; but one or two examples must be given.

The most striking of these is the discovery by Hantzsch of a new class of electrolytes which have been named pseudo-acids and pseudo-bases.* Previous to his work, the electrolytes known to us might be grouped under the four following heads : (1) Acids, which give rise to hydrogen ions ; (2) Bases, which yield hydroxyl ions ; (3) Salts, which dissociate into acidic and basic ions ; and (4) Amphoteric electrolytes, which are capable of producing either hydrogen or hydroxyl ions according to the experimental conditions employed.

Now when an acid solution is neutralized by means of a base, the solution is acidic at the beginning and remains acidic all through the titration until the neutralization-point is reached. On the other hand, if we start with a solution of nitromethane, it is neutral in reaction ; and yet if we slowly add to it a solution of sodium hydroxide, the solution does not become alkaline at once. In fact, we may have to add a considerable quantity of alkali before the next drop produces an alkaline reaction in the liquid. Clearly nitromethane is a neutral substance which, *given time*, can exhibit acidic properties in presence of alkali. It is this *slow neutralization* which distinguishes it from a true acid.

Without going into the details of the evidence, it may be

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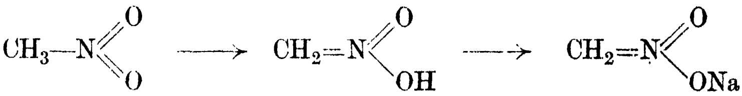
[1] For information on the subject, see Holleman, *Die direkte Einführung von Substituenten in den Benzolkern* (1910), and Obermiller, *Die orientierenden Einflüsse und der Benzolkern* (1909).

* An account of this field is to be found in Stewart's *Physico-chemical Themes*.

said that intramolecular change is the governing factor in the problem. True nitromethane is not acidic; but in presence of bases it may change into an isomeric body, the *aci*-form, which possesses a hydrogen capable of being replaced by alkali: so that the reaction may be represented by the following scheme:—



Normal form. Aci-form. Salt.

The slowness with which nitromethane neutralizes alkalis is obviously due to the fact that the intramolecular change from the normal to the aci-form is not instantaneous, but requires time for its accomplishment.

The discovery of the pseudo-acids resulted in the collapse of Ostwald's hypothesis as to the nature of indicators. Ostwald[1] assumed that indicators underwent a change of colour when dissociated into their ions. Thus undissociated phenolphthalein, in his view, was colourless; but when converted into the easily dissociable sodium salt it broke down into ions which were red in colour. By adding acid to the alkaline solution, the dissociation of the phenolphthalein was restricted; and hence the colour disappeared. Stieglitz[2] suggested, on the other hand, that the production of the colour was due to intramolecular change in the phenolphthalein molecule; and Hantzsch[3] confirmed this, showing that phenolphthalein, for example, changes from the benzenoid to the quinonoid structure under the influence of alkali.

In connection with intramolecular change the case of tetranitromethane may be mentioned.[4] Under normal circumstances, this substance appears to exist in the pure "nitro" form (I.), but in presence of amines or alkyl sulphides it seems slowly to be converted into trinitro-nitrito-methane (II.), as it gives exactly

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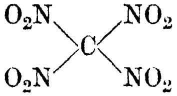
[1] Ostwald, *Die wissenschaftlichen Grundlagen der analytischen Chemie* (1894).

[2] Stieglitz, *J. Amer. Chem. Soc.*, 1903, **25**, 112.

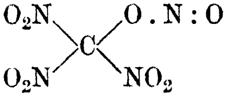
[3] Hantzsch, *Ber.*, 1906, **39**, 1090.

[4] Harper and Macbeth, *T.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824.

the same colour reactions as are observed in the case of alkyl nitrites :—



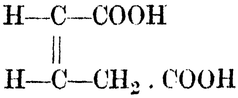
(I.)



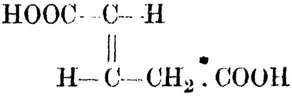
(II.)

This case seems to be a half-way stage towards pseudo-acid formation.

Some of the most surprising results obtained in recent years in the field of isomeric change are those due to Thorpe and his collaborators.[1] Glutaconic acid is known in only one form, though theoretically it should exist in the two stereoisomeric modifications whose formulæ are shown below :



$$\begin{array}{l}\mathrm{H{-}C{-}COOH}\\ \quad\ \ \|\\ \mathrm{H{-}C{-}CH_2\,.\,COOH}\end{array}$$



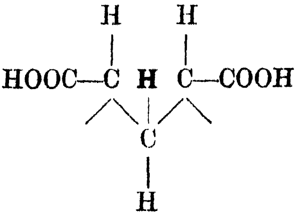
$$\begin{array}{r}\mathrm{HOOC{-}C{-}H}\\ \|\ \ \quad\\ \mathrm{H{-}C{-}CH_2\,.\,COOH}\end{array}$$

Still more strange is the fact that when an α-alkylglutaconic acid is prepared, it is found to be identical with γ-alkylglutaconic acid ; and α-methyl-γ-ethyl-glutaconic acid is identical with γ-methyl-α-ethylglutaconic acid.

$$\mathrm{HOOC{-}CH\mathbf{R}{-}CH{=}CH{-}COOH} \longleftarrow \text{Identical} \longrightarrow \mathrm{HOOC{-}CH_2{-}CH{=}C\mathbf{R}{-}COOH}$$

$$\mathrm{HOOC{-}CH\mathbf{Me}{-}CH{=}C\mathbf{Et}{-}COOH} \longleftarrow \text{Identical} \longrightarrow \mathrm{HOOC{-}CH\mathbf{Et}{-}CH{=}C\mathbf{Me}{-}COOH}$$

In order to account for these facts, it is assumed that the constitution of glutaconic acid is best represented by some formula such as this :



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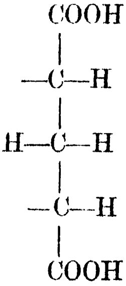
[1] Thole and Thorpe, *J.*, 1911, **99**, 2187, 2208 ; Bland and Thorpe, *J.*, 1912, **101**, 856, 871, 1490, 1557 ; Thorpe and Wood, *J.*, 1913, **103**, 1579, 1752 ; compare Thorpe and Ingold's *Report on Some New Aspects of Tautomerism*, published by the Union Internationale de Chimie Pure at Appliquée.

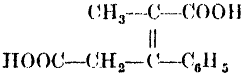
wherein the hydrogen atom printed in heavy type is regarded as a mobile atom in equilibrium between the two unsaturated carbon atoms—a return to Laar's views on tautomerism. If the formula be written with free valencies as a stereo-formula, it is assumed to take the following shape:



$$\begin{array}{rcl} & \mathrm{COOH} & \\ & | & \\ - & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ - & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{COOH} & \end{array}$$

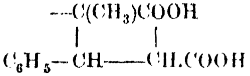
which corresponds to a *meso*-form.

Now if this view be correct, then theoretically an acid of the glutaconic series should exist in three modifications: a *cis*-form, a *trans*-form, and a normal form indicated by the free-valency structure shown above. In practice, β-phenyl-α-methyl-glutaconic acid has actually been obtained in three forms to which the following formulæ have been ascribed:



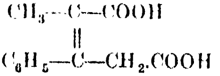
$$\begin{array}{rcl} \mathrm{CH_3}- & \mathrm{C} & -\mathrm{COOH} \\ & \| & \\ \mathrm{HOOC-CH_2}- & \mathrm{C} & -\mathrm{C_6H_5} \end{array}$$

Trans-labile Acid.



$$\begin{array}{rcccl} & -\mathrm{C} & (\mathrm{CH_3}) & \mathrm{COOH} & \\ & | & & | & \\ \mathrm{C_6H_5}- & \mathrm{CH} & — & \mathrm{CH} & .\mathrm{COOH} \end{array}$$

Normal form.



$$\begin{array}{rcl} \mathrm{CH_3}- & \mathrm{C} & -\mathrm{COOH} \\ & \| & \\ \mathrm{C_6H_5}- & \mathrm{C} & -\mathrm{CH_2.COOH} \end{array}$$

Cis-labile Acid.

These results have led to interesting investigations on the problem of three-carbon systems by Thorpe, Ingold, and others; but space will not permit of any further examination of the subject in this place.

At this point something must be said about the progress of stereochemistry *; for after a period of comparative quiescence, this branch of the subject began again to develop rapidly into fresh fields; and even in recent times new discoveries have shown that it is by no means an exhausted vein of research.

In 1899 the only two elements known to be capable of forming asymmetric centres of optical activity were carbon and nitrogen; but since then the list has been greatly increased by the addition

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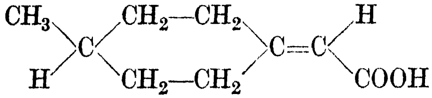
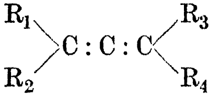
* For a general account of this subject, Stewart's *Stereochemistry* may be consulted.

of sulphur,[1] selenium,[2] tin,[3] silicon,[4] phosphorus,[5] arsenic,[6] cobalt,[7] chromium,[8] rhodium,[9] and iron.[10]

The whole question of molecular symmetry was raised by a paper of Perkin, Pope, and Wallach [11] describing the resolution into optically active components of an acid having the following structure :—



It will be recalled that in one of his earliest publications on stereochemistry, van't Hoff pointed out that optical activity might be expected in compounds of the type :



owing to the fact that, although there is no asymmetric carbon atom in the molecule, the groups R_1, R_2, R_3, and R_4 are tetrahedrally grouped in space, as can easily be seen by considering the arrangement of bonds around the central carbon atom on the van't Hoff hypothesis. The one double bond lies in the plane of the paper, whilst the other must be at right angles to the paper ; and hence a similar grouping of R_1 and R_2 in the plane of the paper and R_3 and R_4 above the plane of the paper must exist. The cyclic compound shown above belongs to the same type, since in its case the ring takes the place of one of the double bonds.

The claim that this substance contained no asymmetric

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[1] Smiles, *J.*, 1900, **77**, 1174 ; Pope and Peachey, *ibid.*, 1072 ; Phillips, *J.*, 1925, **127**, 2552.

[2] Pope and Neville, *J.*, 1900, **81**, 1552.

[3] Pope and Peachey, *P.*, 1900, **16**, 42, 116.

[4] Kipping, *J.*, 1907, **91**, 209.

[5] Kipping and Challenger, *J.*, 1911, **99**, 626 ; Meisenheimer and Lichtenstadt, *Ber.*, 1911, **44**, 356.

[6] Mills and Raper, *J.*, 1925, **127**, 2479 ; compare Burrows and Turner, *J.*, 1921, **119**, 426.

[7] Werner, *Ber.*, 1911, **44**, 1887.

[8] *Ibid.*, 3231.

[9] *Ibid.*, 1912, **45**, 1228.

[10] *Ibid.*, 433.

[11] Perkin, Pope and Wallach, *J.*, 1909, **95**, 1785 ; compare Perkin and Pope, *J.*, 1911, **99**, 1510 ; Mann and Pope, *J. Soc. Chem. Ind.*, 1925, **44**, 833.

carbon atom was contested[1] on the ground that the carbon atom carrying the methyl group is really asymmetrical if the structure of the rest of the molecule be taken into consideration. The matter seems to be one depending upon the interpretation given to the term "asymmetric carbon atom"; and the reader may form his own judgment on the question.

New methods of resolving racemic compounds into their antipodes have been devised. Some of these present nothing essentially novel in conception.[2]

Much more original was the method devised by Marckwald and Meth,[3] which depends upon the difference in rapidity of amide formation between an active amine and the *d*- and *l*-forms of an active acid. Thus when racemic mandelic acid was heated with lævo-menthylamine, it was found that the acid left unacted upon after the process had gone on for ten hours was optically active. This method is based on the same line of reasoning as the method of Marckwald and McKenzie,[4] who showed that when racemic mandelic acid is esterified with menthol the reaction between the menthol and the *d*-form is more rapid than is the case with the *l*-acid; so that by interrupting the process before the acid is completely esterified the residual acid is optically active.

A fresh field was opened up by Marckwald[5] in the accomplishment of the first asymmetric synthesis of an optically active substance. In an asymmetric synthesis, an optically active compound is taken as the starting-point. To this an extra radicle is added, so as to form a new asymmetric carbon atom. The original optically active portion of the molecule is then split off; and if the synthesis is successful, the remainder of the substance, containing the new asymmetric carbon atom, will be optically active. For example, Marckwald utilized methyl-ethyl-malonic acid (I.) which contains no asymmetric carbon atom. He combined this with optically active brucine, thus introducing asymmetry into the molecule (II.). Now on heating this compound, carbon dioxide is split off forming (III.), a compound which contains a new asymmetric carbon

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[1] Everest, *Chem. News*, 1909, **100**, 295; *P.*, 1911, **27**, 285; Marsh, *P*, 1911, **27**, 317; Smith, *J. Chem. Soc. Ind.*, 1925, **44**, 1107.

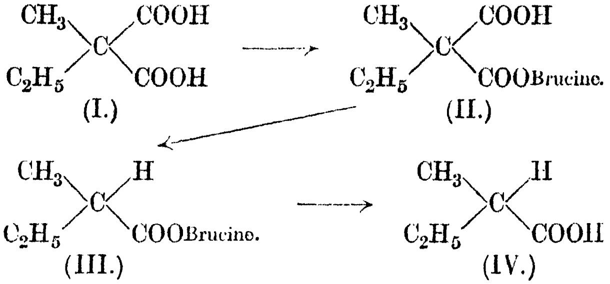
[2] Erlenmeyer, jun., *Ber.*, 1903, **36**, 976; Neuberg, *Ber.*, 1903, **36**, 1192.

[3] Marckwald and Meth, *Ber.*, 1905, **38**, 801.

[4] Marckwald and McKenzie, *Ber.*, 1899, **32**, 2130.

[5] Marckwald, *Ber.*, 1904, **37**, 349, 1368, 4696.

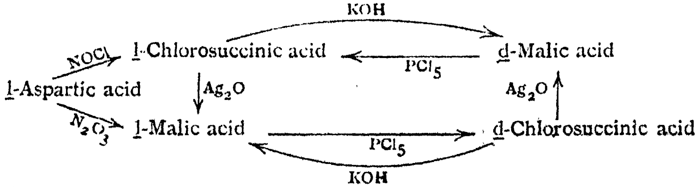
atom. Under the influence of the active brucine, a preference is given to one active form over the other during this process; and when the brucine is split off again, the acid remaining (IV.)



is found to be optically active.

In the whole field of stereochemistry no more puzzling phenomena are known than those grouped under the head of the Walden Inversion; and at the present day we still await a solution of the problem. The data are so complicated that it would be impossible to deal with them fully here: all that can be done is to indicate the nature of the question.[1]

Walden[2] observed that when certain optically active compounds were treated with non-asymmetrical reagents the sign of the rotatory power was altered in some cases, dextro-compounds being converted into lævo-isomers without any marked racemization being observed. The following scheme shows some of these conversions; and it will be seen that lævo-malic acid, for instance, can be changed into dextro-malic acid by the successive use of phosphorus pentachloride and silver oxide; whilst the converse change of dextro-malic acid into the lævo-isomer can be accomplished by the use of the same reagents in the same order:



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[1] For further details and references, see *Ann. Reports*, 1911, 1912, 1926, 1929, and Stewart, *Stereochemistry* (2nd edition).

[2] Walden, *Ber.*, 1893, **26**, 213; 1895, **28**, 1287, 2771; 1897, **30**, 3146; 1899, **32**, 1833, 1855.

Another mysterious case is that of dextro-alanine and its ester.[1] When *d*-alanine is treated with nitrosyl bromide, it produces *l*-*a*-bromopropionic acid; whilst *d*-alanine ester, when subjected to the action of nitrosyl bromide and subsequent hydrolysis, yields the corresponding antipode, *d*-*a*-bromopropionic acid:

$$\text{Dextro-alanine } NH_2\,.\,CH(CH_3)\,.\,COOH \xrightarrow{NOBr} \text{Lævo-}\alpha\text{-propionic acid.}$$

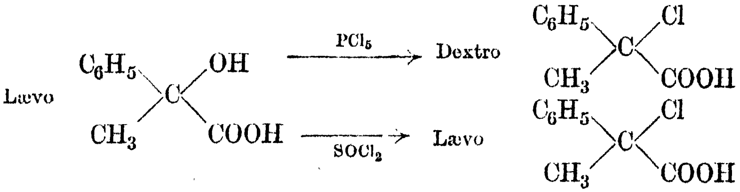
$$\text{Dextro-alanine ester } NH_2\,.\,CH(CH_3).COOEt \xrightarrow[\text{hydrolysis}]{\text{NOBr and}} \text{Dextro-}\alpha\text{-propionic acid.}$$

Again, when silver oxide acts upon an *a*-halogen fatty acid and upon the product obtained by coupling this acid with glycine,[2] the results are optically different:

$$l\text{—}CH_3\,.\,CHBr\,.\,COOH \xrightarrow{Ag_2O} d\text{-}CH_3\,.\,CH(OH)\,.\,COOH$$

$$l\text{—}CH_3\,.\,CHBr\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOH \xrightarrow{Ag_2O \text{ and hydrolysis}} l\text{-}CH_3\,.\,CH(OH)\,.\,COOH$$

Finally, the case of *l*-*a*-hydroxy-*a*-phenylpropionic acid may be mentioned.[3] When this substance is treated with phosphorus pentachloride it yields a *d*-chloro-acid; whilst when thionyl chloride is used, there is no change of rotatory power, the *l*-chloro-acid being formed:



Senter and his collaborators[4] have thrown light upon the matter from a different direction by examining the influence of the solvent on the course of the reaction. In the case of optically active bromophenylacetic acid, $C_6H_5\,.\,CHBr\,.\,COOH$, they have shown that if this be allowed to react with ammonia in aqueous or alcoholic solution, the amino-acid formed has a

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[1] Fischer, *Ber.*, 1907, **40**, 489.

[2] *Ibid.*, 502; Fischer and Raske, *ibid.*, 1052; Fischer and Schoeller, *Annalen*, 1907, **357**, 11.

[3] Mckenzie and Clough, *J.*, 1910, **97**, 1016, 2566.

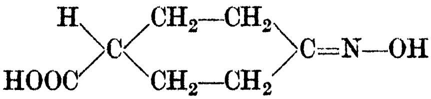
[4] Senter and Drew, *J.*, 1915, **107**, 638; 1916, **109**, 1091; Senter and Tucker, *J.*, 1918, **113**, 140; Senter, Drew, and Martin, *ibid.*, 151.

sign opposite to that of the original bromo-compound; whilst if the solvent be liquid ammonia or acetonitrile, the sign of the rotatory power is not reversed by the reaction. Imino-diphenylacetic acid is formed to some extent during the reaction. When α-bromo-β-phenylpropionic acid, $C_6H_5 . CH_2 . CHBr . COOH$, is treated with ammonia in various solvents, some cinnamic acid is always produced.

One of the most complicated problems in the stereochemical field is that which concerns the numerical value of optical rotatory power. Two subsidiary questions are here involved: first, the influence of the active compound's structure; and second, the effect of the solvent in which it may be dissolved. With regard to the first of these we are still apparently far from any satisfactory conclusion, though many facts have been accumulated by various investigators. Certain rough generalizations with regard to the effect of introducing double or triple bonds in place of single linkages have been made; but we are still far from the time when it may be possible to assess the approximate numerical value of the rotatory power from an examination of the active compound's constitution, as we can do in the case of refractive indices.

With regard to spatial relations which do not produce optical activity, the most far-reaching work is that of Bragg on the X-ray examination of crystal structure; but it would lead us too far if we were to attempt to summarize his results here.

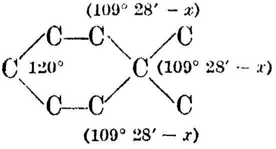
The Hantzsch-Werner theory of *cis-trans*-isomerism in the oximes has been put to a crucial test from which it has emerged intact. Examination of the formula of the oxime of cyclohexanone-4-carboxylic acid, which is shown below, will reveal at once that this structure is a symmetrical one if the oximic hydroxyl group lies in a straight line with the axis of the —C=N— bond.



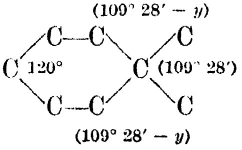
On the other hand, if the oximic hydroxyl group lies to one side or other of the axis of the —C=N— bond (as is demanded by the Hantzsch-Werner theory), then the molecule becomes centro-asymmetrical and should be obtainable in optically active forms. A resolution of this acid into its optical antipodes was carried out successfully by Mills and Bain[1]; and thus the Hantzsch-Werner theory has received its most striking confirmation. Simultaneously, however, grave doubt has been thrown[2] on the applicability of some of the methods hitherto used in the determination of the configurations of the oximes.

In 1885, Baeyer[3] put forward his well-known Strain Theory based upon the assumption that the valencies of a carbon atom normally acted at angles of 109° 28′ with each other but could be diverted during the formation of rings; and that the deviation required to form the cyclic grouping was a measure of the difficulty of forming the ring-compound.[4] Since substitution is known to have marked influence on the stability of rings,[5] it was evident that it also was a factor in stability questions. An important study of this field has been carried out by Thorpe and his collaborators.[6] The data furnished by them are far too voluminous to discuss adequately even in a chapter, so only a brief account can be given of the results obtained.

The normal angle made by the sides of a hexagon is 120°; so that in order to form the ring-compound shown below, two valencies of the quaternary carbon atom must be diverted from their normal position.



Case (a).



Case (b).

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[1] Mills and Bain, *J.*, 1910, **97,** 1866; see also Mills and Schindler, *J.*, 1923, **123,** 312.

[2] Bucherer, *Lehrbuch d. Farbenchemie,* p. 202 (1914); Meisenheimer, *Ber.*, 1921, **54,** 3206; Meisenheimer and Meis, *Ber.*, 1924, **57,** 289; Auwers and others, *Ber.*, 1924, **57,** 446, 800; 1925, **58,** 26, 36; Brady and Bishop, *J.*, 1925, **127,** 1357; Beckmann and others, *Ber.*, 1923, **56,** 341; Meisenheimer and others, *Annalen*, 1925, **444,** 94; Kuhn and Abel, *Ber.*, 1925, **58,** 919, 2088; Boeseken, *Ber.*, 1925, **58,** 1470.

[3] Baeyer, *Ber.*, 1885, **18,** 2277.

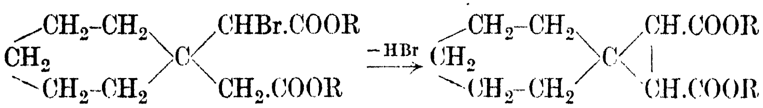
[4] For some account of the application of the Strain Theory, see Stewart, *Stereochemistry*, p. 175 (1919).

[5] See Stewart, *Stereochemistry*, p. 203 (1919).

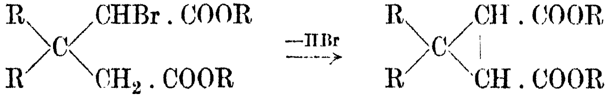
[6] Beesley, Ingold and Thorpe, *J.*, 1915, **107,** 1080; Ingold and Thorpe, *J.*, 1919, **115,** 320; Becker and Thorpe, *J.*, 1920, **117,** 1579; Kon, *J.*, 1921, **119,** 810; compare Kenner and Turner, *J.*, 1911, **99,** 2101; Kenner, *J.*, 1914, **105,** 2685; Ingold, *J.*, 1921, **119,** 305.

The remaining two valencies of the quaternary carbon atom * might then be supposed either (*a*) to distribute themselves evenly in space as indicated in Case (*a*) above, or (*b*) to remain at the normal tetrahedral angle of 109° 28′, as shown in Case (*b*). Inspection will show at once that in Case (*a*) the two carbon atoms external to the ring will be nearer together than they would be in Case (*b*), where the normal angle is maintained.

Now in an open-chain compound, the angles may be assumed to be 109° 28′. Therefore by comparing the behaviour of an open-chain compound with that of a cyclic compound, it should be possible to determine which of the two views is correct. For example, if affairs are correctly represented by Case (*a*), then there should be a greater tendency to form the *spiro*-compound (I.) below than there is to form the analogous open-chain compound (II.); whereas if Case (*b*) represents the true state of things, then the removal of hydrogen bromide should be equally easy in both reactions.



(I.)



(II.)

Examination of a large number of examples has now shown that the *spiro*-compound is much more readily formed than the open-chain one, which indicates that Case (*a*) represents the state of affairs better than Case (*b*); and this is confirmed by the study of the relative stabilities of the fresh rings in the molecule.

Another problem which attracted a certain amount of attention is concerned with what has been termed spatial conjugation. It will be recalled that on the hypothesis of the tetrahedral arrangement of groups around the carbon atom, the first carbon atom in a straight chain may approximate closely in space to

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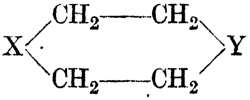
* Those attached to the two carbon atoms not forming part of the ring.

the fifth and sixth atoms of the chain. Similarly it is assumed on account of various reactions that the 1 : 4 positions of a six-membered cyclic compound may also be in some way closely related to each other. From an examination of optically active salts and esters of dicarboxylic acids in which the carboxyl radicles lay at opposite ends of the chain, Hilditch [1] showed that when these groups were situated in the 1 : 5 or 1 : 6 positions with regard to one another, anomalous rotatory powers were observed; from which it follows that the groups must have influenced one another owing to their proximity in space, since structurally they are far removed from each other.

The same problem was attacked in a different way by Clarke.[2] He measured the reactivity of atoms in the positions X and Y in the formula below, wherein X and Y may be =NR, —O— and —S—. All possible combinations of these groups in pairs were investigated:—



It was found that when X and Y are atoms capable of raising their valency (for example: divalent sulphur, which can become quadrivalent, or trivalent nitrogen, which can show pentavalence) and may therefore be supposed to be capable of exhibiting residual affinity, the two atoms X and Y do actually influence each other's reactivities. Further, if X and Y be identical, their reactive power is increased; whereas if X and Y be different (for example X=S and Y=O), their activity is diminished.

A fresh aspect of the question is disclosed when the absorption spectra of stereoisomerides are examined.[3] Since these compounds are structurally identical, the difference in their absorptive power must be ascribed to purely spatial influences. It was found that the difference between the absorption spectra of two isomerides was greatest when the change from one form to the other entailed the relative shifting in space of two unsaturated radicles. When this condition was not present the differences observed were slight.

These pieces of evidence, drawn from such widely differing

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[1] Hilditch, *J.*, 1909, **95**, 1578.

[2] Clarke, *J.*, 1912, **101**, 1788.

[3] Macbeth, Stewart, and Wright, *J.*, 1912, **101**, 599.

fields, certainly point to the probability that spatial conjugation is a factor which may play a marked part in certain cases.

We now come to a subject which lies in the borderland between organic and physical chemistry, namely, the relations between the physical properties of compounds and their chemical structure.[1] The problems comprised in this branch have, for the most part, been solved by organic chemists, owing to the fact that the material of experiment is largely drawn from the carbon compounds. The curious step-motherly fashion in which this important subject has been treated by the ordinary physical chemist is possibly due to the influence of Ostwald, who had a large following among the older group of physical chemists; or it may be ascribed to the fact that few physical chemists have any claim to be ranked as even moderate organic chemists, a fact which handicaps them in this particular line of research. Whatever be the reason, there is no doubt that the relations between chemical constitution and physical properties, so fully recognized by van't Hoff, have not been pursued with either eagerness or success by the physical chemists of the Ostwald school.

Specific heat, boiling-point, and melting-point have occupied less attention in recent years. The influence of chemical structure upon viscosity has furnished a subject for a number of workers, among whom Dunstan and his collaborators have been the most successful. The relations between volume and valency have formed the basis of a considerable amount of ingenious speculation by Traube, Barlow, Pope, and Le Bas.

The physical properties of a molecule may be regarded from either of two different standpoints: for we may assume the molecular properties to be merely the sum of the properties of the various atoms in the molecule; or we may decide to lay most weight upon the structural character of the compound. Unfortunately, this mode of classification breaks down at certain points; for it is found that in the case of some substances the properties of the molecule are apparently compounded partly from purely additive factors and partly from constitutive effects.

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[1] For a complete account of this field up to 1910, the reader should consult Smiles' *Relations between Chemical Constitution and some Physical Properties*. Even a cursory perusal of the book will suggest many subjects for further investigation. See also Kauffman, *Beziehungen zwischen physikalischen Eigenschaften und chemischer Konstitution* (1920).

A certain physical property may be traced as an additive factor throughout a whole series of compounds, and then may finally be so greatly influenced by constitutive factors that the value deduced from additive methods diverges widely from the result of experiment upon the next member of the series. Thus when we speak of additive and constitutive properties we mean merely that in the one case the additive factor is predominant, whilst in the second case the influence of constitution outweighs the purely additive effects.

An example of this is furnished by a relationship which has been detected between surface tension, density, and chemical composition. Macleod[1] discovered that a relation existed between the density and surface tension of substances which could be expressed in the equation :—

$$\gamma = C(D - d)^4$$

Here γ is the surface tension, D the density of the substance as liquid, and d its vapour density, all at the same temperature ; C is a characteristic constant, independent of temperature, in the case of non-associated substances.

Sugden[2] showed that this relationship of Macleod's could be brought into direct touch with chemistry by a simple modification. Taking the fourth root on each side of the equation and multiplying them by M, the molecular weight of the substance under examination, the following relation is obtained :—

$$M\sqrt[4]{C} = \frac{M\sqrt[4]{\gamma}}{(D - d)} = \text{Parachor}$$

The function $M\sqrt[4]{C}$ is termed by Sugden the parachor of the substance.

It is self-evident that when a weight is divided by a density, the quotient represents a volume ; and if, in this case, measurements are made at low temperatures (when d becomes very small) the factor $M/(D - d)$ is simply the molecular volume of the substance under the experimental conditions.

The parachor, then, is the molecular volume of the substance multiplied by the factor $\sqrt[4]{\gamma}$. But this factor represents a measure of the surface tension of the liquid, and the surface

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[1] Macleod, *Trans. Faraday Soc.*, 1923, **19**, 38.

[2] Sugden, *J.*, 1924, **125**, 1177.

tension is a measure of the internal pressure of the material. So, by comparing the parachors of two substances under conditions which make their surface tensions equal, we have a means of comparing their molecular volumes under equal internal pressures.*

When the parachors of a large number of compounds were determined, it was found that the property is mainly an additive one; and the following constants were calculated in the usual manner:—

C = 4·8 Cl = 54·3 Double bond C : C = 23·2
H = 17·1 Br = 68·0 O_2 in esters = 60·0
O = 20·0 I = 91·0 6-membered ring = 6·1

One or two examples will show how close is the agreement between the calculated and the experimental results.

Ethylene bromide

C_2 = 4·8 × 2 = 9·6
H_4 = 17·1 × 4 = 68·4
Br_2 = 68·0 × 2 = 136·0

Calculated = 214·0
Experiment = 215·1

n-Propyl formate

C_4 = 4·8 × 4 = 19·2
H_8 = 17·1 × 8 = 136·8
O_2 = 60 = 60

Calculated = 216·0
Experiment = 216·1

Benzene (Kekulé formula)

C_6 = 4·8 × 6 = 28·8
H_6 = 17·1 × 6 = 102·6
3 Double bonds = 23·2 × 3 = 69·6
6-membered ring = 6·1 = 6·1

Calculated = 207·1
Experiment = 206·3

Further investigation revealed that the parachor, though mainly additive, is in certain cases influenced by constitution. One example of this will suffice here.

It appears that a distinction must be drawn between two kinds of double bonds: the non-polar and the semi-polar.[1] The former adds 23·2 units to the parachor, whilst the latter lowers the parachor value by 1·6 units. On the electronic theory of valency,† the non-polar double bond is supposed to be produced

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* For water at ordinary temperatures the internal pressure is of the order of 11,000 atmospheres.

[1] Sugden, Reed, and Wilkins, *J.*, 1925, **127**, 1525; Sugden and Whittaker, *ibid.*, 1868.

† See Chapter XVI.

by two co-valencies, whilst the semi-polar bond is assumed to consist of one co-valency and one electrovalency. Langmuir assumed that double bonds between carbon atoms were of the non-polar type; and Sugden [1] has suggested that there is free rotation in the case of semi-polar double bonds. An examination of the parachors in the maleic-fumaric acid series proved that there the double bonds had parachoric values corresponding to the non-polar type, which fits in neatly with the cis-trans isomerism characteristic of the series.

From facts such as these it is evident that even in the case of a markedly additive property, constitutional factors make their appearance in the problem. Another example of the same kind may be found in the refractive indices of compounds. In the case of saturated molecules or unsaturated compounds containing centres of residual affinity which are isolated from each other, the refractive power of the substances can be calculated with extraordinary accuracy by simply adding together the predetermined constants of the atoms which go to form the molecule. But if the structure contains a conjugated system of double bonds, the refractivity becomes anomalous and cannot be calculated on an additive basis. In this case, it is evident that constitutive influences are overbearing the purely additive relationship.

This peculiar influence of conjugation makes itself apparent in nearly all optical properties. Magnetic rotatory power—*i.e.* the property of rotating the plane of polarization which is acquired by symmetrical substances when placed in a magnetic field—is calculable, in the main, so long as no conjugation is present in the molecular structure; but substances containing conjugated double bonds are found to exhibit a certain "exaltation" above the calculated value; so that, here also, the constitutional factor outweighs the purely additive effects.

When absorption spectra are examined, it is found that the manner in which the atoms are linked in the molecule may exert far more influence than the nature of the atoms themselves. At the beginning of the century, this subject attracted very wide interest, either in the crude form of "relations between colour and constitution," or in the more accurate survey of the visible and ultra-violet regions by the aid of the

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[1] Sugden, *J.*, 1923, **123**, 1864.

quartz spectrograph. The invention of the sector photometer by Henri for the determination of extinction coefficients in the ultra-violet marked a great stride forward in accuracy of method; and Henri [1] has been enabled to calculate graphs of the absorptive power of certain substances. At the present time, however, absorption spectra have dropped out of the position of interest which they occupied some ten or fifteen years ago.

In the spectroscopic branch an entirely new field was opened up by McVicker, Marsh, and Stewart [2] through the discovery of the Tesla luminescence spectra. In earlier years, the only emission spectra obtainable were those of the elements or of comparatively few stable compounds such as carbon monoxide and carbon dioxide. By using the high-tension Tesla discharge, it is now possible to photograph the emission spectra of highly complex compounds such as benzene and its derivatives; and the extraordinary regularity of the benzene spectrum seems to suggest that through it mathematics may be brought to bear upon some of the fundamental problems of organic chemistry. The Tesla-luminescence spectra are constitutive in character, each class of compound having its own general spectral type. Curiously enough, the influence of conjugation appears to be very small so far as this physical property is concerned.

Fluorescence is another property in which constitutive relations play a preponderant part. So far as visible fluorescence is concerned, Hewitt's theory of double symmetrical tautomerism [3] appears to be the most successful attempt yet made to discover the factors underlying the phenomena. Recent work [4] on the fluorescence of substances in the vapour state, however, suggests that the problem as a whole is by no means easy to solve.

Magnetic susceptibility,[5] when studied from the constitutional standpoint, is found to resemble magnetic rotation in

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[1] Henri, *Etudes de photochimie* (1919).

[2] McVicker, Marsh, and Stewart, *J.*, 1923, **123**, 642, 2147; 1924, **125**, 1743; 1925, **127**, 999; 1926, **129**, 17; *Phil. Mag.*, 1924, **48**, 628; *J. Amer. Chem. Soc.*, 1924, **46**, 1351.

[3] Hewitt, *Z. physikal. Chem.*, 1900, **34**, 1; *J. Soc. Chem. Ind.*, 1903, **22**, 127.

[4] McVicker and Marsh, *J.*, 1923, **123**, 820; Marsh, *ibid.*, 3315; 1924, **125**, 418; Nunan and Marsh, *ibid.*, 2123; Marsh, *Phil. Mag.*, 1925, **49**, 971, 1206.

[5] Pascal, *Bull. soc. chim.*, 1909 (iv), **5**, 1110.

character, being influenced partly by additive factors and partly by the general constitution of the molecule.

Electrical double refraction[1] and dielectric constant[2] have also been worked upon; but they appear to be so highly constitutive in character that only the most general inferences can be drawn from the experimental results.

One of the most highly constitutive properties yet discovered is anomalous electric absorption[3] which seems, so far as our present information goes, to be almost entirely restricted to compounds containing hydroxyl groups.

From the foregoing paragraphs it will be seen that an immense amount of research remains to be done upon the connection between physical properties and chemical structure. We still await some general theory which will co-ordinate the various branches of the subject. From a survey of the data at present available, it seems clear that the more purely electrical a property is, the more does the influence of constitution preponderate. Thus refractive index is largely additive; magnetic rotation and magnetic susceptibility are slightly more constitutive in character; anomalous electric absorption and electrical double refraction are almost entirely constitutive; while the Tesla-luminescence spectra appear to be entirely constitutional properties. It is true that absorption spectra form an apparent exception to this rule.

Photochemistry[4] has grown by leaps and bounds since the beginning of the century and is rapidly reaching the stage when it will be considered a subject in itself. The problems already presented by it are too numerous to be dealt with in this place; although the fringe of the subject is all that has been attacked as yet.

The survey given in the previous pages of the progress of organic chemistry during the present century, though very incomplete, will suffice to indicate the main lines upon which

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[1] Cotton and Mouton, *Ann. Chim. Phys.* (viii), 1907, **11**, 145; 1910, **19**, 153; **20**, 153, 194; 1913, **28**, 209.

[2] Drude, *Z. physikal. Chem.*, 1897, **23**, 309; Walden, *ibid.*, 1903, **46**, 176; 1906, **54**, 139; 1910, **70**, 584.

[3] Drude, *Z. physikal. Chem.*, 1902, **40**, 635; compare Walden, *ibid.*, 1903, **46**, 176.

[4] Accounts of the subject are given in Sheppard's *Photochemistry* (1914), and in Griffith and McKeown's *Photo Processes in Gaseous and Liquid Systems* (1929).

work is proceeding at the present day; and it should be sufficient to show that fresh subjects of research are still plentiful. The newer trend towards a study of natural products comes as a relief after the long supremacy of the purely synthetic work of the late nineteenth century; and it may be emphasized in this place that in the near future the study of quite simple reactions will offer many points of interest. We are far too apt to be captivated by the application of old reactions to new syntheses; and it seems likely that more interesting and useful work could be carried out by an examination of even such obvious problems as the hydration and dehydration of simple organic compounds.

CHAPTER II

SOME CARBOHYDRATE CONSTITUTIONS

A.—INTRODUCTORY

AMONG organic compounds, the carbohydrate class occupies a unique position, since in one form or another its members have become almost indispensable to modern civilization. Sugar and starch occur in our foodstuffs. The growing plant's cell-walls are formed from cellulose, which is thus the keystone of agriculture. Cellulose in the form of wood finds applications as fuel, as a building material, and in the construction of furniture. It is the basis of the manufacture of cheap paper; it is an essential raw material in the making of cinema-films; and it is utilized in the making of many commercial explosives. On it, too, the cotton trade is founded; and the recent rise of artificial silk represents yet another field of application for the carbohydrates. Even in pathology this group has a marked importance, since glycogen forms a reserve supply of nutriment in the animal body, and glucose acts as a danger-signal in cases of diabetes.

On the chemical side, the study of the carbohydrate group is of considerable historical interest; for a narrative of it is found to fall naturally into successive chapters and to illustrate in an exceptionally striking manner the influence of new theories and fresh methods upon the progress of chemical science.

In the early days of organic chemistry, the sugars offered the greatest difficulties to investigators. Unguided by any clear ideas of chemical structure, the chemists who attacked the carbohydrate group had to content themselves with purely empirical and descriptive results; and the complexity of the subject must have disappointed many an eager investigator. A glance at the edition of Gmelin's *Handbuch der organischen Chemie* published in the middle of last century will reveal how chaotic the subject must have appeared at that time, even to the most expert. If research had closed at this point, our knowledge would have been confined to a series of facts, most of which seemed to bear little relationship to one another and all of which appeared to lack any power of suggestion for a fresh start. Pure practice had failed to clarify the subject.

Then came the great days of the structural chemistry evolved by Kekulé, and a fresh light was thrown upon the whole field. Baeyer and Zincke were not slow to see the possible applications of constitutional ideas in the sugar group, and more or less modern formulations of the saccharides made their appearance. Almost on the heels of this came van't Hoff's extension of chemical formulæ into three dimensions ; and with that advance the hitherto incomprehensible complexity of the carbohydrate problem began to fade out.

But even with all this, the riddle of the carbohydrates still had difficulties of its own : for the physical character of many members of the group offered resistance to the normal processes of purification ; and the task of disentangling from each other a series of closely-similar materials presented practical stumbling-blocks which even the finest experimental skill could hardly surmount. Fischer's discovery of the phenylhydrazones and osazones was necessary before any real advance could be made. The utilization of phenylhydrazine, coupled with the application of the structural and stereochemical ideas which had come into vogue, produced a complete change in one aspect of the carbohydrate chemistry. In an almost incredibly short period, Fischer carried to a successful conclusion a vast research which ended with the determination of the structure and spatial configurations of all the known pentoses and hexoses. At one sweep, our knowledge of the monosaccharides had been extended, clarified, and consolidated.

With the close of Fischer's activity in this region of organic chemistry, the general interest in the carbohydrate group suffered what was, perhaps, a natural decline. In the special branch which he had attacked but little remained for subsequent investigators ; and there was a quite comprehensible diffidence shown by other researchers in entering the field. Thus, for a time, the subject was studied, if at all, on a scale much more modest than that to which Fischer had accustomed our minds.

The action of enzymes on various sugars was investigated and enzymatic syntheses were worked out; whilst further examination was made of the constitutions of various members of the sugar group. But though much valuable information was thus acquired, the results lacked something which had illuminated the previous period. They formed a mass of valuable data, but behind them there was no single intellect concentrated on a huge problem and seeing it as a whole. Even the scientific mind is capable of appreciating the romantic side of science; and undoubtedly the picture of a single personality mastering a vast region of investigation produces a more definite impression than does the work of a group of independent investigators attacking a problem piecemeal. On the whole, then, this period of sugar chemistry suffered in interest by comparison with the brilliancy of the Fischer era; and for a time it seemed as though the carbohydrates had sunk back into obscurity, so far as the general interest of organic chemists was concerned.

The third period in the history of sugar chemistry opened almost simultaneously with the beginning of the present century. Fischer's researches had cleared up the field of the monosaccharides; but our knowledge of the polysaccharides was left in almost the same condition as it had been before he entered upon the study of the carbohydrates. The new attack was opened by Purdie and his collaborators. It seems desirable to sketch the main outlines of the succeeding campaign in this place, so as to lend some perspective to the details which will be given in later sections.

Like Fischer, the new investigators had armed themselves with a fresh weapon. As phenylhydrazone formation had been the key to the monosaccharides, so methylation was to throw light upon the constitutions of the much more complex carbohydrates. The attack was launched on a modest scale by the preparation of a crystalline tetramethyl-glucose.[1]

The methylation of sundry other members of the sugar group was rapidly taken in hand. Galactose,[2] sucrose, and maltose[3] were subjected to methylation; and in 1906 an extension of the method into a fresh region showed that the new

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[1] Purdie and Irvine, *J.*, 1903, **83**, 1026.

[2] Irvine and Cameron, *J.*, 1904, **85**, 1081.

[3] Purdie and Irvine, *J.*, 1905, **87**, 1025.

process could be applied to determine the structure of the typical natural glucoside, salicin.[1]

In 1910, an entirely fresh field was entered by Denham and Woodhouse,[2] who applied a new method of methylation by means of which they were able to introduce methyl radicles into cellulose. Starch also came within the range of investigation about the same period.

A modification of the new methylation method enabled it to be applied to the preparation of glucosides and methylated glucosides[3]; and the simplification of work in such cases facilitated the constitutional study of sucrose, lactose, maltose, and cellobiose.[4]

The preparation of these numerous methylated carbohydrates, and the identification of the fission-products of the simpler polysaccharides after hydrolysis, represent in themselves a gigantic piece of work; but to see the matter in true perspective it must be borne in mind that all this labour was undertaken merely as a first step towards the solution of the most intricate problems in the carbohydrate field. Stage by stage, the investigation was consolidating the ground for the final attack upon the constitutions of the most complex naturally-occurring carbohydrates. One by one, the structures of the simpler materials were determined; the modes of linking one monosaccharide nucleus to another were established: and it was not until all had been made ready that a real attempt was made to discover the molecular groupings of inulin, cellulose, starch, and glycogen. The research has now entered this ultimate stage; and although at present it is too soon to speak of finality, nevertheless our knowledge of the polysaccharides has grown almost out of recognition within the last few years.

The remainder of this chapter is mainly concerned with the developments produced by the application of methylation in the carbohydrate group. While studying it, the reader may perhaps be inclined to suppose that it represents a record of easy and steady progress along well-defined lines; but it should be borne in mind throughout that in actual practice the carbohydrates

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[1] Irvine and Rose, *J.*, 1906, **89**, 814.

[2] Denham and Woodhouse, *J.*, 1913, **103**, 1735.

[3] Haworth, *J.*, 1915, **107**, 8.

[4] Haworth and Leitch, *J.*, 1918, **113**, 188; 1919, **115**, 809; Haworth and Hirst, *J.*, 1921, **119**, 193.

present the most unexpected difficulties, both in experimental work and in the interpretation of results obtained. Consultation of the original papers will soon remove any false ideas on this subject which might be produced by the simplicity of text-book presentation.

B.—THE PHENOMENA OF MUTAROTATION

When a monosaccharide such as glucose is dissolved in water, the optical rotatory power of the solution gradually alters until at last it reaches a constant value. The final stage can be reached more rapidly, either by heating the solution or by adding some catalyst such as ammonia. This change in the value of the rotatory power is known as mutarotation.

As an explanation of this behaviour, it was suggested [1] that mutarotating sugars exist in isomeric forms which, in solution, gradually change into one another. This explanation was later on supported by definite evidence. For example, when *d*-glucose is recrystallized from alcohol, it melts at 146° C. This form is termed α-glucose. If a concentrated solution of α-glucose be heated for several hours to 105°–106° C. and be then treated with alcohol, a fresh form, β-glucose,* is obtained, which melts at 148°–150° C.†

These two modifications of glucose differ in solubility, the β-form being the more soluble. A more interesting difference comes to light when their rotatory powers are examined.[2]

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[1] Erdmann, *Jahresbericht*, **1855,** 672; **1856,** 639; Dubrunfaut, *Compt. rend.*, 1856, **42,** 739; Bechamp, *ibid.*, 896.

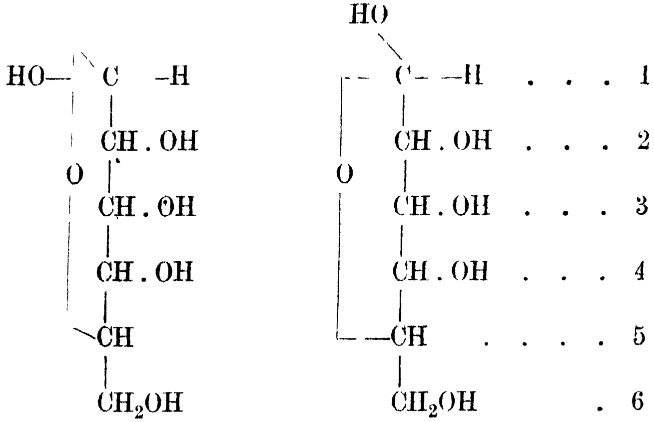
* This substance was originally termed γ-glucose, as the name β-glucose had been given to an equilibrium mixture of α- and β-glucose. On the discovery that this mixture was not an individual, the name β-glucose was transferred to the pure second variety. The term γ-glucose now denotes a peculiar active form of glucose, different from both α- and β-forms.

† Hudson and Dale (*J. Amer. Chem. Soc.*, 1917, **39,** 320) have shown that either of the two forms of glucose can be conveniently obtained by using acetic acid as a crystallizing medium. α-Glucose is prepared by evaporating at ordinary temperature a mixture of two parts sugar, one part water, and four parts of glacial acetic acid. β-Glucose is obtained from a mixture of ten parts of sugar, one part of water, and twelve parts of glacial acetic acid by heating the solution on a boiling water-bath and subsequently allowing crystals to form.

[2] References to the literature of mutarotation are to be found in a paper by Hudson (*J. Amer. Chem. Soc.*, 1910, **32,** 889). See also Baker, Ingold, and Thorpe, *J.*, 1924, **125,** 268; Lowry, *J.*, 1925, **127,** 1371; Lowry and Richards, *ibid.*, 1385.

When 8 per cent. solutions are used, the initial rotatory power of the α-modification is +110°, but, on standing, it gradually falls to +52°. The initial rotatory power of the β-modification is +19°, but it slowly increases, on standing, to +52°. This value, +52°, obviously represents the rotation of a mixture of the two forms after they have come into equilibrium with each other.

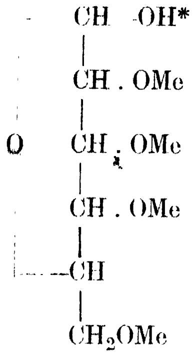
To account for mutarotation, Tollens [1] suggested that sugar structures contain an oxide ring, which would bring into existence two fresh stereoisomeric forms of the sugar. The formulæ below represent the spatial arrangements round the terminal atom of the sugar chain in the two cases.



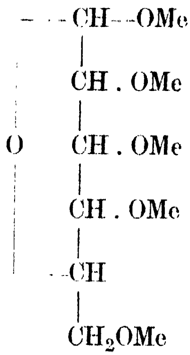
Support was lent to this hypothesis by the discovery that the alkyl glucosides occur in two stereoisomeric forms, which can be represented by replacing the hydroxyl groups attached to the carbon atoms (1) in the above formulæ by methoxyl radicles. A further proof of the correctness of Tollens' views is found in the behaviour of the methylated sugars and their glucosides. Tetramethyl-glucose exhibits mutarotation, whereas the corresponding tetramethyl-derivatives of the methylglucosides are devoid of mutarotatory power.[2]

[1] Tollens, *Ber.*, 1883, **16**, 923.

[2] Purdie and Irvine, *J.*, 1904, **85**, 1049.



Tetramethyl-glucose.



Tetramethyl-methylglucoside.

As can be seen from these formulæ, the methylglucoside has no power of structural alteration, since it is completely methylated; whereas in tetramethyl-glucose the hydrogen atom marked with the asterisk might be assumed to wander and thus produce a new oxide-ring having a stereochemical position different from the original one.

If still further proof is needed in favour of the presence of an oxide-ring, it is to be found in the results of methylation; but as these will be discussed in detail in later sections of this chapter, it is unnecessary to go into the matter at this point.

The existence of an oxide-ring of some sort in the sugar structures is now generally admitted. But this by no means disposes of the problem, since the question at once presents itself: what is the nature of the ring? Since glucose, for example, contains five hydroxyl groups, each of which—theoretically—might play its part in the formation of an oxide-ring, it is evident that further evidence will be required in order to assign a definite ring-structure to the substance.

Very brief consideration will show how difficult is the problem thus presented to the chemist. In the first place, the ease with which mutarotation occurs, and the readiness with which the sugars react in the open-chain aldehydic form with phenylhydrazine and other similar reagents, are sufficient to prove that the oxide-ring is anything but a stable grouping. Under the action of even the mildest reagents a structural or stereochemical rearrangement may occur which may change the number of atoms in the ring or alter the spatial configuration of the molecule. Thus, even among the monosaccharides, it is difficult to gain absolute certainty as to the cyclic grouping, and in the polysaccharides this difficulty is increased. During the action of hydrolytic agents, the original ring-structure may be ruptured and a fresh type of ring may present itself in the constitution of the fission-products, so that a study of their architecture might lead to completely erroneous inferences with regard to the type of ring present in the parent molecule.

In order to avoid this pitfall, it is obviously essential to put out of action all the hydroxyl groups in the carbohydrate molecule which might serve as centres for the formation of an oxide-ring different from that which is normally present. Various methods might be suggested, such as acetylation or benzoylation; but the drawbacks of such solutions of the problem are self-evident in the case of the polysaccharides. In this group, information can be gained only by splitting up the molecule by hydrolysis; and in the presence of hydrolytic agents there would be no guarantee that acetyl or benzoyl groups would remain *in situ.** What is required, evidently, is some substituent which will resist hydrolysis and will not migrate during hydrolytic reactions. Since this desideratum has been discovered in the methyl radicle, the methylation of the hydroxyl groups has become a process of fundamental importance in the study of carbohydrate constitution.

C.—The Alkylation of the Carbohydrates

Before describing the practical methods employed in the alkylation of the carbohydrates, a typical example may be chosen in order to show the rationale of the processes employed; and for this purpose the stages leading up to the complete methylation of glucose may be selected. These are indicated in the following scheme[1]:—

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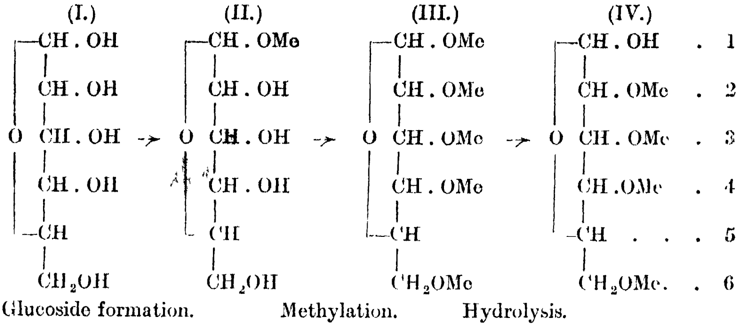
* For examples of the migration of acetyl groups in the acetylated rhamnoses, see Fischer, Bergmann, and Rabe, *Ber.*, 1920, **53**, 2362. Compare also the kindred phenomena in the depside series which are described in Chapter VIII.

[1] Irvine, *J.*, 1923, **123**, 988.



The first stage is the formation of the methylglucoside in which the reducing group of the sugar is protected by the new methyl radicle. In the next stage, the methylating agent attacks the remaining hydroxyl groups of the molecule, the process culminating in the formation of the tetramethyl-methylglucoside (III.). When this is subjected to acid hydrolysis, the only methyl group removed is that related to the original reducing group of the sugar, so that the tetramethyl-derivative (IV.) is produced. This substance, as the formula shows, has four hydroxyl groups (in the 2 : 3 : 4 : 6-positions) masked by the alkyl radicles, and it is thus possible to study the properties of the reducing group in position 1 in the absence of many factors which might normally complicate the problem.

Further consideration will show that if a sugar derivative contains any group or groups capable of subsequent removal by hydrolysis, it is possible to methylate the unoccupied hydroxyl radicles and ultimately to obtain identifiable partly-methylated sugars. Thus the method of alkylation leads ultimately to an exact knowledge of the constitution of the compound subjected to methylation; but in order to make the identification it is essential to have a whole series of known reference-compounds in the form of more or less completely alkylated simple sugars. The preparation and identification of these substances occupied one of the longest and most laborious sections of the new attack on the carbohydrate constitutions.

We must now turn to the practical methods which have been devised in order to introduce alkyl groups into the carbohydrate molecules.

The pioneers in this branch of the subject were Purdie and

Irvine,[1] who showed that sugars and glucosides would be alkylated by acting on them with alkyl iodides and dry silver oxide, a process generally termed for convenience "the silver oxide method." Since silver oxide has an oxidizing action on the reducing group of some sugars, it is usual to prepare the methylglucoside and utilize it for methylation, instead of the sugar itself.* In this case, methylation is initially conducted in methyl alcohol solution. When several alkyl groups have been introduced into the sugar, the new derivative is soluble in methyl iodide, and thus the presence of methyl alcohol is no longer necessary.

The silver oxide method has the disadvantages that it is applicable only to carbohydrates for which a suitable solvent can be found; also that there is always a risk of the sugar being oxidized by the silver oxide; and finally, that the reagents are expensive. On the other hand, owing to the mild conditions under which methylation proceeds, no profound alterations in the constitution of the sugars need be feared when this method is employed. Racemizations, Walden inversions, or glucosidal interconversions do not complicate the problem. Thus the silver oxide method has furnished a safe means of preparing a large number of standard alkylated sugars which serve as comparison materials when other methylation methods, more violent in action, are employed.

A fresh reagent for the methylation of the carbohydrates was discovered ten years later by Denham and Woodhouse.[2] They were engaged in an attempt to methylate cellulose; and since the insolubility of this material in normal solvents stood in the way of an application of the silver-oxide method, they tried the effect of methyl sulphate. By impregnating cellulose with a 15 per cent. solution of sodium hydroxide and then treating the material with methyl sulphate, they readily obtained methyl-derivatives of cellulose.

Two years later, Haworth[3] showed that methyl sulphate

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[1] Purdie and Irvine, *J.*, 1903, **83**, 1021; 1904, **85**, 1049; Irvine and Cameron, *ibid.*, 1071.

* The methylglucosides, being more soluble in organic media than the parent sugars, are on this account better fitted for use in the silver oxide method of alkylation.

[2] Denham and Woodhouse, *J.*, 1913, **103**, 1735.

[3] Haworth, *J.*, 1915, **107**, 8.

could be utilized very simply for the alkylation of less complex carbohydrates. The sugar, such as sucrose, was dissolved in a minimum quantity of water and the solution was introduced into a flask furnished with a condenser and two tap-funnels which contained respectively methyl sulphate and a 30 per cent. sodium hydroxide solution. The flask was placed on a water-bath maintained at 30°–40° C. and the reagents were run in from the tap-funnels with constant stirring, the temperature being raised to 70° C. in the later stages. The methylated sugar is extracted by means of chloroform, after any excess methyl sulphate has been destroyed; and the final purification is attained by vacuum distillation at low pressure. Haworth's method has the advantage that it proceeds in definite stages; so that homogeneous products, representing the intermediate steps in the alkylation process, can be isolated. Thus the production of mixtures of unchanged and partly-alkylated materials, which are found in using the silver oxide method, is avoided; and consequently the final purification of the end-product is simpler.

Yet another method of alkylation has been rendered possible by Werner's discovery that diazomethane can be easily obtained from nitroso-methylurea; and that alkylation by means of this reagent can be carried out in alcoholic solution.[1] The substance to be alkylated is dissolved in dry alcohol along with a small excess of nitroso-methylurea. Sodium ethoxide is added; and the diazomethane thus liberated, immediately attacks the hydroxyl groups. Diazomethane is especially suitable for the methylation of phenolic groups in certain glucosides.[2]

D.—THE OXIDE-RINGS IN THE SUGAR

1. *General*

As was mentioned in a previous section, the existence of an oxide-ring in the sugar molecule was suggested in order to account for the phenomena of mutarotation.[I] At a later stage, Fischer's preparation of two isomeric methylglucosides[II] and the isolation of glucose itself in isomeric forms furnished further

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[1] E. A. Werner, *J.*, 1919, **115**, 1093.

[2] Herzig and Schönbach, *Monatsh.*, 1912, **33**, 673.

support to the idea. Another branch of the evidence came to light when Purdie and Irvine[1] showed that the methylation of either methylglucoside yielded two isomeric tetramethyl-glucosides which on hydrolysis gave the same tetramethyl-glucose; and that from this tetramethyl-glucose the two original tetramethyl-glucosides could be obtained by ordinary glucoside formation. Though the evidence in favour of a ring-structure is by no means conclusive, it has been sufficient to satisfy most experts; and since in cyclic anhydrides and lactones a five-membered grouping is found to be the most stable type, the oxide-ring of the sugars was tacitly assumed to contain four carbon atoms and one oxygen atom.

In his original work on the methylglucosides, Fischer[2] obtained three products. Two of these he regarded as stereoisomeric compounds, giving them the names of α- and β-methylglucosides. The third substance, being difficult to purify, was not closely investigated; but Fischer assumed that it was glucose dimethyl-acetal. In 1914, however, Nef[3] put forward the view that the two methylglucosides were structural isomers and not stereoisomeric compounds; and thus the problem of the nature of the oxide-ring was raised in an acute form, since if the glucosides were structural isomers the oxide-rings in the two compounds must be different from each other.

Fischer[4] in his reply was able to show that the α- and β-glucosides were structurally identical; but being thus led to a re-examination of the supposed glucose dimethyl-acetal, he was forced to conclude that it also was a methylglucoside, to which he gave the name γ-methylglucoside.* This discovery of Fischer's was sufficient to establish that more than one kind of oxide-ring was possible in the sugar group; for the difference between the γ-glucoside and the other two must be a structural one, since the two stereochemical possibilities have already been utilized to account for the existence of the α- and β-glucosides. But if two types of ring were possible, there was no guarantee

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[1] Purdie and Irvine, *J.*, 1904, **85**, 1059.

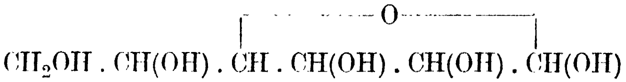
[2] Fischer, *Ber.*, 1893, **26**, 2405; 1895, **28**, 1151, 1434.

[3] Nef, *Annalen*, 1914, **403**, 204.

[4] Fischer, *Ber.*, 1914, **47**, 1980.

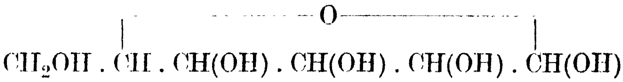
* It should be noted that Fischer used the prefix γ- as a mere convenient symbol and that he did not mean to imply that the prefix had the same significance which it bears in, for instance, γ-lactone.

that the normal type was a five-membered structure; and so the whole problem had to be approached from a fresh direction. In the group of aldoses, the two most probable structures appeared to be the five-membered butylene-oxide type and the six-membered amylene-oxide structure:



$$CH_2OH\,.\,CH(OH)\,.\,CH\,.\,CH(OH)\,.\,CH(OH)\,.\,CH(OH)$$

Butylene-oxide structure.



$$CH_2OH\,.\,CH\,.\,CH(OH)\,.\,CH(OH)\,.\,CH(OH)\,.\,CH(OH)$$

Amylene-oxide structure.

and it was at this point that the investigators reaped some of the fruits of the laborious work undertaken in the original preparation of the methylated sugars.

In dealing with sensitive materials like the carbohydrates, the possibility of isomeric change cannot be left out of account in considering the results of oxidation reactions; and the advantage of methylated sugars over other derivatives is to be found in the fact that the former can be oxidized without any change occurring in the relative positions of the various alkyl groups.[1] Thus the final products give a definite clue to the original grouping of the molecule.

2. *Rhamnose*

In order to make the method clear, the case of rhamnose[2] will be chosen, since it is free from complexities which arise in some other cases owing to mixtures being formed on methylation. When methylated by several different methods, rhamnose is invariably found to give on hydrolysis a single trimethyl-

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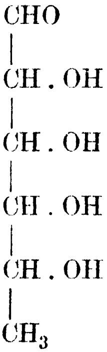
[1] Irvine, Fyfe, and Hogg, *J.*, 1915, **107**, 539; Irvine and Oldham, *J.*, 1921, **119**, 1744; Pryde, *J.*, 1923, **123**, 1808; Haworth and Baker, *J.*, 1925, **127**, 365; Levene, *J. Biol. Chem.*, 1924, **60**, 167.

[2] Hirst and Macbeth, *J.*, 1926, **129**, 22.

derivative. A glance at the rhamnose formula (written in the open-chain way to avoid any prejudice about the position of the ring) will show that a number of choices can be made for the positions of the three methoxy-groups :

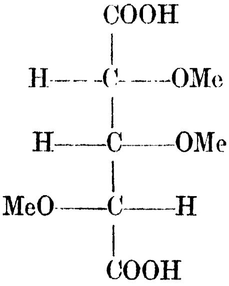


$$\begin{array}{l} CHO \\ | \\ CH\,.\,OH \\ | \\ CH\,.\,OH \\ | \\ CH\,.\,OH \\ | \\ CH\,.\,OH \\ | \\ CH_3 \end{array}$$

Rhamnose.

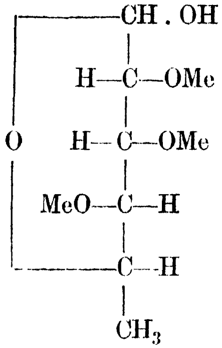
The hydroxyl group which is unattacked by methylation is obviously the one which has lost its hydrogen atom in order to form the cyclic chain of the oxide-ring ; and thus if the positions of the three methoxy-radicles can be ascertained, the point of attachment of the oxide-ring is also established.

Now on oxidation with nitric acid, trimethyl-rhamnose yields *l*-arabo-trimethoxy-glutaric acid, the space formula of which is :

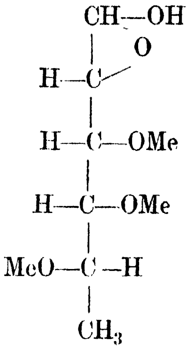


$$\begin{array}{rcl} & COOH & \\ & | & \\ H- & C & -OMe \\ & | & \\ H- & C & -OMe \\ & | & \\ MeO- & C & -H \\ & | & \\ & COOH & \end{array}$$

This result proves beyond doubt that the three methoxy-groups in trimethyl-rhamnose lie on three directly-connected carbon atoms. But this limits the possible formulæ of trimethyl-rhamnose to the two which are shown below :

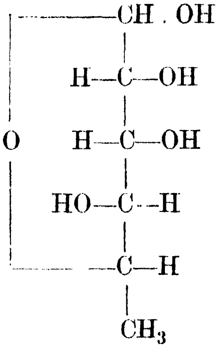


Trimethyl-rhamnose.



Alternative formula.

The choice thus lies between an ethylene-oxide ring and an amylene-oxide grouping; and on stereochemical and other grounds the amylene-oxide arrangement appears to be the only probable one. The formula of rhamnose itself must therefore be that shown below.



Rhamnose.

This example brings out clearly the value of sugar-methlyation in problems of this type. In a similar manner it was proved that the pentoses xylose and arabinose also contain the amylene-oxide structure.[1]

3. *The Glucoses*

At first sight, the structure of glucose appears to present a problem of much greater difficulty than that of the rhamnose constitution. In 1925, an amylene-oxide ring structure for the

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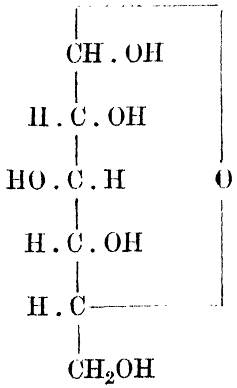
[1] Hirst and Purves, *J.*, 1923, **123**, 1352; Hirst and Robertson, *J.*, 1925, **127**, 358.

glucose molecule was suggested[1]; and evidence in favour of this view[2] was found in the work of Hudson. This investigator[3] had shown, from an examination of two dozen lactones derived from the polyhydroxy-acids of the sugars, that a striking parallelism could be traced between the sign of rotation of the lactone and the position of the lactone ring assuming that ring-formation took place through the γ-carbon atom of the chain. No exceptions to the Hudson Rule have yet been detected. On the other hand, if the lactone ring were formed through the α-, β-, or δ-atom of the sugar chain, Hudson's Rule should fail in 8, 10, and 12 cases respectively out of the twenty-four. By applying the Hudson Rule to the case of the lactone derived from tetramethyl-glucose, Charlton, Haworth, and Peat came to the conclusion that glucose must contain the amylene-oxide ring; so that the glucose molecule should have the structure:



Glucose.

Strong evidence in favour of the amylene-oxide structure has been contributed by the study of the oxidation-products of tetramethyl-glucose. On methylation, glucose yields a tetramethyl derivative. If an amylene-oxide ring exists in the glucose structure, then this tetra-methyl derivative must be the 2 : 3 : 4 : 6 compound shown in formula (I.); whereas if a butylene-oxide ring is present, the tetramethyl-derivative will be the 2 : 3 : 5 : 6 compound shown in (II.).

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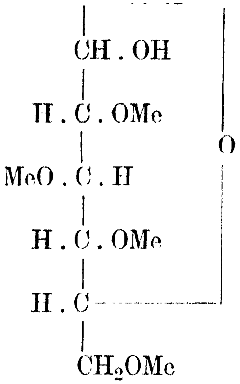
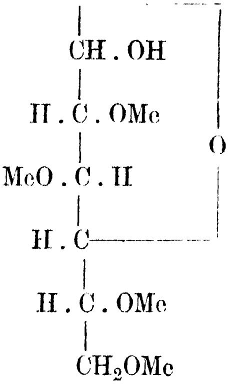
[1] Haworth, *Nature*, 1925, **116**, 430.

[2] Charlton, Haworth, and Peat, *J.*, 1926, **129**, 89.

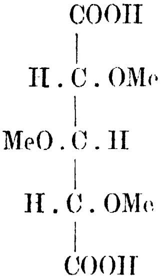
[3] Hudson, *J. Amer. Chem. Soc.*, 1910, **32**, 338.



(I.)

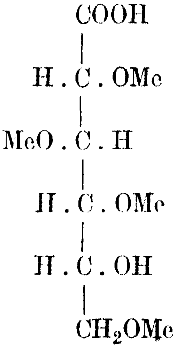


(II.)



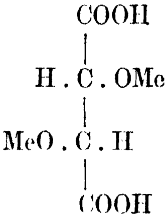
$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{MeO\,.\,C\,.\,H} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{COOH} \end{array}$$

(III.)



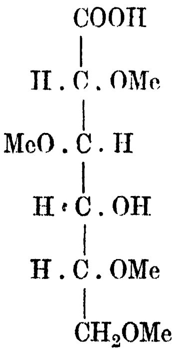
$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{MeO\,.\,C\,.\,H} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{H\,.\,C\,.\,OH} \\ | \\ \mathrm{CH_2OMe} \end{array}$$

(IV.)



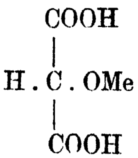
$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{MeO\,.\,C\,.\,H} \\ | \\ \mathrm{COOH} \end{array}$$

(V.)



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{MeO\,.\,C\,.\,H} \\ | \\ \mathrm{H\,.\,C\,.\,OH} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{CH_2OMe} \end{array}$$

(VI.)

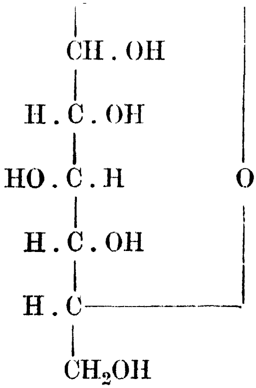


$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H\,.\,C\,.\,OMe} \\ | \\ \mathrm{COOH} \end{array}$$

(VII.)

If the amylene-oxide ring be present in the molecule, the first result of oxidation would be the production of the tetramethyl-gluconic acid (IV.). Thereafter, *d*-dimethoxy-succinic acid (V.) would be formed if the break took place between the fourth and fifth atoms of the chain, or else the product would be inactive xylo-trimethoxy-glutaric acid (III.), if rupture occurred between the fifth and sixth atoms of the chain. If the butylene-oxide ring be present, on the other hand, the first product would be the tetramethyl-gluconic acid shown in (VI.). On further oxidation, this might yield methoxy-malonic acid (VII.) and also the same dimethoxy-succinic acid (V.) as would be obtained from the amylene-oxide structure. From this it is evident that the presence or absence of the xylo-trimethoxy-glutaric acid (III.) is the crucial test in deciding between the two possible ring-structures.

This field has been investigated by Hirst,[1] who detected xylo-trimethoxy-gluconic acid among the oxidation products; and by means of the reasoning already given, he was able to establish definitely that the true formula of glucose is:



Glucose.

The foregoing examples will suffice to illustrate the methods by which the presence of the amylene-oxide ring has been established in the cases of certain normal sugars. It will be remembered, however, that the existence of a third methylglucoside suggests the probability that more than one type of ring-structure

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[1] Hirst, *J.*, 1926, **129**, 350.

is possible in the sugar molecule; and this idea gains further support from the readiness with which sucrose and other fructosides are hydrolysed, for their lability suggests that they are constituted differently from the normal type.

Irvine, Fyfe, and Hogg, simultaneously with Fischer,[1] discovered the existence of the third methylglucoside, which they isolated in the course of an attempt to prepare glucosamine from glucose; and their investigations of it carried our knowledge considerably further. Fischer[2] observed that the γ-methylglucoside differed from the α- and β-forms in its indifference to emulsin, as well as in its extraordinary sensitiveness towards acids. Irvine, Fyfe, and Hogg found that in addition to these properties, the γ-glucoside is characterised by (1) the remarkable ease with which it enters into condensation with acetone; (2) its capacity of reducing alkaline potassium permanganate, which is so striking as to suggest unsaturation; (3) its tendency to unite with one atomic proportion of oxygen to give a neutral product; and (4) the ready auto-condensation of this oxy-compound to give a product allied to the disaccharides. These properties were practically unique in the sugar group.

Irvine, Fyfe, and Hogg, on methylating this γ-methylglucoside by means of silver oxide, obtained a tetramethyl-γ-methylglucoside which was found to differ completely in properties from the methylation-products of the α- and β-methylglucosides. It reduced permanganate instantaneously in the cold and was readily hydrolysed by hydrochloric acid in conditions which leave the α- and β-forms intact. The hydrolysis product is a tetramethylated hexose, termed tetramethyl-γ-glucose, which is a liquid, instead of being solid like the normal tetramethyl-glucose obtained from either the α- or the β-methylglucoside.

The reaction with permanganate suggests the possibility that the γ-methylglucoside contains an unsaturated linking and might therefore be allied to glucal, for which Fischer[3] had proposed the following formula:

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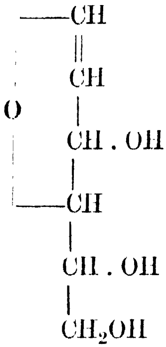
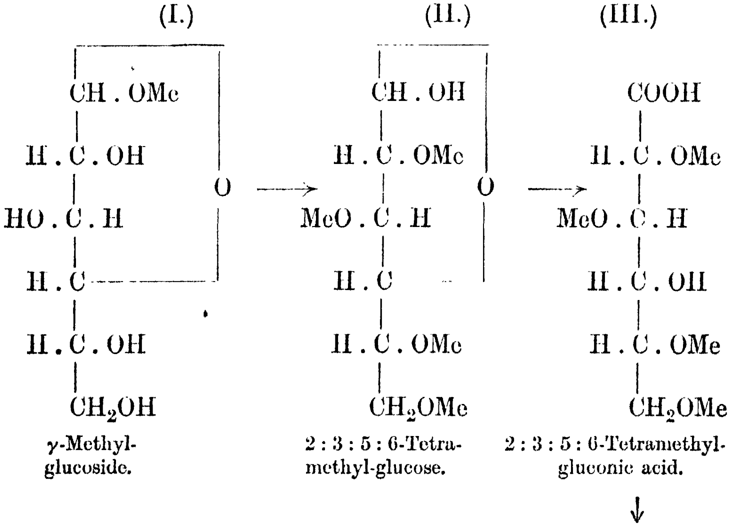
[1] Irvine, Fyfe, and Hogg, *J.*, 1915, **107**, 524.
[2] Fischer, *Ber.*, 1914, **47**, 1980.
[3] Fischer, *Ber.*, 1914, **47**, 196.



Glucal.

The most convincing evidence on the point is the following.[1] When γ-methylglucoside (I.) is methylated and then hydrolysed, it yields 2 : 3 : 5 : 6-tetramethyl-glucose (II.). Oxidation of this with bromine water gives 2 : 3 : 5 : 6-tetramethyl-gluconic acid (III.). The lactone of this (IV.), when digested with hot nitric acid, is oxidised to oxalic acid and *d*-dimethyl-tartaric acid (V.).



(I.) γ-Methyl-glucoside.

(II.) 2 : 3 : 5 : 6-Tetra-methyl-glucose.

(III.) 2 : 3 : 5 : 6-Tetramethyl-gluconic acid.

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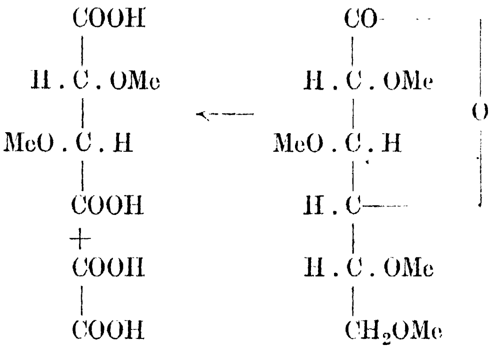
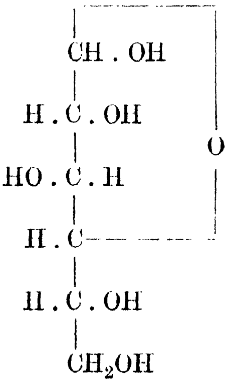
[1] Haworth, Hirst, and Miller, *J.*, 1927, 2436; Haworth, *Constitution of Sugars* (1929), p. 42.

(V.) (IV.)



As there is no doubt about the structure [1] of the lactone (IV.) it is easy to work backwards to the structure of γ-glucose itself, which can be inferred from that of the γ-methylglucoside (I.). On this evidence, γ-glucose must have the structure shown below.



γ-Glucose.

4. *The Fructoses*

Since fructose is associated with glucose in the sucrose molecule, it seemed advisable to determine whether fructose also was capable of existing in a labile form, as this would open

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[1] Haworth, *Constitution of Sugars* (1929), p. 19.

the way to the investigation of the sucrose structure. The results obtained in this field by Irvine and Robertson[1] were of unexpected complexity. Clear evidence was obtained that fructose reacts in two forms. (1) A compound containing a normal oxide-ring and existing in two modifications termed the α- and β-forms. On methylation each of these gives rise to a tetramethyl-fructoside which may be hydrolysed to a tetramethyl-fructose. These, like the parent sugar, are lævo-rotatory and may be supposed to have the same type of oxide-ring. This fructose type is not attacked by permanganate, should not combine readily with acetone, and should give rise to stable fructosides. It is represented by the ordinary crystalline form of fructose. (2) A more reactive compound, now known as γ-fructose. This variety of fructose is highly reactive, combines readily with acetone, and reduces permanganate solution. Fructosides derived from this type of fructose are hydrolysed by acids in low concentrations.

The views of Irvine and Robertson received strong support from other facts discovered at a later stage.[2] It is well known to every chemist that when dextro-rotatory cane-sugar (sucrose) is hydrolysed with dilute acids, the resulting mixture of glucose and fructose is lævo-rotatory, whence is derived the term "inversion" to describe the process. The origin of the change in rotatory power is found in the fact that the dextro-rotatory sucrose molecule is split up into a dextro-rotatory glucose molecule and a lævo-rotatory fructose molecule of much higher rotatory power. The result of this is that the mixture possesses lævo-rotation. Now when sucrose is methylated and hydrolysed, the octamethyl-sucrose splits up into tetramethyl-glucose and tetramethyl-fructose; but *no inversion of the sign of the rotatory power is observed.* This apparent anomaly is due to the fact that the methylated fructose residue differs from ordinary fructose in being strongly dextro-rotatory instead of showing lævo-rotation. This furnishes conclusive proof that the fructose molecule is capable of existing in two different forms. As combined in the sucrose molecule, it is in the γ-form; and during the inversion of sugar it reverts to the normal stable fructose type. If this intramolecular rearrangement is pre-

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[1] Irvine and Robertson, *J.*, 1916, **109**, 1305.

[2] Haworth and Law, *J.*, 1916, **109**, 1314.

vented by methylation, which locks the molecular structure, then the product of inversion is the tetramethyl-derivative of the γ-form and not a derivative of the normal form. This conception of the matter is reinforced by the fact that tetramethyl-fructose[1] derived from the methylation of methyl-fructoside differs greatly in physical and chemical character from the tetramethyl-fructose obtained from octamethyl-sucrose. The former compound is stable towards permanganate, the sucrose product is unstable in presence of permanganate; and the two substances present the contrast in rotatory power which was referred to above.

Fructose, then, exists in two structurally different forms. With regard to the normal variety, the following evidence throws light on the constitution.

Fructose yields two methyl-fructosides, which are designated as α- and β-methyl-fructoside.[2] Methylation[3] of β-methyl-fructoside (I.) yields 1 : 3 : 4 : 5-tetramethyl-fructose (II.). Since there is no reducing group in the terminal position, this substance might be expected to be more stable than corresponding compounds derived from the aldoses; and in practice it is found that bromine water has very slight effect on the methylated fructoside. Digestion with nitric acid,[4] however, leads to oxidation of the $-CH_2OMe$ group, with the production of trimethyl-fructuronic acid (III.). (Arabo-trimethoxy-glutaric acid is formed as a by-product in this reaction.) When trimethyl-fructuronic acid is oxidized with acidified permanganate it yields *d*-2 : 3 : 4-trimethyl-δ-arabonolactone (IV.), which proves to be an optical enantiomorph of the product obtained by the action of bromine water upon *l*-trimethyl-arabinose. Further oxidation converts (III.) into *d*-arabo-trimethoxy-glutaric acid (V.), which is the optical antipode of the compound obtained by oxidation of *l*-trimethyl-arabinose.

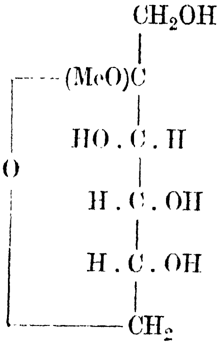
[1] Purdie and Paul, *J.*, 1907, **91**, 296.

[2] Hudson, *J. Amer. Chem. Soc.*, 1916, **38**, 1216.

[3] Purdie and Paul, *J.*, 1907, **91**, 289; Steele, *J.*, 1918, 257.

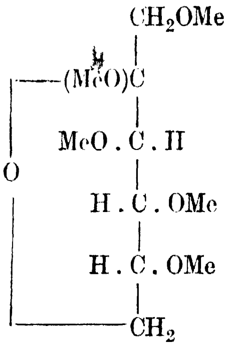
[4] Haworth and Hirst, *J.*, 1926, 1858; Haworth, Hirst, and Learner, *J.*, 1927, 1040; Haworth, *Constitution of Sugars* (1929), p. 34.

(I.)



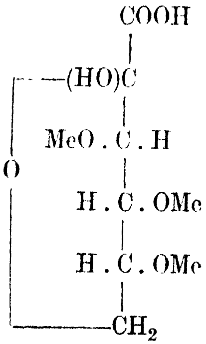
Normal β-methyl-fructoside.

(II.)



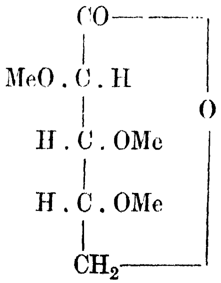
1 : 3 : 4 : 5-tetramethyl-fructose.

(III.)



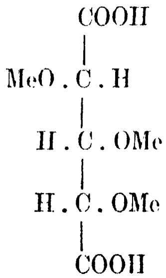
Trimethyl-
fructuronic acid.

(IV.)



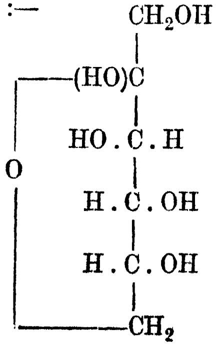
d-2 : 3 : 4-Trimethyl-
δ-arabonolactone.

(V.)



d-Arabo-trimethoxy-
glutaric acid.

These results seem to leave no doubt that normal fructose has the following structure :—

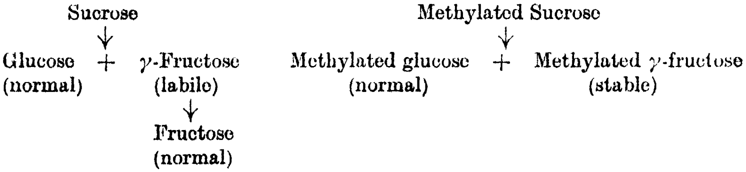


E.—The Disaccharides

1. *Sucrose*

As most first-year students know, the hydrolysis of cane sugar yields a mixture of glucose and normal fructose; from which evidence it seems a simple matter to infer the constitution of the disaccharide. Further investigation, however, proved that matters were not quite so simple as they appeared.

Methylation of sucrose produces octamethyl-sucrose; and when this is hydrolysed, it yields a mixture of methylated glucose and methylated fructose. The octamethyl-sucrose has a rotation $[\alpha]_D = +66{\cdot}5^\circ$, whilst the mixture after hydrolysis has $[\alpha]_D = 56{\cdot}5^\circ$; so that there is no change of sign as a consequence of the hydrolysis, and the case is not similar to the production of ordinary invert sugar from sucrose. To account for these phenomena, Haworth and Law [1] suggested that in the sucrose molecule, the fructose fragment exists in the γ-structure, but that when sucrose is hydrolysed, the liberated fructose reverts to the normal constitution. In the case of the methylated sucrose, however, the liberated fructose cannot change its structure owing to the presence of the methyl groups, and hence the substance produced by hydrolysis in this instance is a methylated γ-fructose and not a methyl derivative of normal fructose.



This idea received confirmation from further investigations by Haworth,[2] who isolated the pure methylated fructose fragment from the hydrolysis products of octamethyl-sucrose, and proved that it was a tetramethyl-fructose with properties different from those of the tetramethyl-derivative obtained from normal fructose.

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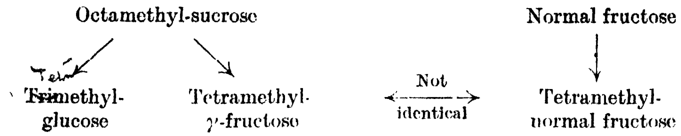
[1] Haworth and Law, *J.*, 1916, **109**, 1314.

[2] Haworth, *J.*, 1920, **117**, 199.



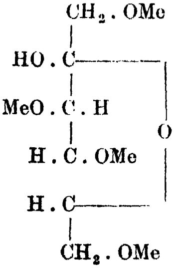
Evidently, in order to establish the constitution of sucrose, it is essential to determine the structure of tetramethyl-γ-fructose. This was achieved in the following manner.[1]

Sucrose was methylated and hydrolysed. The tetramethyl-γ-fructose (I.) thus obtained was treated with nitric acid, whereby a terminal group was oxidised, with the loss of a methoxyl radicle. The resulting trimethyl-fructuronic acid (II.) reduced Fehling's solution; but when the reducing group was protected by methylation, the reducing power vanished.

When the trimethyl-fructuronic acid (II.) was treated with permanganate and dilute sulphuric acid, it yielded 2 : 3 : 5-trimethyl-*d*-arabonolactone (III.), which had a rotation equal in magnitude but opposite in sign to that of the lævo-variety, which had previously been isolated from *l*-trimethyl-γ-arabinose. Further oxidation with nitric acid converted the lactone from sucrose into *l*-dimethyl-tartaric acid (IV.).

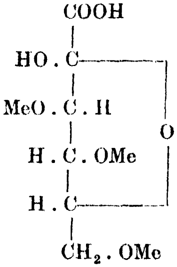
The only manner in which these results can be fitted together satisfactorily is shown in the following formulæ :—

(I.)



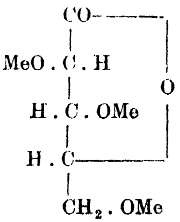
1 : 3 : 4 : 6-Tetramethyl-fructose.

(II.)



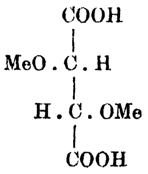
Trimethyl-fructuronic acid.

(III.)



d-2 : 3 : 5-Trimethyl-γ-arabonolactone.

(IV.)

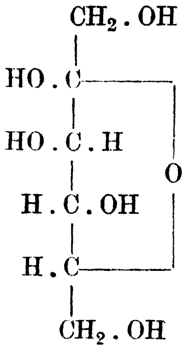


l-Dimethyl-tartaric acid.

---

[1] Haworth, Hirst and Nicholson, *J.*, 1927, 1513; Avery, Haworth and Hirst, *ibid.*, 2308; Haworth, Hirst and Learner, *ibid.*, 2432.

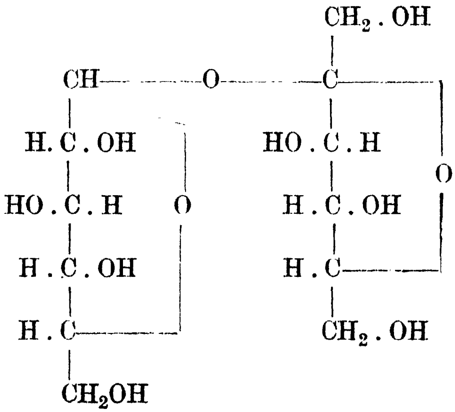
This establishes the following constitution of γ-fructose :—



γ-Fructose

And now, since the glucose fragment of sucrose is a normal glucose, it is possible to link up the normal glucose and γ-fructose portions in the following manner, through the unmethylated group in the formula (I.) above, so as to form the complete sucrose molecule :—

Sucrose



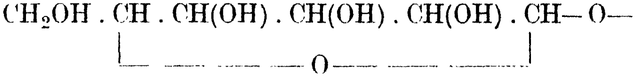
Normal glucose fragment. γ-Fructose fragment.

As has already been pointed out, when sucrose undergoes hydrolysis, the labile γ-fructose thus liberated is immediately transformed into the stable variety of fructose.

2. *Maltose*

When treated with dilute acids, the disaccharide maltose yields glucose exclusively as a hydrolysis product. It must, therefore, be built up from two glucose molecules; and the main point of interest lies in the determination of the manner in which the two monose molecules are united. But the importance of the maltose constitution ranges far beyond the structure of a single compound. The fact that diastase breaks down the starch molecule with the liberation of maltose is sufficient to indicate the prominence which the maltose structure attains in the chemistry of the higher carbohydrates.

For reasons which have already been given in connection with other sugars, it would be useless to attack the maltose problem through maltose itself, since during the hydrolytic degradation reactions there might be changes in the structures of the two glucose nuclei. As in other cases, methylation is the best available method of preventing such alterations, and this was first utilized by Purdie and Irvine[1] early in this century. Unfortunately, the action of silver oxide proved to be more complicated than had been hoped, since oxidation occurred at the reducing group of the sugar; yet one decisive result was attained. Crystalline tetramethyl-glucose was isolated from the reaction-products; and this revealed the structure of one-half of the maltose molecule to be the following, if the amylene-oxide formula for glucose be adopted:



$$CH_2OH\,.\,\underbrace{CH\,.\,CH(OH)\,.\,CH(OH)\,.\,CH(OH)\,.\,CH}_{O}—O—$$

The non-reducing glucose residue of Maltose.

A second attack on the problem was made later on by Irvine and Dick,[2] by means of complete methylation of methylmaltoside and an identification of the hydrolytic fission products; but it also met with unexpected obstacles, since the preparation of methylmaltoside, by the method employed, was found to involve the degradation of the sugar so that a methylated pentose appeared among the reaction-products.

A third attempt to solve the problem was made by Haworth and Leitch,[3] who applied the methyl-sulphate method to maltose in two stages, the first step being intended to convert maltose into methylmaltoside which was to be completely methylated

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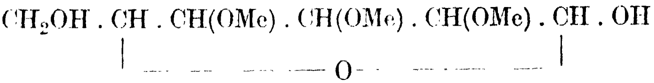
[1] Purdie and Irvine, *J.*, 1905, **87**, 1022.

[2] Irvine and Dick, *J.*, 1919, **115**, 593.

[3] Haworth and Leitch, *J.*, 1919, **115**, 809.

in the second application of the reagent. The methylated methylmaltoside was then hydrolysed, and two methylated glucoses were identified in the products, one being tetramethylglucose. The new point of interest was reached when it was found that the second product was a trimethyl-glucose ; and since this must be the key to the structure of the second half of the maltose molecule, its nature is of vital importance.

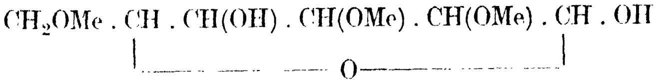
The sugar isolated by Haworth and Leitch was a syrup and was believed by them to be the liquid trimethyl-glucose in which the terminal $-CH_2OH$ group is unsubstituted. Adopting the amylene-oxide structure, such a substance has the formula



$$\mathrm{CH_2OH\,.\,\underbrace{CH\,.\,CH(OMe)\,.\,CH(OMe)\,.\,CH(OMe)\,.\,CH}_{O}\,.\,OH}$$

Implicit in this formulation is the conception that the two hexose nuclei in maltose are united through a terminal alcohol group ; since only such groups are available for the purpose, owing to the remainder being blocked by methyl radicles.

The foregoing view of the trimethyl-glucose isolated from maltose could not, however, be reconciled with the results obtained in the methylation of starch and glycogen, which will be dealt with presently ; and at a later date it was shown by Irvine and Black [1] (and independently by Cooper, Haworth, and Peat [2]) that this trimethyl-glucose is not 2 : 3 : 4-trimethylglucose (as had been assumed) but instead was 2 : 3 : 6-trimethyl-glucose :



$$\mathrm{CH_2OMe\,.\,\underbrace{CH\,.\,CH(OH)\,.\,CH(OMe)\,.\,CH(OMe)\,.\,CH}_{O}\,.\,OH}$$

At first sight, this correction may appear to settle the problem of the maltose structure, since apparently we have now a knowledge of both halves of the maltose molecule. Confidence in this view must be shaken, however, when it is recalled that the number of diglucoses which can qualify for this mode of linkage is much greater than the stereochemical possibilities will permit. Thus the enigma of the maltose constitution apparently remains as insoluble as before.

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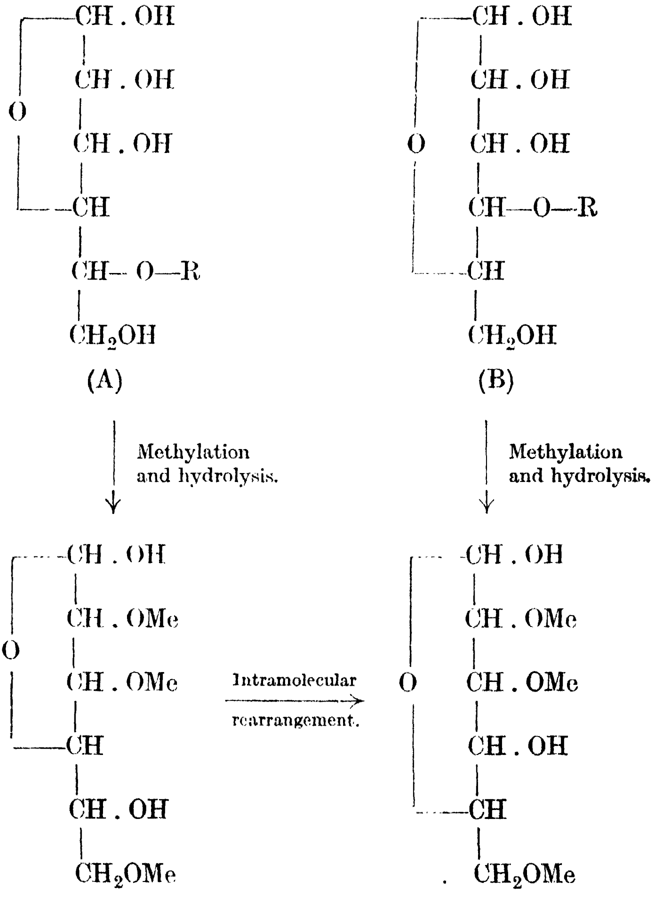
[1] Irvine and Black, *J.*, 1926, **129**, 862.

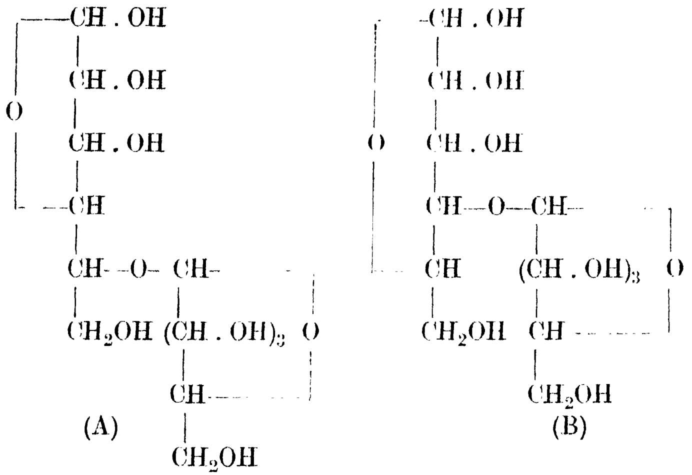
[2] Cooper, Haworth, and Peat, *J.*, 1926, **129**, 876.

Irvine and Black have pointed out a possible explanation of the phenomena. Suppose that two disaccharides had the structures shown respectively in (A) and (B), in which R represents in each case the non-reducing hexose residue shown on p. 56. On methylation, the compound (B) would yield the stable form of 2 : 3 : 6-trimethyl-glucose by direct reaction between the reagents. The compound (A), however, might yield the same derivative if an intramolecular change takes place subsequent to (or during) methylation and hydrolysis as shown in the formulæ :



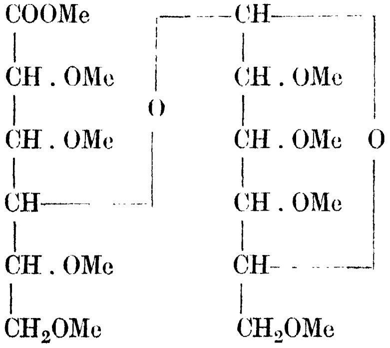
Unstable Type. Stable Type.

This reasoning leaves open a choice between two possibilities in deciding upon a formula for maltose:



Alternative formulæ for Maltose.

The choice between these alternatives can be made on the following evidence.[1] Maltose was oxidized to maltobionic acid. By methylating this last substance, octamethyl-maltobionate was obtained.



Octamethyl-maltobionate.

On hydrolysis, this yields 2 : 3 : 5 : 6-tetramethyl-γ-glucono-lactone

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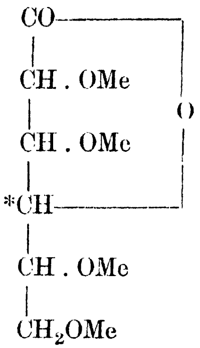
[1] Haworth and Peat, *J.*, 1926, **129**, 3094.



from the left-hand section of the structure. This establishes the position of the linkage between the two sugar groups as being at the point marked with an asterisk, and this proves that the maltose formula (B) is correct.

3. *Lactose*

The constitution of lactose has been inferred by methods analogous to those which have just been described. On complete methylation,[1] lactose yields a heptamethyl-methyllactoside, the cleavage products of which, after hydrolysis, are found to be 2 : 3 : 6-trimethyl-glucose and a tetramethyl-galactose. This last substance has been shown [2] to contain an amylene-oxide ring ; so the lactose structural formula must be identical with one of the alternative formulæ for maltose which have just been given. The difference between the two sugars lies in the configurations of the non-reducing portion of the molecules. In maltose, this has the glucose configuration, whilst in lactose the non-reducing portion has the same configuration as the galactose molecule.

The constitution of the disaccharide cellobiose has been attacked in an analogous manner ; but as its structure is intimately connected with the cellulose constitution, a discussion of its molecular arrangement will fall into place more appropriately at a later stage, in the section dealing with cellulose.*

F.—GENTIANOSE

This substance is a trisaccharide, $C_{18}H_{32}O_{16}$, which is found in gentian roots. On partial hydrolysis with acids or by means of invertin, it can be decomposed into *d*-fructose and a disaccharide

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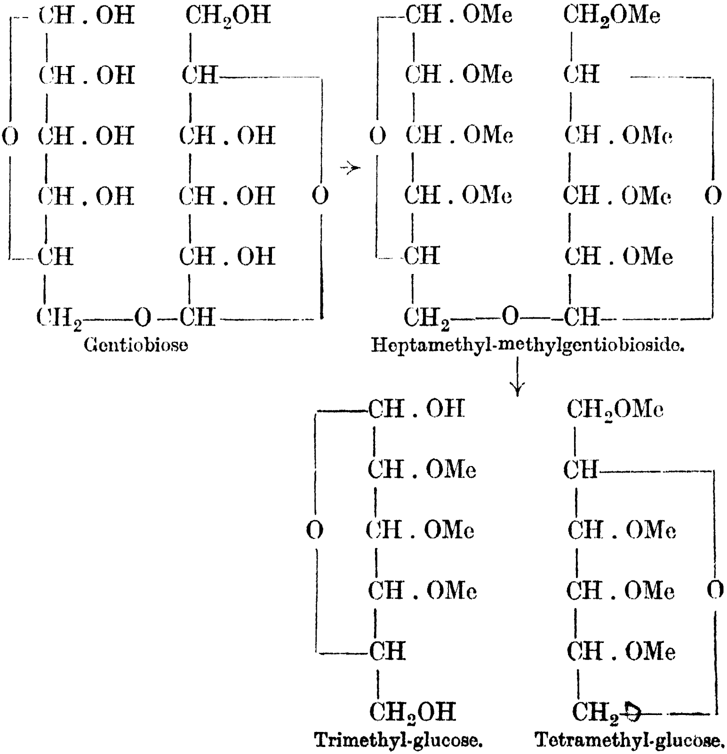
[1] Haworth and Leitch, *J.*, 1918, **113**, 188.

[2] Pryde, *J.*, 1923, **123**, 1808 ; Haworth, Ruell, and Westgarth, *J.*, 1924, **125**, 2468.

* See p. 76.

named gentiobiose. Gentiobiose can be synthesized from glucose by the action of emulsin,[1] but this merely proves that gentiobiose is built up from two glucose molecules and tells nothing with regard to which hydroxyl group of one sugar molecule is attacked by the aldehyde radicle of the second glucose molecule during the condensation.

Haworth and Wylam[2] have cleared up the matter in the following manner. Gentiobiose was methylated by means of methyl sulphate followed by an application of the silver-oxide method; and in this way a heptamethyl-methylgentiobioside was obtained. On hydrolysis, this heptamethyl-derivative broke up into two methylated monoses which are now known to be 2 : 3 : 4-trimethyl-glucose and 2 : 3 : 4 : 6-tetramethyl-glucose. These facts indicate that the decomposition of gentiobiose can be expressed by the following formulæ:



Gentiobiose

Heptamethyl-methylgentiobioside.

Trimethyl-glucose.

Tetramethyl-glucose.

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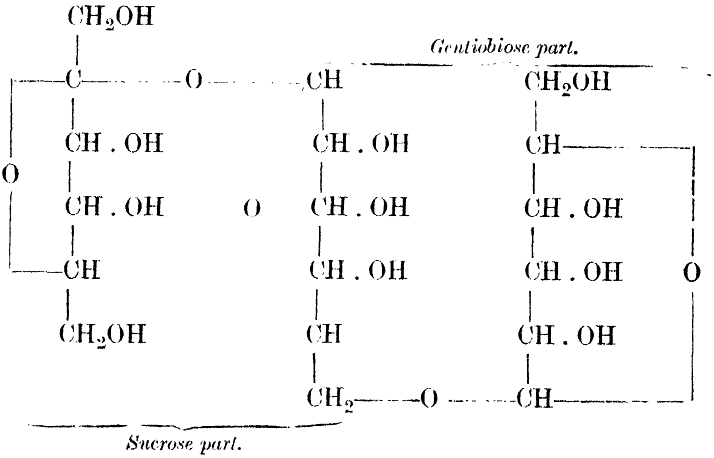
[1] Bourquelot, Hérissey, and Coirre, *Compt. rend.*, 1913, **157**, 732; compare Georg and Pictet, *Helv. Chim. Acta*, 1926, **9**, 444.

[2] Haworth and Wylam, *J.*, 1923, **123**, 3120.

Now the trisaccharide gentianose is built up from gentiobiose and fructose, since it can be decomposed into these constituents on hydrolysis; but further light is thrown on the gentianose structure by the fact that some emulsin preparations split the gentianose molecule at a different point, producing sucrose and glucose. Assuming that the γ-fructose nucleus exists in the butylene-oxide form,* this suggests that the full structure of gentianose can be written thus:



Gentianose molecule.

G.—SOME GLUCOSIDE CONSTITUTIONS

1. *General*

In the foregoing pages, an outline has been given of the methods by which the constitutions of the monosaccharides and the simpler polysaccharides can be investigated. The next series of compounds is the glucoside class with which the present section is concerned; and here also it will be found that methylation has played the part of a master-reaction, since it has furnished the main evidence in the subject.

Any exhaustive study of a glucoside must include the following problems:

I. The sugar and the non-saccharine constituent must be identified. This can be achieved by subjecting the glucoside to hydrolysis either with dilute acid or by the action of an enzyme.

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* See p. 55.

II. The mode of union between the sugar and the remainder of the glucoside must be determined. In cases where the non-saccharine constituent contains only a single hydroxyl group, no doubt can exist on this point; but if the sugar be combined with a polyhydroxy-molecule, the complexity of the problem is considerably increased.

III. Since glucosides exist in α- and β-forms, the configuration of the material under examination must be ascertained. This question can generally be answered by a study of the action of emulsin on the glucoside, since this enzyme is apparently a specific enzyme for β-alkylglucosides. If emulsin hydrolyses the given glucoside, it is fairly safe to infer that the glucoside is derived from β-glucose.

IV. After settling these three points, there still remains the investigation of the cyclic grouping in the sugar nucleus; and it is with this last problem that we are mainly concerned here.

2. *Salicin*

Our knowledge of the intimate constitution of salicin is due to the work of Irvine and Rose.[1] When salicin is hydrolysed by emulsin, it yields glucose and saligenin (salicylic alcohol). This proves that it is the glucoside of saligenin and, further, that it is a β-glucoside, since it is sensitive to emulsin. Since saligenin contains a phenolic hydroxyl as well as a primary alcoholic radicle, it is evident that the sugar has two possible points of attack during the formation of the glucoside from its constituents. The choice between these is easily made. When the glucoside salicin is oxidized with nitric acid, it yields helicin, which is the glucoside of salicylic aldehyde:

$$C_6H_{11}O_5 . O . C_6H_4 . CHO$$

Obviously, from this evidence, salicin must contain a primary alcoholic group which is oxidized to the aldehyde radicle; and hence it must be inferred that the primary alcoholic group is present in salicin. This implies that the linkage in the glucoside is through the phenolic oxygen; and the structure of salicin must therefore be

$$C_6H_{11}O_5 . O . C_6H_4 . CH_2OH$$

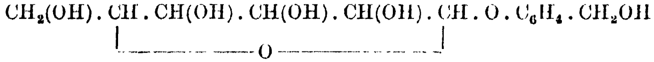
---

[1] Irvine and Rose, 1906, **89**, 814.

Irvine and Rose methylated salicin and obtained a pentamethyl-salicin. The obvious succeeding step would seem to be the hydrolysis of this substance and an identification of the tetramethyl-glucose which must thus be obtained ; but unfortunately owing to the properties of the pentamethyl-derivative, this method broke down. Irvine and Rose solved the problem in another way. From tetramethyl-glucose and salicylic alcohol, they prepared a synthetic glucosidal product and on methylating this in turn, they obtained a pentamethyl-glucoside identical in every respect with the pentamethyl-derivative produced by methylating natural salicin.

This establishes the fact that the glucose nucleus in salicin has the same oxide-ring as ordinary glucose, since methylation of the two compounds leads to the same end-product. And since it has been established in a foregoing section that the tetramethyl-glucose employed contains the amylene-oxide ring, it is evident that this ring is also present in the salicin molecule.

The structure of salicin can therefore be expressed by the formula :



$$CH_2(OH).\underbrace{CH.CH(OH).CH(OH).CH(OH).CH}_{O}.O.C_6H_4.CH_2OH$$

Salicin.

3. *Indican*

On hydrolysis, indican yields *d*-glucose and indoxyl. Macbeth and Pryde[1] have established the normal nature of the sugar structure by the following method. Indican was methylated by the silver oxide method and a tetramethyl-indican was thus formed. Now since the indoxyl part of the molecule might possibly be affected by the methylation, it was essential to prove that all the four methyl groups were attached to the sugar nucleus. For this purpose, the production of indirubin was utilized as a test. Baeyer[2] showed that indoxyl and isatin yield indirubin by condensation ; and this reaction has been shown to be satisfactory as a method of estimation.[3] On

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[1] Macbeth and Pryde, *J.*, 1922, **121**, 1660.

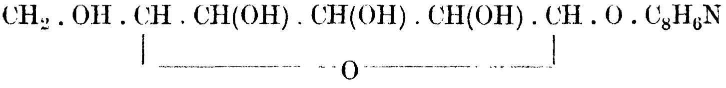
[2] Baeyer, *Ber.*, 1881, **14**, 1745.

[3] Beyerinck, *Proc. K. Akad. Wetensch. Amsterdam*, 1899, **2**, 120 ; Orchardson, Wood, and Bloxam, *J. Soc. Chem. Ind.*, 1907, **26**, 4.

submitting tetramethyl-indican to the reaction, Macbeth and Pryde found that indirubin was freely produced, proving that the methylation does not affect the indoxyl portion of the glucoside molecule.

In order to hydrolyse the methylated indican and isolate the methylated sugar, advantage was taken of a method devised by Irvine and Rose whereby the methylated glucoside is treated with methyl alcohol containing 1 per cent. hydrogen chloride. This reagent overcomes the somewhat stubborn resistance which these alkylated glucosides present to ordinary hydrolytic agents. As was to be expected, the product of the hydrolysis under these conditions was a mixture of α- and β-tetramethyl-methylglucoside, the indoxyl group being replaced by a methyl radicle.

Since the tetramethyl-methylglucosides obtained from indican are the same as those obtained by the methylation of the ordinary α- and β-methylglucosides derived from glucose, it is evident that indican's sugar constituent has the same type of oxide-ring as glucose itself; and the formula of indican can be written thus:



$$CH_2 . OH . \underbrace{CH . CH(OH) . CH(OH) . CH(OH) . CH}_{O} . O . C_8H_6N$$

Indican.

4. *Arbutin*

Macbeth and Mackay [1] have established by similar methods the existence of the normal amylene-oxide ring in the glucoside arbutin. On hydrolysis, arbutin yields glucose and hydroquinone; and since it is attacked by emulsin, it must be regarded as a β-glucoside. On methylation with methyl sulphate and alkali, it yielded a pentamethyl-arbutin. Since on hydrolysis with 1 per cent. hydrogen chloride in methyl alcoholic solution, the pentamethyl-arbutin liberated a mixture of α- and β-tetramethyl-methylglucosides, it is evident that the methylated arbutin has one methyl group in the hydroquinone nucleus and four methyls in the sugar portion, for hydrolysis does not remove methyls attached to the normal hydroxyl groups of the sugars. On examination, the tetramethyl-glucose obtained by the hydrolysis

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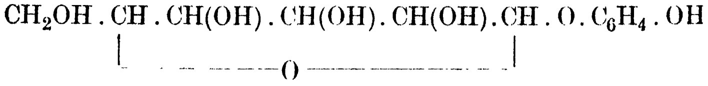
[1] Macbeth and Mackay, *J.*, 1923, **123**, 717.

of the methylglucoside mixture was found to be identical with the tetramethyl-derivative yielded by ordinary *d*-glucose. This proves that the normal amylene-oxide structure is present in arbutin, which therefore must have the formula :



$$CH_2OH.\underbrace{CH.CH(OH).CH(OH).CH(OH).CH}_{O}.O.C_6H_4.OH$$

Arbutin.

This inference is confirmed by the fact that Macbeth and Mackay succeeded in synthesizing from tetramethyl-glucose and hydroquinone monomethyl-ether a pentamethyl-arbutin identical with that obtained from natural arbutin by methylation.

5. *Amygdalin*

The present survey of the glucosides may be closed with an account of the synthesis of amygdalin.[1] Amygdalin occurs naturally in bitter almonds and has the composition expressed by $C_{20}H_{27}O_{11}N$. On treatment with zymase, it is split up into one molecule of glucose and one molecule of *l*-mandelonitrile-glucoside, from which the single remaining glucose molecule can be removed by hydrolysis with emulsin. This behaviour suggests that amygdalin contains a biose and that its structure can be represented thus :

$$C_6H_5—CH(CN)—O—C_{12}H_{22}O_{11}$$

The biose has been found [2] to be gentiobiose, the structure of which has been elucidated in an earlier part of this chapter.

When glucose is treated with emulsin, gentiobiose is formed.[3] By the action of acetic anhydride saturated with hydrogen bromide, Campbell and Haworth converted gentiobiose into hepta-acetyl-β-bromo-gentiobiose by simultaneous bromination and acetylation. This product was condensed with *dl*-mandelic ethyl ester in presence of silver oxide ; and the resulting material was identified as hepta-acetyl-*dl*-amygdalinic ethyl ester. From it, the amide of amygdalinic acid was prepared by the action of

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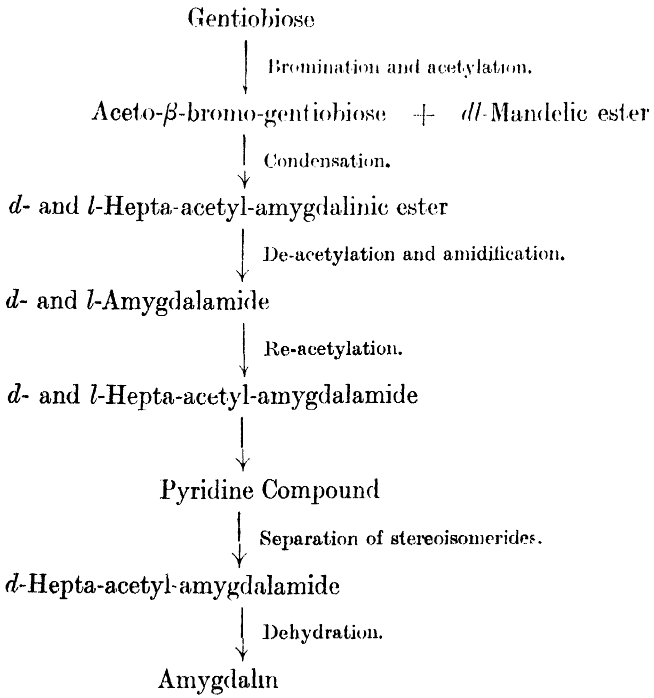
[1] Campbell and Haworth, *J.*, 1924, **125**, 1337.

[2] Haworth and Wylam, *J.*, 1923, **123**, 3120.

[3] Bourquelot, Hérissey, and Coirre, *Compt. rend.*, 1913, **157**, 732.

alcoholic ammonia, the acetyl groups being split off during the amide-formation. Re-acetylation in presence of pyridine yielded a pyridine compound with hepta-acetyl-amygdalamide; and the stereoisomeric forms were separated from each other by fractional crystallization. Water was then removed from the acetylated amide by digestion with phosphoric oxide in xylene solution; and in this way hepta-acetyl-amygdalin was obtained, from which amygdalin itself can be prepared by de-acetylation with alcoholic ammonia.[1]

As this series of reactions is rather difficult to follow, a table may be useful to indicate their inter-relationship.



H.—GLUCOSAN AND THE SYNTHETIC DEXTRINS

When heated to about 170° C., glucose loses water and yields a compound named glucosan. This material has the composition

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[1] Fischer and Bergman, *Ber.*, 1917, **50**, (*B*), 1065.

$C_6H_{10}O_5$, has no sweet taste, and regenerates glucose when boiled with water and dilute acids. A crystalline form of the substance can be obtained by the action of alkalis upon certain glucosides.[1] Curiously enough, a large yield of crystalline *l*-glucosan is produced when starch or cellulose is distilled under reduced pressure.[2] This compound has been shown to be related to β-glucose, so it may be shortly described as β-glucosan.[3]

From the simple formula $C_6H_{10}O_5$ and the fact that β-glucosan regenerates glucose when treated with dilute acids, it seems evident that β-glucosan is one of the numerous anhydro-glucoses which theoretically can be obtained by the removal of one molecule of water from a molecule of glucose.

This view of β-glucosan has brought in its train another idea, which at one time seemed to suggest that β-glucosan might prove the key-substance in a much wider field. Since the complex polysaccharides like starch and cellulose have the general formula $(C_6H_{10}O_5)_n$, it was suggested by Pictet that they were simply polymers of β-glucosan, so that the β-glucosan molecules form the bricks from which the cellulose edifice is built. Unfortunately for the simplicity of the subject, this view of the cellulose structure has been decisively disproved [3] in the following way.

When cellulose is methylated, the product is a trimethyl-cellulose which, on hydrolysis, yields a crystalline trimethyl-glucose.[4] Thus if cellulose is a polymer of β-glucosan, it follows that trimethyl-cellulose must be a polymerized form of trimethyl-β-glucosan; and Pictet's views can be subjected to a rigid test by preparing trimethyl-β-glucosan from β-glucosan, converting it into trimethyl-glucose, and then comparing this trimethyl-glucose with the trimethyl-glucose obtained by the degradation of methylated cellulose. The diagram will make the matter clear.

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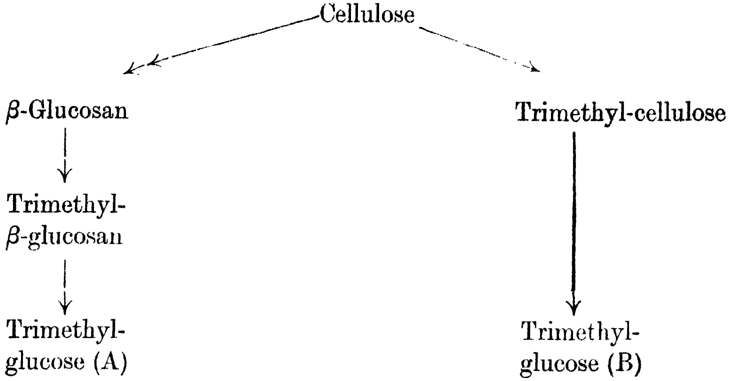
[1] Tanret, *Bull Soc. chim.*, 1894 (3), **11**, 949; Vongerichten and Muller, *Ber.*, 1906, **39**, 241.

[2] Pictet and Sarasin, *Compt. rend.*, 1918, **166**, 38; *Helv. Chim. Acta*, 1918, **1**, 187; Sarasin, *Arch. Sci. phys. nat.*, 1918 (4), **46**, 5; Pictet, *Helv. Chim. Acta*, 1919, **2**, 698; 1920, **3**, 649.

[3] Irvine and Oldham, *J.*, 1921, **119**, 1744.

[4] Denham and Woodhouse, *J.*, 1913, **103**, 1735.



If the two trimethyl-glucoses (A) and (B) are identical, then obviously the β-glucosan unit must be present in the cellulose molecule. If (A) is different from (B), then some constitutional change must have occurred in the stage marked by the double-headed arrow.

In practice, Irvine and Oldham found that the two compounds (A) and (B) were entirely different in character. One is a liquid, the other is a solid with m.p. 123°–124° C. On heating, the one derived from trimethyl-β-glucosan regenerates its parent, whereas the compound (B) is stable when heated. The glucosan derivative yields a characteristic crystalline β-methylglucoside; the compound (B) is the 2 : 3 : 6-isomer, which gives a difficultly crystallizable glucoside. These facts prove conclusively that the compounds (A) and (B) are entirely different; and hence it must be inferred that the β-glucosan nucleus is not present, as such, in the cellulose structure, but is brought into existence during a deep-seated change which takes place during the preparation of β-glucosan from cellulose.

The interest of β-glucosan does not, however, disappear on this account, and some description will now be given of its polymerization. Pictet[1] found that under the influence of platinum black or zinc chloride β-glucosan yields various polymers which are optically active and show the characteristics of dextrins. Irvine and Oldham,[2] using zinc as a catalyst, further increased our knowledge in this field. The following list shows the various derivatives hitherto obtained.

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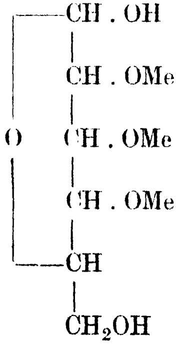
[1] Pictet, *Helv. Chim. Acta*, 1918, **1**, 226; 1921, **4**, 788.

[2] Irvine and Oldham, *J.*, 1925, **127**, 2903.

	Pictet	*Irvine and Oldham*
$(C_6H_{10}O_5)_2$	Diglucosan	
$(C_6H_{10}O_5)_3$		Triglucosan
$(C_6H_{10}O_5)_4$	Tetraglucosan	Tetraglucosan
$(C_6H_{10}O_5)_6$	Hexaglucosan	
$(C_6H_{10}O_5)_7$		Heptaglucosan
$(C_6H_{10}O_5)_8$	Octaglucosan	

Curiously enough, the compounds prepared by Irvine and Oldham differ from those obtained by Pictet in that they each contain three hydroxyl groups for each C_6 unit, as can be shown by acetylation. But these three hydroxyl groups are not uniformly distributed as are the hydroxyl groups in a cellulose and hexa-amylose. Cellulose on methylation and hydrolysis yields 2 : 3 : 6-trimethyl-glucose exclusively. The synthetic dextrins of Irvine and Oldham, on the other hand, break up into sugars which are now believed to be 2 : 3 : 4 : 6-tetramethyl-glucose, 2 : 3 : 4-trimethyl-glucose, and a dimethyl-glucose. This establishes that the natural and synthetic molecules are constituted on entirely different plans.

The structures of the synthetic dextrins have not yet been definitely established ; but a few words may be devoted to the problem which they present. In the first place, the constitution of β-glucosan itself may be examined. It was found by Irvine and Oldham [1] that β-glucosan on consecutive methylation and hydrolysis yielded a trimethyl-derivative which is now recognized as 2 : 3 : 4-trimethyl-glucose :



2 : 3 : 4-Trimethyl-glucose.

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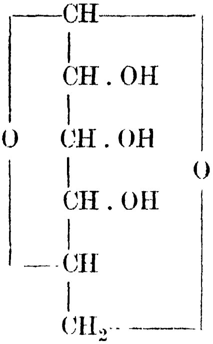
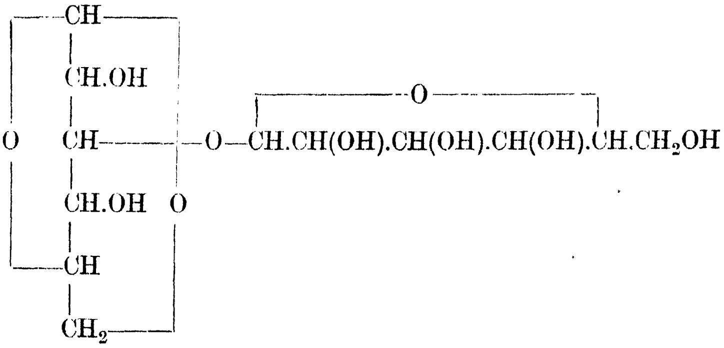
[1] Irvine and Oldham, *J.*, 1921, **119**, 1744.

The second oxide-chain of the glucosan molecule must therefore be formed by the elimination of a molecule of water from the two remaining hydroxyl groups of the sugar ; and thus it seems probable that β-glucosan has the structure shown below :



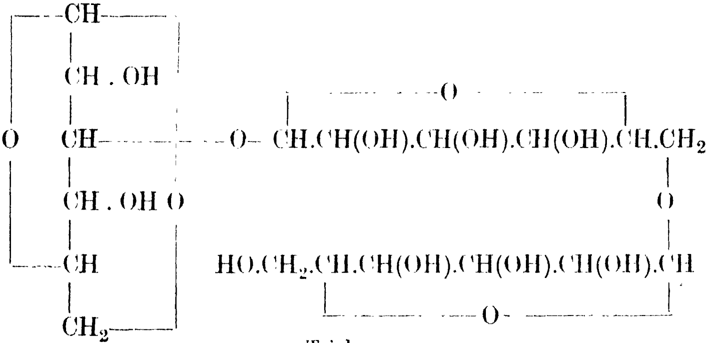
β-Glucosan.

Now when diglucosan is methylated, a dimethyl-glucose is obtained on hydrolysis ; and in the light of recent information, this sugar appears to be either 2 : 3- or 2 : 4-dimethyl-glucose. This gives a key to possible ways in which the second glucose nucleus is attached to the glucosan which forms the other half of the diglucosan molecule. The formula below shows the result when the methylated sugar is assumed to be the 2 : 4-derivative, which is believed to be the more probable constitution.



Glucosan nucleus. Diglucosan. Glucose chain.

The probable constitutions of the higher polyglucosans are suggested by the fact that all the polymers above diglucosan yield 2 : 3 : 4-trimethyl-glucose as a result of successive methylation and hydrolysis. Inspection of the formula given above for diglucosan will reveal at once that the glucosan nucleus in it can yield only a dimethylated sugar, since there are only two free hydroxyl groups in the structure. On the other hand, the glucose chain in the molecule has its 2 : 3 : 4-hydroxyl groups free and could thus yield the methylation product which is required. Hence any extension of the chain must take the "glucose chain" structure and not the "glucosan" structure. The formula for triglucosan therefore must be of the following type :



Triglucosan.

As Irvine and Oldham point out, the polymerization of glucosan may involve reactions of two types : association and condensation. For instance, a tetraglucosan might be imagined to come into existence : (1) by the successive formation of di, tri-, and tetraglucosan ; or (2) by the production of diglucosan and a subsequent association of two diglucosan molecules to form a tetraglucosan without the intermediate triglucosan stage. It seems highly probable that if two such processes could be traced out, the final tetraglucosans would be found to differ from each other in constitution.

I.—Some Polysaccharides

1. *Inulin*

Among the reserve-materials of certain plants, the compound inulin [1] occupies an important position. It is a non-reducing

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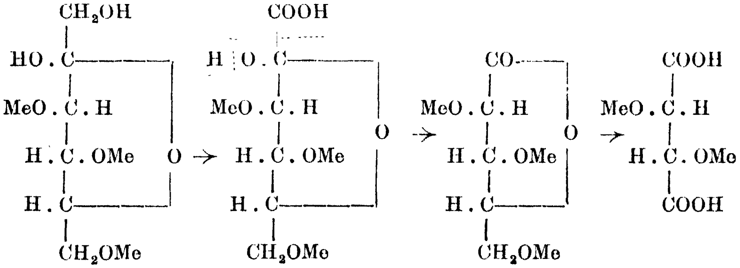
[1] Irvine and Steele, *J.*, 1920, **117**, 1474 ; Irvine, Steele, and Shannon, *J.*, 1922, **121**, 1060 ; Karrer and Lang, *Helv. Chim. Acta*, 1921, **4**, 249 ; Haworth and Learner, *J.*, 1928, 619 ; Drew and Haworth, *ibid.*, 2690 ; Freudenberg and others, *Ber.*, 1928, **61**, [*B*], 1735 ; Pringsheim and others, *ibid.*, 2018 ; 1929, **62**, [*B*], 2378 ; *Annalen*, 1928, **462**, 231 ; Schlubach and Elsner, *Ber.*, 1928, **61**, [*B*], 2358 ; 1929, **62**, [*B*], 1493.

compound and yields exclusively fructose when it is hydrolysed. It differs from starch in various ways, one or two of which may be mentioned here. With iodine, starch gives the well-known starch-iodine blue colour; whereas inulin has no such property. Starch is decomposed to maltose by diastase; but inulin is stable in presence of diastase. Starch is much less rapidly hydrolysed than inulin when dilute acids are employed; and the end-product of the hydrolysis is *d*-glucose instead of being *d*-fructose as in the case of inulin.

When inulin was treated with methyl sulphate, the reaction progressed in one stage to the formation of a dimethyl-inulin corresponding to the formula $[C_6H_8O_3(OMe)_2]_n$; and a further operation was required to obtain the final product, trimethyl-inulin, $[C_6H_7O_2(OMe)_3]_n$. On hydrolysis with 1 per cent. oxalic acid at 100° C., trimethyl-inulin was converted smoothly into trimethyl-fructose,* which appeared to belong to the γ-series.

The constitution of this fructose derivative was established by a series of reactions indicated in the formulæ below:



(I.) (II.) (III.) (IV.)

The trimethyl-fructuronic acid (II.) was proved to be identical with the trimethyl-fructuronic acid derived from sucrose, so that obviously both inulin and sucrose contain the same kind of fructose (γ-fructose). The positions of the methyl-groups can be established by working back from the final *l*-dimethoxy-succinic acid (IV.); and since this proves that in the original inulin molecule the hydroxyl groups in positions 1 and 2 are not methylated, it is clear that these groups are involved in the

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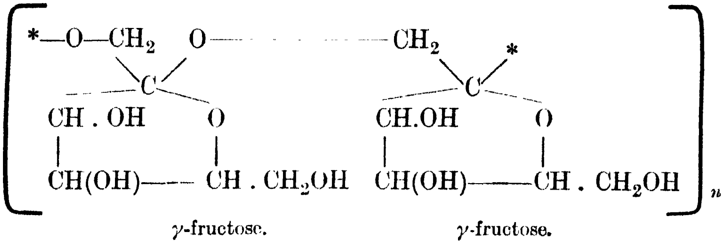
* The yield of trimethyl-fructose from trimethyl-inulin exceeds 90 per cent., which seems to prove beyond doubt that all the fructose units of inulin are of the γ-type.

linking together of the various fructose nuclei from which inulin is built up.

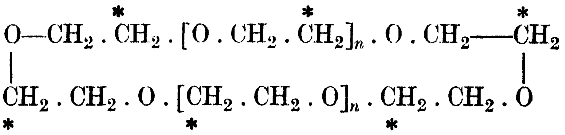
The general formula for inulin which would comply with these requirements is this :—



wherein the two valencies indicated by asterisks are assumed to link still further γ-fructose units to the complex in the same fashion.

This leaves still undetermined the total number of fructose units which go to form the inulin molecule. It appears from the evidence with regard to the molecular weight of inulin that there must be at least twenty-four fructose units involved in its architecture ; but it should be noted that in these determinations the inulin molecule has been found to break down and results have been obtained which point to its resolution into smaller complexes containing anything from twelve fructose units downwards, the number of units being even in each case.

Haworth and Hirst [1] have pointed out that this view of the inulin structure, based on the work of Haworth and Learner, can be extended in the following way. Ethylene oxide is readily induced to polymerise ; and if the higher polymers be assumed to have a cyclic structure, they would conform to the following formula :



$$\begin{array}{l} O-CH_2\,.\,\overset{*}{C}H_2\,.\,[O\,.\,CH_2\,.\,\overset{*}{C}H_2]_n\,.\,O\,.\,CH_2-\overset{*}{C}H_2 \\ |\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad | \\ \underset{*}{C}H_2\,.\,CH_2\,.\,O\,.\,[\underset{*}{C}H_2\,.\,CH_2\,.\,O]_n\,.\,\underset{*}{C}H_2\,.\,CH_2\,.\,O \end{array}$$

Now to convert this into a possible inulin formula, it is only necessary to substitute for each methylene group marked with an asterisk the γ-fructose ring :—

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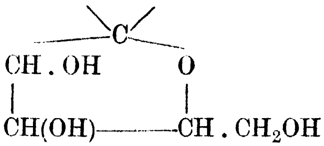
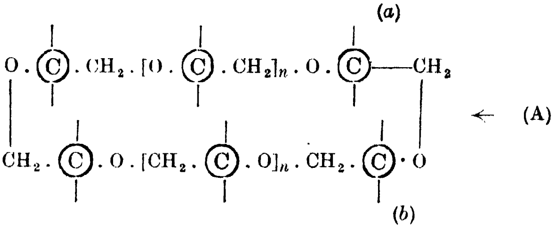
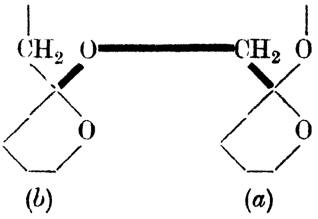
[1] Haworth and Hirst, *Ann. Reports*, 1929, **26**, 102.



For the sake of simplicity, this ring may be represented by the symbol Ⓒ in which the two lines represent the γ-fructose ring viewed along its own plane, which is assumed to lie vertical to the paper. Substituting these symbols in the foregoing formula, the following arrangement is obtained :—



The chains may be assumed to lie fairly close together in space so as to form a flattened loop ; and in this case the γ-fructose rings of inulin will occur side by side in pairs in a plane vertical to that of the ethylene oxide chain.* If the space-model of this system were inspected from the point (A) two γ-fructose rings would be seen (*a* and *b*) ; and pairs of such units would be perceived at regular intervals throughout the model.



On hydrolysis, an inulin of this structure would break up by scission at the oxygen links ; and the result would be groups of the type $(C_6H_{10}O_5)_n$, where *n* is an even number.

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* Thus in the formula shown, the ethylene oxide chain would lie in the plane of the paper, as shown, whilst the γ-fructose rings would be seen end-on, since their planes would be perpendicular to the paper.

2. *Cellulose*

The problem of cellulose's constitution bristles with difficulties which at first sight may well seem insuperable. Owing to the insolubility of the material in ordinary solvents, chemical purification is beset with quite abnormal hindrance. The colloidal character of the material throws out of account any normal method of ascertaining the molecular weight. And the possibility that intramolecular change or degradation will follow the use of even mild reagents puts the final touch of hopelessness to the picture.

A normal cotton cellulose is represented by the formula $(C_6H_{10}O_5)_n$; and the fact that glucose alone has been identified among the products of hydrolysis can be taken to indicate that the cellulose molecule has an architecture based on the glucose unit. But it must be borne in mind that the hydrolysis of cellulose is by no means easy to achieve. It requires the use of rather drastic reagents; and secondary reactions seem inevitable during the process.

If it be assumed that cellulose is a polyglucose anhydride, the case resembles that of inulin; and there are, theoretically, two possibilities which must be borne in mind. In the first place, cellulose may be regarded as an arrangement of simple anhydrohexose units, $(C_6H_{10}O_5)$, united by polymerization in unknown numbers. Or, as an alternative, it may be assumed that n molecules of a hexose are directly connected together by the elimination of n molecules of water.* In either case, a complete hydrolysis of cellulose should proceed according to the equation:

$$(C_6H_{10}O_5)_n + nH_2O = nC_6H_{12}O_6$$

But in actual practice, the hydrolysis of cellulose is hemmed in by difficulties. From time to time accounts have appeared in the literature describing how practically quantitative yields of glucose have thus been obtained; but these have been adversely criticized by Irvine and Soutar.[1] These two investigators carried out careful experiments in which only

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* Or $(n\text{-}1)$ molecules of water, if n be a sufficiently large integer.

[1] Irvine and Soutar, *J.*, 1920, **117**, 1489.

actually isolated glucose was taken into account; and they were able to prove that the glucose yield from cellulose on this basis was a minimum of 85 per cent., which compares very favourably with the normal yields of reactions in the sugar group, since these rarely reach 80 per cent. Later, Monier-Williams [1] recorded a yield of 90·67 per cent. of the theoretical quantity, his result also being based on actually-isolated glucose. Finally, Irvine and Hirst [2] obtained an over-all yield of hexose from cellulose amounting to no less than 95·1 per cent. of the theory. From these figures it seems not unwarranted to suppose that cotton cellulose is essentially composed of glucose units.

Even when it is proved that cellulose is based on the glucose unit, however, the problem is only in its beginnings; for the main difficulty obviously presents itself when an attempt is made to discover the manner in which the various monose nuclei are linked together in the polysaccharide structure.

Here, again, the method of methylation has proved an indispensable weapon, though the difficulties of it were enhanced by the insolubility of cellulose. Discarding the silver oxide method, Denham and Woodhouse [3] discovered that methyl groups can be introduced very simply by impregnating cellulose with 15 per cent. solution of sodium hydroxide and then applying methyl sulphate. The process was found to take place in stages, more methyl groups being introduced with each successive treatment of the material.

Denham and Woodhouse [4] found that their methylated celluloses when subjected to the action of hydrolysing agents, did not lose the methyl radicles; so that in this way a new line of attack on the cellulose problem was laid open. On subjecting to hydrolysis a methylated cellulose containing 25 per cent. of methoxyl, a trimethyl-glucose was isolated among the reaction-products; and thus a definite reference-compound was obtained.

Denham and Woodhouse were able to identify this crystalline trimethyl-glucose as the 2 : 3 : 6-derivative; so that, adopting the amylene-oxide structure, its constitution is expressed by

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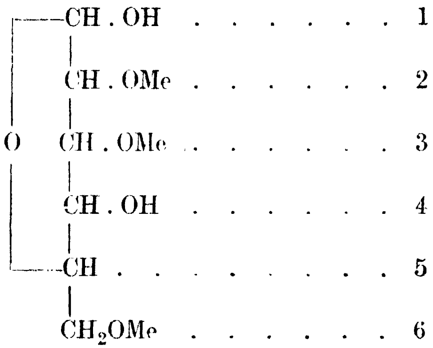
[1] Monier-Williams, *J.*, 1921, **119**, 803.

[2] Irvine and Hirst, *J.*, 1922, **121**, 1585.

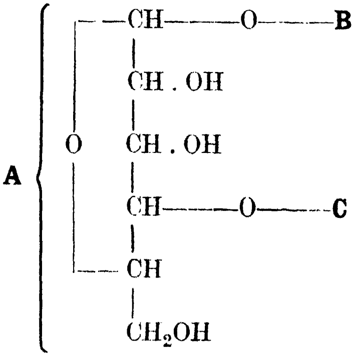
[3] Denham and Woodhouse, *J.*, 1913, **103**, 1735; Denham, *J.*, 1921, **119**, 77.

[4] Denham and Woodhouse, *J.*, 1917, **111**, 244.



2 : 3 : 6-Trimethyl-glucose from cellulose.

A glance at this formula will show that the positions 1 and 4 in the molecule have not borne free hydroxyl groups during the methylation of cellulose; and therefore these two points must be the positions at which the remaining parts of the cellulose molecule are linked on. Thus on the evidence up to this point it is safe to say that the cellulose molecule is composed of three parts (**A**, **B**, and **C**) which are linked together as shown in the following scheme:



First sketch of the cellulose constitution.

A further glimpse of the cellulose constitution is gained from cellobiose. This disaccharide is related to cellulose as maltose is to starch, and is obtained from cellulose by incomplete hydrolysis either by means of acetic anhydride and concentrated sulphuric acid (acetolysis) or else by bacterial action.[1]

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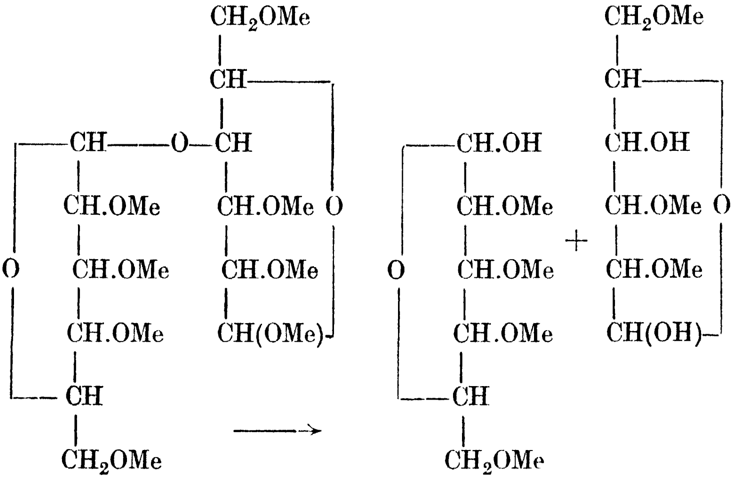
[1] Pringsheim, *Z. physiol. Chem.*, 1912, **78**, 266.

Cellobiose is obviously composed of two glucose nuclei; and for the present purpose the essential point is the manner in which these are linked. To solve this problem, the methylation method was employed by Haworth and Hirst[1]; and by using in succession methyl sulphate and the silver oxide method, they obtained a heptamethyl-methylcellobioside. On hydrolysis, this last compound yielded two substances which are now known to be 2 : 3 : 4 : 6-tetramethyl-glucose and 2 : 3 : 6-trimethyl-glucose.

From these fragments, the structure of heptamethyl-methylcellobioside can be reconstituted in the following form: *



Heptamethyl-methyl-cellobioside. 2 : 3 : 4 : 6-Tetramethyl-glucose. 2 : 3 : 6-Trimethyl-glucose.

From this structure it appears that the 2 : 3 : 6-trimethyl-glucose fragment is linked to the rest of the molecule through hydroxyl group 4 †; and this is the important point so far as the present argument is concerned. Since cellobiose is an intermediate degradation compound between cellulose and glucose, it is

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[1] Haworth and Hirst, *J.*, 1921, **119**, 193; 1926, **129**, 1858; Charlton, Haworth and Peat, *ibid.*, 89; compare Zemplen, *Ber.*, 1926, **59**, 1254.

* It is evident from this that cellobiose is identical in structure with maltose (see p. 55). Maltose is a glucose-α-glucoside, whereas cellobiose is a glucose-β-glucoside.

† Or hydroxyl group 5.

probable that cellulose also must contain this cellobiose linking.

A second trimethyl-cellulose has been obtained [1] by acting on cellulose with methyl sulphate at 20° C. This variety is quite different from the earlier type. It is quite insoluble in water, but dissolves in acetic acid, chloroform, and tetrachloro-ethane. On hydrolysis this trimethyl-cellulose yields 2 : 3 : 6-trimethyl-glucose. The yield [2] of trimethyl-cellulose is 93 per cent. and that of the trimethyl-glucose is 91 per cent.

A third line of attack upon the cellulose constitution lies through the field of acetolysis. This process of simultaneous acetylation and hydrolysis carried out by means of acetic anhydride and concentrated sulphuric acid is not by any means a simple succession of acylation and decomposition; but in its broad outlines Irvine and Robertson [3] believe that it can be represented as a series of rather ill-defined steps such as are indicated below:

$$\begin{tikzcd}
\text{Cellulose} \arrow[r] & \text{Acetylated cellulose} \arrow[d] \\
 & \text{Acetylated cellulose dextrins} \arrow[d, two heads] \\
\text{Glucose penta-acetate} & \text{Cellobiose octa-acetate} \arrow[l]
\end{tikzcd}$$

wherein the stage marked with the double-headed arrow represents the formation of compounds in which the maximum depolymerization of cellulose has taken place, whilst the specific hydrolytic action responsible for the formation of cellobiose octa-acetate is at a minimum.

By studying quantitatively the results of acetolysis, Irvine and Robertson were able to isolate trisaccharide derivatives in a yield equivalent to 35 per cent. of the original cellulose; and since the total isolated acetates represented only 76 per cent. of the material, it is evident that these trisaccharide derivatives are a most important constituent of degraded cellulose. This

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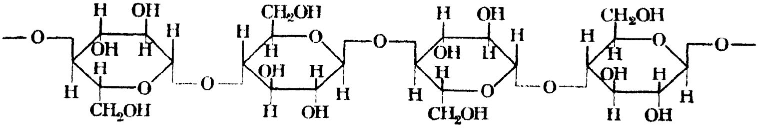
[1] Urban, *Cellulosechem.*, 1926, **7**, 73.

[2] Freudenberg and Braun, *Annalen*, 1928, **460**, 288; Freudenberg, *ibid.*, **461**, 130.

[3] Irvine and Robertson, *J.*, 1926, **129**, 1488.

suggests that at least one-third of the cellulose structure is based on a tri-glucose unit.

Piecing together the evidence now available, the following formula [1] has been put forward to represent cellulose, and it is supported by an interpretation of the crystal lattice of cellulose which has been obtained by X-ray spectra measurements : [2]



The extreme complexity of the cellulose problem may be indicated by a reference to the work of Hess and Pringsheim on the acetates of cellulose. Determinations of the molecular weight of cellulose diacetate in acetic acid solution [3] yielded a mean value closely corresponding to that which would be given by the diacetate of a glucose-anhydride. Peculiar phenomena were observed when the solutions were allowed to stand ; for the molecular weight remained constant for some days and then gradually increased to an enormous value, and no halt was made at the figure corresponding to the dimeric form $(C_6H_{10}O_5)_2$. The material isolated from these solutions at the end of the process is identical with the initial crystalline substance, and when redissolved, it passes through the same series of stages. Crystalline cellulose triacetate behaves analogously.

When glucose triacetate was heated to 235° C. in presence of naphthalene, Pringsheim and his collaborators [4] found that its molecular weight fell to 288, which corresponds to that of anhydroglucose triacetate. Removal of the acetyl radicles yields an anhydroglucose named cellosan, which is soluble in water and has a molecular weight corresponding to the simple formula $C_6H_{10}O_5$. A similar procedure has been employed in the case of lichenin, which is a cellulose derived from Iceland

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[1] Haworth, *Helv. Chim. Acta*, 1928, **11**, 534 ; Freudenberg, *Annalen*, 1928, **461**, 130.

[2] Meyer and Mark, *Ber.*, 1928, **61**, [*B*], 1982 ; *Z. angew. Chem.*, 1928, **34**, 935 ; Hauser, *Ind. Eng. Chem.*, 1929, **21**, 124.

[3] Hess and Schultze, *Annalen*, 1926, **448**, 99 ; Hess, *Koll.-Chem. Beih.*, 1926, **23**, 93.

[4] Pringsheim and others, *Annalen*, 1926, **449**, 163.

moss; and in this case a substance lichosan is formed, which also is a glucose anhydride.

The Röntgen diagrams of cellulose hydrate, oxycellulose (derived from oxidation of viscose), and hydrocellulose (prepared by the reduction of viscose), have been found [1] identical with the diagram for lichenin, which shows that all these materials have the same crystalline constituents. This evidence suggests that cellulose and lichenin are both built up from basal units which have the character of glucose anhydrides.

It is evident that we are still left in doubt as to the ultimate constitution of cellulose; and the final elucidation may not come for some years yet. In the foregoing pages, enough has been said to show the complexity of the problem and the difficulty of arriving at any final solution at present.

3. *Starch*

It was first pointed out by Nägeli [2] that the natural grains of starch consist of two independent materials. The inner portion of the granules consists of a material now named amylose; whilst the external part of the granules contains a substance termed amylopectin.[3] The two constituents can be separated from each other by treating the granules with alkali, in which the amylose dissolves, leaving the amylopectin behind.[4] The amylopectin may also be obtained by treating starch paste with barley diastase whereby the amylose portion is completely converted into maltose, whilst the amylopectin is hardly attacked.[5] Amylopectin is believed to be a phosphoric ester derived from the amylose polysaccharides [5]; so that the central problem of starch is centred in the polysaccharides which form the main portion of the natural material.

By using different modes of disintegration, starch can be converted into the following degradation-products, which are

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[1] Ott, *Helv. Chim. Acta*, 1926, **9**, 31.

[2] Nägeli, *Die Stärkekorner*, 1858.

[3] Maquenne and Roux, *Ann. Chim. Phys.*, 1904 (viii), **2**, 109; 1906 (viii), **9**, 179.

[4] Gatin-Gruzewska, *Compt. rend. Soc. biol.*, 1908, **64**, 178; *Compt. rend.*, 1908, **146**, 540; see also Ling and Nanji, *J.*, 1923, **123**, 2666.

[5] Ling and Nanji, *J.*, 1923, **123**, 2666.

placed in order of increasing simplicity: (1) the amyloses; (2) the maltoses; (3) glucose; and (4) β-glucosan. A few words are necessary with regard to the first two of these; the final pair have been dealt with in earlier sections of this chapter.

The amyloses were first brought within the reach of easy investigation by Schardinger,[1] who, by the action on starch of *Bacillus macerans* from retting vats, obtained three crystalline materials which he termed dextrins. Further investigation of these substances led to the discovery that they could be represented by the general formula $(C_6H_{10}O_5)_n$, and that simpler materials could be obtained from them by heating with zinc chloride.[2] In this way two hexa-amyloses and one tetra-amylose were identified among the natural products and from them by depolymerization a tri-amylose and a di-amylose were prepared. The complete series is shown below:[3]

Hexa-amylose (two forms) . . .	$[(C_6H_{10}O_5)_2]_3$
Tetra-amylose	$[(C_6H_{10}O_5)_2]_2$
Triamylose	$(C_6H_{10}O_5)_3$
Diamylose	$(C_6H_{10}O_5)_2$

The next degradation-products of starch are the maltoses. When starch is treated with malt diastase, the main product is maltose; but along with this a subsidiary product has been detected which is named *iso*-maltose. In the case of amylopectin, the *iso*-maltose becomes the principal end-product.[4]

From the foregoing, it is easily seen that the degradation of the starch molecule * can be represented as a gradual simplification of the initial carbohydrate $(C_6H_{10}O_5)_n$ through various stages, during which *n* becomes smaller and smaller until at last a single C_6 chain in glucose represents the final halting-point in the series. In reality, however, the problem is not quite so simple as this; for enzyme action may be synthetic as well as analytic; and quite possibly some of the intermediate compounds

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[1] Schardinger, *Wiener Klin. Wochensch.*, 1904, No. 8; *Zentr. Bakt. Parasitenk.*, 1908 (ii), **22,** 98.

[2] Pringsheim and Langhans, *Ber.*, 1912, **45,** 2533; Pringsheim and Eissler, *Ibid.*, 1913, **46,** 2959.

[3] Pringsheim, *Die Polysaccharide*, p. 167 (1923).

[4] Ling and Nanji, *J.*, 1923, **123,** 2666.

* We are concerned here only with the carbohydrate constituents and not with the inorganic ester residues.

are not direct fission-products of starch but are really synthetic materials produced by the combination of two simpler fragments of the starch molecule.

Here, as in many previous cases, the method of methylation has furnished the necessary clue to the outlines of molecular constitution; but its application was found to be less easy than in most of the previous investigations. While no pronounced hindrance was observed in the methylation of glucose, glucosan, or maltose, the alkylation of the polyamyloses presented marked difficulty, which has been ascribed to steric hindrance.[1] Thus diamylose yielded only a tetramethylamylose, though further hydroxyl groups were present in the molecule; tetra-amylose gave only an octamethyl-derivative.

For the purpose of complete methylation, β-hexa-amylose was chosen, since an examination of it would serve a double purpose. In the first place, it is one of the most complex of the starch degradation-products and hence its nature is important. Secondly, the suggestion had been made that hexa-amylose was not a true chemical individual, but was merely a fresh form of triamylose [2]; and methylation promised to present a solution of the problem thus raised.

No less than twenty-two successive methylation operations were necessary with methyl sulphate before a completely alkylated material was obtained. The final substance had the formula $C_{54}H_{96}O_{30}$, and its molecular weight in camphor solution was observed to be 1210, which is remarkably close to the theoretical 1224. The compound is therefore hexa-(trimethylamylose): the completely methylated derivative of hexa-amylose with three methyl groups attached to each C_6 unit in the molecule.

On hydrolysing this polymethyl-derivative, the only sugar detected was 2 : 3 : 6-trimethyl-glucose. In the light of our modern knowledge this result implies that β-hexa-amylose has a symmetrical molecule in which each glucose residue belongs to the amylene-oxide type and the positions 1 and 4 are involved in the linkage.

At this point difficulties arose which have now been overcome, but seem worthy of mention, since they throw some light

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[1] Irvine, Pringsheim, and MacDonald, *J.*, 1924, **125**, 942.

[2] Karrer and Burklin, *Helv. Chim. Acta*, 1922, **5**, 181.

on the complexity of the problem presented by carbohydrate research.

The weight of evidence in the possession of organic chemists at this date certainly suggested that in the series of degradations: starches → polyamyloses → maltose, the maltose skeleton should remain intact. But according to the maltose formula then current, the methylation and hydrolysis of the polyamyloses should have yielded 2 : 3 : 4-trimethyl-glucose and not, as was actually found, the 2 : 3 : 6-derivative. Two possible explanations presented themselves. In the first place, the action of diastase on starch and the polyamyloses might not be purely analytic, and the maltose produced during the fermentation of starch might be derived synthetically from glucose, and thus maltose would not be a unit in the starch molecule at all and there would be no genetic relationship between starch and maltose. This hypothesis offered a possible, though not satisfying, explanation of the results. The second view of the case suggested that probably the current formula for maltose was incorrect. Further investigation by Irvine and Black[1] established the present-day formula of maltose, which is found to harmonize with the results detailed above in connection with hexa-amylose.

Turning now to the methylation of starch itself,[2] it was found that certain variations presented themselves which are not without interest. When the silver oxide method is applied to a previously methylated starch containing less than two methoxyl groups per C_6 unit, the methylation is definitely arrested at the dimethyl stage, the methoxyl content being arrested at 33 per cent., which points to the introduction of only two methyl groups into each C_6 unit in the starch molecule. With methyl sulphate and alkali, methylation proceeds until the methoxyl content attains 36–37 per cent., a value which indicates that only seven hydroxyl groups out of nine have been attacked. That there are actually nine hydroxyls capable of action is shown by the fact that the partly-methylated starch was capable of acetylation to the exact extent required to substitute the remaining unmethylated hydroxyl radicles. It was noted that as the methyla-

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[1] Irvine and Black, *J.*, 1926, **129**, 862; Cooper, Haworth, and Peat, *ibid.*, 876.

[2] Irvine and MacDonald, *J.*, 1926, **129**, 1502.

tion of the starch advanced, the colour-reaction with iodine ceased to occur. The final stage of methylation, attained after twenty-four treatments, gave a methoxyl content of 43·7 per cent., which agrees closely with that required for trimethyl-starch.* There are thus three definite halting-places in the methylation-process corresponding to the following methoxyl percentages:

	Percentage OMe found	Ratio of OMe groups to initial OH groups
I. Dimethyl-starch . . .	32·7	6 : 9
II. Methylated starch . .	36·3	7 : 9
III. Trimethyl-starch . . .	43·7	9 : 9

The hydrolysis of all three types has been carried out; but in this place only trimethyl-starch need be considered. The final products were isolated as methylglucosides; and from trimethyl-starch a good yield of the glucoside of 2 : 3 : 6-trimethyl-glucose was obtained, no trace of any other sugar being found. Starch, then, contains in each C_6 residue three free hydroxyl groups which lie in the 2 : 3 : 6-positions.

We are now in a position to consider the inferences which can be drawn from the foregoing experimental evidence. These are due to Irvine and MacDonald.[1] It should be clearly understood that in the remainder of this section, the term "starch" applies to those constituents of natural non-homogeneous starch which differ from each other in their degree of polymerization but which all are convertible into 2 : 3 : 6-trimethyl-glucose.

In the first place, since β-glucosan on methylation yields 2 : 3 : 4-trimethyl-glucose whereas starch gives rise to the 2 : 3 : 6-derivative, it seems clear that starch is not built up on the glucosan model.

The relationship of starch to maltose and *iso*maltose next demands consideration. The three disaccharides maltose, cellobiose, and *iso*cellobiose, all yield 2 : 3 : 6-trimethyl-glucose; and it appears very probable that *iso*maltose would behave similarly. Now an inspection of the formulæ below will show that they represent isomeric structures and contain residues with different types of oxide-ring; yet each of them would be convertible into

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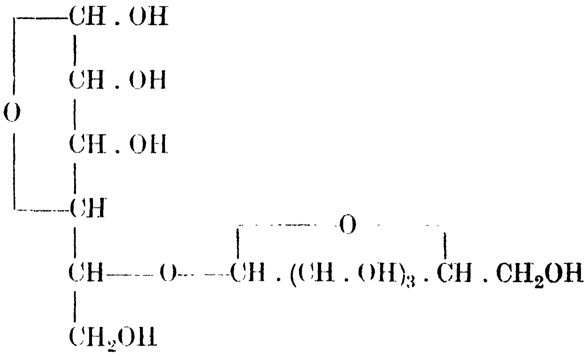
* That is, a starch containing three methyl radicles in each C_6 unit.

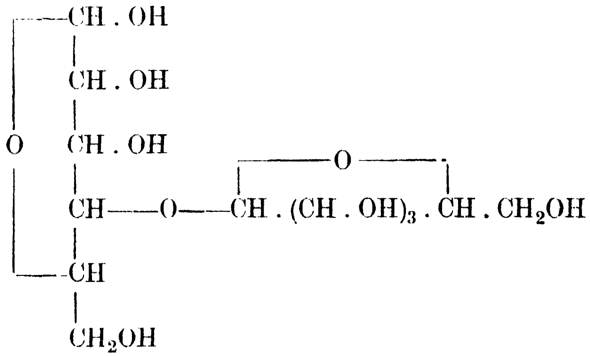
[1] Irvine and MacDonald, *J.*, 1926, **129**, 1502.

2 : 3 : 6-trimethyl-glucose if Type I. yielded the γ-form of the sugar as an intermediate stage, whilst Type II. underwent direct methylation.

Type I.

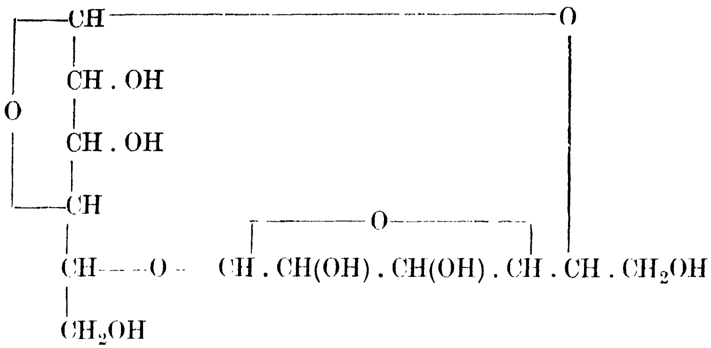


Type II.



Cellobiose and *iso*cellobiose form one structural pair; and it may be assumed that maltose and *iso*maltose form the other pair. It is impossible with our present knowledge to assign maltose and cellobiose to their respective types; but for the sake of the present argument it will be sufficient to ascribe Formula I. to maltose and Formula II. to cellobiose. This is, of course, an intentionally arbitrary decision.

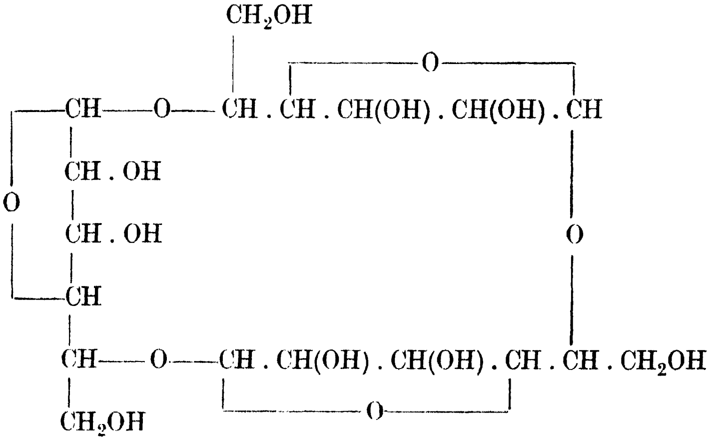
If it be assumed that starch is based on an anhydrodisaccharide unit, the simplest formula for the unpolymerized molecule could then be written thus :



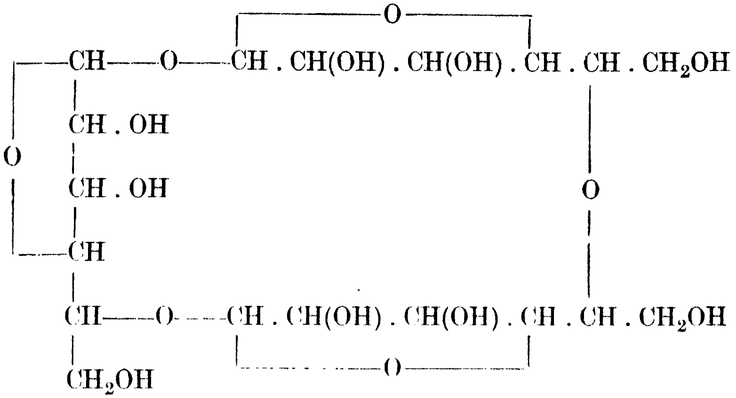
Maltosan formula.

If in the process of hydrolysis, one anhydro-linking of this molecule opened and a subsequent adjustment of the unstable oxygen ring in the non-reducing glucose component occurred, this "maltosan" would give maltose as a unique disaccharide at the end of the reaction. Thus there is a possibility that maltosan may be one of the molecular units of starch. At the same time it must be noted that this maltosan formula for starch does not admit the experimental fact that starch can give rise to a trihexosan or triamylose. Evidently, in order to fit this evidence, it is necessary to consider a starch constitution based on the union of three glucose residues.

Two formulæ are suggested by Irvine and MacDonald as possible structures on this basis.



Symmetrical formula (A).



Unsymmetrical formula (B).

As Irvine and MacDonald point out, neither of these formulæ gives a complete expression of the biochemical properties of starch. Formula (A) represents a compound which on hydrolysis would yield only maltose and glucose. Formula (B) represents a substance from which by hydrolysis maltose, *iso*maltose, and a non-reducing disaccharide could be obtained. Thus neither structure will account for the experimental fact that starch is convertible into maltose in one set of conditions, but into *iso*maltose in other circumstances.

So far as purely chemical reactions are concerned, the formula (B) gives the better expression of the behaviour of starch. It accounts for the phenomena in methylation, which is arrested at the dimethyl stage (when 6 hydroxyl groups out of 9 have been substituted) and slows down abruptly when 7 hydroxyl groups out of the 9 have been attacked.

From the foregoing account, it is easy to see that we have advanced very considerably in our knowledge of the starch constitution ; but there are still three main questions which demand answers before the enigma can be regarded as solved. The amyloses occur in two series to which the names α- and β- have been given. The relations of these must be made clear in the final starch formulation. Again, the above formulæ represent only one set of possible couplings of the hexose residues ; and more research will be necessary before a certain choice can be made from among all the possible modes of linking. Finally, when the nature of the basal unit of starch has been accurately determined, there will still remain the determination of the degree of polymerization required to produce a material with the physical properties of natural starch.

4. *Glycogen*

In the animal body, glycogen plays the part of a reserve material, and its physiological importance has led to much research. On the chemical side, its composition is known to be representable by $(C_6H_{10}O_5)_n$; and on hydrolysis it yields maltose in certain conditions and glucose when the hydrolysis is a complete one. These facts indicate that there must be a certain resemblance between glycogen and starch, a resemblance which is increased when it is recalled that starch is the reserve material in plant life.

On methylating glycogen, Macbeth and Mackay[1] obtained after several applications of methyl sulphate a substance having a methoxyl content equal to about 37 per cent. Since the methylation of two hydroxyls in each glucose unit would give 32 per cent. methoxyl, whilst tri-methylation corresponds to 45 per cent. methoxyl, it is clear that Macbeth and Mackay's material is probably a mixture of dimethyl-glycogen and trimethyl-glycogen. Further methylation was not found practicable, either by means of methyl sulphate or by using the silver oxide method; but the presence of three free hydroxyl groups in the glucose nucleus of the molecule was established by acetylation.

On hydrolysis of the methylated glycogen containing 37 per cent. of methoxyl, two main products were obtained which eventually were decomposed into 2 : 3 : 6-trimethyl-glucose and dimethyl-glucose. The resemblance here to the behaviour of starch is obvious; and Macbeth and Mackay suggest that both starch and glycogen are built up from the same basal units. If this be so, the structures proposed by Irvine and MacDonald and given in the preceding section of this chapter, are equally applicable to glycogen.

J.—SOME CYCLIC DERIVATIVES OF THE SUGARS

As long ago as 1837, Biot observed that the addition of boracic acid to a tartaric acid solution had the effect of increasing the rotatory power. A generation later, Vignon obtained similar

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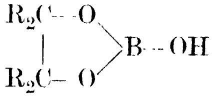
[1] Macbeth and Mackay, *J.*, 1924, **125**, 1513.

results by adding borax to a mannite solution: and since then, the phenomenon has been found in many cases in which polyhydroxy-compounds have been examined. Borax has an alkaline reaction; but when sugar is added to a borax solution, the mixture assumes an acidic character. Van't Hoff[1] suggested that the boracic acid formed a cyclic ester with the hydroxy-compound:—

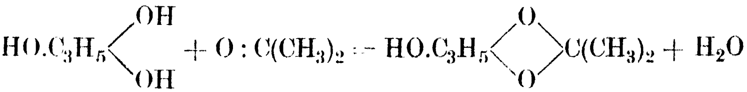


and as cyclic groupings in a molecule are known to increase rotatory power, this explanation fitted the facts.

From an examination of a large number of substances, Walden[2] inferred that the maximum action of the type is exerted by elements of the sixth Group of the Periodic System (molybdenum, tungsten, and uranium), the oxides of which show no marked acid or basic character.

The use of this method of heightening rotatory power in the case of polyhydroxy-compounds of low rotation is so obvious that it need not be described in detail.

A fresh cyclic type was discovered by Fischer, who found that acetone could be condensed with certain polyhydroxy-compounds by employing a catalyst such as hydrogen chloride, zinc chloride, or anhydrous copper sulphate, which assist the elimination of water. For example, glycerine[3] yields acetone-glycerine (isopropylidene-glycerine).



$$HO.C_3H_5(OH)_2 + O:C(CH_3)_2 = HO.C_3H_5O_2C(CH_3)_2 + H_2O$$

Glucose[4] reacts in an analogous manner with two molecules of acetone, forming a diacetone compound.

Members of this class of sugar derivatives are found to be stable in presence of alkali, but they are readily hydrolysed in presence of acid. The converse is the case with another group of cyclic substances[5] which are produced when carbonyl chloride

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[1] Van't Hoff, *The Arrangement of Atoms in Space* (1898), p. 151.

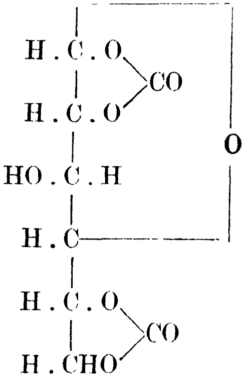
[2] Walden, *Ber.*, 1905, **38**, 345.

[3] Fischer, *Ber.*, 1895, **28**, 1169.

[4] *Ibid.*, **28**, 1145, 2496.

[5] Haworth and Porter, *J.*, 1929, 2796.

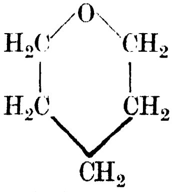
acts upon sugars. These "sugar carbonates" are more stable in acid solutions than the corresponding acetone-compounds; but they are unstable in presence of alkali. As an example of them, glucose carbonate will serve. It is obtained by condensing glucose with carbonyl chloride in pyridine or in mildly alkaline solutions, and it has the structure shown below:—



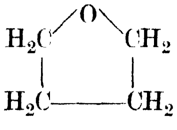
Glucose carbonate.

It is obvious that, in combination with the methylation process, the formation of the acetone-sugars and the sugar carbonates offers most interesting possibilities, some of which have already been realised.[1]

In connection with cyclic groupings, mention must be made of the new nomenclature for the sugar group which has been put forward by Haworth.[2] The normal sugars, with their rings of five carbon atoms and one oxygen atom, are obviously related to tetrahydro-pyrane; whilst the sugars with four carbon atoms and one oxygen atom in their rings are similarly related to tetrahydro-furan.



Tetrahydro-pyrane.



Tetrahydro-furan.

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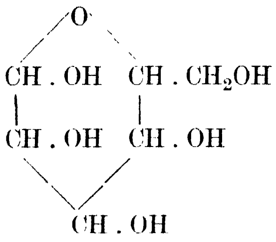
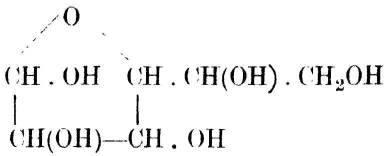
[1] See Haworth, *Constitution of Sugars* (1929), Chapter VII.

[2] *Ibid.*, p. 46; Goodyear and Haworth, *J.*, 1927, 3136.

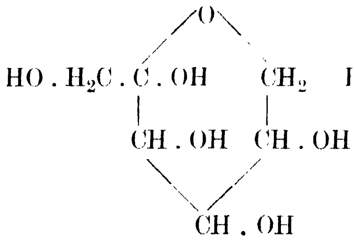
The suggested nomenclature entitles the first set pyranoses, and the second type furanoses. The following examples will make the matter clear :



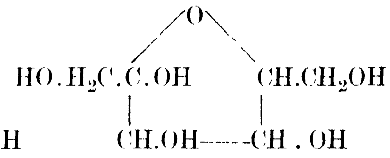
Normal aldohexose
Gluco-pyranose.



γ-Aldohexose
Gluco-furanose.



Normal ketohexose
Fructo-pyranose.



γ-Ketohexose
Fructo-furanose.

One very considerable advantage offered by this new nomenclature is the chance it gives of making a completely fresh start and getting rid of the current jumble of terms such as normal, γ-, amylene-oxide ring, 1 : 4-oxide ring, and so forth. Also, a ring-formula of this type is already familiar in connection with cis-trans isomerism in cyclic compounds ; and Haworth's suggestion, if adopted, will make it much easier to visualize the spatial relationships of the various groups in the sugar molecule.

K.—Conclusion

The foregoing account, lengthy as it is, does not pretend to include all the researches on members of the carbohydrate class which have been carried out during the last ten or fifteen years. Had any effort at completeness been made, the material would have filled a volume instead of a chapter. Since selection of some sort was rendered inevitable by the limitation of available space, it seemed best to pick out from the mass of data those parts which have the greatest theoretical interest and which have the further quality of lending themselves to a logical treatment. As the preceding sections show, this work on the carbohydrates exhibits in a vivid manner how even the most intricate structural problems can be approached with success. In this research the reader can recognize the various stages through which the investigation has passed. First came the initial idea of fixing the labile structures of the carbohydrates by means of methylation, and close on this followed the devising of experimental methods of putting the idea into practice. In the next stage, numbers of definite methylated sugars were prepared which were to serve as comparison compounds in the identification of the fission-products of the methylated carbohydrates of complex constitution. This stage was the longest and most difficult—though it has been passed over lightly in the present chapter—since it represents an enormous amount of detailed work in the case of each sugar examined. At the end of it, all was ready for a great advance; and in the final stage, the most striking feature is the rapidity with which intricate problem after intricate problem is finding its solution.

CHAPTER III

THE SESQUITERPENE GROUP

1. *Introductory*

THE compounds known as terpenes are usually, for convenience, divided into three classes: the hemiterpenes with the formula C_5H_8; the true terpenes, which are reduced benzene derivatives, with the composition $C_{10}H_{16}$; and the sesquiterpenes having the general formula $C_{15}H_{24}$. The hemiterpenes do not occur in nature; but the most characteristic member of the class, isoprene, is obtained by the distillation of rubber, so that evidently the C_5H_8 skeleton is to be found among natural products. The true terpenes, with ten carbon atoms in their structure, are widely distributed, occurring as they do in the saps of many plants. With them are associated the sesquiterpenes.

The investigation of the terpene group as a whole has fallen into fairly well-marked chronological stages. The third quarter of the nineteenth century was devoted to clearing up the problems presented by the cyclic terpenes. At the end of the century, interest passed to the group of olefinic terpenes; and considerable progress was made in that field. The sesquiterpenes have only recently been taken in hand; and even at the present day our knowledge of the field is scanty; though enough has been done to lay bare the outlines of the subject and to suggest the lines along which future work will probably proceed.

The main object of the present chapter is to indicate the inter-relationships of certain among these sesquiterpenes and to describe some of the information which has been gained as to the constitution of these substances.

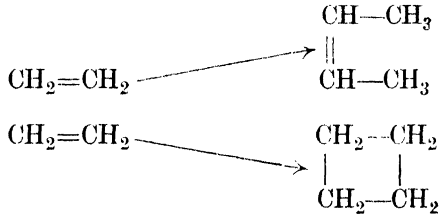
Before entering upon individual problems, however, it seems well to devote a paragraph or two to certain general questions which may serve to simplify the subject.

Inspection of the table below will bring out immediately the simple relationships which the formulæ of the terpenes and of rubber bear to one another :

Hemiterpenes	C_5H_8			—	C_5H_8
Terpenes	C_5H_8	×	2	=	$C_{10}H_{16}$
Sesquiterpenes . . .	C_5H_8	×	3	=	$C_{15}H_{24}$
Rubber	C_5H_8	×	n	=	$(C_5H_8)_n$

These figures suggest at once that the whole terpene group is built up on a basis composed of five carbon and eight hydrogen atoms ; and it will be convenient at this point to examine the various stages of saturation which may result from the polymerization of the C_5H_8 unit.

Two molecules, each containing an ethylenic linkage, can be supposed to unite in either of two ways : (1) to form an open chain ; and (2) to yield a cyclic compound.



Now clearly from the above formulæ it is seen that the linking of the two ethylenic molecules in an open chain has resulted in the disappearance of one ethylenic bond ; whilst when a cyclic structure is produced, two ethylenic bonds disappear.

Let this be applied to the case of the sesquiterpenes. In order to link together three of the fundamental C_5H_8 nuclei, two junctions are necessary : $C_5H_8—C_5H_8—C_5H_8$. Each of these junctions implies the disappearance of one ethylenic bond, if the new molecule has an open-chain structure. Since each isoprene molecule contains two ethylenic linkages, there are six double bonds present at the start. Two of these are used up in forming the long chain ; which leaves four double bonds present in the final product.

Now the formation of a cyclic structure from this long open chain will demand the disappearance of another double bond ; so that obviously a monocyclic sesquiterpene will have only three ethylenic linkages left in its structure.

Further ring-formation to produce a dicyclic sesquiterpene will entail the elimination of yet another double bond, leaving two ethylenic linkages in the dicyclic sesquiterpene molecule.

By the same reasoning, a tricyclic sesquiterpene must have only a single ethylenic bond and a tetracyclic grouping must be a saturated hydrocarbon.

For the sake of clarity, these facts may be put in the form of a table.

Sesquiterpene Type	*Number of Double Bonds*
Olefinic	4
Monocyclic	3
Dicyclic	2
Tricyclic	1
Tetracyclic	0

It may be recalled that the same rules hold good in the group of ordinary terpenes of the composition $C_{10}H_{16}$. These may also be regarded as derived from a polymerization of hemiterpenes containing two double bonds; and the same reasoning leads to the conclusion that olefinic terpenes derived from two hemiterpene molecules should contain three double bonds; whilst monocyclic terpenes such as limonene should contain two ethylenic linkages; and dicyclic members of the group like camphene should have only a single ethylenic bond in their structures. This is, of course, exactly what is found in practice.

In distinguishing between members of the sesquiterpene class, the refractivities of the various sesquiterpene structures yield some assistance. The values calculated for the molecular refractivities of the different isomeric forms are:

Open-chain type	69·60
Monocyclic type	67·87
Dicyclic type	66·13
Tricyclic type	64·40
Tetracyclic type	62·66

These values differ from each other sufficiently to make the refractivity of some help in classifying the various sesquiterpenes, and in suggesting the chemical methods of attack which can best be utilized in determining the constitution of a given substance. An illustration of this will be given in a later section when the constitution of zingiberene is discussed.

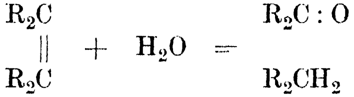
2. *Farnesol, Nerolidol, and Farnesene*

Farnesol[1] has the composition $C_{15}H_{26}O$. It is found in musk kernels, in the flowers of certain acacias (*e.g. Acacia Farnesiana*) and other plants; and it appears to be the main cause of the odour of lindens.

On oxidation, farnesol yields a substance farnesal, which has the composition $C_{15}H_{24}O$. Since its reactions prove farnesal to be an aldehyde, it is clear that farnesol is a primary alcohol. When the oxime of farnesal is dehydrated, it yields a nitrile. On hydrolysis, this nitrile yields farnesenic acid and also a ketone with the composition $C_{13}H_{22}O$. This ketone has been identified as dihydro-pseudo-ionone:

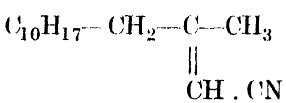
$$(CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3) : CH . CH_2 . CH_2 . CO . CH_3$$

This formation of a ketone by hydrolysis recalls the case of pulegone, which breaks up with the production of methylcyclohexanone and acetone when it is hydrolysed.* The reaction is evidently an addition of water to a double bond in this fashion:



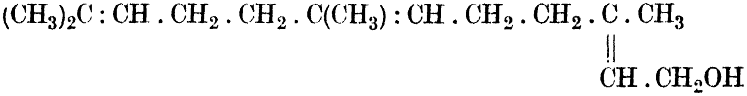
$$\begin{array}{c} R_2C \\ \| \\ R_2C \end{array} + H_2O = \begin{array}{c} R_2C : O \\ \\ R_2CH_2 \end{array}$$

On this basis, the nitrile mentioned above must have the constitution represented by:



$$\begin{array}{l} C_{10}H_{17}-CH_2-C-CH_3 \\ \qquad\qquad\quad\;\; \| \\ \qquad\qquad\quad CH . CN \end{array}$$

and the primary alcohol farnesol must be:



$$\begin{array}{l} (CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3) : CH . CH_2 . CH_2 . C . CH_3 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \| \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH . CH_2OH \end{array}$$

Farnesol.

Isomeric with farnesol, there is a second alcohol known as

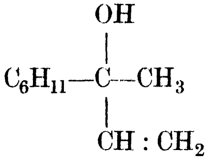
---

[1] Haarmann and Reimer, D.R.P. 149603, 150501; Kerschbaum, *Ber.*, 1913, **46**, 1732; Harries and Haarmann, *ibid.*, 1737; Semmler and others, *Ber.*, 1917, **50**, 1836.

* See Vol. I., p. 190.

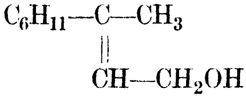
nerolidol[1] (originally named peruviol) which occurs in orange blossom and Peru bark. On treatment with acetic anhydride, nerolidol is rearranged into farnesol, which indicates a close relationship between the two substances. Further, on oxidation, nerolidol yields the same acid, farnesenic acid, which is obtained by the oxidation of farnesol.

This behaviour is an exact parallel to that shown by linalool among the ordinary olefinic terpenes, since it is converted by the action of acetic anhydride into nerol :



$$C_6H_{11}-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle CH:CH_2}{|}}{C}}-CH_3$$

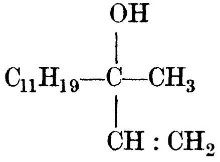
Linalool.



$$C_6H_{11}-\underset{\underset{\displaystyle CH-CH_2OH}{\|}}{C}-CH_3$$

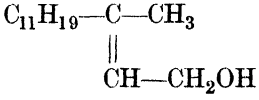
Nerol.

Ruzicka[2] was led by this similarity to suggest that the formulæ of nerolidol and farnesol had analogous endings to their chains so that their formulæ might be written thus :



$$C_{11}H_{19}-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle CH:CH_2}{|}}{C}}-CH_3$$

Nerolidol.



$$C_{11}H_{19}-\underset{\underset{\displaystyle CH-CH_2OH}{\|}}{C}-CH_3$$

Farnesol.

This view was confirmed by the complete synthesis of nerolidol in the following manner. Geranyl chloride (I.) was treated with acetoacetic ester, yielding the dihydro-pseudo-ionone (II.). Condensation of this with acetylene in presence of sodamide resulted in the formation of dehydronerolidol (III.), which on reduction with sodium in moist ether was converted into nerolidol (IV.). This synthetic nerolidol corresponds exactly with natural nerolidol in chemical properties, though of course it was optically inactive whereas natural nerolidol is dextro-rotatory.

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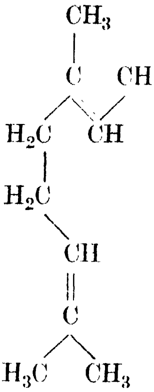
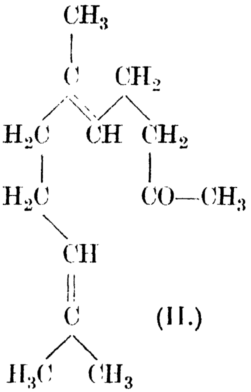
[1] Hesse and Zeitschel, *J. pr. Chem.*, 1902, **66**, 503 ; Thoms, *Arch. Pharm.*, 1897, **237**, 271.

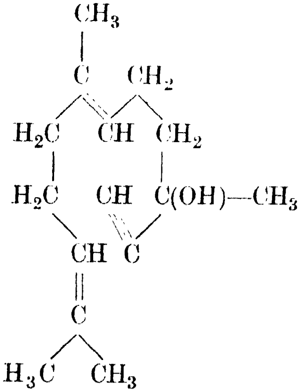
[2] Ruzicka, *Helv. Chim. Acta*, 1923, **6**, 483.



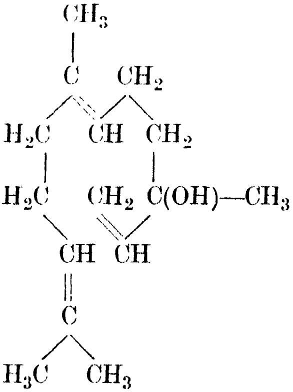
(I.)



(II.)

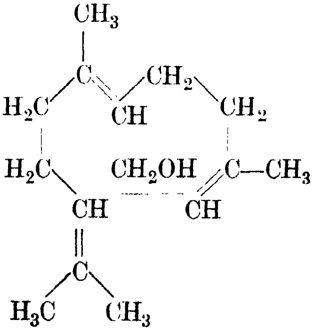


(III.)



(IV.) Nerolidol.

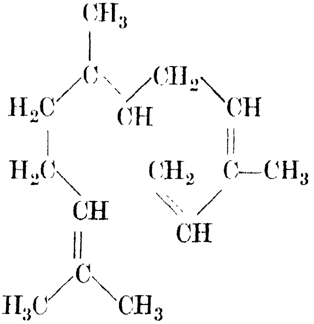
Farnesol is therefore the corresponding analogue of nerol :



Farnesol.

And the formulæ of farnesal and farnesenic acid are got by substituting —CHO and —COOH for the $—CH_2OH$ group in the above.

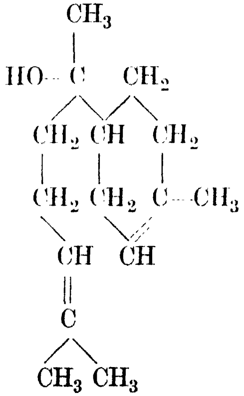
So far, we have been concerned with oxygen derivatives; but we may now turn to the corresponding terpene, farnesene. This is obtained, along with farnesol, when nerolidol is treated with acetic anhydride. It seems probable that its structure is this:



Farnesene.

3. *Bisabolol and Bisabolene* [1]

Farnesene, when acted upon for some hours by cold acetic acid in presence of sulphuric acid, gives rise to the acetate of a monocyclic sesquiterpene alcohol. This alcohol is believed to be α-bisabolol, for which the structure below has been suggested.



α-Bisabolol.

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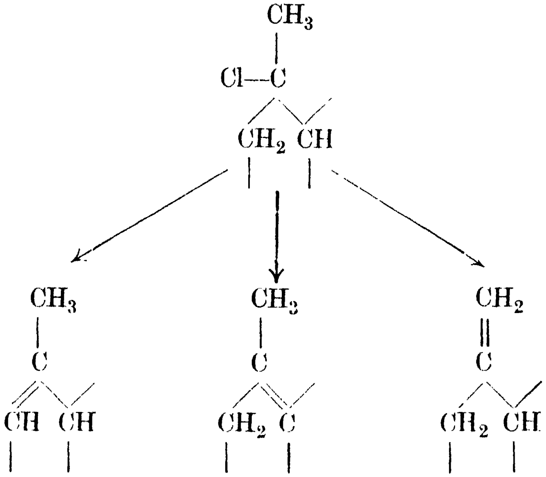
[1] **Ruzicka, *Helv. Chim. Acta*, 1923, 6, 483; Ruzicka and Capato, *ibid.*, 1925, 8, 259.**

The alcohol is separable from farnesol by means of phthalic anhydride, which attacks farnesol but leaves bisabolol unaffected.

The same closure of the farnesol open chain to a monocyclic grouping is brought about by means of 90 per cent. formic acid.

The bisabolol obtained by either of these methods can be converted into a trihydrochloride which is identical with the trihydrochloride obtained from natural bisabolene.

When this synthetic trihydrochloride is heated with acetic acid and sodium acetate, it is converted into a monocyclic sesquiterpene which has been shown to be the same as natural bisabolene. The concordance in properties is not absolutely exact between the natural and synthetic products, probably owing to the fact that hydrogen chloride may be eliminated in three different ways from the molecule :



The synthetic bisabolene is thus in all probability a mixture of two or three hydrocarbons which are very difficult to separate ; and hence a slight divergence between its properties and those of the natural material is to be expected. In boiling-point, density, and refractive index, the values are very close in the case of the two compounds.

Ozonization of either synthetic or natural bisabolene yields [1] acetone, lævulinic acid, and succinic acid. This is easily accounted for, if bisabolene has the following structure.

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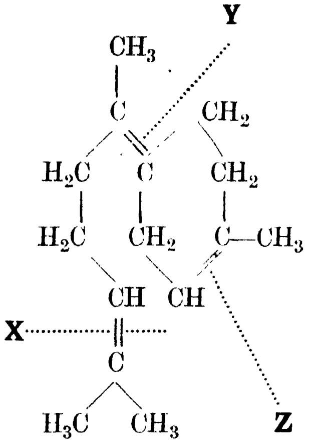
[1] Ruzicka and Veen, *Annalen*, 1929, **468**, 133.



Bisabolene.

Rupture of the molecule at **X** yields acetone ; and further fission at **Y** and **Z** gives rise to two molecules of lævulinic acid, from which succinic acid can be produced by oxidation.

4. *Cadalene and Eudalene*

At this point it seems advisable to indicate how the nature of the sesquiterpene skeletons can be ascertained, since a knowledge of the relationships between the various members of the class is thus made simpler.

In 1903, Vesterberg[1] observed that when abietic acid was heated with excess of sulphur to 200° C. and subsequently to 250° C. a small yield of the hydrocarbon retene was obtained. This process evidently is a method of removing hydrogen and so converting a reduced member of the benzene series into its parent. For some reason, this discovery of Vesterberg's does not seem to have attracted the attention it deserved ; and it was only after a number of years that it found a wider application.

Ruzicka and Meyer[2] applied Vesterberg's method to the sesquiterpene cadinene, and in this way they obtained a new hydrocarbon, cadalene, which has the formula $C_{15}H_{18}$. Since this substance, from its formula, should be highly unsaturated,

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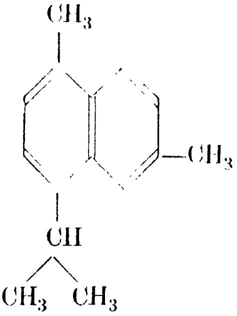
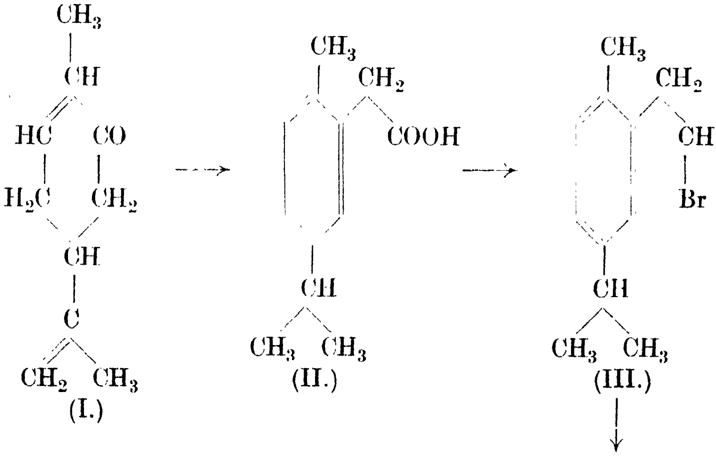
[1] Vesterberg, *Ber.*, 1903, **36**, 4200.

[2] Ruzicka and Meyer, *Helv. Chim. Acta*, 1921, **4**, 505.

it was tested with bromine; but it refused to absorb the halogen. This behaviour suggests a benzenoid character; and that idea is strengthened by cadalene forming a picrate. Potassium permanganate oxidizes cadalene readily at ordinary temperatures; and this suggests the elimination of one or more side-chains attached to a benzenoid nucleus, which, from the molecular formula, might be of the naphthalene type.

By this time the structure of farnesol was known, and a consideration of its formula led Ruzicka and Seidel [1] to the idea that cadinene might have an analogous constitution and that therefore cadalene might be a naphthalene derivative of the following type:





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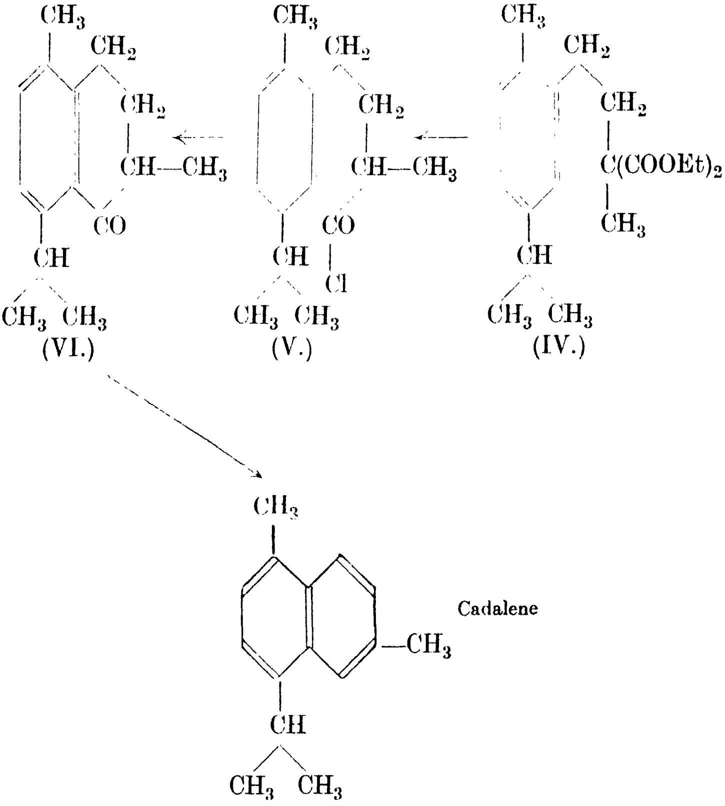
[1] Ruzicka and Seidel, *Helv. Chim. Acta*, 1921, **5**, 369.


(VI.) (V.) (IV.)

Cadalene

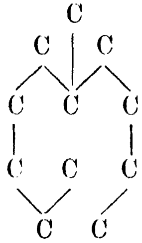
(VII.)

This view they tested by synthesizing this derivative of naphthalene in the following way. Carvone (I.) was converted into 2-cymylacetic ester (II.) by using zinc and bromacetic ester. The cymylacetic acid, obtained from the ester, was reduced to the corresponding alcohol by Bouveault's method; and the alcohol was then converted into the bromide (III.). This bromide was acted on by methyl-malonic ester, whereby the compound (IV.) was produced. This ester was hydrolysed; carbon dioxide was split off from one carboxyl group; and the chloride (V.) of the resulting acid was prepared. On acting on this with aluminium chloride, an internal Friedel-Crafts reaction occurred, with the production of the required naphthalene skeleton (VI.). The compound (VI.) was then converted into the corresponding hydrocarbon by reduction with sodium in alcohol, followed by heating with sulphur. The final compound (VII.) proved to be identical with cadalene derived from sesquiterpenes.

This synthesis evidently establishes the structure of the cadinene skeleton beyond dispute. But investigation shows that cadinene is not the base of all the sesquiterpenes. For instance,[1] when the sesquiterpene alcohol eudesmol and the sesquiterpene selinene are dehydrogenated by the Vesterberg method, the reactions take the course shown below :

$$C_{15}H_{26}O + 3S = C_{14}H_{16} + H_2O + 2H_2S + CH_3 . SH$$
$$C_{15}H_{24} + 3S = C_{14}H_{16} + 2H_2S + CH_3 . SH$$

In each case, it will be noticed, a carbon atom is split off the skeleton of the sesquiterpene derivative ; and in both cases the hydrocarbon produced is eudalene and not cadinene. Since eudalene is an aromatic compound, this behaviour suggests that the eliminated carbon atom must lie in a position which would block the conversion of the sesquiterpene into an aromatic ring-compound ; so that it has to be eliminated when ring-formation occurs. Now by analogy, it seems reasonable to suppose that the ring-compound formed is a naphthalene derivative ; and this implies that the eliminated carbon atom must be attached originally to one of the two carbon atoms common to the two benzene nuclei in the naphthalene structure :



If it were attached anywhere else, it would merely become the nucleus of a normal substituent group ; whereas in this particular position it must be removed before cyclization can occur, since these two atoms in the naphthalene structure carry no substituent groups.

This view of the position of one methyl group in the eudalene structure leaves the remainder of the constitution unsettled ;

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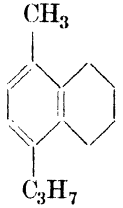
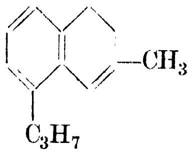
[1] Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, **1922, 5, 345.**

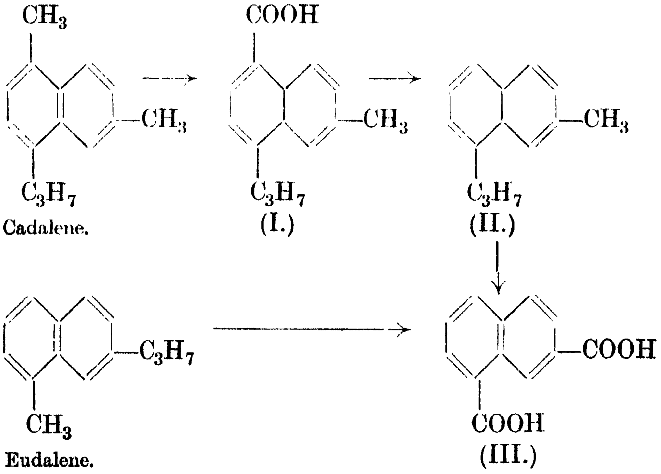
and the next point is to establish the location of the remaining substituents. The first possibility which need be considered is that eudalene is *apo*-cadalene. If so, it must have either of the following structures :





This conception of eudalene's constitution is negatived decisively by the fact that Ruzicka and Mingazzini[1] synthesized both these compounds and found them to be different from eudalene.

A fresh hypothesis is suggested by the following evidence. When cadalene is oxidized with chromic acid,[2] it yields a naphthoic acid, which proved to be 6-methyl-4-isopropyl-1-naphthoic acid (I.). On heating this with soda-lime, the carboxyl group is eliminated ; and on oxidizing the methyl-isopropyl-naphthalene (II.) thus formed, the product is 1 : 7-naphthalene dicarboxylic acid (III.) Now the same acid is produced from eudalene on oxidation. Since eudalene is not *apo*-cadalene, the only possible explanation of these reactions is the one indicated in the formulæ below :



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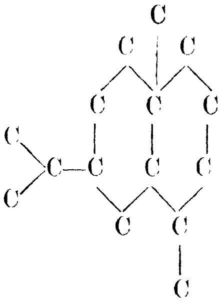
[1] Ruzicka and Mingazzini, *Helv. Chim. Acta*, 1922, **5**, 710.

[2] Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, **5**, 345.

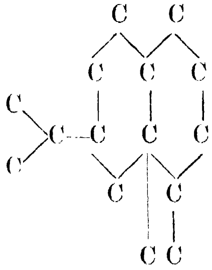
Eudalene is therefore a position-isomer of *apo*-cadalene (II.), the situations of the methyl and isopropyl groups being exchanged.

This view has been confirmed by a synthesis of eudalene[1] on the same lines as that already described in the case of cadalene.

Since it has already been shown that the carbon atom eliminated during the formation of eudalene from the sesquiterpenes must be attached to one or other of the central atoms of the naphthalene structure, only two possible sesquiterpene skeletons can be made to agree with the facts :



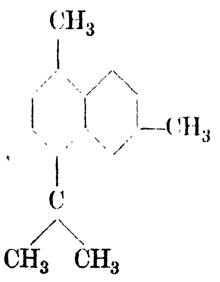
(I.)



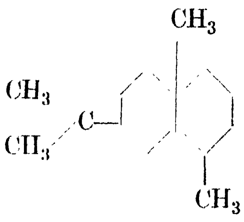
(II.)

Since (II.) cannot be derived from three molecules of isoprene owing to the contiguity of the two methyl radicles which it entails, the skeleton (I.) is to be preferred.

It is thus established that two main types of skeleton exist in the sesquiterpene series : the cadalene type and the eudalene type :



Cadalene Type.



Eudalene Type.

The manner in which skeletons of these types can be built up from isoprene molecules is suggested in the formulæ below :

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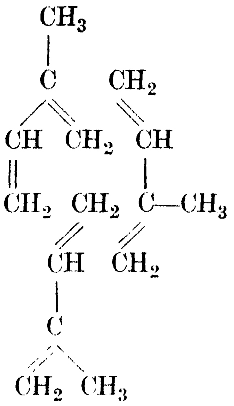
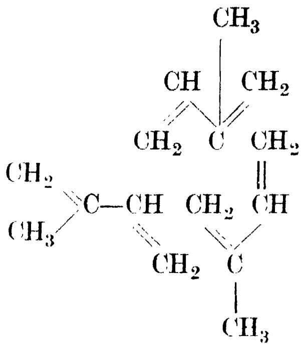
[1] Ruzicka and Stoll, *Helv. Chim. Acta*, 1922, 5, 923.



Cadalene Type.



Eudalene Type.

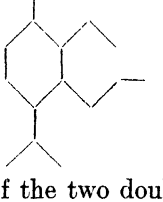
It will be seen from the above arrangements that the three isoprene molecules could be linked together into (1) an olefinic open chain; (2) a monocyclic grouping with three side-chains; or (3) a reduced naphthalene derivative with three side-chains.

5. *Cadinene and the Cadinols*

Cadinene is a widely-distributed sesquiterpene found in oleum cadinum, oil of cubebs, galbanum oil, the oil of angostura rind, juniper wood, and many other sources.

It is optically active, showing that it contains at least one asymmetric carbon atom; and it takes up two molecules of hydrogen chloride, which indicates that it has two double bonds in its structure.

On dehydrogenation by Vesterberg's method or with platinum black in vacuo at 300° C. it yields cadalene,[1] which establishes the fact that it contains the skeleton:



This leaves the positions of the two double bonds still in doubt.

Since the isopropyl group appears in cadalene, it seems probable that it exists also in cadinene; which leads to the

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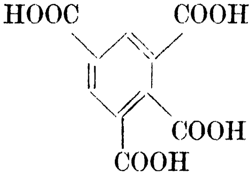
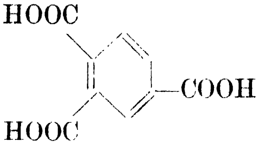
[1] Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, **7**, 84.

inference that both the cadinene double bonds are situated in the cyclic portion of the structure. Now on ozonization, cadinene yields a product which contains all the carbon atoms of cadinene. This disposes of the possibility that both double bonds are in the same ring of the structure, since in this case the carbon atoms between the two double bonds would be eliminated during the decomposition of the ozonide. Further, attempts to reduce cadinene with sodium and amyl alcohol proved unsuccessful, which suggests that the two double bonds do not form a conjugated system.

Oxidation with manganese dioxide and sulphuric acid leads to the production of mellophanic acid (I.) and trimellitic acid (II.):



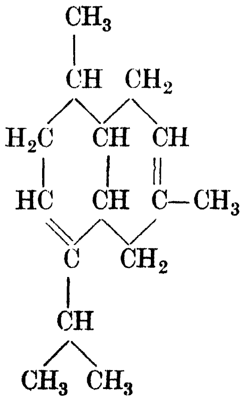
(I.)

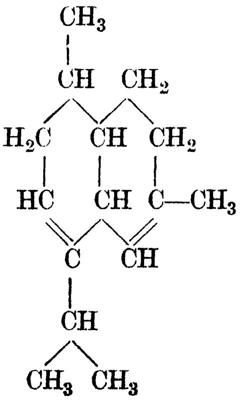


(II.)

which seems curious, as the formation of prehnitic acid instead of mellophanic might have been expected from the skeleton of the compound.

It will be seen that this information still leaves the determination of the true positions of the double bonds open for further research. At present, all that can be done is to adopt tentatively the conclusion arrived at by Ruzicka and Stoll, who regard cadinene as being possibly a mixture of two compounds with the structures shown below:



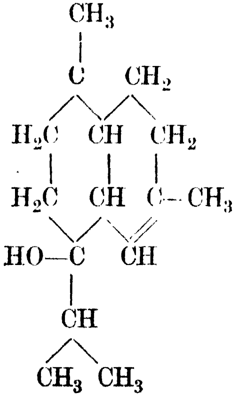


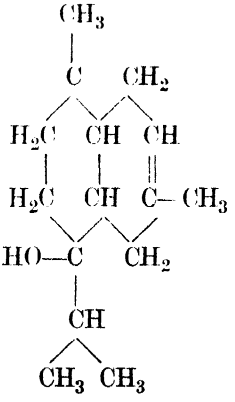
Closely related to cadinene is the sesquiterpene alcohol cadinol [1] which is found in galbanum oil. By the loss of a molecule of water, cadinol is converted into cadinene, so that it evidently contains the cadalene skeleton. Since the hydroxyl group of cadinol fails to interact with phthalic anhydride, it may be inferred that cadinol is a tertiary alcohol.

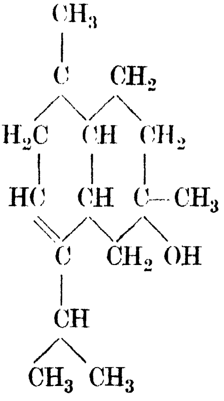
With some difficulty, cadinol was reduced to dihydrocadinol by means of hydrogen and platinum black; and on boiling the dihydro-derivative with 90 per cent. formic acid, a dihydrocadinene was produced.

On ozonizing this dihydrocadinene, a keto-aldehyde and a keto-acid were produced by the disruption of the remaining single bond. By ozonizing cadinene itself, a compound $C_{15}H_{24}O_2$ was obtained, which was conjectured to be an unsaturated keto-alcohol. This substance when treated with 95 per cent. formic acid yielded a ketone $C_{15}H_{22}O$, containing two double bonds. On oxidation with manganese dioxide and sulphuric acid, this ketone yielded only mellophanic acid.

In order to account for these rather confusing results, Ruzicka and Stoll suggested that "cadinol" is really a mixture of three substances corresponding to the formulæ shown below. It will be seen that even this does not entirely clear away the whole of the problem's difficulties.


α-Cadinol.


β-Cadinol.


γ-Cadinol.

The action of concentrated formic acid upon cadinene has

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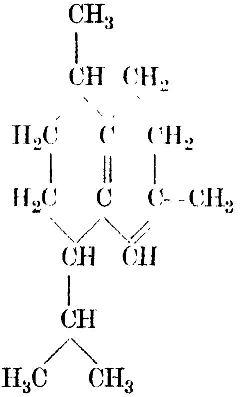
[1] Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, 7, 94.

been studied independently by Robertson, Kerr, and Henderson.[1] The chief product was found to be a sesquiterpene (or mixture of sesquiterpenes) which refused to form any stable compound with hydrochloric acid.

On heating cadinene with glacial acetic and sulphuric acids, Henderson and Robertson[2] obtained an isocadinene, which seems to be produced also by heating cadinene in a sealed tube with glacial acetic acid. This last product easily resinified in air, decolorized permanganate solution and absorbed bromine with the liberation of hydrogen bromide. It refused to yield a solid nitrosochloride, nitrosite, or nitrosate. Further investigation[3] has shown that this isocadinene is probably identical with a sesquiterpene previously obtained from cade oil[4] and differs from cadinene only in the positions of the double bonds. The physical properties of isocadinene show so close a resemblance to those of one of the hydrocarbons synthesized by Ruzicka and Capato, as mentioned above, that it seems almost certain that all three compounds have a common structure.

Henderson and Robertson suggest the following formula for isocadinene :



Isocadinene.

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[1] Robertson, Kerr, and Henderson, *J.*, 1925, **127**, 1944.

[2] Henderson and Robertson, *J.*, 1924, **125**, 1992.

[3] *Ibid.*, 1926, **129**, 2811.

[4] Tröger and Feldmann, *Arch. Pharm.*, 1898, **236**, 692.

6. *Zingiberene* [1]

This sesquiterpene, found in ginger oil, presents certain points of interest owing to sundry anomalies in its behaviour. Its molecular refraction is 68·37, which obviously lies between the values 69·60 and 67·87, which have been calculated for an open-chain and a monocyclic sesquiterpene. It ought therefore to have in its structure at least two, and possibly three, double bonds. In practice, however, it takes up only two molecules of hydrogen chloride; and it refuses to form a trihydrochloride. Further, it was found impossible to regenerate zingiberene from the dihydrochloride.

A partial explanation of these anomalies is to be found on the basis of two assumptions. First, if zingiberene is a monocyclic sesquiterpene containing two conjugated double bonds, the well-known optical effect of conjugation might tend to raise its refractivity above the normal calculated value for this class. Secondly, under the action of hydrochloric acid, zingiberene might become converted into a dicyclic structure by ring-closure; and this new isozingiberene might not be reconvertible into the original hydrocarbon.

In the first place, it is necessary to prove that in zingiberene there are actually three double bonds. This has been done by reducing the hydrocarbon with hydrogen in presence of platinum black, whereby hexahydro-zingiberene, $C_{15}H_{30}$, is formed. From this it is clear that zingiberene is actually a monocyclic sesquiterpene.

Secondly, it is necessary to clear up the question of the possible conjugation of the bonds in the zingiberene structure. On reducing zingiberene with sodium and alcohol, two hydrogen atoms are attached to the molecule, producing dihydro-zingiberene, $C_{15}H_{26}$. The molecular refraction of this dihydro-derivative was found to be 68·36, whilst the calculated value, on the basis of two isolated double bonds in the molecule, is 68·25. The agreement here is close enough to prove that the two double bonds in the molecule are isolated from each other;

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[1] Semmler and Becker, *Ber.*, 1913, **46,** 1814; Ruzicka, Meyer, and Mingazzini, *Helv. Chim. Acta*, 1922, **5,** 359; Ruzicka and Veen, *Annalen*, 1929, **468,** 143.

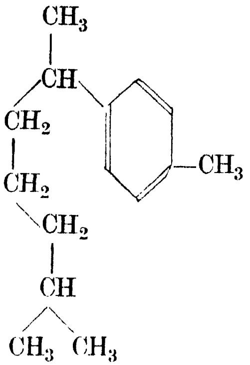
and when it is compared with the marked divergence between observed and calculated values in the case of zingiberene itself, it is sufficient to suggest that during the reduction the conjugated system has been attacked and replaced by a single ethylenic linkage.

Thirdly, we must consider the conversion of zingiberene into isozingiberene. By treating zingiberene with glacial acetic acid and sulphuric acid for some hours, isozingiberene was produced. Its refractive index was found to be 66·50, whilst that calculated for a dicyclic sesquiterpene is 66·13; so that the agreement between the values is fair. Further, on reduction with hydrogen and platinum black, isozingiberene yields a tetrahydro-derivative instead of the hexahydro-compound obtained under similar conditions from zingiberene; which shows that one double bond of zingiberene has disappeared during the formation of isozingiberene. This evidence proves conclusively that isozingiberene is a dicyclic sesquiterpene.

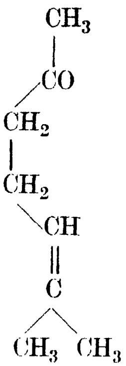
Fourthly, the question of the action of hydrogen chloride must be examined. When isozingiberene is treated with hydrogen chloride in dry ether, it yields the same dihydrochloride as that which is obtained from zingiberene itself under identical conditions. This proves that the dihydrochloride arises from isozingiberene, which has only two double bonds; and that it is formed from zingiberene itself only after a cyclization has taken place under the action of the hydrogen chloride. On treatment with alcoholic potash, the dihydrochloride regenerated isozingiberene without any accompanying zingiberene. This evidence shows definitely that zingiberene itself is converted into isozingiberene before any attachment of hydrochloric acid occurs.

Fifthly, both zingiberene and isozingiberene yield cadalene on treatment with sulphur by Vesterberg's method. This proves that both the monocyclic and dicyclic hydrocarbon have the cadalene skeleton as their bases.

Sixthly, when hexahydro-zingiberene is dehydrogenated by passing it over palladised charcoal, ζ-*p*-tolyl-β-methylheptane (I.) is formed, which on oxidation with chromic acid yields acetic, oxalic, and terephthalic acids. The dehydrogenation product (I.) has been synthesised by acting on methyl-heptenone (II.) with magnesium *p*-tolyl bromide and subsequently subjecting the resulting compound to dehydration and catalytic reduction.

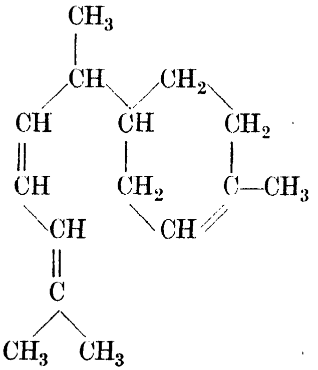


(I.)

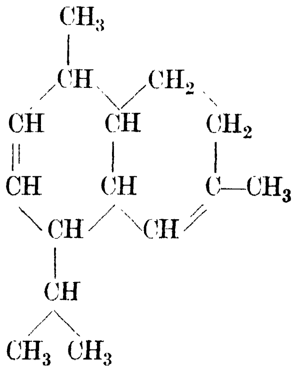


(II.)

Fitting together the foregoing evidence, the following structures may be ascribed to zingiberene and isozingiberene :



Zingiberene.



Isozingiberene.

The position of the methyl group in the side-chain of zingiberene (and that of the corresponding methyl radicle in the isozingiberene formula) is not the same as that which was proposed by Semmler. He placed the methyl group on the adjacent atom of the side-chain ; but obviously his proposed structure could not yield cadalene.

It will be seen from the foregoing that the zingiberene problem presents some points of interest ; and that it illustrates the manner in which refractive index can be utilized as an aid in the field of the sesquiterpenes.

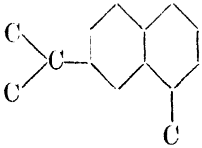
7. *The Selinenes*

The compounds hitherto discussed in this chapter have all been based on the cadalene skeleton; but with the selinenes we reach the eudalene group.

Celery-seed oil contains a sesquiterpene originally termed selinene, but now known as β-selinene in order to distinguish it from an isomeric hydrocarbon which is obtained from it in the following way. Like cadinene, β-selinene yields a bis-hydrochloride; and by careful treatment of this hydrochloride with caustic soda in methyl-alcohol solution, an isomer of natural selinene is produced. This α-selinene, as it is termed, unites with hydrochloric acid again to form the same bishydrochloride as is obtained from β-selinene; but the two hydrocarbons are not identical, being structurally isomeric with each other.

This is easily proved from the results of ozonization.[1] The β-selinene gives a good yield of a diketone, $C_{13}H_{20}O_2$, along with minor quantities of acidic oxidation-products. The α-selinene, on the other hand, produces only a small yield of this ketone; and its main product is a dicarboxylic acid, $C_{14}H_{22}O_4$. On further oxidation with alkaline bromine solutions, both the ketone and the dicarboxylic acid are converted into the same tricarboxylic acid, $C_{12}H_{18}O_6$.

When treated with sulphur by the Vesterberg method[2] both selinenes yield eudalene; so that both of them contain the skeleton:



In order to account for the convertibility of β-selinene into α-selinene through a bishydrochloride common to both compounds, the simplest assumption is that the difference between the two sesquiterpenes is merely in the position of a double bond with respect to one carbon atom in the molecule.

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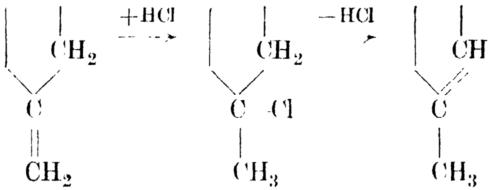
[1] Semmler and Risse, *Ber.*, 1912, **45,** 3301, 3725.

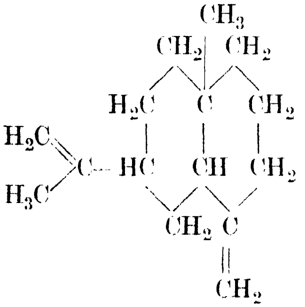
[2] Ruzicka, Meyer and Mingazzini, *Helv. Chim. Acta*, 1922, **5,** 345.

In α-selinene, the bond is supposed to be in the ring; whilst in β-selinene it is assumed to unite a methylene group to the rest of the molecule:

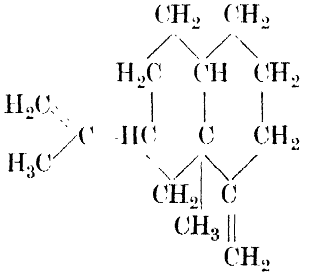


β-Selinene. α-Selinene.

If this view be adopted, it helps to make clear one of the difficulties of the selinene problem; but we have still to define the position of the methyl group which disappears during the conversion of selinene into eudalene. Two positions are possible for this group, as was pointed out in an earlier section of this chapter; so that even on the above assumptions, natural selinene may be either (I.) or (II.).



(I.)



(II.)

When α-selinene is boiled with alcoholic sulphuric acid, the double bond of the isopropylene group apparently migrates into the ring and a mixture of two substances is formed. These have been termed δ- and ε-selinene.[1]

The oxidation of (I.) would yield a tricarboxylic acid (I*a*.), whilst the oxidation of (II.) would yield an acid of the structure (II*a*.).

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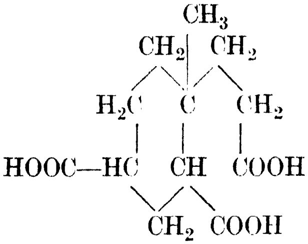
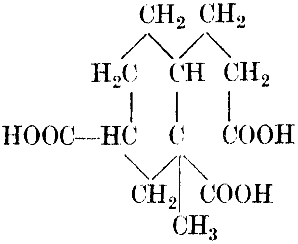
[1] **Ruzicka and Stoll, *Helv. Chim. Acta*, 1923, 6, 846.**

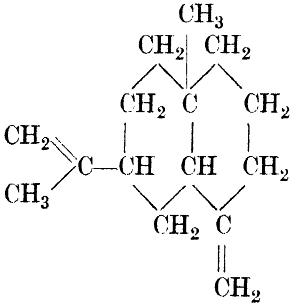


(I*a*.)

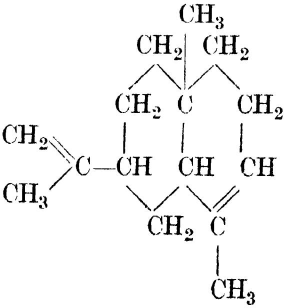


(II*a*.)

Now the actual tricarboxylic acid obtained from both forms of selinene is easily esterified [1] to a tri-ester. An acid of formula (II*a*.), on the contrary, would be subject to steric hindrance owing to one of the —COOH groups being attached to a tertiary carbon atom. The evidence, therefore, is in favour of the tricarboxylic acid having the formula (I*a*.); and hence the position of the eliminated methyl group is probably as shown in formula (I.). The structures of the two selinenes are thus, in all likelihood, those which are shown below :



β-Selinene.



α-Selinene.

8. *Eudesmol*

The structure of this sesquiterpene alcohol from eucalyptus has been settled in the following manner.[2]

Application of the Vesterberg method proves that eudesmol has the same carbon skeleton as that of selinene :—

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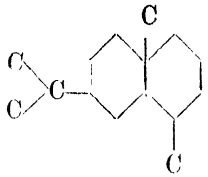
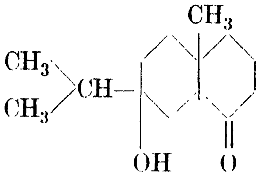
[1] Ruzicka and Stoll, *Helv. Chim. Acta*, 1923, **6**, 846.

[2] Ruzicka and Capato, *Annalen*, 1927, **453**, 62.



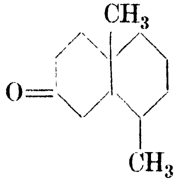
On ozonolysis, eudesmol loses one carbon atom and yields a methyl-isopropyl-decalolone, which has this structure :—



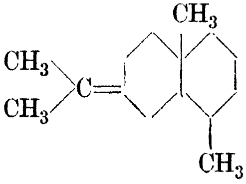
This establishes the position of one double bond in the eudesmol architecture.

If the hydroxyl group of eudesmol lay in the isopropyl side-chain, then eudesmol's bishydrochloride would be identical with that of selinene, which is not found to be the case. The hydroxyl radicle, therefore, must be directly attached to the ring at some point.

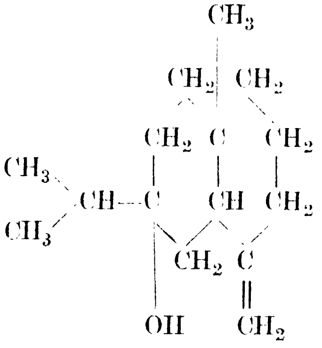
When eudesmol is reduced and then dehydrated, the product, dihydro-eudesmene, can be ozonized to a dimethyl-decalone of the following constitution :—



The position of the oxygen atom in this compound was evidently occupied by the group : $C(CH_3)_2$ in dihydro-eudesmene, which therefore must have the structure :—



Since this double bond came into existence by the removal of water from dihydro-eudesmol, and since the hydroxyl group involved was not attached to the side-chain, it is obvious that the —OH must be attached to the ring-carbon atom ; and hence the eudesmol structure can be expressed thus :—



Eudesmol.

9. *a-Santalol*

Sandalwood oil contains a large number of ethereal oils such as santene, C_9H_{14}, teresantalol, $C_{10}H_{16}O$, the santalenes, $C_{15}H_{24}$, and β- and α-santalol. In the present section the constitution of this last substance will be discussed.[1] To save continual repetition, the α- will be omitted and the compound will be referred to simply as santalol.*

Santalol has the formula $C_{15}H_{24}O$. On oxidation with chromic acid, it yields an aldehyde, santalal, $C_{14}H_{21}.CHO$. This proves santalol to be a primary alcohol.

Further oxidation converts santalal into a lower aldehyde, ekasantalal, $C_{11}H_{17}.CHO$, which is also obtained direct from santalol by ozonization. This indicates that santalol has three carbon atoms separated from the rest of its structure by a double bond which is attacked by the ozone.

[1] Semmler and others, *Ber.*, 1907, **40,** 1120 ; 1908, **41,** 1488 ; 1909, **42,** 584 ; 1910, **43,** 1722, 1890 ; 1913, **46,** 2300.

* The reader is advised to consult the scheme on p. 122 as an aid to the comprehension of this section.

From ekasantalal, through its oxime and nitrile, the acid $C_{11}H_{17}$. COOH, ekasantalic acid, is obtained, which can also be produced by direct oxidation of santalol with potassium permanganate. This last reaction shows that ekasantalic acid contains no double bond; for if it did, then further oxidation by the permanganate would take place. But if it contains no double bond in its structure, ekasantalic acid must be a tricyclic substance. Evidently this tricyclic system of ekasantalic acid is the kernel of the santalol structure. We shall return to it later.

On heating with acetic anhydride and sodium acetate, ekasantalal yields the acetate of its enolic form:

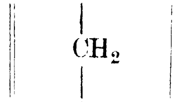
$C_{10}H_{15}.CH_2.CHO$	$C_{10}H_{15}.CH:CH(OH)$	$C_{10}H_{15}.CH:CH.O.CO.CH_3$
Ekasantalal.	Enolic form.	Ekasantalal acetate.

This reaction proves that ekasantalal has at least one hydrogen atom attached to the carbon carrying the aldehydic radicle, as otherwise enolization could not take place.

On oxidation, ekasantalal acetate yields *nor*ekasantalic acid, $C_{10}H_{15}$. COOH, which is obviously the lower homologue of ekasantalic acid, $C_{11}H_{17}$. COOH.

*Nor*ekasantalic acid on reduction yields the aldehyde *nor*ekasantalal, C_9H_{13} . CH_2 . CHO, which forms an acetate like ekasantalal and can thus be converted into teresantalic acid, C_9H_{13} . COOH.

Finally, when teresantalic acid is boiled with dilute sulphuric acid, it loses carbon dioxide and is converted into santene, C_9H_{14}, which has been shown by synthesis [1] to have the following structure:—



Santene.

The scheme given below shows the various steps outlined in the foregoing paragraphs.

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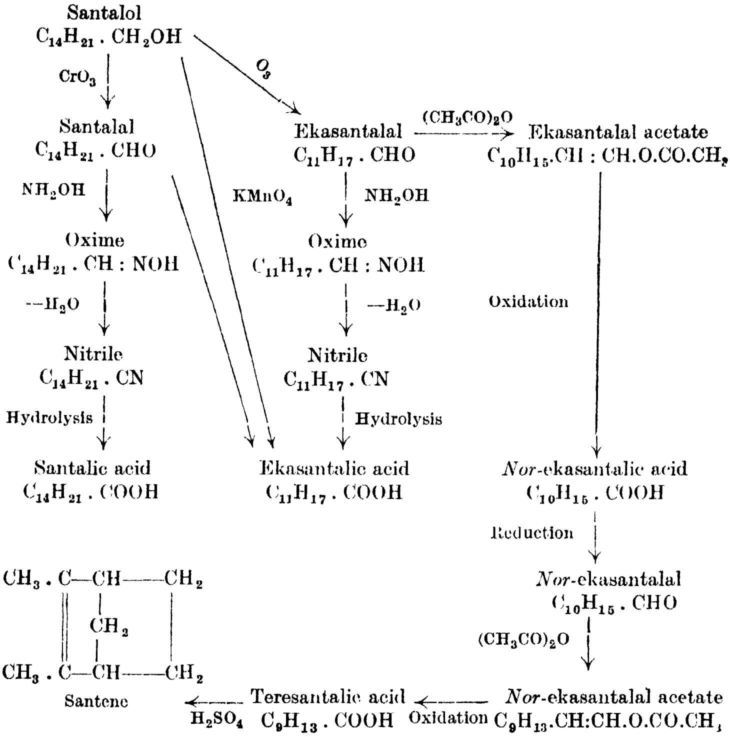
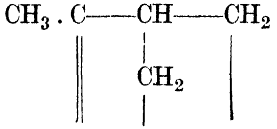
[1] Komppa and Hintika, *Bull. Soc. chim.*, 1917 (4), **21**, 13.



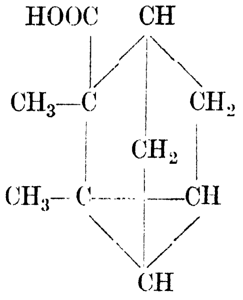
In order to establish the santalol constitution, it is now necessary to retrace these steps in the inverse order, beginning with the known constitution of santene:



Santene.

In order to pass from santene back to teresantalic acid, a carboxyl group must be fitted into the molecule. At the same time, a further condition must be fulfilled. Santene is an unsaturated compound and its double bond offers a point of attack to oxidizing agents. No such group can be present in teresantalic acid. If it were, then teresantalic acid would be oxidized as soon as it was formed during the oxidation of *nor*-

ekasantalal acetate. The only plausible way of getting round this difficulty is to assume that teresantalic acid is a tricyclic substance—a conclusion supported by the refractivity of the compound. Semmler, from a complete examination of the properties of teresantalic acid, has attributed to it the structure shown below; and this seems the most probable, though it cannot be said to be absolutely proved.



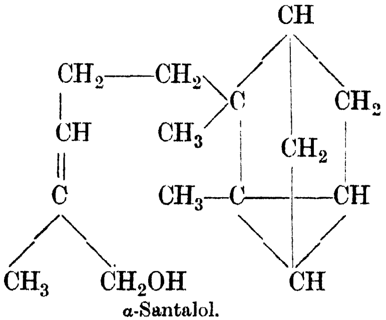
Teresantalic Acid.

The rest of the reconstruction is simple. Since santalol is a primary alcohol, the alcoholic radicle must lie at the extreme end of the chain which is attached to the tricyclic system.

Further, since ozone breaks off three carbon atoms from the santalol system, there must be a double bond between the third and fourth carbon atoms of the side-chain.

Lastly, this side-chain must be attached to the tricyclic system at the point where the carboxyl group lies in teresantalic acid.

This reasoning leads to the following structure for santalol :—



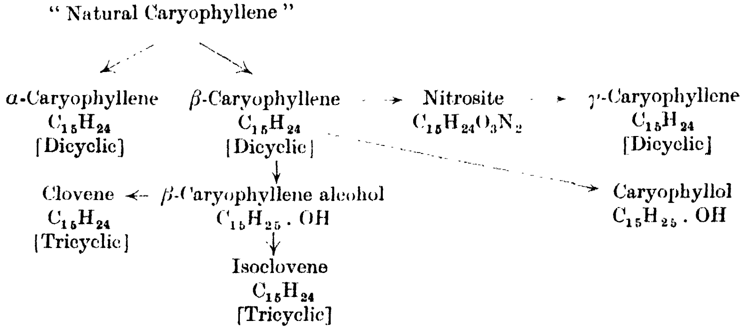
a-Santalol.

A possible alternative to this is a formula in which the side-chain is a normal one throughout, instead of having the branch shown at the end of it in the above formula. This matter is at present unsettled.

10. *The Caryophyllenes and Clovenes*

Eugenol occurs in the buds of *Eugenia caryophyllata Thunb.*, but in addition to it Wallach and Walker [1] isolated a second terpene fraction to which they gave the name caryophyllene. By the action of nitrosyl chloride, Deussen [2] obtained from "natural caryophyllene" two independent nitrosochlorides, one of which was optically inactive, the other optically active. Thus "natural caryophyllene" is a mixture of inactive α-caryophyllene and active β-caryophyllene. By the action of sodium nitrite and acetic acid, β-caryophyllene yields a nitrosite which, on boiling with alcohol, is converted into γ-caryophyllene. On heating "natural caryophyllene" with glacial acetic and dilute sulphuric acids, hydration occurs and the product is caryophyllene alcohol, which on dehydration yields a fresh hydrocarbon clovene.[3] By a modification of the dehydration process, Henderson, McCrone, and Robertson obtained, along with clovene, a second hydrocarbon which they termed isoclovene.[4] By using silver acetate in glacial acetic acid, Henderson, Robertson and Kerr [5] obtained a second hydration-product of caryophyllene, which they termed caryophyllol.

The following scheme will make these relationships clearer.



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[1] Wallach and Walker, *Annalen*, 1892, **271**, 283.

[2] Deussen, *Annalen*, 1907, **356**, 1.

[3] Wallach and Walker, *Annalen*, 1892, **271**, 283.

[4] Henderson, McCrone, and Robertson, *J.*, 1929, 1368.

[5] Henderson, Robertson, and Kerr, *J.*, 1926, **129**, 62.

With regard to the number of rings in each of these compounds, the evidence is fairly clear. A dicyclic sesquiterpene, $C_{15}H_{24}$, must contain two double bonds in its structure ; whilst a tricyclic one has only a single bond. Now α-caryophyllene forms a nitrosochloride, by which process one double bond is saturated ; and this nitrosochloride takes up one molecule of halogen acid, proving the presence of a second double bond in the molecule.[1] The nitrosite of β-caryophyllene is obviously formed by the attachment of N_2O_3 to one double bond ; and it takes up a molecule of halogen acid, which establishes the presence of a second double bond.[1] The fact that γ-caryophyllene contains two double bonds is proved by its forming a bishydrochloride.[2] In the cases of clovene and isoclovene, the necessary evidence is furnished by refractive index measurements.[3] The molecular refractions of the various $C_{15}H_{24}$ types, calculated from the usual formula, are as follows :—

Openchain	compound	with	4	double	bonds	$[R_L]_D = 69·60$
Monocyclic	,,	,,	3	,,	,,	$[R_L]_D = 67·87$
Dicyclic	,,	,,	2	,,	,,	$[R_L]_D = 66·13$
Tricyclic	,,	,,	1	,,	,,	$[R_L]_D = 64·40$
Tetracyclic	,,	,,	0	,,	,,	$[R_L]_D = 62·66$

The experimental value for clovene is $[R_L]_D = 64·1$, and for isoclovene it is $[R_L]_D = 64·11$, both values being close to the 64·40 required for a tricyclic substance.

Beyond this stage, only tentative suggestions can be made, since the degradation-products have not thrown much light on the structures of the compounds.

Attempts to dehydrogenate the components of natural caryophyllene failed to produce any hydrocarbon of the naphthalene series ; and this has been adduced as a proof that a bridged ring is present in all of them.

It will be sufficient here to set down the formulæ which have been provisionally proposed.

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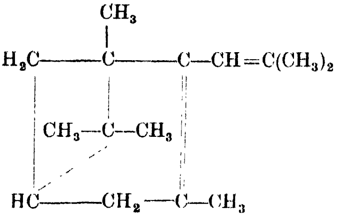
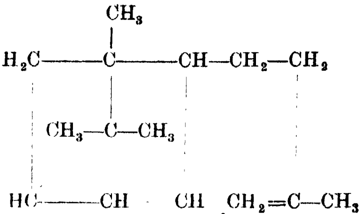
[1] Deussen, *Annalen*, 1912, **388**, 157 ; *J. pr. Chem.*, 1914, [2], **90**, 325.

[2] Deussen, *Annalen*, 1907, **356**, 20 ; 1908, **359**, 251 ; 1912, **388**, 154.

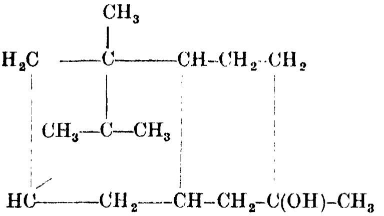
[3] Henderson, McCrone, and Robertson, *J.*, 1929, 1368.



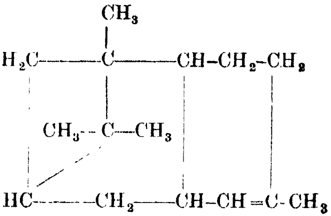
β-Caryophyllene.
(Semmler)



γ-Caryophyllene.
(Deussen)



β-Caryophyllene Alcohol.
(Henderson)



Clovene.
(Henderson)

It must be admitted, however, that β-caryophyllene yields no dihydro-derivative on treatment with sodium and alcohol, as it might be expected to do if it really contained a pair of conjugated double bonds ;[1] whilst the reported occurrence of unsymmetrical dimethyl-succinic acid among the oxidation products is not accounted for by the formula.

11. *Some other Terpenes*

The foregoing pages have given some information about the methods now being applied to the determination of certain terpene structures; and although, in the available space, a complete account of the field is impossible, yet enough has been said to indicate the broad outlines of the subject.

Before concluding this chapter, a few words may be devoted to some cases in which the application of the Vesterberg method has revealed the skeletons of sesquiterpenes and polyterpenes, though we have to await further research before we can elucidate the finer details of the various structures.

The sesquiterpene calamenene, from calamus oil, the corresponding alcohol calamenol, and a sesquiterpene alcohol from Javanese citronella oil, have all been shown to have a kinship with cadalene.[2]

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[1] **Deussen, *J. pr. Chem.*, 1926, 114, 63.**

[2] **Ruzicka, Meyer, and Mingazzini, *Helv. Chim. Acta*, 1922, 5, 345.**

CHAPTER IV

THE DITERPENES AND TRITERPENES

1. *The Camphorenes*

THE investigation of the diterpenes and the triterpenes is as yet only in its beginnings; and it is unnecessary in this volume to do more than indicate the lines on which work is proceeding in this fresh field. Two examples will suffice: the diterpenes α- and β-camphorene, $C_{20}H_{32}$, and the dihydro-triterpene squalene, which has the formula $C_{30}H_{50}$.

When oil of camphor is distilled under reduced pressure, the fraction which comes over at 180°–190° C. under 11 mm. pressure is separable into two hydrocarbons [1] having the molecular weight corresponding to $C_{20}H_{32}$. One of these substances—α-camphorene—is distinguished by the fact that it yields a tetrahydrochloride, $C_{20}H_{36}Cl_4$, when it is treated with hydrogen chloride.

The hydrocarbon regenerated from this tetrahydrochloride had a molecular refraction of 90·6, which is very close to the value (90·49) calculated for a molecule containing four ethylenic linkages. This is confirmed by the fact that on catalytic reduction [2] the hydrocarbon takes up eight hydrogen atoms and forms an octahydride, $C_{20}H_{40}$.

Of especial interest is the fact that α-camphorene has been detected among the dimyrcenes which are formed [3] when myrcene is heated for several hours in a sealed tube at 250°–260° C. This reaction not only indicates a genetic relationship between

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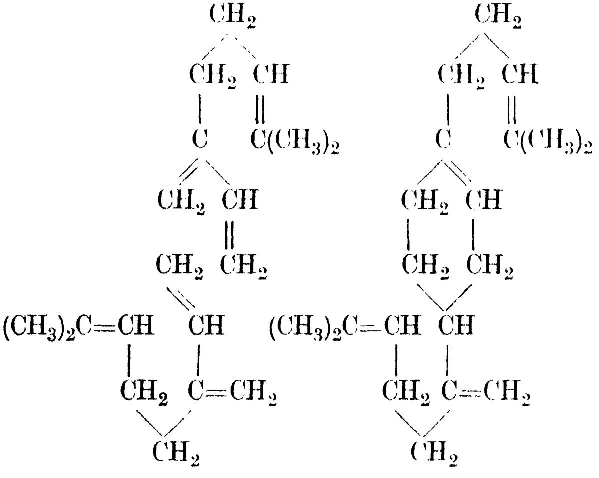
[1] Semmler and Rosenberg, *Ber.*, 1913, **46**, 771.

[2] Semmler and Jonas, *Ber.*, 1914, **47**, 2077.

[3] *Ibid.*, 1913, **46**, 1566.

myrcene and α-camphorene but also represents a direct synthesis of the higher terpene from the lower one. This myrcene polymerization is formulated by Ruzicka and Stoll [1] in the following way :—



Ruzicka and Stoll found that boiling with 95 per cent. formic acid converts α-camphorene into a bicyclic diterpene, whilst further treatment results in the formation of a tricyclic diterpene. These two ring-closures are paralleled by analogous cyclizations in the olefinic terpene group.*

If the cyclization occurs with the two side-chains in the positions shown in the formulæ, the ring-closure should produce an anthracene derivative having the structure shown in (A). On the other hand, if one of the side-chains swings round through 180° about an axis passing through the 1 : 4-positions of the central ring in the α-camphorene formula, subsequent cyclization should yield a phenanthrene derivative with the structure shown in (B).

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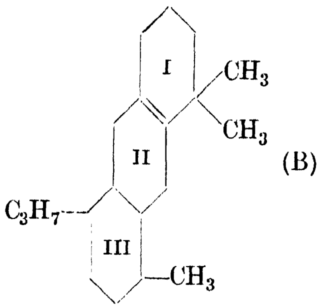
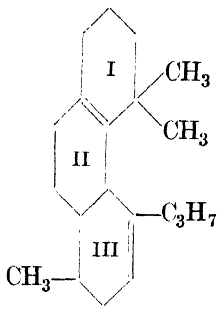
[1] Ruzicka and Stoll, *Helv. Chim. Acta*, 1924, **7**, 271.

* In this connection it may be mentioned that α-camphorene can be obtained from linalool by heating the terpene alcohol in a sealed tube with anhydrous oxalic acid.



(A)

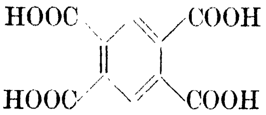
Iso-tricyclocamphorene.



(B)

Tricyclocamphorene.

Now when the tricyclic hydrocarbon is oxidized with sulphuric acid and manganese dioxide, pyromellitic acid is one of the degradation products :—



Pyromellitic acid.

This acid could obviously be produced from the central portion (II.) of Formula (A); whereas a compound of the structure shown in Formula (B) might yield pyrogallic acid from ring (I.) or prehnitic acid from ring (II.) or ring (III.), but no pyromellitic acid could be obtained from it.

The tricyclic hydrocarbon must therefore have the structure (A); and from this it follows that α-camphorene is represented by the formula given above.

Further evidence in favour of this formula is found when α-camphorene is reduced to the octahydro-derivative, $C_{20}H_{40}$, and this derivative is oxidized with manganese dioxide and sulphuric acid. Some terephthalic acid is thus obtained, which obviously results from conversion of the central ring of α-camphorene into a benzene nucleus and a subsequent oxidation of the two para side-chains to carboxyls.

Less is known about the second constituent of the high-boiling fraction of camphor oil. When the oil is treated with hydrogen chloride to produce the tetrahydrochloride of α-camphorene, an oily residue remains which, on boiling with alcoholic potash, yields β-camphorene. Its molecular refraction is 88·61, which suggests that it may be bicyclic in structure.

2. *The Squalenes*

The terpenes are so much associated with the vegetable kingdom that it is somewhat surprising to encounter a member of the class among the products of animal metabolism ; all the more so, since hydrocarbons seem to offer but little hold for the reagents which play the main part in the vital processes of the vertebrates. And when it is further noted that squalene is apparently a triterpene and thus more complex than most of the vegetable congeners, it must be admitted that it has exceptional points of interest.

Squalene was discovered by Tsujimoto,[1] who ascribed to it the composition $C_{30}H_{50}$; and it appears to be identical with spinacene.[2] The hydrocarbon occurs in the livers of elasmobranch fish, chiefly in the *Squalidæ* from which its name is derived. The determination of its constitution is not entirely completed ; but the main lines have been worked out by Heilbron and his collaborators.[3]

If six molecules of isoprene united to form an open chain, the resulting compound would obviously have the formula $C_{30}H_{48}$; and the original twelve ethylenic linkages would be reduced to seven during the process of chain-formation. Saturation of one of these double bonds by hydrogen would yield a compound containing six ethylenic bonds and having the composition $C_{30}H_{50}$, which is the same as that of squalene. As a first guess, therefore, it is worth while to consider whether squalene has a constitution which in any way corresponds to this conception.

I. When squalene is reduced with hydrogen and a nickel catalyst, the hydrogenation proceeds through six well-marked stages ; and the final product is squalane, $C_{30}H_{62}$. If the reduction is stopped after the hydrogen absorbed is just sufficient

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[1] Tsujimoto, *J. Chem Ind. Japan*, 1906, **9**, 953.

[2] Chapman, *J.*, 1917, **111**, 56.

[3] Heilbron, Kamm, and Owens, *J.*, 1926, 1630 ; Heilbron, Hilditch, and Kamm, *ibid.*, 3131 ; Harvey, Heilbron, and Kamm, *ibid.*, 3136 ; Heilbron, Owens, and Simpson, *J.*, 1929, 873 ; Heilbron and Thompson, *ibid.*, 883.

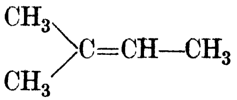
to saturate five double bonds, the product is not homogeneous; from which it appears that the original "squalene" may be a mixture of isomers.

II. When squalene is treated with hydrogen chloride, the product on analysis proves to have the composition $C_{30}H_{56}Cl_6$, whence it seems clear that squalene contains six ethylenic bonds. Examination shows that this product is a mixture of three separable, crystalline, hexahydrochlorides, which confirms the view that the original "squalene" is really a mixture of three isomeric hydrocarbons.*

III. From each of these isomeric hexahydrochlorides, a hydrocarbon $C_{30}H_{50}$ can be regenerated by the same method as is employed for this purpose among the ordinary terpenes.

IV. When boiled with acetic anhydride containing 1 per cent. of sulphuric acid, squalene passes through a series of isomeric changes; and from refractive index measurements it appears that the first product is a bicyclic compound; then a tricyclic isomer is produced; and in the final stage, only two double bonds seem to be left in the molecule. Here, again, the resemblance to the terpenes is striking. Further, this power of ring-closure is lost when squalene is partially reduced by taking up three, four or five gramme-molecules of hydrogen per molecule of the hydrocarbon.

V. Dry distillation of squalene yields products which, on analysis, were found to have compositions corresponding to C_5H_8, $C_{10}H_{16}$, and $C_{15}H_{24}$. The lowest-boiling of these hydrocarbons was proved to be an amylene; and since on oxidation with permanganate it yielded acetone, its structure must be:—



$$\left.\begin{array}{l}CH_3\\ \\ CH_3\end{array}\right\rangle C{=}CH{-}CH_3$$

The isolation of this substance, having the same skeleton as isoprene, tends further to confirm the idea that squalene belongs to the terpene class. Even more interesting is the fact that among the higher-boiling decomposition products of squalene there appears a hydrocarbon with physical constants which agree surprisingly with those of the sesquiterpene bisabolene.

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* An alternative possibility is that the original material is homogeneous, but undergoes isomerization in presence of hydrogen chloride or at the temperature 150° C. which is required for catalytic reduction.

VI. By treating squalene in acetone solution with solid permanganate, two ketones were obtained. One of these was identified as dihydro-ψ-ionone ; the other was, almost certainly,* methylheptenone.

VII. Oxidation with chromyl chloride in carbon disulphide yielded formaldehyde, acetaldehyde, and succinic acid.

VIII. Ozonolysis of squalene in the usual way led to the detection of a number of fission products, of which the following are the most important : carbon dioxide (8·5 per cent.), formaldehyde, formic acid, succinic acid (28 per cent.), acetone, lævulinic acid, lævulinic aldehyde, and a complex ozonide, $C_8H_{14}O_6$, which appears to be derived from methyl-heptenone.

IX. From the results just described, it is evident that oxidation splits up the squalene molecule too completely, leaving intact no fragments of a size sufficient to act as guides to the molecular structure. A way round this difficulty is found by reducing squalene with hydrogen sufficient to saturate five out of the six double bonds ; and then ozonizing the reduced material. From what has already been said, it is clear that here the ozone is being applied to a mixture of isomeric hydrocarbons. By this method, the following substances were obtained among the disruption products : methyl-heptenone, hexahydro-ψ-ionone, a ketone with the formula $C_{19}H_{38}O$, another ketone containing twenty-three or twenty-four carbon atoms, as well as γ-methyl-*n*-valeric acid, $C_6H_{13} . COOH$, and 4 : 8-dimethyl-nonoic acid, $C_{10}H_{21} . COOH$. Finally, an acid was detected corresponding to the formula $C_{16}H_{33} . COOH$.

The evidence contained in sections I.–IX. above is not sufficient to determine the structures of the squalenes in every detail ; but there are facts enough to allow the broad outlines of the squalene constitutions to be laid down.

From I., it is plain that " squalene " is a mixture of isomers.

From II., it follows that " squalene " is a mixture of three isomers, each of which contains in its structure six double bonds.

From III., it is clear that the squalenes have a strong resemblance to the olefinic terpenes.

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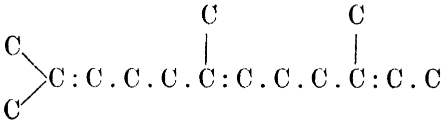
* As will be seen later, though methyl-heptenone was not completely identified here, there is other evidence which leaves no doubt as to the nature of this ketonic fission-product.

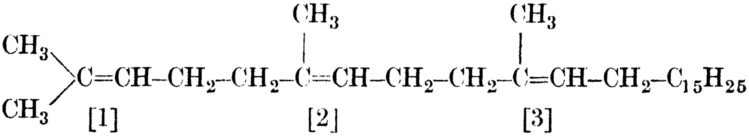
From IV., the closeness of this parallelism becomes even more apparent.

From V., it seems evident that at least one of the squalene isomers must contain the skeleton :—



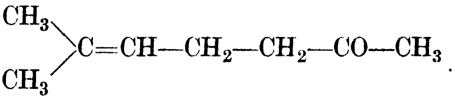
$$\begin{matrix}C\\ C\end{matrix}\!>\!C:C.C.C.\overset{C}{\overset{|}{C}}:C.C.C.\overset{C}{\overset{|}{C}}:C.C$$

since this is the open chain corresponding to the grouping of atoms in bisabolene. Thus, at a single stroke, the arrangement of fifteen out of the thirty carbon atoms in this squalene chain has been ascertained ; and by filling in the necessary hydrogen atoms and tacking on the missing complex, the following formula for the squalene is obtained :—



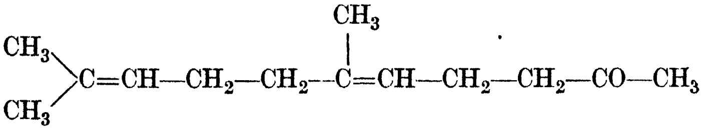
$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!>\!\underset{[1]}{C=CH}-CH_2-CH_2-\underset{[2]}{\overset{CH_3}{\overset{|}{C}}=CH}-CH_2-CH_2-\underset{[3]}{\overset{CH_3}{\overset{|}{C}}=CH}-CH_2-C_{15}H_{25}$$

This structure is in agreement with the facts mentioned in VI., as very little consideration will show. If the double bond marked [1] remains intact while oxidation breaks the bond marked [2], then methyl-heptenone :



$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!>\!C=CH—CH_2—CH_2—CO—CH_3$$

will appear as a decomposition product. If both the double bonds [1] and [2] remain unaffected, whilst the chain is oxidized at the ethylenic linkage [3], the result will be the formation of dihydro-ψ-ionone :



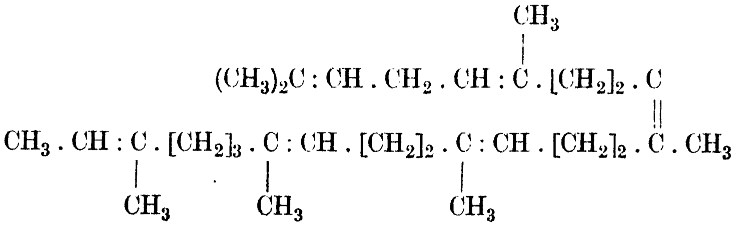
$$\begin{matrix}CH_3\\ CH_3\end{matrix}\!>\!C=CH—CH_2—CH_2—\overset{CH_3}{\overset{|}{C}}=CH—CH_2—CH_2—CO—CH_3$$

With the data summarized in VII., the formula is only in partial agreement. Succinic acid would result from oxidative rupture of the bonds [1] and [2] or of the bonds [2] and [3]. But the production of formaldehyde and acetaldehyde cannot so easily be accounted for, and this point must be reserved for later consideration in connection with the remainder of the structure which has been treated en bloc in the foregoing formulation.

The facts mentioned in VIII. can, in the main, be brought into conformity with the formula. Oxidation at the bond [2] would yield methyl-heptenone; and from this, in turn, by further oxidation, the production of acetone, lævulinic aldehyde, lævulinic acid, and succinic acid could be produced.

This structure would account for the production of marked yields of carbon dioxide, formaldehyde, and formic acid during the oxidation of squalene with ozone.

Neither of the foregoing formulæ accounts satisfactorily for the production of γ-methyl-valeric acid and 4 : 8-dimethyl-nonoic acid. The possibility that these are oxidation products of methyl-heptenone and hexahydro-ψ-ionone must be excluded, as the conditions employed in the decomposition of the ozonides rule out such a solution completely. Further, along with the acid $C_{10}H_{21} . COOH$ is found the ketone $C_{19}H_{38}O$; and these two fragments are obviously complementary, since together they contain the whole thirty carbon atoms of the squalene chain. Obviously, to produce these fragments, the chain must break between the eleventh and twelfth carbon atoms from one end of it ; and at this point there must be a double bond. No such bond is found in this position in either of the foregoing structures ; so that a third formula is needed to account for these facts :—

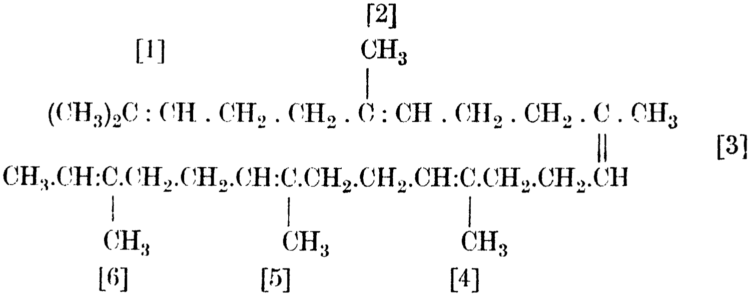


$$\begin{array}{r} (CH_3)_2C : CH . CH_2 . CH : \overset{\displaystyle CH_3}{\overset{|}{C}} . [CH_2]_2 . C \\ \| \\ CH_3 . CH : \underset{\displaystyle CH_3}{\underset{|}{C}} . [CH_2]_3 . \underset{\displaystyle CH_3}{\underset{|}{C}} : CH . [CH_2]_2 . \underset{\displaystyle CH_3}{\underset{|}{C}} : CH . [CH_2]_2 . C . CH_3 \end{array}$$

If this compound were reduced until the only double bond left intact was that which is printed vertically on the right-hand side of the formula above, then on oxidation this bond would break and the fragments of the squalene would be two in number : an acid, $C_{10}H_{21} . COOH$ (4 : 8-dimethyl-nonoic acid), from the reduced top section ; and the ketone $C_{19}H_{38}O$ from the section indicated in the lower line of the formula.

Turning now to the final series of facts grouped under IX., it is evident that two of the fragments are mutually complementary. Hexahydro-ψ-ionone, $C_{13}H_{26}O$, and the acid $C_{16}H_{33}$. COOH between them contain the complete set of thirty carbon atoms in squalene ; and it seems clear that these two compounds arise through a scission of the molecule at the double bond [3].

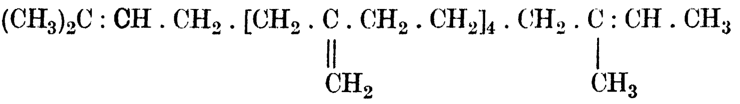
On the basis of the foregoing evidence, Heilbron and his collaborators have suggested the following formula to represent the hydrocarbon which gives rise to the decomposition products discussed in the foregoing paragraphs :—



$$\begin{array}{l}
\qquad\qquad\qquad [1] \qquad\qquad\qquad\qquad\quad \overset{[2]}{CH_3} \\
(CH_3)_2C:\overset{}{C}H.CH_2.CH_2.\overset{|}{C}:CH.CH_2.CH_2.C.CH_3 \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \| \qquad\qquad [3] \\
CH_3.CH:\underset{\underset{[6]}{CH_3}}{\underset{|}{C}}.CH_2.CH_2.CH:\underset{\underset{[5]}{CH_3}}{\underset{|}{C}}.CH_2.CH_2.CH:\underset{\underset{[4]}{CH_3}}{\underset{|}{C}}.CH_2.CH_2.CH
\end{array}$$

The top line of this formula contains the portion which has been definitely settled by the evidence already submitted. As regards the lower line, it is clear that fission at the double bond [6] would yield acetaldehyde. And, obviously, if the double bonds [6], [5], and [4] are all hydrogenated, fission could take place at the bond [3], with the production of $C_{16}H_{33}$. COOH.

For the second squalene isomer, Heilbron and his collaborators suggest the following structure :—



$$(CH_3)_2C:CH.CH_2.[CH_2.\underset{\underset{CH_2}{\|}}{C}.CH_2.CH_2]_4.CH_2.\underset{\underset{CH_3}{|}}{C}:CH.CH_3$$

Further, if the single unreduced bond in the decahydro-squalene lies between the sixth and seventh atoms in the top line of the formula, the ozonolysis should yield γ-methyl-n-valeric acid, which is again in agreement with the experimental results.

Thus by assuming these three formulæ for the squalenes, it is possible to account satisfactorily for the decomposition products obtained in practice; and the fact that three formulæ are necessary is in very neat agreement with the production of three individual hexahydrochlorides from natural squalene.

CHAPTER V

RUBBER

1. *Introductory*

THE exact distribution of credit among the pioneers in the chemistry of rubber produced a most unedifying amount of controversy[1]; and insinuations were made by at least one German chemist which appear to overstep the bounds of normal scientific polemics. In these circumstances, it seems desirable to give an outline of the history of the subject in its earlier stages.

In 1860 Williams[2] observed that when rubber is distilled it yields what are now known as isoprene and dipentene. On leaving isoprene in a partly-filled bottle for some months, he noticed that it became oxidized and was converted into a viscid liquid. When this viscid material was distilled, at one point in the process the liquid solidified to " a pure white spongy elastic mass " which, when burned, gave off the characteristic odour of burning rubber. The material in question, on analysis, yielded the following results: 78·8 per cent. carbon, 10·7 per cent. hydrogen, and 10·5 per cent. oxygen. This composition corresponds to isoprene plus half an atom of oxygen.

Bouchardat[3] in 1879 found that when hydrochloric acid solution is allowed to act upon isoprene, one of the products, after the reaction has proceeded for a fortnight or three weeks, is a non-volatile body having the composition C=87·1 per cent., H=11·7 per cent., and Cl=1·7 per cent. If the chlorine be disregarded—and Bouchardat believed that its presence was due to contamination by foreign chlorinated compounds—these

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[1] For a complete account of this see Pond, *J. Amer. Chem. Soc.*, 1914, **36**, 165. See also Luff, *J. Soc. Chem. Ind.*, 1916, **35**, 983.

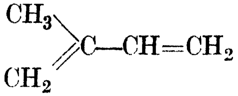
[2] Williams, *Phil. Trans.*, 1860, **150**, 245; *Proc. Roy. Soc.*, 1860, **10**, 516.

[3] Bouchardat, *Compt. rend.*, 1879, **89**, 1117.

results agree closely with the formula $(C_5H_8)_x$. The substance thus produced "possesses the elasticity and other characteristics of rubber. It is insoluble in alcohol; it swells up in ether, also in carbon disulphide in which it dissolves in the manner of natural rubber." When submitted to dry distillation "it forms the same volatile hydrocarbons as rubber." "All these properties appear to identify this polymer of isoprene with the substance from which isoprene is formed, namely rubber."

Harries[1] in 1913, criticized this work of Bouchardat and attempted to prove that Bouchardat's method does not yield the products described. Unfortunately for his contentions, he had read the original paper so carelessly that he apparently attempted a repetition of the work by the employment of hydrochloric acid *gas* whereas Bouchardat used aqueous hydrochloric acid. When an attempt is made to repeat an author's work it is usual to employ his own method; not to try a new one and then declare that the described method "seems almost excluded." Harries also[2] asserted that Bouchardat had not proved the identity of his product with true rubber. It is difficult to see what more Bouchardat could have done, considering the date at which he worked; and this attitude in the critic becomes more astonishing when it is recalled that in 1910–11 Harries made use of tetrabromides, nitrosites, and ozonides as tests to distinguish rubber; but in 1912–13 he discarded these as being inefficient, and concentrated his attention upon the rate of decomposition of the ozonides with water.[3]

The next stage in the history of synthetic rubber is marked by Tilden's paper of 1882.[4] Tilden showed that when turpentine vapour is passed through a red-hot tube, isoprene:



$$\begin{array}{l} CH_3\diagdown \\ \qquad\quad C{-}CH{=}CH_2 \\ CH_2\diagup\!\!\!\diagup \end{array}$$

Isoprene.

is formed; and he also stated that, by the action of nitrosyl chloride, isoprene was converted into rubber. Ten years later,

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[1] Harries, *Annalen*, 1913, **395**, 211.

[2] Harries, *Gummi-Zeitung*, 1910, **24**, 853.

[3] Harries, Lecture at Vienna, 12th March, 1910; *Chem. Zeit.*, 1910, **34**, 316; *Annalen*, 1913, **395**, 211.

[4] Tilden, *Chem. News*, 1882, **46**, 220.

Tilden[1] made public the fact that some isoprene which had been kept in a bottle for a long time had undergone change. "In place of the limpid colourless liquid the bottles contained a dense syrup in which were floating several large masses of solid, of a yellowish colour. Upon examination this turned out to be indiarubber." These original samples have now been tested by the ozone method and were found to be true rubber.[2] It may be noted that this work of Tilden's should be regarded as a real synthesis of rubber, and stands in a different category from Bouchardat's. Bouchardat obtained his isoprene by distilling rubber; so that his work consisted of *re-synthesizing* rubber from its decomposition products. Tilden, on the other hand, obtained his isoprene from turpentine, and may thus claim to have made a true synthesis of rubber.

Harries,[3] not having been able to repeat Tilden's work, contented himself with the statement that Tilden "never proved that he had rubber in his hands."

About 1899 or 1900, Kondakoff[4] showed that other members of the isoprene series could be converted into rubber-like materials by various methods.

In the earlier part of the present century, the uses of rubber were greatly extended; and as a natural consequence there was a marked effort to produce the material by artificial means on a manufacturing scale.

In 1909 Hofmann[5] discovered that isoprene may be converted into rubber by the action of heat. This is claimed as the first technical method of rubber synthesis. If it be a practical method it appears curious that, during the war, Germany was in great difficulties owing to lack of rubber.

In 1908 a British syndicate quietly set to work upon the problem of the commercial synthesis of rubber.[6] A method of obtaining isoprene from fusel oil was worked out, thereby

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[1] Tilden, Paper read before the Philosophical Society of Birmingham, 1892.

[2] Tilden, *Chemical Discovery and Invention in the Twentieth Century*, 1916; Pickles, *J.*, 1910, **97**, 1085.

[3] Harries, Vienna Lecture, 1910.

[4] Kondakoff, *On Synthetic Rubber* (in Russian) (1912); *J. pr. Chem.*, 1900, **62**, 175; 1901, **63**, 113; **64**, 109. See also Harries' Vienna Lecture and *Annalen*, 1911, **383**, 186.

[5] See Duisberg, *Eighth International Congress of Applied Chemistry*, 1912, **28**, 50, 86.

[6] See Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

ensuring that the raw material should not be too expensive. In the course of some experiments, it occurred to Matthews to study the influence of sodium upon isoprene ; and in July, 1910, he sealed the two substances up in a tube. Inspection of the tube in August showed that the contents had become viscid and contained a proportion of remarkably good rubber. The vessel was resealed and left till September, when it was found to contain a solid mass of amber-coloured rubber. A patent was applied for on 25th October, 1910.

Meanwhile Harries, the Badische Anilin und Soda Fabrik, and Bayer and Co. were also at work, and the race was becoming a close one. Harries' story is as follows.[1] He claimed that in February, 1910, he observed, during a purification of isoprene by distilling it over sodium, that the metal had an "altering" (verändernde) action upon the hydrocarbon. The fact that rubber-like materials resulted from the process was first established "in September or October," which is rather vague. He stated that on 28th October, 1910, he verbally communicated his discovery to a representative of the Elberfeld Farbenfabriken in Berlin, and suggested that a patent should be taken out by them. This patent was applied for in Germany on 12th December, 1910, seven weeks after the British syndicate had applied for their English patent.*

If Harries' story be subjected to the same rigid scrutiny as he himself gave the work of Bouchardat and Tilden, the only evidence which could be regarded as relevant would be the actual date of the patent application, as no corroboration has been offered by the other details.† In any case, under modern conditions, priority of discovery counts for less than priority of publication ; and on that basis the Germans lost the race.

The controversy which arose out of this defeat was marked by especial bitterness on the part of Harries[2] ; and it is a matter for congratulation that chemical polemics are not usually conducted in that spirit.

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[1] Harries, *Annalen*, 1912, **395**, 211.

* It appears that Aschan independently discovered the sodium polymerization process at a slightly later date. (See Aschan, *Naphtenverbindungen*, 1929, p. 321).

† The first scientific publication by Harries on the subject is dated 26th June, 1911 (*Annalen*, **383**, 188), and he there stated (before the controversy arose) that he made the discovery at the *end* of 1910 (Ende des Jahres 1910).

[2] Harries, *Annalen*, 1912, **395**, 211.

2. *The Properties and Constitution of Natural Rubber*

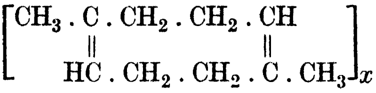
Natural rubber or caoutchouc is a transparent, tough elastic substance having no definite melting- or boiling-point.* It absorbs water, increasing in volume as it does so. It is soluble in several organic liquids, such as benzene, chloroform, carbon tetrachloride, dipentene, ligroin, and carbon disulphide. Its composition corresponds to the formula $(C_5H_8)_x$. It is unsaturated, combining readily with oxygen and chloride; and it yields nitrosites and nitrosates with nitrous fumes. When distilled, it breaks down into a mixture of hydrocarbons of which the chief are isoprene and dipentene. When heated with sulphur or when treated with solutions of sulphur dichloride in carbon disulphide, it becomes "vulcanized," the process resulting in the rubber retaining its elastic properties over a wider range of temperature than when raw. When a high percentage of sulphur is introduced, vulcanite is produced.

Apart from the actions of halogens and nitrous fumes upon rubber, which have led to little, our knowledge of its constitution depends upon its behaviour with ozone.

Harries [1] stated that when rubber is treated with ozone and the resulting ozonide is decomposed with water, the only isoluble products are lævulinic aldehyde, lævulinic acid, and the peroxide of lævulinic aldehyde. The acid is evidently a secondary product of reaction.

The molecular weight of the ozonide shows that its composition is $C_{10}H_{16}O_6$, which points to the fact that the structure from which it was derived must have contained two double bonds, each of which has taken up one molecule of ozone.

In order to account for these results, Harries had to resort to an hypothesis which will hardly recommend itself to many chemists. He assumed, from the production of lævulinic aldehyde and its peroxide, that rubber has the following structure:



$$\left[\begin{array}{l} CH_3 . \overset{}{C} . CH_2 . CH_2 . CH \\ \qquad\ \ \| \qquad\qquad\qquad\ \ \| \\ \qquad HC . CH_2 . CH_2 . C . CH_3 \end{array}\right]_x$$

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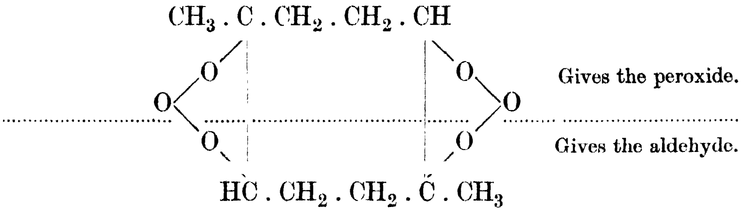
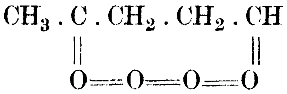
* It appears from some work of Harries that natural Para rubber occurs in at least three forms: oily, soluble, and insoluble.

[1] Harries, *Ber.*, 1905, **38**, 1195.

and that the ozonide has the constitution :



The breakdown of the ozonide is supposed to take place along the dotted line, the lower half of the molecule producing lævulinic aldehyde, $CH_3 . CO . CH_2 . CH_2 . CHO$, whilst the upper half yields the peroxide :—



$$\begin{array}{c} CH_3 . C . CH_2 . CH_2 . CH \\ \| \qquad\qquad\qquad \| \\ O{=}O{=}O{=}O \end{array}$$

But at this point difficulties arise ; for how can the cyclo-octadiene ring polymerize without destroying the double bonds in it ? And if it does polymerize through the agency of the double bonds, how can they be left unchanged to attack the ozone molecules in order to produce the ozonide ?

Harries endeavoured to gain credence for his hypothesis by adducing the fact that cyclo-octadiene—which should be analogous to his assumed eight-membered ring—does actually polymerize readily ; but inadvertently, no doubt, he omitted to mention that one of the products of this polymerization is a di-cyclo-octadiene consisting of thin, pointed leaflets of m.p. 114° C. ; whilst the other polymer is also a crystalline body.[1] The analogy with the properties of rubber is hardly close enough to support the eight-membered ring theory to any extent worth considering.

For his final demonstration of the presence of an eight-membered ring in the rubber molecule, Harries relied upon the following statements.[2] When the dihydrochloro-derivative of rubber is subjected to the action of pyridine,[3] he found that a substance *different* from rubber is regenerated.* On ozoniz-

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[1] Willstätter and Veraguth, *Ber.*, 1905, **38**, 1975.

[2] Harries, *Ber.*, 1913, **47**, 2590.

[3] *Ibid.*, 733.

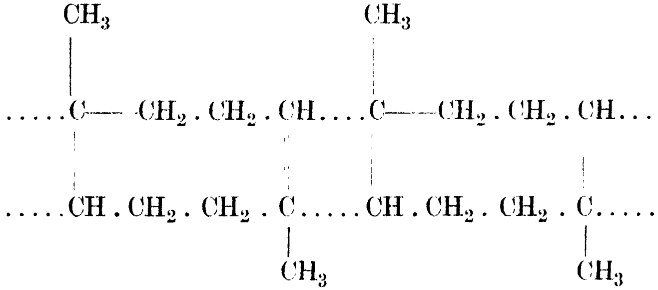
* "Dieser (the regenerated substance) ist nicht mehr identisch mit dem natürlichen Kautschuk."

ing this, he claimed to have isolated a cyclo-octadione derivative among the products. Therefore, according to his argument, the *original* rubber must have contained an eight-membered ring. The fallacy in reasoning is not worth dwelling upon, as it subsequently turned out[1] that he had made a "regrettable error"* and had mistaken an open-chain di-ketone,

$$CH_3 . CO . CH_2 . CH_2 . CH_2 . CO . CH_3,$$

for a cyclo-octadione derivative. It seems hardly worth while to comment on the value of such evidence; though Harries still contended that it established the presence of an eight-membered ring in the rubber molecule.

Harries[2] proposed to regard the polymerization of the eight-membered rings as a mere kind of loose addition, so that the polymer breaks down into cyclo-octadiene molecules under the influence of ozone. In other words, he regarded rubber as being built up from a large number of separate cyclo-octadiene molecules clinging together by means of Thiele's partial valencies, somewhat in the following style:—



$$\begin{array}{l}
\overset{\displaystyle CH_3}{|}\overset{\displaystyle CH_3}{\vdots} \\
.....C — CH_2 . CH_2 . CH....C — CH_2 . CH_2 . CH... \\
\vdots \vdots\vdots| \\
.....CH . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\overset{}{\underset{|}{C}}}.....CH . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{C}}.....
\end{array}$$

Pickles[3] has adduced several reasons why this conception should not be accepted without further evidence. In the first place, if ozone has the power of depolymerizing this peculiar compound, there seems no reason to deny the same depolymerizing property to other reagents. On this basis, bromine would first break down the colloidal rubber to independent cyclo-

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[1] Harries, *Ber.*, 1914, **48**, 784.

* "Ein bedauerlicher Irrtum."

[2] Harries, *Ber.*, 1905, **38**, 1195, 3985.

[3] Pickles, *J.*, 1910, **97**, 1085.

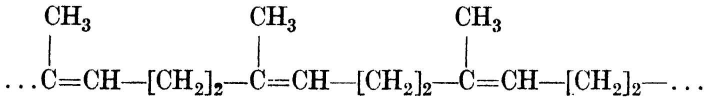
octadiene derivatives which would then yield a simple tetrabromo-compound, $C_{10}H_{16}Br_4$; but in actual practice the bromo-derivative of rubber appears to be almost as complex as rubber itself.*

Again, nitrous fumes might be expected to resemble ozone in their effects; but their action on rubber, as studied by Harries himself, produces complicated substances with compositions,† established by molecular weight determinations, corresponding to $C_{20}H_{30}O_{14}N_6$ and even $C_{40}H_{62}O_{24}N_{10}$.

Yet another objection to the physical polymerization idea is to be found in the behaviour of rubber when heated. Under ordinary pressure, heated rubber shows exactly the phenomena ordinarily observed when a complex substance undergoes complete disruption; whilst if the heating be done under reduced pressure, cyclo-octadiene derivatives are not formed, but instead it is found that the simplest compound in the distillate contains at least twenty carbon atoms.‡

This does not exhaust the evidence against Harries' idea; but it is sufficient to indicate some of the weak points of his hypothesis.

Pickles proposed a formula which certainly avoids these difficulties. He suggested that rubber consists of long chains built up from the group C_5H_8 by normal polymerization :—



$$\ldots\overset{\displaystyle CH_3\atop|}{C}{=}CH{-}[CH_2]_2{-}\overset{\displaystyle CH_3\atop|}{C}{=}CH{-}[CH_2]_2{-}\overset{\displaystyle CH_3\atop|}{C}{=}CH{-}[CH_2]_2{-}\ldots$$

The oxidation results require that the two ends of the chain should be linked together; and Pickles assumed that at least eight C_5H_8 complexes are included in a ring. To account for the ozone results, Pickles proposed the hypothesis that after the formation of the ozonide, the linkage between the carbon

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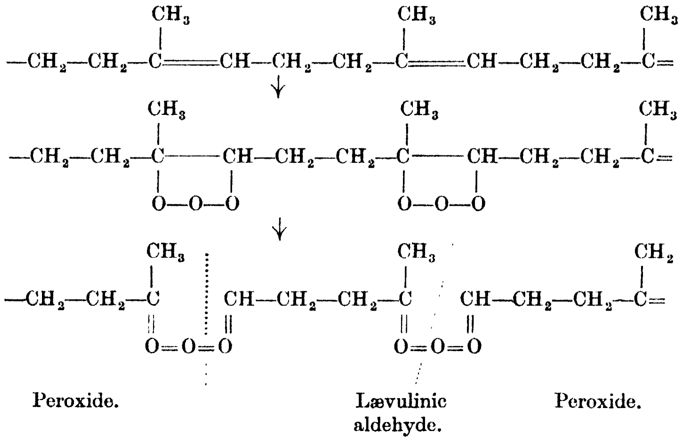
* Harries (*Annalen*, 1911, **383**, 227) endeavoured to get round this by suggesting that the bromo-derivative is an adsorption compound, an hypothesis for which he adduced no evidence.

† Harries (*Annalen*, 1911, **383**, 227) asserted, in reply to this, that most terpene nitrosites are bimolecular, which would reduce the rubber nitrosite to $C_{10}H_{15}O_7N_3$, thus making the C_8 ring possible.

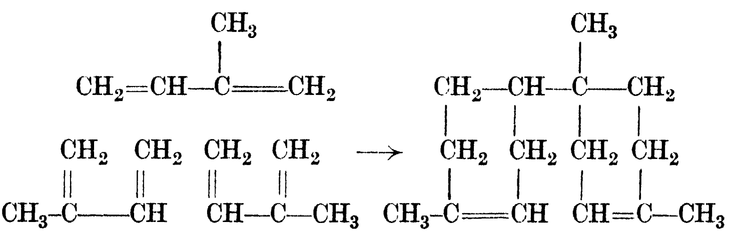
‡ Harries made no reply to this argument.

atoms is ruptured whilst the ozonide chain remains intact till later :—



This proposal certainly throws less strain upon the chemist's credulity than is demanded by Harries' hypothesis; and it appears to be supported by the work of Ostromisslenski.[1]

Another view of rubber's constitution is due to Boswell.[2] He assumed that three molecules of isoprene combine to form a cyclic compound, $C_{15}H_{24}$, containing two double bonds :—



In virtue of its two ethylenic linkages, this substance is assumed to enter into combination with further molecules of isoprene, yielding structures like the following :—

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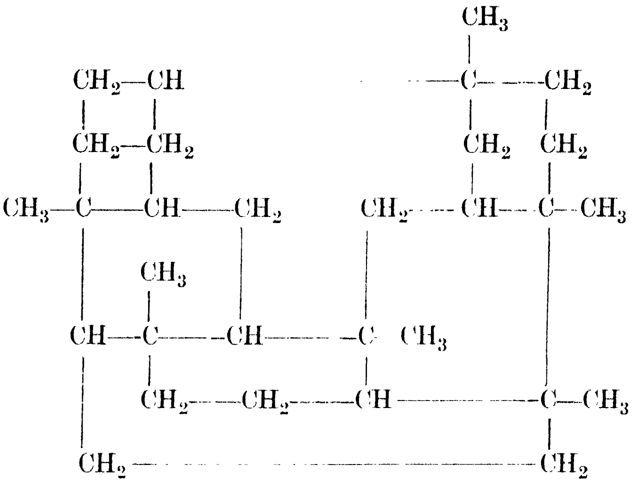
[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1932.

[2] Boswell, *Canadian Chemistry and Metallurgy*, 1922, **6**, 238; *Trans. Roy. Soc. Canada*, 1922, **16**, iii, 27.



which is assumed to be the structure of the rubber molecule. In support of this hypothesis, the following evidence can be quoted. By the action of hydrogen peroxide or potassium permanganate upon rubber, Boswell obtained a derivative $C_{25}H_{40}O_2$, which he believed to be formed by the loss of the central C_5H_8 group from the rubber molecule formulated above and its replacement by two oxygen atoms. By the action of hydrogen peroxide on rubber, a second oxidation product, $C_{15}H_{24}O$, was isolated, which Boswell assumed to result from further oxidation of the compound $C_{25}H_{40}O_2$ during which two more isoprene groups are eliminated. When oxidized by air, rubber was found to yield a highly-oxygenated derivative, $C_{25}H_{40}O_2$, wherein, on Boswell's view, the five isoprene groups are connected by oxygen atoms. After this, any further oxidation produces rupture of the molecule. The action of iodine on rubber is peculiar in that when iodine alone is used, the reaction is slow; but in presence of oxygen it is rapid; and it yields a compound $C_{25}H_{40}O_9$, if hydrogen peroxide be employed along with the iodine. It was suggested by Boswell that the iodine atom served to link together various isoprene nuclei within the molecule.

The main disadvantage of Boswell's formula is that it fails to make clear the action of ozone upon the rubber molecule. To get over this difficulty, he assumed that the first action of ozone is a depolymerizing one and that the ozonide is formed after a rearrangement of the five isoprene nuclei thus produced. Boswell points out, however, that the ozone method does not give a quantitative yield of ozonide from rubber nor does it even produce a constant quantity of ozonide from a given amount of rubber.[1] It is therefore by no means certain that Harries' ozonide is a homogeneous material and the sole product of the ozonization of rubber. Obviously this throws still further doubt upon Harries' views of the constitution of rubber.

3. *The Anglo-French Synthesis of Rubber*

In devising a manufacturing process on a large scale, the first point to be considered is the possible supply and price of the raw material involved.[2] A synthesis of rubber on a commercial scale might imply a demand running up to 100,000 tons ; and before proceeding further it is necessary to make sure that this demand can be filled without producing a shortage in the raw material.

Turpentine appeared at first sight to be a suitable starting-point ; but the imports of that substance into this country in the years previous to 1910 were found to average less than 29,000 tons per annum ; so that the additional demand for three times that quantity would disturb the market and cause a rise in price which it would be difficult to estimate. Acetone was also ruled out by the question of cost ; since, in order to compete with natural rubber, the artificial substitute must be manufactured at a price not exceeding one shilling per pound.*

The choice of the syndicate fell upon starch, which was readily obtainable at a low price. An alliance was made with Fernbach, of the Pasteur Institute ; and this investigator worked out a fermentation process whereby starch (from maize or potatoes) is convertible into fusel oil by one method and into acetone by another. The fusel oil thus obtained was found to contain an exceptionally high percentage of butyl alcohol.

The next stage in the process consists in treating butyl alcohol with hydrochloric acid gas, whereby it is converted into butyl chloride.

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[1] Olivier, *Rec. trav. chim.*, 1921, **40**, 665.

[2] For a complete account of the history of the syndicate's work, see Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

* These figures refer, of course, to pre-war prices.

By the action of chlorine, a mixture of dichloro-derivatives is obtained from the butyl chloride; and an apparatus was devised which checked the formation of more highly halogenated compounds. The final product contains a mixture of 1,2-, 1,3- and 1,4- dichlorobutane.

Contrary to what might have been expected, these substances, when passed over heated soda-lime, all give rise to the same product: butadiene: $CH_2 : CH . CH : CH_2$. Apparently intramolecular change takes place in the case of 1,2-dichlorobutane, or its product, under the influence of the soda-lime.

The final stage, conversion of the butadiene into artificial rubber, is carried out by allowing the hydrocarbon to stand in contact with a small quantity of sodium, the length of time required ranging from hours to weeks and being dependent upon temperature conditions.

Another method of obtaining artificial rubber has been suggested by Perkin, starting from amyl alcohol. The alcohol is converted into amyl chloride; the latter is then chlorinated, as in the case of butyl alcohol, producing a series of dichloro-derivatives which, when passed over heated soda-lime, yield isoprene. By treatment with metallic sodium, the isoprene polymerizes to an artificial rubber which is different in constitution from the butadiene rubber.

4. *Natural Rubber and the Artificial Rubbers*

It must be clearly borne in mind that the synthetic rubbers, though they have many resemblances to natural rubber, are not identical with it in chemical constitution. Some of them, as is evident from their raw materials, are obviously different; whilst even in the case of isoprene polymers we cannot safely assert that their identity with natural rubber is proved.[1]

Harries [2] stated that the autopolymerization of isoprene gives rise in the main to what he called a " normal " product; but that along with this is formed, in small yield, a different substance, on his ring-hypothesis, the formulæ of these bodies are shown below :—

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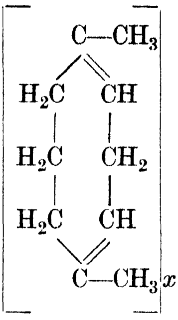
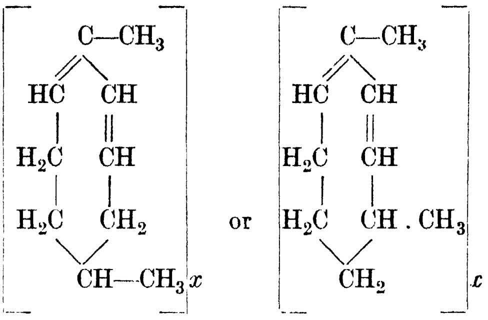
[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 1071.

[2] Harries, *Annalen*, 1911, **383**, 184.



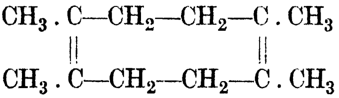
Normal form.



By-product.

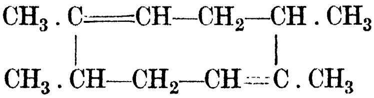
The proof adduced in favour of the by-product structure was that he thought he isolated methyl-glyoxal among the decomposition products of the ozonide.*

In the case of the polymer of dimethyl-butadiene, two ozonides were obtained which, on decomposition, yielded acetonylacetone and some strong reducing substances. From this Harries deduced that along with the "normal" polymer in this case there must be produced another which yields the reducing material, assumed by him to be a keto-aldehyde. For the two forms which he believed to exist he devised the following formulæ which may possibly be established when any definite evidence in their support is produced :—



$$\begin{array}{ccccccc} CH_3\,.\,C & - & CH_2 & - & CH_2 & - & C\,.\,CH_3 \\ \quad\;\, \| & & & & & & \| \quad\;\; \\ CH_3\,.\,C & - & CH_2 & - & CH_2 & - & C\,.\,CH_3 \end{array}$$

Normal form giving
Acetonylacetone.



$$\begin{array}{ccccccc} CH_3\,.\,C & = & CH & - & CH_2 & - & CH\,.\,CH_3 \\ \quad\;\, | & & & & & & | \quad\;\;\; \\ CH_3\,.\,CH & - & CH_2 & - & CH & = & C\,.\,CH_3 \end{array}$$

By-product giving a
Keto-aldehyde.

Further results were given in a later paper.[1] An examination of the rate of decomposition of various ozonides was carried out by the following method. About 10 grammes of the ozonide were suspended in 100 grammes of water and heated under a reflux to 120°–125° C. Every quarter (or half) hour the mixture was shaken until the ozonide stuck to the walls of the vessel; the clear liquid was then poured off; the vessel and ozonide were dried for some hours *in vacuo* and then weighed: the

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* "Unter diesen wurde ein Produkt festgestellt, welches ich für Methylglyoxal ansprechen möchte."

[1] Harries, *Annalen*, 1912, **395**, 211.

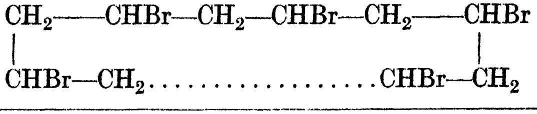
decanted liquid was poured back and a fresh experiment begun. From the loss of weight in the ozonide the amount of decomposition was calculated.

Harries stated that the rates of ozonide decomposition were similar for natural rubber and for autopolymerized isoprene. Divergency was noted in the case of a rubber obtained from piperylene, $CH_3 . CH : CH . CH : CH_2$, which is not astonishing in view of the fact that piperylene-rubber gives ozonide decomposition products differing entirely from those of natural rubber.

The decomposition curves of the ozonides derived from the rubbers obtained by the sodium-polymerization process differ, according to Harries, from the curve for the ozonide of natural rubber; but it must be noted that he himself pointed out that even natural rubbers differ among themselves in the readiness with which they form ozonides.

The same method was applied to synthetic 1 : 5-cyclooctadiene; and Harries stated that its ozonide breaks down at almost exactly the same rate as the ozonide of butadiene-rubber. From this he claimed to have proved that his eight-membered ring hypothesis is correct; but it appears that if Pickles' postulates as to the structure of the ozonide were applied to this case the argument for his formula would hold just as well. The matter must therefore be regarded as *sub judice*, the more so since the real value of the decomposition-velocity method is by no means thoroughly tested yet.

Ostromisslenski[1] obtained by the polymerization of vinyl bromide a material which he termed caouprene bromide. This exists in three forms $\alpha \rightarrow \beta \rightarrow \gamma$ which, when submitted to the action of ultra-violet light, are capable of change in the direction shown by the arrows. Boiling with anhydrous acetic acid has a similar effect. The bromide of Harries' butadiene-rubber, which also exists in three modifications, is either identical or isomeric with caouprene bromide. Ostromisslenski did not accept Harries' eight-membered ring hypothesis, but regarded caouprene bromide as constituted in the following manner :—



$$\begin{array}{l} CH_2\text{——}CHBr\text{—}CH_2\text{—}CHBr\text{—}CH_2\text{——}CHBr \\ |\hspace{22em}| \\ CHBr\text{—}CH_2\ldots\ldots\ldots\ldots\ldots\ldots CHBr\text{—}CH_2 \end{array}$$

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[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 204.

where the dotted line represents an unknown number of —$CH_2.CHBr$— groups. Both caouprene bromide and butadiene-rubber bromide, when treated with zinc dust, yield the same rubber, apparently butadiene-rubber.

The work of Ostromisslenski[1] has been so fertile in this field that it seems regrettable that his papers are published in a language which few British chemists can read. He apparently made a very complete investigation of the methods of preparing butadiene, no fewer than twenty-nine of these being described in a single paper.

Ostromisslenski differed from Harries with regard to the classification of the rubber-like materials produced by synthetic methods. In his view, the physical properties of the product are better indices of its nature than the results of decomposition-reactions have proved to be. For example, a determination may be made of the temperatures at which an artificial rubber acquires and loses its elastic properties; and if these temperatures agree approximately with those for natural rubber, Ostromisslenski considered that the synthetical substance is "normal." If, on the other hand, there is little agreement here and if the range of temperature over which the artificial product remains elastic is different from the range found for natural rubber, then the artificial product should be regarded as "abnormal."

The complexity of the processes whereby synthetic rubbers are formed is well illustrated by some of Ostromisslenski's results. When isoprene is kept at a temperature of 80°–90°, it forms an open-chain dimeric form named β-myrcene. This substance, on polymerization by the sodium process, yields a "normal" rubber; whereas isoprene itself, when treated with sodium, gives rise to an "abnormal" polymer.

$$\begin{tikzcd}
\text{Isoprene } C_5H_8 \arrow[r, "\text{Sodium}"] \arrow[d] & \text{Abnormal rubber} \\
\beta\text{-Myrcene } C_{10}H_{16} \arrow[r, "\text{Sodium}"] & \text{Normal rubber}
\end{tikzcd}$$

Further variation seems to be induced by the presence of carbon dioxide. If the sodium polymerization be conducted in a carbon dioxide atmosphere, the end-product is a type of

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[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1915, 47, 1374, 1472, 1494, 1507, 1928, 1932, 1937, 1941.

rubber differing from that obtained in the normal sodium process since it is less easily dissolved in or attacked by benzene.[1]

Lebedeff[2] investigated the polymerization of divinyl derivatives containing conjugated double bonds. The reaction products contain cyclohexene compounds as well as a resinous material derived from cyclo-octadiene. Low temperatures and the action of light favour the formation of the cyclo-octadiene compounds: while cyclohexene derivatives are produced at higher temperatures. Substances of the allene type give rise to cyclobutane compounds.

Further consideration of the details of the rubber problem[3] would require more space than is available in a volume of this size; but in conclusion it may be well to refer to the results obtained from an X-ray examination of rubber.

Katz[4] discovered by this means that when rubber is stretched it develops a strongly-marked crystalline structure, which disappears on the release of the tension or on heating the material. Thus in the unstretched state, rubber is apparently amorphous; but on extension it yields an X-ray photograph rather like that given by asbestos. The structure of the stretched material appears to be built up from a series of crystallites which are all oriented in such a way that a certain crystallographic axis points in the direction of the tension.[5] The possibility of a crystal unit containing four C_5H_8 groups has been inferred from the measurements.

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[1] Holt, *Z. angew. Chem.*, 1914, **27**, 156.

[2] Lebedeff, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 949; 1911, **43**, 820.

[3] A survey is given by Dinsmore, *Ind. Eng. Chem.*, 1926, **18**, 1142.

[4] Katz, *Kolloid-Z.*, 1925, **36**, 300.

[5] Hauser and Mak, *Koll. Chem. Beih.*, 1926, **23**, 64; Hauser, *Ind. Eng. Chem.*, 1929, **21**, 249.

CHAPTER VI

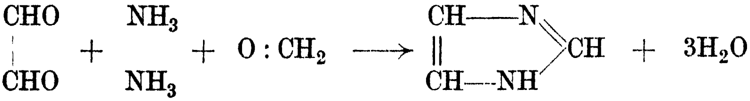
RECENT WORK ON THE ALKALOIDS

In this chapter no attempt can be made to describe all the investigations which have been carried out upon the alkaloids during the last few years. Much of the work which has been done is of value mainly because it is paving the way towards a final solution of sundry constitutions; but in itself it is of little interest, since it is only a link in a chain of which we cannot as yet see the end. Consequently the inclusion of accounts of it here would serve very little purpose.

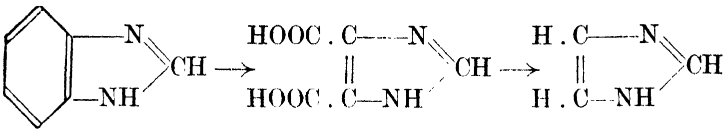
A number of fields have been completely cleared up in recent times, however, and it seems best to devote most of the space available here to some description of the results attained in these particular regions of the subject. A certain scrappiness of treatment is unavoidable, since the various alkaloidal groups which thus come under consideration are isolated from each other in almost every respect. Nevertheless, even this disjointedness will serve to depict fairly well the present condition of the research which is going on among the alkaloids.

A.—The Glyoxaline Group

The parent substance of the glyoxaline group may be obtained by condensing together glyoxal, ammonia, and formaldehyde:



It may also be produced by oxidizing benzimidazole with permanganate and then heating the dicarboxylic acid so formed:



An examination of the purine structure will show that it may be regarded as containing a glyoxaline ring condensed with a pyrimidine nucleus; so that the purine derivatives may be considered as partly derived from glyoxaline: but it is not necessary to lay too much stress upon this relationship since the uric acid group is sufficiently distinct to permit of its being regarded as a class by itself.

1. *The Constitutions of Pilocarpine and Pilocarpidine*

Pilocarpine occurs in jaborandi leaves in conjunction with several related alkaloids: pilocarpidine,[1] isopilocarpine,[2] pilosine,[3] ψ-pilocarpine,[4] and ψ-jaborine.* The general structure of pilocarpine has been established in the following manner:—

The composition of pilocarpine is $C_{11}H_{16}N_2O_2$. Although it contains two nitrogen atoms it does not yield an amide with acetyl chloride; so it is clear that both nitrogen atoms must be tertiary ones. Oxidation[5] with permanganate produces from pilocarpine a mixture of methyl-urea, homopilopic acid, and pilopic acid. As pilopic acid is derived from homopilopic acid by further oxidation, it will be best to examine first the constitution of homopilopic acid.

Homopilopic acid is a lactonic acid, containing one lactone ring and one free carboxyl radicle. From the stability of the lactonic structure, the substance is evidently a γ-lactone. Its composition is $C_8H_{12}O_4$.

When fused with caustic potash, homopilopic acid gives α-ethyltricarballylic acid:

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[1] Harnack, *Annalen*, 1887, **238**, 230.

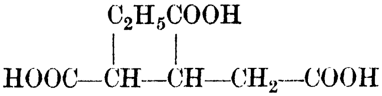
[2] Petit and Polonowsky, *J. Pharm. Chim.* (vi.), 1897, **5**, 370, 430; **6**, 8.

[3] Pyman, *P.*, 1912, **28**, 267.

[4] Petit and Polonowsky, *Chem. Zentr.*, 1897 (i), 1126.

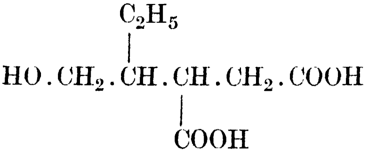
* The supposed alkaloid jaborine appears to be a mixture (Jowett, *J.*, 1900, **77**, 474, 851; 1901, **79**, 581, 1331).

[5] Jowett, *J.*, 1900, **77**, 474, 851; 1901, **79**, 581, 1331; compare Pinner, *Ber.*, 1900, **33**, 1424, 2537; 1901, **34**, 727; 1902, **35**, 204, 2443; 1905, **48**, 1510.



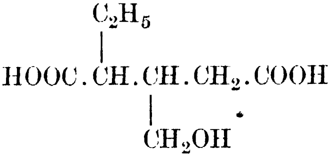
$$\mathrm{HOOC{-}\overset{\displaystyle C_2H_5}{\overset{|}{C}H}{-}\overset{\displaystyle COOH}{\overset{|}{C}H}{-}CH_2{-}COOH}$$

This substance must arise from a hydroxy-acid (the parent of the lactonic homopilopic acid) by the action of the potash; and for this hydroxy-acid three formulæ are possible, from which we must select the correct one:



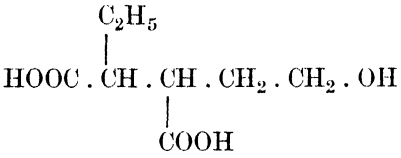
$$\mathrm{HO.CH_2.\overset{\displaystyle C_2H_5}{\overset{|}{C}H}.\underset{\displaystyle COOH}{\underset{|}{C}H}.CH_2.COOH}$$

(I.)



$$\mathrm{HOOC.\overset{\displaystyle C_2H_5}{\overset{|}{C}H}.\underset{\displaystyle CH_2OH}{\underset{|}{C}H}.CH_2.COOH}$$

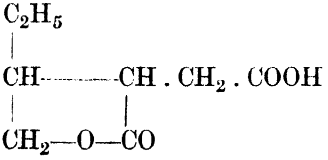
(II.)



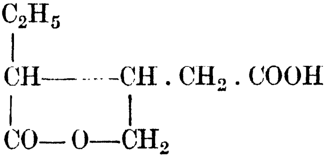
$$\mathrm{HOOC\,.\,\overset{\displaystyle C_2H_5}{\overset{|}{C}H}\,.\,\underset{\displaystyle COOH}{\underset{|}{C}H}\,.\,CH_2\,.\,CH_2\,.\,OH}$$

(III.)

Now pilopic acid appears to be derived from homopilopic acid by loss of carbon dioxide and oxidation of the carbon atom which carried the destroyed carboxyl radicle. Of all the possible γ-lactonic formulæ derived from the three acids shown above, only two can fulfil this condition—

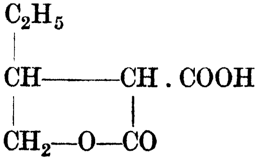


(A.)

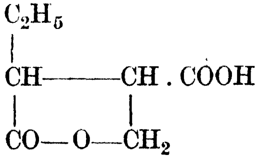


(B.)

The corresponding formulæ for pilopic acid would therefore be:



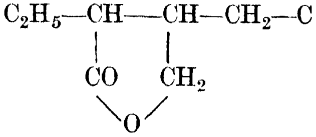
(a.)



(b.)

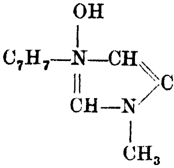
Now, owing to the fact that in (a) there are two carboxyl radicles (one in lactone form) attached to the same carbon atom, we should expect such a compound to lose carbon dioxide easily on heating as malonic acid does. Pilopic acid, however, is stable even at 200° C. It seems most probable, therefore, that pilopic acid has the formula (b); which leads us to the formula (B) for homopilopic acid.

By this reasoning, pilocarpine itself must contain the skeleton



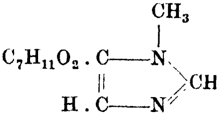
in addition to a group $C_3H_5N_2$, which disappears completely on oxidation. With regard to the structure of this last complex we must look for further evidence.

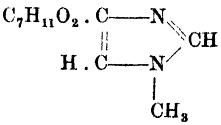
When derivatives of glyoxaline are allowed to interact with alkyl halides, ammonium compounds are formed which break down under the action of caustic potash, yielding primary amines. Now when pilocarpine is submitted to this series of reactions, it gives rise to equimolecular quantities of methylamine, methyl alcohol, and $C_7H_7 . NH_2$, plus two molecular proportions of formic acid. This decomposition can be accounted for by assuming that its methyl iodide addition product is transformed by caustic potash into an ammonium hydroxide of the following structure :—

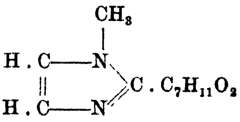


$$+ 4H_2O = CH_3NH_2 + C_7H_7NH_2 + CH_3OH + 2HCOOH$$

Thus pilocarpine itself may have one of the following structures :—*







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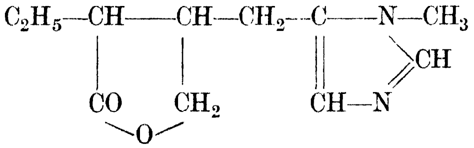
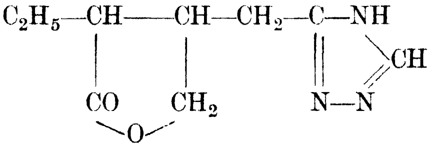
* It is assumed that the union between the glyoxaline group and the rest of the molecule is originally through carbon, a wandering of the homopilopic group taking place during the decomposition.

An examination of the dimethyl-glyoxalines by Pyman[1] led to the conclusion that pilocarpine must be a 1 : 5-derivative of glyoxaline. The following formula has therefore been ascribed to it :—



Pilocarpine

The alkaloid pilocarpidine[2] appears to be the imine corresponding to pilocarpine, so that its structure can be expressed by



Pilocarpidine.

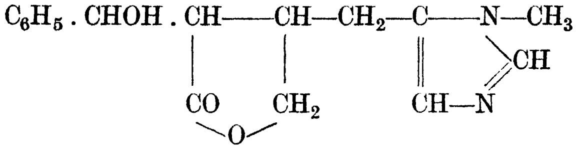
2. *Isopilocarpine and Pilosine*

The oxidation of pilocarpine and isopilocarpine gives rise to the same products ; which shows that the two substances are closely allied in structure. Their chemical properties are also very similar ; and the absorption spectra of their nitrates are identical.[3] Further, pilocarpine and isopilocarpine, when treated with alcoholic potash, are both converted into an equilibrium mixture containing chiefly isopilocarpine. From evidence of this kind, Jowett[4] regards isopilocarpine as a stereoisomer of pilocarpine ; and this view appears to cover all the more important reactions of the alkaloids.

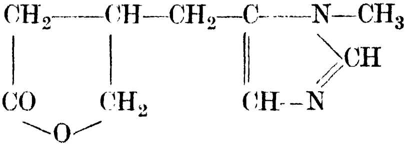
The constitution of pilosine has been investigated by Pyman.[5] He found that on distillation with potash solution it yields benzaldehyde and a substance called pilosinine, which closely resembles pilocarpine in physiological action. He ascribed to the two substances the following structures :—

---

[1] Pyman, *J.*, 1910, **97**, 1814 ; 1922, **121**, 2616.
[2] Späth and Kunz, *Ber.*, 1925, **58**, [*B*], 513.
[3] Dobbie, *cf.* Hartley, *P.*, 1903, **19**, 122.
[4] Jowett, *J.*, 1903, **83**, 438 ; 1905, **87**, 794.
[5] Pyman, *P.*, 1912, **28**, 267.



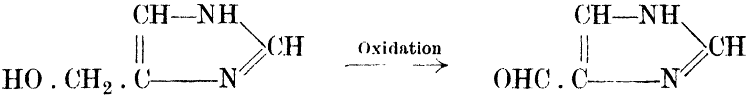
Pilosine.



Pilosinine.

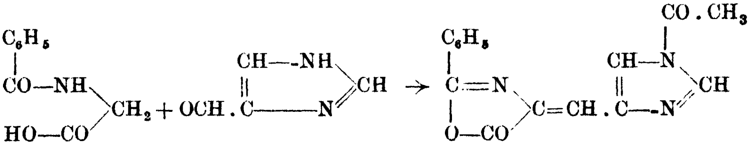
3. *The Synthesis of Histidine*

By heating together potassium thiocyanate and the hydrochloride of diamido-acetone, amido-methyl-glyoxaline mercaptan is produced ; and when this is added to dilute nitric acid, it yields 4-hydroxymethyl-glyoxaline (I.), which forms the raw material of the histidine synthesis.[1] Oxidation with chromic acid converts it into glyoxaline formaldehyde (II.) :



(I.) (II.)

By means of acetic anhydride, the formaldehyde derivative is condensed with hippuric acid to form 2-phenyl-4-[1-acetyl-glyoxaline-4-methylidine]-oxazolone (III.) :



Hippuric acid. (II.) (III.)

When this oxazolone derivative is boiled with very dilute sodium carbonate solution, the acetyl group is split off and the oxazolone ring opens. If, now, the calculated quantity of an acid be added, the compound (IV.) results. Reduction of

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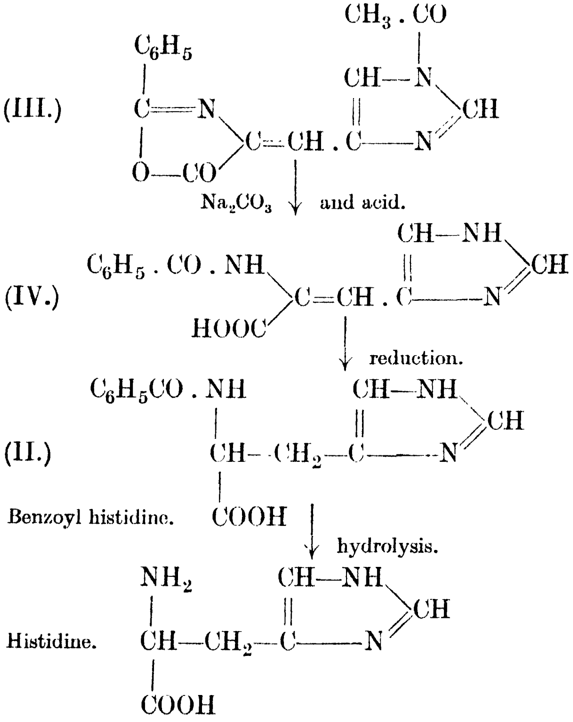
[1] Pyman, *J.*, 1916, **109**, 186.

this produces benzoyl-histidine (V.) from which histidine itself is obtained by hydrolysis—



B.—Some Derivatives of Ergot and their Allies

The examination of ergot has resulted in the detection in it of numerous compounds of physiological interest, for several of its products have marked influence upon the blood pressure and in other directions as well.

Tanret [1] discovered an active principle in ergot; but it was not until further work had been done by Barger and Carr [2] that the composition of the materials was made clear. The last two authors isolated two substances, ergotoxine, $C_{35}H_{41}O_6N_5$, and ergotinine, $C_{35}H_{39}O_5N_5$. It will be noticed that ergotoxine

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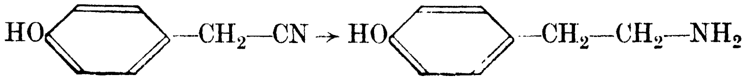
[1] Tanret, *Compt. rend.*, 1875, **81**, 896; 1878, **86**, 888; *Ann. Chim. Phys.*, 1879 (v.), **17**, 493.

[2] Barger and Carr, *J.*, 1907, **91**, 336.

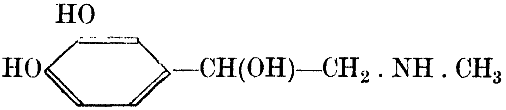
contains a molecule of water more than ergotinine; and subsequent investigation[1] proved that ergotinine is the lactone of ergotoxine, which is therefore a carboxylic acid. Both ergotoxine and ergotinine give on destructive distillation isobutyryl-formamide, $(CH_3)_2CH . CO . CO . NH_2$. Beyond this, nothing definite is known as to their constitution.

Further examination of ergot[2] brought to light another physiologically active substance, *p*-hydroxy-phenyl-ethylamine. This compound is also found in putrid meat.[3] It has been synthesized by the reduction, with sodium and alcohol, of *p*-hydroxy-phenyl-acetonitrile:—

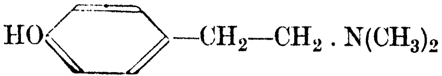


It has also been obtained in even better yield by acting on anisaldehyde, $CH_3O . C_6H_4 . CHO$, with nitromethane to form $CH_3O . C_6H_4 . CH : CH . NO_2$, which is then reduced to the amine. Demethylation of the methoxy-group completes the process.[4]

The structure of this substance is interesting, since its skeleton occurs in adrenaline,[5] the active principle of the adrenal gland and also in hordenine,[6] which is present in barley—



Adrenaline.



Hordenine.

Yet another active substance[7] was found in ergot: 4-β-amino-ethyl-glyoxaline, which is obviously closely related to histidine—

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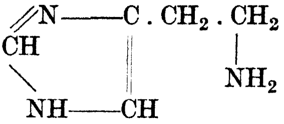
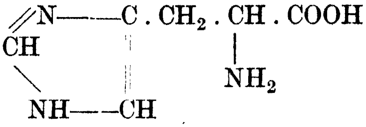
[1] Barger and Ewins, *J.*, 1910, **97**, 284.
[2] Barger, *J.*, 1909, **95**, 1123.
[3] Barger and Walpole, *J. Physiol.*, 1909, **38**, 343.
[4] Rosenmund, *Ber.*, 1909, **42**, 4778.
[5] Jowett, *J.*, 1904, **85**, 192.
[6] Léger, *Compt. rend.*, 1906, **142**, 108; **143**, 234, 916.
[7] Barger and Dale, *J.*, 1910, **97**, 2592.

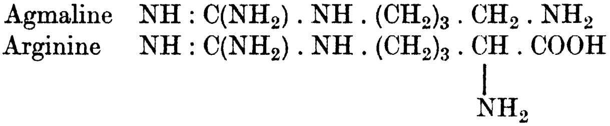


4-β-amino-ethyl-glyoxaline.



Histidine.

Finally, a substance, agmaline,[1] has been extracted from ergot; and it is found that it is related to the naturally occurring amino-acid arginine in exactly the same way as the glyoxaline derivative mentioned above is related to histidine:



$$\begin{array}{ll}\text{Agmaline} & NH : C(NH_2) . NH . (CH_2)_3 . CH_2 . NH_2 \\ \text{Arginine} & NH : C(NH_2) . NH . (CH_2)_3 . \underset{\displaystyle NH_2}{\underset{|}{CH}} . COOH\end{array}$$

C.—The Areca Nut Alkaloids

An examination of the seeds of the betel-nut palm (*Areca Catechu*) by various workers [2] resulted in the discovery of five alkaloids: arecaidine (also known as arecaine), arecoline, guvacine, guvacoline, and arecolidine. Another substance,[3] iso-guvacine, has also been detected; but its identity is a matter of doubt, and suggestions have been made that it is mainly arecaidine.

Arecaidine, $C_7H_{11}O_2N$, furnishes a methyl ester, which is found to be identical with the alkaloid arecoline, $C_8H_{13}O_2N$. The formulæ of the two alkaloids can therefore be written:

Arecaidine $(C_6H_{10}N)COOH$ Arecoline $(C_6H_{10}N)COOCH_3$

The most obvious way of accounting for the group $C_6H_{10}N$ is to assume that it represents a methylated tetrahydropyridine nucleus; and if this view were correct, then arecaidine would have the following structure: $CH_3 . N : C_5H_7 . COOH$. Obviously this leaves still unsettled the positions of the carboxyl group and the double bond in the tetrahydropyridine ring.

These two points were simultaneously cleared up by the

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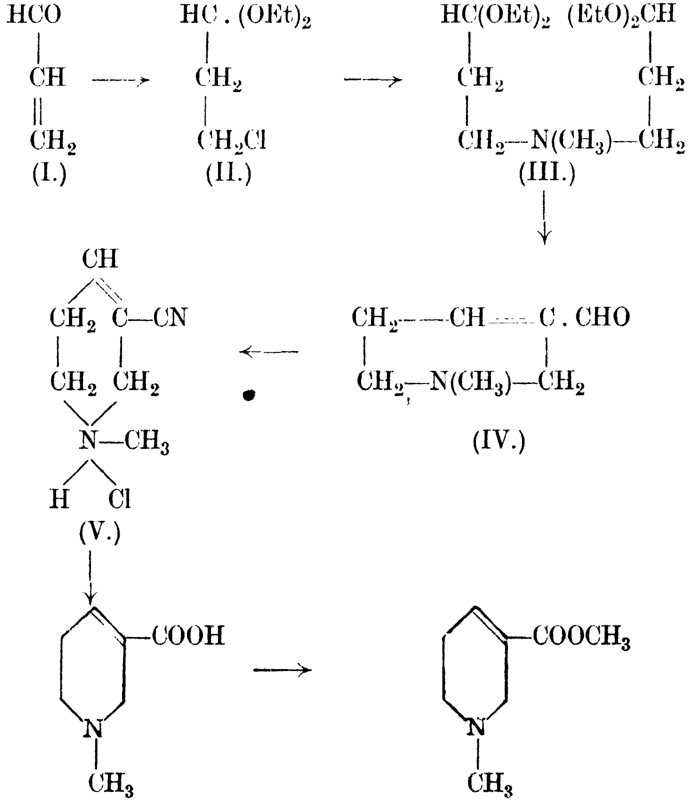
[1] Engeland and Kutscher, *Zentr. Physiol.*, 1910, **24**, 479.

[2] Bombelon, *Pharm. Ztg.*, 1886, 146; Jahns, *Ber.*, 1888, **21**, 3404; 1890, **23**, 2972; 1891, **24**, 2615; *Arch. Pharm.*, 1891, **229**, 669; Emde, *Apoth Ztg.*, 1915, **30**, 240; Hess, *Ber.*, 1918, **51**, 1004.

[3] Trier, *Z. physiol. Chem.*, 1913, **85**, 391; Winterstein and Weinhagen, *ibid.*, 1918, **104**, 48.

complete synthesis of arecaidine devised by Wohl and Johnson.[1] By acting on acrolein (I.) with alcohol and hydrogen chloride, β-chloropropaldehyde acetal (II.) was produced. Condensation of this acetal with methylamine yielded β-methyl-iminodipropaldehyde tetra-ethyl-acetal (III.). The action of strong hydrochloric acid on (III.) gave rise to N-methyl-Δ^3-tetrahydropyridine-3-aldehyde (IV.). Oximation, followed by dehydration of the oxime by means of thionyl chloride, resulted in the formation of 3-cyano-N-methyl-Δ^3-tetrahydropyridine hydrochloride (V.). On hydrolysis, the acid obtained was found to be identical with arecaidine (VI.); and esterification of this acid produced arecoline, which therefore has the formula (VII.).



(vi) Arecaidine. (vii) Arecoline.

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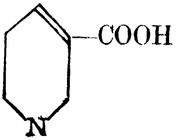
[1] Wohl and Johnson, *Ber.*, 1907, **40**, 4712.

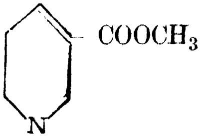
The constitution of the second pair of alkaloids, guvacine, $C_6H_9O_2N$, and guvacoline, $C_7H_{11}O_2N$, presented more difficulty than might have been expected. This, in the main, was due to Jahns, who failed to detect a carboxyl radicle in guvacine; and his results led to the view that there could be no structural kinship between guvacine and arecaidine, although the formulæ differ only by a methylene group—which naturally suggests that arecaidine might be methyl-guvacine.

This last view was taken by Trier in 1913, but was not then accepted. Five years later, Freudenberg[1] demonstrated that guvacine was identical with Δ^3-tetrahydropyridine-3-carboxylic acid, which had been synthesized by Wohl and Losanitsch[2] in 1907. This substance, on methylation, yields an N-methyl-derivative which proved to be identical with arecaidine; and on esterification with methyl alcohol, Wohl and Losanitch's acid produces a methyl ester identical with guvacoline.

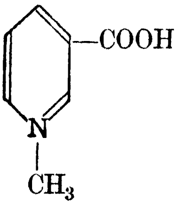
The formulæ for the four substances are therefore those which are shown below:



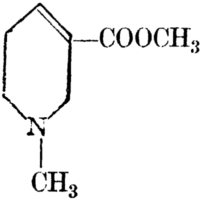
Guvacine.



Guvacoline.



Arecaidine.



Arecoline.

The fifth alkaloid, arecolidine, $C_8H_{13}O_2N$, is believed[3] to be 3 : 4-dimethoxy-1-methyl-1 : 2-dihydropyridine; but the evidence available is hardly sufficient to establish this formula definitely.

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[1] Freudenberg, *Ber.*, 1918, **51**, 976, 1669.

[2] Wohl and Losanitsch, *Ber.*, 1907, **40**, 4701.

[3] Emde, *Apoth. Ztg.*, 1915, **30**, 240.

D.—RICININE

The difficulties in the way of determining chemical constitution have seldom been better illustrated than in the case of this alkaloid derived from the castor bean. It has the comparatively simple composition $C_8H_8O_2N_2$; yet in the course of a chequered career as a subject of investigation, it has been associated in one way or another with pyrrol, glyoxaline, and pyridine; and one proposed formula even contained divalent carbon.

By heating ricinine with concentrated hydrochloric acid, Macquenne and Philippe[1] obtained a compound $C_6H_7O_2N$. Winterstein[2] isolated a base $C_7H_9O_2N$, by heating ricinine with 57·4 per cent. sulphuric acid to 140° C. When ricinine is treated with dilute potassium carbonate solution, it yields ricininic acid; and from this, by oxidation with chromic acid and dilute sulphuric acid, Böttcher[3] obtained methylamine, oxalic acid, and hydrocyanic acid. These three reactions form the keys to the ricinine constitution.

Since the two compounds $C_6H_7O_2N$ and $C_7H_9O_2N$ differ from each other by CH_2, it seemed probable that the second is the methyl derivative of the first; and the reactions of the parent substance suggested that it was a pyridone derivative.

Späth and Tschelnitz[4] identified this pyridone by the synthetic method. By treating the silver salt of 2 : 4-dihydroxy-1-methyl-pyridine (I.) with methyl iodide, they obtained the dimethyl ether (II.). On further treatment with methyl iodide, this yielded a substance which must be either 4-methoxy-1-methyl-1 : 2-dihydropyrid-2-one (III.) or 2-methoxy-1-methyl-1 : 4-dihydropyrid-4-one (IV.).

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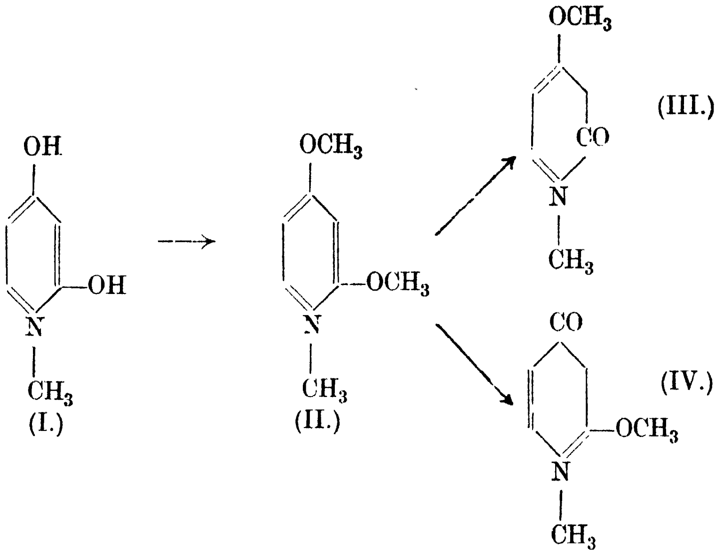
[1] Macquenne and Philippe, *Compt. rend.*, 1904, **138**, 506; **139**, 840.

[2] Winterstein and others, *Arch. Pharm.*, 1917, **255**, 513.

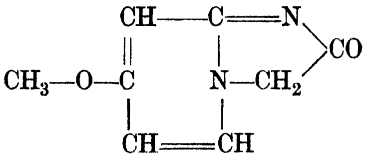
[3] Böttcher, *Ber.*, 1918, **51**, 673.

[4] Späth and Tschelnitz, *Monatsh.*, 1921, **42**, 251.


(I.) (II.) (III.) (IV.)

This synthetic substance proved to be identical with the compound $C_7H_9O_2N$ derived from ricinine ; and on demethylation it yielded a parent substance identical with the ricinine derivative $C_6H_7O_2N$. In this way the main skeleton of the ricinine molecule is established, since it must contain either the grouping (III.) or (IV.), and these differ only in the position of a methyl radicle.

At this point Späth was apparently misled by some analogies drawn by Böttcher between ricinine and histidine on the strength of the Weidel reaction, the ferric chloride colour, and a liberation of hydrocyanic acid during an oxidation with chromic and sulphuric acid which he had carried out. Späth therefore suggested that the remaining part of the ricinine molecule was a glyoxaline ring which might be joined on as shown below :



Further investigation by Späth and Koller [1] showed that the glyoxaline hypothesis was erroneous. Böttcher had found that

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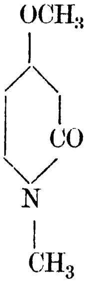
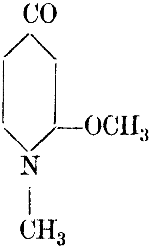
[1] Späth and Koller, *Ber.*, 1923, **56**, 880.

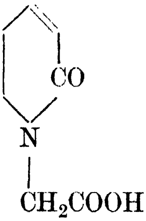
on treatment with potassium hydroxide, ricinine was converted into a so-called ricinic acid. On treating this substance with phosphorus oxychloride, Späth and Koller found that it yielded a compound $C_7H_5ON_2Cl$, which corresponds to a replacement of one hydroxyl group by a chlorine atom. On reducing this chlorine compound by means of hydrogen and palladized barium sulphate, a substance was obtained which was termed ricinidine, having the composition $C_7H_6ON_2$. That this body was a nitrile is shown by its hydrolysis to a carboxylic acid $C_7H_7O_3N$.

Now in view of the fact that ricinine must contain either of the skeletons :

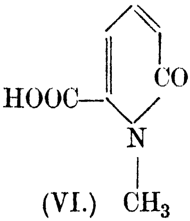




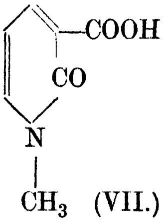
it is clear that there are only three possible carboxylic acids derivable from it in the manner described.



(V.)



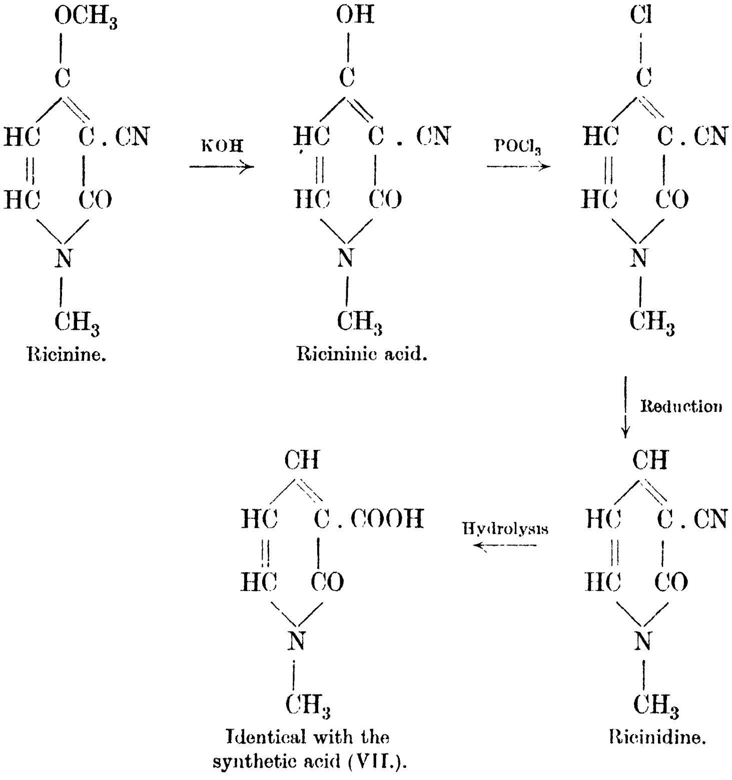
(VI.)



(VII.)

Späth and Koller synthesized all three ; and it was found that the one corresponding to the structure (VII.) was identical with the acid $C_7H_7O_3N$ derived from ricinine.

This fixes the position of the carboxyl group in the acid, and hence establishes the position of the corresponding nitrile group in ricinidine and ricininic acid; so that the reactions mentioned above can be formulated as follows :—

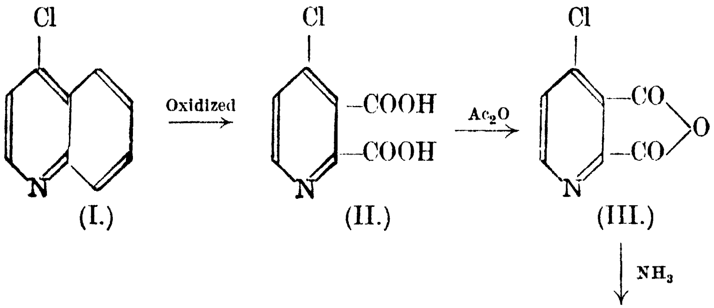


Ricinine.

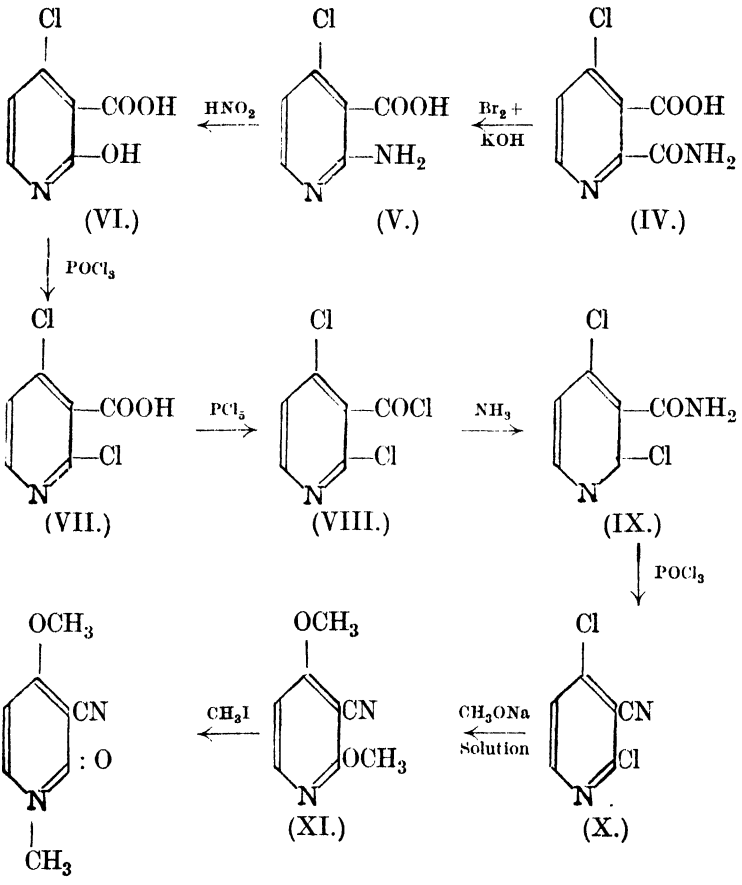
Ricininic acid.

Ricinidine.

Identical with the synthetic acid (VII.).



(I.) (II.) (III.)



Ricinine has been synthesized by Späth and Koller[1] in the following manner. By oxidizing the chloroquinoline (I.) with potassium permanganate, the di-carboxylic acid (II.) is obtained. This is converted, by treatment with acetic anhydride, into the anhydride (III.), from which the amide (IV.) is prepared and converted by Hofmann's reaction into the amine (IV.). Treatment of this amine with nitrous acid produces the hydroxy-compound (VI.) from which, by successive treatment with phosphorus oxychloride and phosphorus pentachloride, the derivatives (VII.) and (VIII.) are made. The acyl chloride

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[1] Späth and Koller, *Ber.*, 1923, **56**, 2454.

(VIII.), with ammonia, gives the amide (IX.); and this is converted into the nitrile (X.) by means of phosphorus oxychloride. This nitrile, when boiled with a solution of sodium methylate in methyl alcohol, was changed into the dimethoxy-derivative (XI.). The final step was the conversion of (XI.) into ricinine, which was accomplished by heating with methyl iodide in an evacuated tube at 120°–130° C.

The constitution of the hydroxy-acid (VI.) was proved by reducing it with hydrogen and palladized barium sulphate to 2-hydroxy-pyridine-3-carboxylic acid and hence to 2-hydroxy-pyridine. This establishes the positions of the carboxyl and hydroxyl radicles, since the 4-position is originally occupied by a chlorine atom. From this evidence, there can be no doubt as to the constitution of the compound (XI.); and since it has already been proved by earlier work that the methoxy-group of ricinine is in the 4-position, the constitution of the alkaloid is now beyond dispute.

E.—The Harmaline Group

The seeds of the plant *Peganum harmala* contain three alkaloids:

Harmaline[1]	$C_{13}H_{14}ON_2$
Harmine[2]	$C_{13}H_{12}ON_2$
Harmalol[3]	$C_{12}H_{12}ON_2$

From a comparison of the formulæ, it appears likely that harmaline is dihydroharmine.[4] This proves to be the case; for both compounds yield the same tetrahydroharmine on reduction, and harmaline is converted into harmine by gentle oxidation. When boiled with hydrochloric acid, both harmine and harmaline are demethylated, showing that each of them contains a methoxy-group. The products of these reactions[5] are respectively harmol, $C_{12}H_{10}ON_2$, and harmalol, $C_{12}H_{12}ON_2$. Harmine is a

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[1] Goebel, *Annalen*, 1841, **38**, 363.

[2] Fritsche, *Annalen*, 1847, **64**, 365.

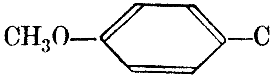
[3] O. Fischer, *Ber.*, 1897, **28**, 2481; 1905, **38**, 329; *Prince Luitpold Festschrift*, Erlangen, 1901 (see *Chem. Soc. Abstracts*, 1905, i. 229).

[4] O. Fischer, *Ber.*, 1897, **28**, 2481.

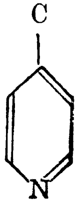
[5] O. Fischer and Tauber, *Ber.*, 1897, **39**, 2482.

secondary base; for with methyl iodide it yields first methyl-harmine and then methyl-harmine methiodide.

On oxidation with strong nitric acid,[1] harmaline gives harminic acid, $C_8H_6N_2(COOH)_2$, and *m*-nitro-anisic acid. The production of this last substance shows that the harmine molecule must contain the grouping:



Oxidation of harminic acid with dilute nitric acid [2] produced some isonicotinic acid; so that the harmine structure must have in it the nucleus



Further, Perkin and Robinson [3] found that harmine condenses with benzaldehyde to yield a benzylidene-harmine; which suggests by analogy that harmine contains a methyl group in the α-position to a nitrogen atom, like α-picoline. Finally, by the elimination of the methoxy-group from harmine, O. Fischer [4] obtained a compound harman, $C_{12}H_{10}N$, which proved to be the key to the problem.

Perkin and Robinson in 1912 suggested that harmine contained a fused system of benzene, pyrrol, and pyridine rings. The results of oxidation, given above, indicate that the pyrrol ring is in the centre, since derivatives of both the other rings appear among the disintegration-products.

Now in 1903, Hopkins and Cole [5] obtained a base by oxidizing tryptophane with ferric chloride; and this base was identified by Perkin and Robinson [6] with O. Fischer's harman.

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[1] O. Fischer and Boesler, *Ber.*, 1912, **45**, 1934.

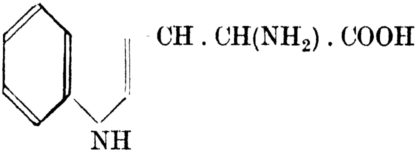
[2] O. Fischer and others, *Ber.*, 1914, **47**, 99.

[3] Perkin and Robinson, *J.*, 1912, **101**, 1778.

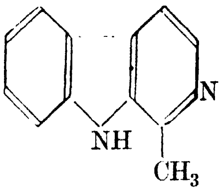
[4] O. Fischer, *Luitpold Festschrift*, 1901.

[5] Hopkins and Cole, *J. Physiol.*, 1903, **29**, 451.

[6] Perkin and Robinson, *J.*, 1919, **115**, 933, 971.

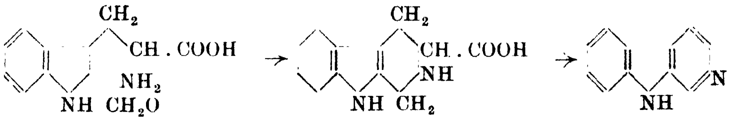


Tryptophane.

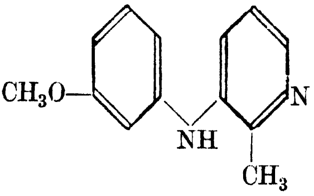


Harman.

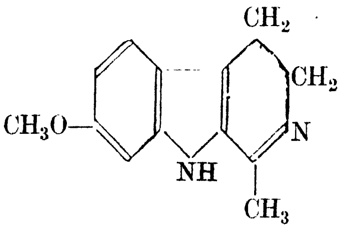
It will be noticed that this conversion of tryptophane into harman demands an extra pair of carbon atoms, which are probably derived from decomposition products of another tryptophane molecule. Their exact provenance is not of major importance, however. The main point is that the indol nucleus of tryptophane can give rise to harman; so that the presence of the same indol kernel in harman is made probable.[1] Tryptophane can be condensed with formaldehyde to yield *nor*harman, which seems to place the matter beyond doubt.



Fitting together the above evidence, Perkin and Robinson arrived at the following formulæ for harmine and harmaline:



Harmine.



Harmaline.

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[1] See also Kermack, Perkin, and Robinson, *J.*, 1921, **119**, 1602; 1922, **121**, 1872.

F.—THE ANHALONIUM OR CACTUS ALKALOIDS

No less than seven alkaloids have been identified as cactus products:

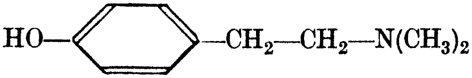
Hordenine (anhaline)	$C_{10}H_{15}ON$
Mezcaline	$C_{11}H_{17}O_2N$
Anhalamine	$C_{11}H_{15}O_3N$
Anhalonidine	$C_{12}H_{17}O_3N$
Pellotine	$C_{13}H_{19}O_3N$
Anhalonine	$C_{12}H_{15}O_3N$
Lophophorine	$C_{13}H_{17}O_3N$

The earlier work on the subject was carried out by Heffter[1] and it was known that the seven bases had a close chemical kinship with each other. In physiological action, also, they show marked resemblances.[2] From the latter standpoint, the most interesting is mezcaline, derived from so-called "Mezcal Buttons" (the buds of *Anhalonium Lewinii*), as it has the power of producing wonderful colour visions when used as a drug.

As will be seen immediately, the anhalonium alkaloids not only form a group which is interesting in itself, but in addition they throw some light upon the relationships between the normal cyclic alkaloid type and those open-chain nitrogen derivatives which possess physiological action entitling them to membership of the alkaloidal class.

1. *Hordenine*

The simplest of the anhalonium alkaloids is hordenine, $C_{10}H_{15}ON$. Originally termed anhaline, this substance was later found to be identical[3] with the known compound hordenine[4] which is present in sprouted barley, and which has been identified as *p*-hydroxy-phenyl-dimethyl-ethylamine:



Hordenine.

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[1] Heffter, *Ber.*, 1894, **27**, 2975; 1896, **29**, 216; 1898, **31**, 1193; 1901, **34**, 3004.

[2] Mogilewa, *Arch. expt. Path. Pharmak*, 1903, **49**, 137.

[3] Späth, *Monatsh.*, 1919, **40**, 129.

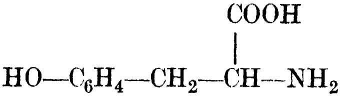
[4] Léger, *Compt. rend.*, 1906, **142**, 108 **143**, 234, 916.

Since hordenine is the dimethyl derivative of *p*-hydroxyphenyl-ethylamine, it might be supposed that the latter would be used as a starting-point in the hordenine synthesis. Owing, however, to the readiness with which hordenine, when formed, passes into the tetra-alkyl ammonium salt form, it is found better to set out from phenyl-ethyl alcohol. This substance is converted into the corresponding chloride which, when treated with dimethylamine, yields the base $C_6H_5 . CH_2 . CH_2 . N(CH_3)_2$. The missing hydroxyl radicle in the para-position is introduced by nitration, reduction, and diazotization in the usual manner. Another method consists in the methylation of *p*-methoxyphenyl-ethylamine followed by the action of hydriodic acid which splits off the methyl radicle of the methoxy-group.

The interest of the hordenine structure extends far beyond the constitution of a single alkaloid. Inspection shows that it contains the same skeleton as tyrosine :

$HO—C_6H_4—C—C—N$

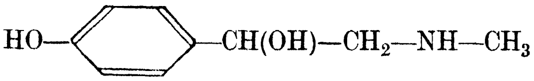
Hordenine skeleton.



$$HO—C_6H_4—CH_2—\overset{\overset{COOH}{|}}{C}H—NH_2$$

Tyrosine.

and as tyrosine is a common product in the decomposition of proteins, it seems evident that natural hordenine has a protein origin. Further, the hordenine skeleton is found in various alkaloidal structures, as an examination of the adrenaline formula will show at a glance :



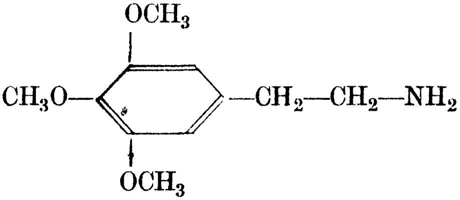
Adrenaline.

A somewhat analogous structure is traceable in papaverine, laudanosine, narcotine, hydrastine, and berberine ; whilst narceine contains the chain of phenyl-dimethyl-ethylamine complete. These relationships, taken in conjunction with the tyrosine formula, are obviously capable of furnishing food for interesting speculations with regard to the genesis of the alkaloids.

With regard to the effect of structure upon physiological properties, it is interesting to note that the conversion of the alcohol adrenaline into the ketone adrenalone does not destroy the physiological activity ; nor is the presence of the methyl radicle attached to the nitrogen atom essential. One hydroxyl radicle in the benzene nucleus appears to be sufficient. A marked influence is exerted by the introduction of a methyl radicle in the α- or β-position; for compounds containing this grouping are much less active than the parent substances.

2. *Mezcaline*

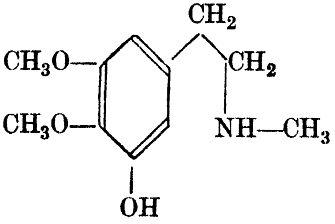
The second anhalonium alkaloid, mezcaline, has been synthesized[1] in the following manner, which establishes its constitution beyond doubt. Gallic acid is methylated by means of methyl sulphate. The trimethoxy-gallic acid so formed is converted into the acyl chloride by means of phosphorus pentachloride; and this acyl chloride is then reduced by means of hydrogen and palladized barium sulphate with the production of trimethoxy-benzaldehyde. On treatment with nitromethane in the ordinary way, this aldehyde yields the corresponding nitro-styrene: $(CH_3O)_3C_6H_2 . CH : CH . NO_2$. Reduction of this compound proceeds in two stages, the oxime being formed first and then the amine of the structure shown below, which has been proved to be identical with mezcaline:



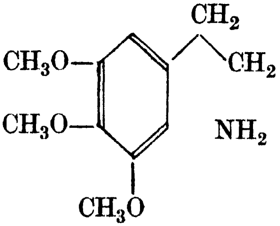
Mezcaline.

3. *Anhalamine*

Owing to certain superficial resemblances between mezcaline and anhalamine it was at first supposed that they were built up on the same skeleton. Anhalamine being a secondary base, it seemed possible that it had a formula of this type:



Anhalamine.



Mezcaline.

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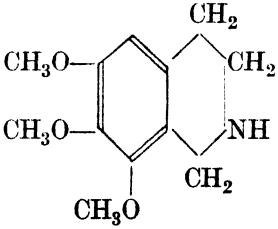
[1] Späth, *Monatsh.*, 1919, **40**, 129.

wherein one of the carbon atoms of mezcaline has been transferred from the oxygen to nitrogen. This view was disproved in the following manner. Both anhalamine and mezcaline were further methylated, an extra methyl radicle being introduced in each case. On the foregoing assumption, this operation should convert both of them into the same trimethyoxy-N-methyl derivative. In practice, however, the methylation led to the production of two different compounds. Further, when the methyl-anhalamine thus formed was oxidized, no trace of trimethyl-gallic acid, $(CH_3O)_3C_6H_2 . COOH$, could be detected among the oxidation products. This establishes definitely the fact that trimethyl-anhalamine does not contain the simple skeleton $(CH_3O)_3C_6H_2—C$. It therefore cannot be like mezcaline to this extent.

The only other plausible suggestion is that the anhalamine secondary nitrogen atom forms part of a reduced pyridine ring: in other words, that anhalamine is a tetrahydro-isoquinoline derivative. But the formation of an isoquinoline ring demands an extra carbon atom in addition to the side-chain of mezcaline, as can be seen from the formula above. Since mezcaline and anhalamine both contain eleven carbon atoms, then, if the resemblance between the alkaloids is to be retained at all, this extra carbon atom can be obtained only by the demethylation of one of the mezcaline methoxy-groups.

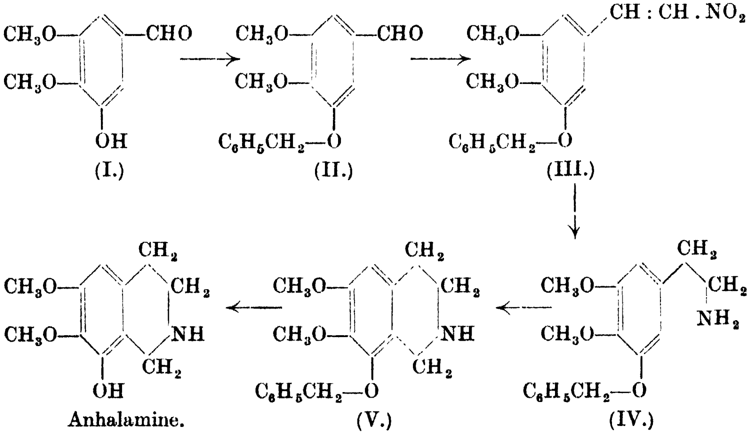
This reasoning leads to the conclusion that anhalamine is a tetrahydro-*iso*quinoline with one hydroxyl and two methoxyl groups in the benzenoid portion of the molecule. Now when mezcaline is treated with formaldehyde, it yields an isoquinoline derivative which must obviously have the structure:



This substance, on treatment with *m*-nitrobenzoyl chloride, yields an N-*m*-nitrobenzoyl derivative; and this last compound is found to be identical with the corresponding N-*m*-nitrobenzoyl derivative of methyl-anhalamine. This proves that the oxygen atoms in mezcaline and anhalamine are attached to corresponding carbon atoms ; so that anhalamine is a pyrogallol derivative like mezcaline.

Which pair of the pyrogallol hydroxyl groups has been methylated in anhalamine remained to be settled ; and this has been done by synthesis.[1]

The compound 5-hydroxy-3 : 4-dimethoxy-benzaldehyde (I.) was benzylated, yielding (II.), whereby the hydroxyl group is shielded by the easily removable benzyl radicle. This substance was then condensed with nitromethane in the usual way, whereby (III.) was formed. On reduction this gave the amine (IV.) which was then condensed with formaldehyde to give the tetrahydro-isoquinoline derivative (V.). On digestion with hydrochloric acid, the benzyl group was split off, the hydroxyl group being regenerated. The product was found to be identical with anhalamine.



4. *Anhalonidine*

The synthesis of anhalonidine[2] has been achieved ; but the method employed leaves a choice open between two possible formulæ for the alkaloid. The 5-benzyloxy-3 : 4-dimethoxy-

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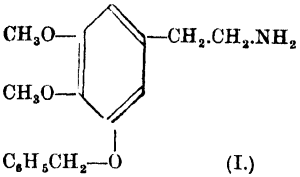
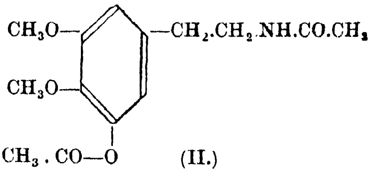
[1] Späth and Röder, *Monatsh.*, 1922, 43, 93.

[2] Späth, *Monatsh.*, 1923, 43, 477.

phenyl-ethylamine (I.) described above was treated with hydrochloric acid, whereby the benzyl radicle was removed. Acetic anhydride converts the product into the O—N-diacetyl derivative (II.).

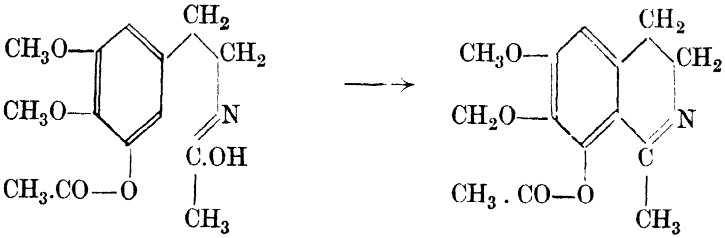


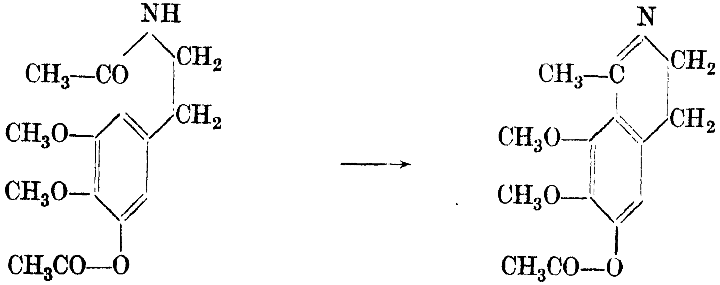
(I.)



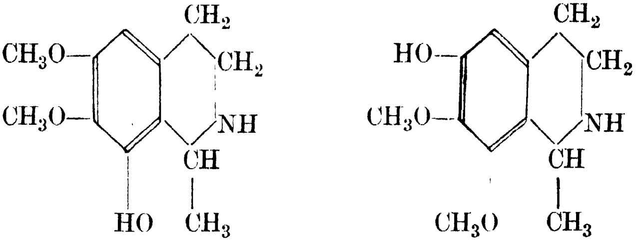
(II.)

On heating (II.) with phosphorus pentoxide in toluene solution, a base was formed which may obviously have either of two constitutions, as shown in the formulæ below :





On reducing the base with tin and hydrochloric acid, a compound is produced which is identical with anhalonidine. Anhalonidine must therefore have a structure corresponding to either (A) or (B) below ; but at present there is not enough evidence to settle the question, though Späth inclines to favour formula (A) on general grounds.



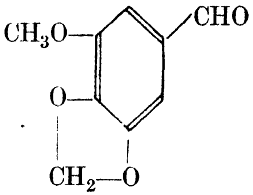
(A) Anhalonidine. (B)

5. *Pellotine*

Pellotine has been shown to be the N-methyl derivative of anhalonidine. By methylating the above-mentioned dihydro-isoquinoline compound before reduction with tin and hydrochloric acid, and then carrying out the reduction as before, it is possible to obtain pellotine.[1] Here, again, the structure is indeterminate, since it may correspond to the N-methyl derivative of either formula (A) or (B) in the foregoing section.

6. *Anhalonine and Lophophorine*

Späth and Gangl [2] synthesized anhalonine by a method quite analogous to that described above in the case of anhalamine with the exception that instead of hydroxy-dimethoxy-benzaldehyde they began with the substance which they obtained by the



ozonization of myristicine. This aldehyde was condensed with nitromethane, and the product subjected to reduction, acetylation, and dehydration. The result must be a compound having either formula (X) or formula (Y).

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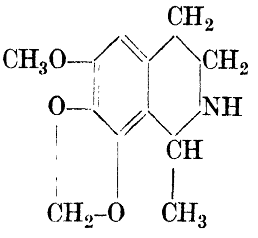
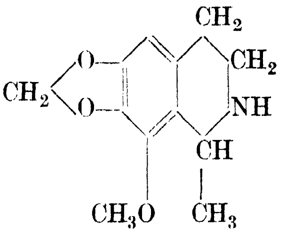
[1] Späth, *Monatsh.*, 1923, **43**, 477.

[2] Späth and Gangl, *Monatsh.*, 1923, **44**, 103.



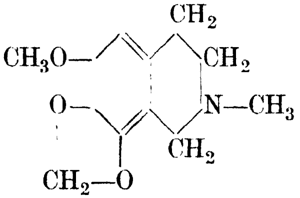
(X) Anhalonine.



(Y)

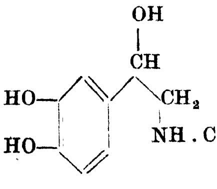
Now a compound corresponding to the N-methyl derivative of the formula (Y) was synthesized by means of magnesium methyl iodide and cotarnine ; and this body proved to be different from the N-methyl derivative of anhalonine. The structure of anhalonine must therefore correspond to formula (X) given above.

Lophophorine has been shown by Späth to be identical with the N-methyl derivative of anhalonine, so that its structure is obviously that which is derived from the anhalonine formula :

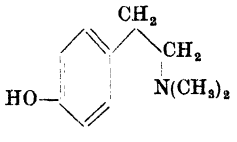


Lophophorine.

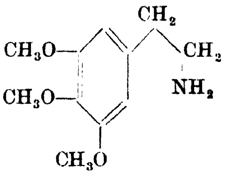
The formulæ of the complete series of alkaloids (or methyl ethers of known constitution), as well as that of adrenaline, are given below so as to bring out the resemblances in structure between the various members of the group.



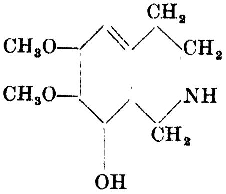
Adrenaline.



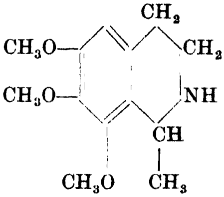
Hordenine
(Anhaline).



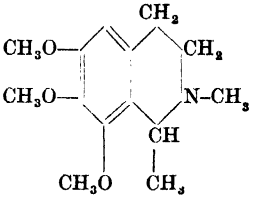
Mezcaline.



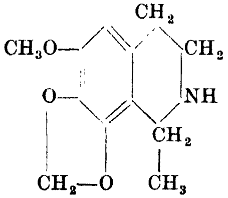
Anhalamine.



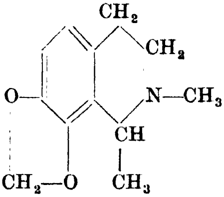
Anhalonidine methyl ether.



Pellotine methyl ether.



Anhalonine.



Lophophorine.

G.—The Angostura Alkaloids

The two principal alkaloids found in cusparia or angostura bark are cusparine, $C_{19}H_{17}O_3N$, and galipine, $C_{20}H_{21}O_3N$. More recently, a third alkaloid, galipoline, has been obtained. A fourth supposed component, galipidine, is now believed to be identical with galipine ; and the existence of cusparidine is doubtful.

Troeger [1] and his collaborators observed that on oxidation galipine yielded a carboxylic acid. On demethylating this and heating the product, carbon dioxide was lost, and a substance C_9H_7ON was obtained, which on heating with zinc dust yielded quinoline. The original carboxylic acid is therefore a derivative of a methoxy-quinoline. Further, among the galipine oxidation products he believed that he had detected anisic acid and veratric acid ; and on this basis he assumed that galipine must contain (1) a quinoline nucleus with (2) a methoxy-group in the 7-position (to account for his anisic acid) and (3) a veratryl complex attached to some point of the quinoline ring (to account for his veratric acid). On the basis of this and other evidence, he attributed to galipine the structure :

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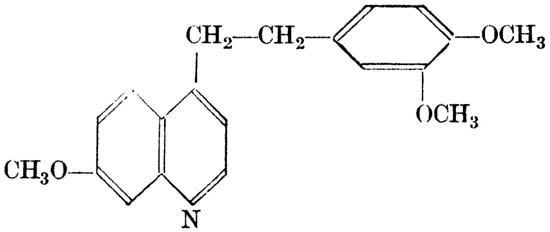
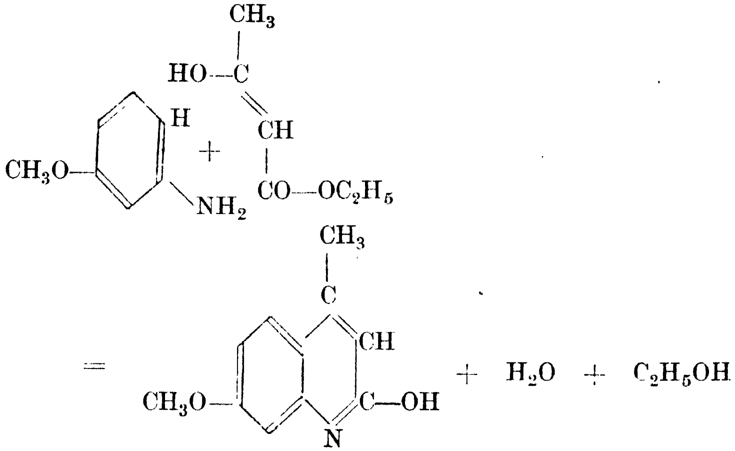
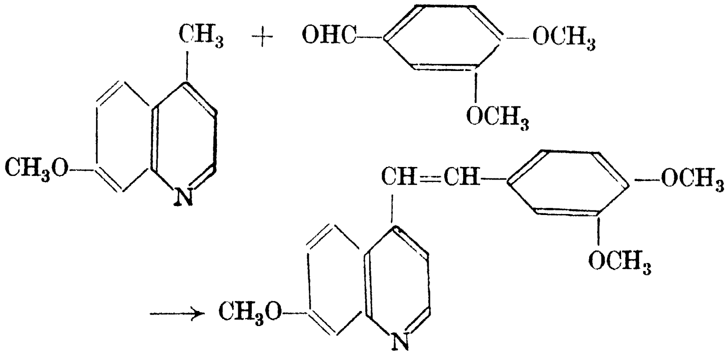
[1] Troeger and others, *Arch. Pharm.*, 1914, **252**, 459 ; 1920, **258**, 250.



Späth and Brunner [1] tested this by synthesis in the following way. Acetoacetic ester was condensed with *m*-methoxy-aniline



and the product was converted into 2-chloro-7-methoxy-4-methyl-quinoline ; and thence, by reduction, into 7-methoxy-4-methyl-quinoline. This last substance was condensed with 3 : 4-dimethyoxy-benzaldehyde by means of zinc chloride :



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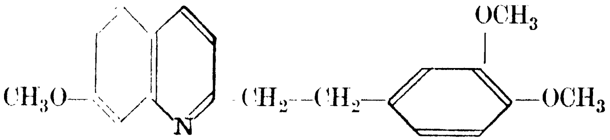
[1] **Späth and Brunner, *Ber.*, 1924, 57, 1243.**

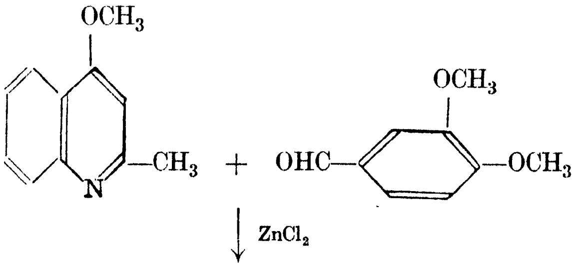
and on reduction the product yielded a substance with a structure identical with Troeger's proposed formula for galipine. Since the synthetic material had properties different from natural galipine, Troeger's formula was proved to be incorrect. By a somewhat analogous synthesis it was shown that a compound with the structure



was not identical with galipine.

These results suggest that the methoxy-group of galipine is not situated in the benzenoid ring at all; and a further hint of this was obtained when it was recalled that the methyl iodide addition product of galipine easily changes into a methyl-galipine. This behaviour is analogous to the change of α- or γ-methoxy-quinolines into N-methyl-quinolines, which makes it probable that the methoxy-radicle of galipine is really in the pyridine portion of the structure.

Following this line of thought, Späth and Eberstaller[1] synthesized galipine in the following manner. Veratryl aldehyde was condensed with 4-methoxy-2-methyl-quinoline by heating with zinc chloride. The product was reduced by means of hydrogen and palladized charcoal and was found to be identical with natural galipine. The formulæ below will make the various steps clear.



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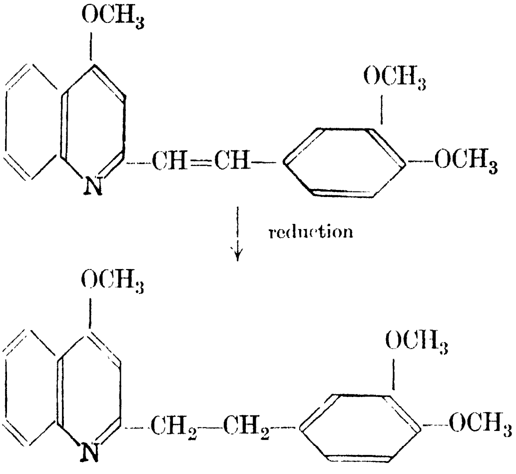
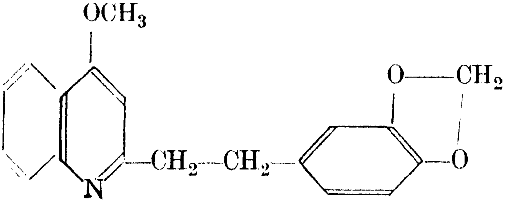
[1] Späth and Eberstaller, *Ber.*, 1924, **57**, 1687.



Galipine.

By an exactly similar condensation and reduction, cusparine was obtained[1] from 4-methoxy-1-methyl-quinoline and piperonal; so that its structure is therefore



Cusparine.

As galipine has the composition $C_{20}H_{21}O_3N$, whilst the alkaloid galipoline[2] has the formula $C_{19}H_{19}O_3N$, it appears probable that galipine is a methylated galipoline. This idea is confirmed by the fact that galipoline, on methylation, yields galipine; but as there are three methoxy-groups in galipine, this reaction does not indicate the position of the unmethylated hydroxyl group in the galipoline structure. The matter has now been settled by the synthesis of galipoline, on lines analogous to those indicated in the case of the other alkaloids; and it has been shown that the hydroxyl group of the galipine quinoline nucleus is free in galipoline. This alkaloid is therefore 4-hydroxy-2-β-3′:4′-dimethoxy-phenyl-ethyl-quinoline.

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[1] Späth and Brunner, *Ber.*, 1924, **57**, 1243.

[2] Späth and Papaioanou, *Monatsh.*, 1929, **52**, 129.

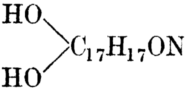
H.—THE PHENANTHRENE GROUP

1. *The Relations between Morphine, Codeine, and Thebaine*

The general resemblance between morphine, codeine, and thebaine can be seen by the comparison of their compositions :

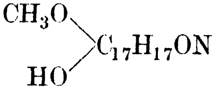
$C_{17}H_{19}O_3N$	$C_{18}H_{21}O_3N$	$C_{19}H_{23}O_3N$
Morphine.	Codeine.	Thebaine.

Morphine contains two hydroxyl groups, one of which is phenolic,[1] while the other is an alcoholic radicle.[2] When morphine is methylated, codeine is formed, which has no phenolic properties. This establishes that codeine is methyl-morphine and carries its methyl radicle on the phenolic oxygen atom of morphine. The third oxygen atom in morphine and codeine is indifferent to reagents and is therefore assumed to be ethereal in character.[3] When subjected to Zeisel's reaction, thebaine loses two methyl radicles ; so that evidently it contains two methoxyl groups. The formulæ of the three substances may therefore be written as below :



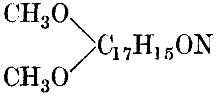
$$\begin{matrix} HO \\ HO \end{matrix} \rangle C_{17}H_{17}ON$$

Morphine.



$$\begin{matrix} CH_3O \\ HO \end{matrix} \rangle C_{17}H_{17}ON$$

Codeine.



$$\begin{matrix} CH_3O \\ CH_3O \end{matrix} \rangle C_{17}H_{15}ON$$

Thebaine.

wherein the third oxygen atom is assumed to be ethereal in character.

All three alkaloids are tertiary bases and each of them contains a phenanthrene nucleus, as will be seen later.

2. *Methylmorphimethine.*[4]

I. Codeine unites directly with one molecule of methyl iodide, forming codeine-methyl-ammonium iodide. When this compound is boiled with caustic soda it yields a tertiary base, $C_{19}H_{23}O_3N$, which is known as methylmorphimethine. The process is evidently one of exhaustive methylation,* and the result proves that in codeine the nitrogen atom forms part of a ring.

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[1] Matthiessen and Wright, *Proc. Roy. Soc.*, 1869, **17**, 364.

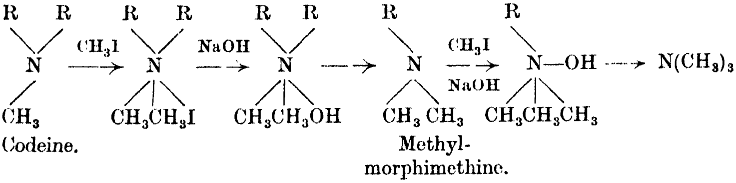
[2] Hesse, *Annalen*, 1884, **222**, 203.

[3] Vongerichten, *Annalen*, 1882, **210**, 105.

[4] Knorr, *Ber.*, 1889, **22**, 182.

* See Vol. I., p. 48.

II. When methyl iodide is allowed to unite with methylmorphimethine, a quaternary ammonium iodide is produced which can be converted into the corresponding methylmorphimethine-methyl-ammonium hydroxide in the usual way. On heating, this hydroxide decomposes; and among the products trimethylamine is found. This proves that the nitrogen atom in methylmorphimethine-methyl-ammonium hydroxide is attached to three methyl radicles. Now since only one methyl group was introduced into the molecule in Stage I. and a second one in Stage II. it follows that the third methyl radicle must have been attached to the original nitrogen atom in codeine. Codeine, therefore, contains a nitrogen atom attached by two of its valencies to a cyclic grouping, whilst the third valency holds a methyl radicle. The course of the various reactions may be symbolized as follows, RR being used to represent the remainder of the codeine structure:



III. When treated with acetic anhydride,[1] methylmorphimethine yields hydroxy-ethyl-dimethylamine:

$$HO . CH_2 . CH_2 . N(CH_3)_2$$

This chain might have been attached to the parent molecule either by the intermediation of the oxygen atom or of a carbon atom. By actual synthesis of the ether type of compound from the decomposition products,[2] it was proved that this structure was not the one sought; so that the side-chain is not attached to the rest of the codeine molecule by means of the oxygen atom. The linkage is therefore one between two carbon atoms; and the oxygen atom of hydroxy-ethyl-dimethylamine is not part of the original molecule, but is supposed to appear

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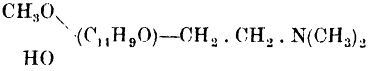
[1] Knorr, *Ber.*, 1889, **22**, 181, 1113; 1894, **27**, 1144; Knorr and Smiles, *ib.*, 1902, **35**, 3009.

[2] *Ibid.*, 1905, **38**, 3143.

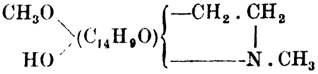
as the result of a reaction between water and the primary decomposition-product: a vinyl derivative.*

IV. Summarizing the information gained in the foregoing paragraphs, it is clear that methylmorphimethine may be represented by (1) while codeine corresponds to (2).



$$\begin{matrix}CH_3O\diagdown \\ \quad (C_{11}H_9O)—CH_2 . CH_2 . N(CH_3)_2 \\ HO\end{matrix}$$

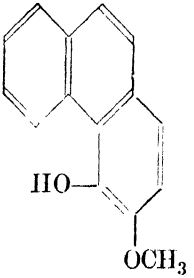
(1).



$$\begin{matrix}CH_3O\diagdown \\ \quad (C_{14}H_9O)\left\{\begin{matrix}—CH_2 . CH_2 \\ \qquad | \\ ———N . CH_3\end{matrix}\right. \\ HO\diagup\end{matrix}$$

(2).

V. The second product obtained when methylmorphimethine is decomposed with acetic anhydride is a methoxy-hydroxy-phenanthrene which has been shown, by synthesis,[1] to have the structure:



3. *The Structures of Morphine and Codeine*

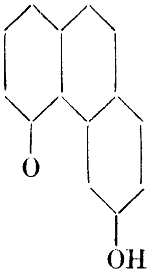
I. The whole of the seventeen carbon atoms in the morphine molecule are now accounted for: since there are fourteen in the phenanthrene nucleus; two in the ring of which nitrogen forms a member; and one in the methyl radicle attached to the nitrogen atom. The next step is to determine, if possible, the position of the ethereal oxygen atom in the molecule. Proof has been given above that this oxygen atom does not serve to connect the nitrogen chain with the molecular nucleus; so it evidently must be linked with two carbon atoms of the phenanthrene group. Since a ring composed of four carbon and one oxygen

---

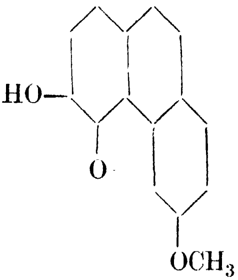
* The primary product is assumed to be $CH_2 : CH . N(CH_3)_2$ which is then supposed to add on a molecule of water at the double bond.

[1] Pschorr and Sumuleanu, *Ber.*, 1900, **33**, 1810, 1824; Pschorr and Vogtherr, *Ber.*, 1902, **35**, 4412.

atom is a fairly stable one, it is concluded that this grouping occurs in morphine; and this view is supported by evidence drawn from the effect of the Grignard reagent upon the analogous oxygen atom in thebaine.[1] Although the evidence is not perfect, it is generally accepted that morphine contains the skeleton shown in (3)—



(3).



(4).

II. The position of the remaining hydroxyl radicle has been determined in the following way. When codeine is oxidized by means of potassium permanganate or chromic acid,[2] it gives the corresponding ketone codeinone, the group —CH(OH)— being changed to a carbonyl radicle. On treatment with acetic anhydride,[3] codeinone yields 3-methoxy-4,6-dihydroxy-phenanthrene, which places the hydroxyl group in position 6 as shown above in the formula (4).

III. It has now been shown that morphine contains a phenanthrene nucleus with six substituents attached to it: two places being occupied by the ends of the nitrogen ring, two by the hydroxyl groups and two by the ethereal oxygen. On counting the hydrogen atoms in this structure, it will be found that the total is six less than the number actually required by the formula for morphine. From this it is clear that morphine contains a partially reduced nucleus. The position of one of the reduced nuclei is indicated by the alcoholic hydroxyl in morpnine; since this must be attached to a hexahydro-ring.

IV. The only remaining problem is the attachment of the

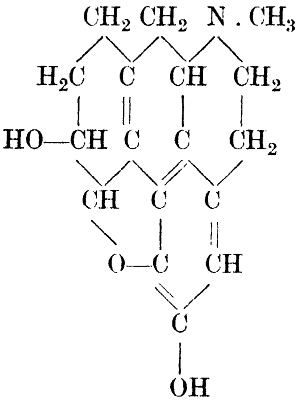
---

[1] Freund, *Ber.*, 1903, **38**, 3234.

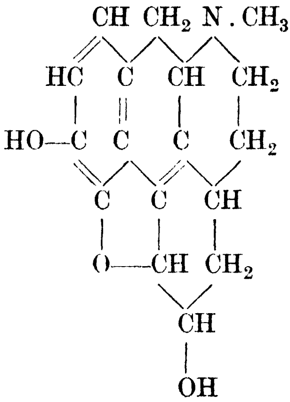
[2] Ach and Knorr, *Ber.*, 1903, **36**, 3067.

[3] Knorr, *Ber.*, 1903, **36**, 3077.

nitrogen ring to the nucleus. There is no conclusive evidence on the point; and it will be sufficient to give here two of the formulæ suggested, one by Collie,[1] the other by Pschorr.*



Collie's formula.



Pschorr's formula.

Whatever formula be adopted for morphine, the corresponding codeine formula is obtained by substituting a methyl radicle for the hydrogen of the phenolic hydroxyl group.

It will be noticed that in each of the above morphine formulæ there are three asymmetric carbon atoms, from the presence of which it is reasonable to deduce that morphine will exist in two or more isomeric forms. In actual practice it is found that in addition to morphine itself there exist three isomeric bases: α-, β-, and γ-isomorphine; and in the case of codeine there are also three extra isomers: isocodeine, pseudocodeine and allopseudocodeine. Four isomeric methylmorphimethines [2] have also been found.

The case of the codeines is sufficient to throw some light upon the problem. When phosphorus chloride acts upon codeine, the hydroxyl group of the alkaloid is replaced by a chlorine

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[1] Collie, private communication.

* This formula is based on Pschorr's formula for apomorphine (Pschorr, Jäckel and Fecht, *Ber.*, 1902, **35**, 4379; Pschorr, Einbeck and Spangenberg, *Ber.*, 1907, **40**, 1984, 1995, 1998).

[2] Grimaux, *Compt. rend.*, 1881, **93**, 591; Hesse, *Annalen*, 1884, **222**, 223; Knorr, *Ber.*, 1894, **27**, 1144; Knorr and Smiles, *ibid.*, 1902, **35**, 3009; Schryver and Lees, *J.*, 1901, **79**, 1; Knorr and Hawthorne, *Ber.*, 1902, **35**, 3010.

atom, yielding chlorocodide; but when this chlorocodide is reconverted into a hydroxyl derivative there is no regeneration of the original codeine, for any one of the three isomeric bodies may be produced according to the experimental conditions.[1]

Now when codeine and isocodeine are oxidized with chromic acid, they yield the same codeinone, which proves them to be structurally identical but stereoisomeric on account of the arrangement of the —CH(OH)— groups in space, a difference which vanishes when the secondary alcoholic radicle is oxidized to a carbonyl group. By the same test, pseudocodeine and allopseudocodeine are also two stereoisomers, but since the codeinone in this case is different from that derived from codeine itself, it is clear that structure isomerism must be taken into account in order to explain the difference between codeine and pseudocodeine. The correctness of this view seems to be established by the fact that pseudocodeinone, derived from pseudocodeine, can be broken down to 3-methoxy-4,8-dihydroxyphenanthrene; whereas codeine itself yields with the same treatment 3-methoxy-4,6-dihydroxyphenanthrene. The isomerism of codeine and pseudocodeine therefore arises from the fact that the —CH(OH)— group occupies the position 6 in one molecule and the position 8 in the other.

These reactions enable us to compare the formulæ of Collie and Pschorr. The Collie formula agrees with the facts; whereas in the Pschorr formula the position 8 is already occupied by the isoquinoline ring. From this it is evident that Collie's formula is the more correct of the two.

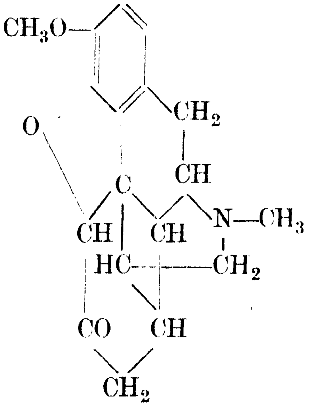
Further evidence in favour of Collie's view and against Pschorr's formula is to be found in the following facts. When codeinone is treated with dilute hydrochloric acid it yields a secondary base thebenine; whereas when strong hydrochloric acid is employed, the tertiary base morphothebaine is produced. Both these substances are isomeric with codeinone. Now when each of these compounds is methylated two different trimethoxy-derivatives are formed, which, on oxidation, give rise to two different trimethoxy-carboxylic acids derived from phenanthrene:—

---

[1] Schryver and Lees, *J.*, 1900, **77**, 1024; 1901, **79**, 563; 1907, **91**, 1408; Knorr and Hörlein, *Ber.*, 1906, **39**, 4409; 1907, **40**, 3844.

$$\begin{tikzcd}
\text{Morphothebaine} \arrow[d, "\text{Methylate and oxidize}"] & \text{Codeinone} \arrow[l, "\text{Conc. HCl}"'] \arrow[r, "\text{Dil. HCl}"] & \text{Thebenine} \arrow[d, "\text{Methylate and oxidize}"'] \\
\text{Phenanthrene-3, 4, 6-trimethoxy-carboxylic acid} \arrow[d, "\text{Heat}"] & & \text{Phenanthrene-3, 4, 8-trimethoxy-carboxylic acid} \arrow[d, "\text{Heat}"'] \\
\text{3, 4, 6-trimethoxy-phenanthrene.} & & \text{3, 4, 8-trimethoxy-phenanthrene.}
\end{tikzcd}$$

In the space available here, it is quite impossible to enter into a full description of all the niceties of the morphine problem. An interesting and complete review of the whole subject has been made by Gulland and Robinson,[1] as a result of which they reached the conclusion that the best formula for codeinone is that shown below :



Codeinone.

This formula may be rewritten as shown below, which brings it into parallel with the Collie and Pschorr formulæ for morphine which were given above.

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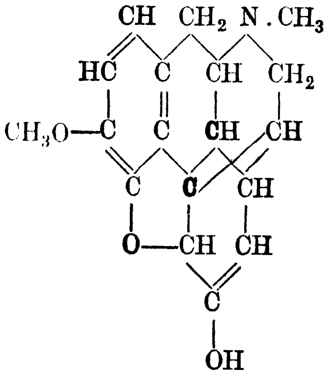
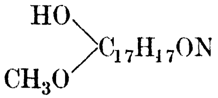
[1] Gulland and Robinson, *J.*, 1923, **123**, 980.



If this structure be further rearranged by breaking the long bond across the *iso*quinoline ring and replacing it by a double bond between the two carbon atoms printed in heavy type (with the consequent shift of a hydrogen atom), then the new structure will be found to be that suggested by Pschorr.* The reader is advised to consult this paper of Gulland and Robinson. To it is appended a bibliography of the subject which will be found useful to those who desire to go further into the field.

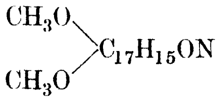
4. *Thebaine*

An examination of the formulæ for codeine and thebaine



$$\left.\begin{matrix}HO\\CH_3O\end{matrix}\right>C_{17}H_{17}ON$$

Codeine.



$$\left.\begin{matrix}CH_3O\\CH_3O\end{matrix}\right>C_{17}H_{15}ON$$

Thebaine.

will show that thebaine apparently contains a structure similar to codeine, except that it has two hydrogen atoms less in its nucleus. It is reasonable to assume that in thebaine there is a double bond which does not exist in the codeine molecule.

When thebaine is hydrolysed with dilute acid, it yields codeinone,[1] a ketone also derivable from codeine by oxidation. The most satisfactory explanation of these reactions is based on the assumption that thebaine is the ether derived from the enolic form of codeinone :—

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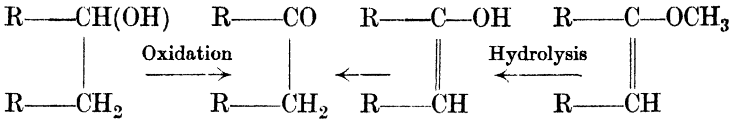
* I am indebted to Dr. Graham for this suggestion.

[1] Knorr, *Ber.*, 1906, **39**, 1409 ; Freund, *ibid.*, 844.

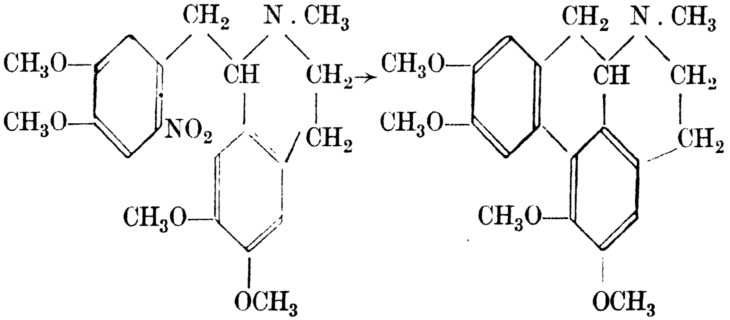


Codeine. Codeinone. Enolic form. Thebaine.

This view is in agreement with all the facts ; and can be applied to either of the codeine formulæ given above.

5. *Glaucine*

The connection between the isoquinoline and the phenanthrene alkaloids is clearly brought out by the conversion of laudanosine into glaucine. Nitration of laudanosine produces nitro-laudanosine (I.) which is then reduced to amino-laudanosine. This last substance is then diazotized ; and when the diazo-derivative is heated with copper powder, racemic glaucine (II.) is formed, which can be resolved into optical antipodes by means of tartaric acid.



Nitro-laudanosine. Glaucine.

(I.) (II.)

6. *The Relations between the Isoquinoline and Phenanthrene Alkaloids*

There are certain similarities in the structures of the isoquinoline and phenanthrene alkaloids which are apt to be overlooked when the various substances are considered individually as we have done in the preceding pages ; and it seems advisable to point out here some of the resemblances which can be detected.*

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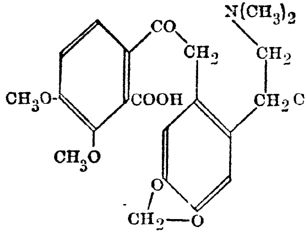
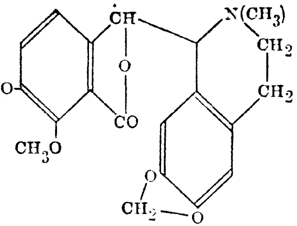
* I am indebted to Professor Collie for notes on this point.

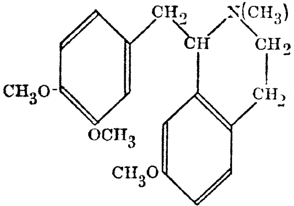
RELATIONS BETWEEN ISOQUINOLINE AND PHENANTHRENE ALKALOIDS.



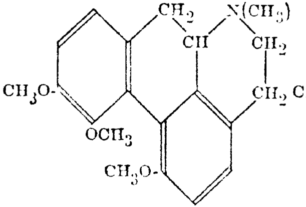
Narceine



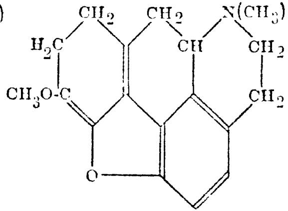
Hydrastine



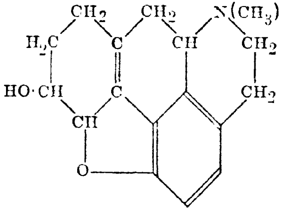
Laudanosine OCH3



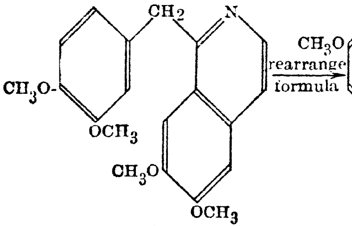
Glaucine OCH3



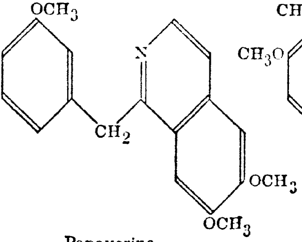
Thebaine OCH3



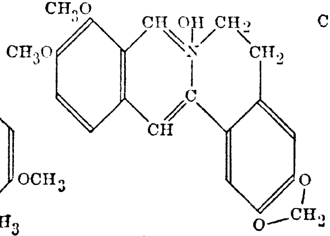
Morphine OH



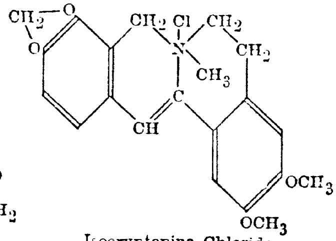
Papaverine



Papaverine



Berberine



Isocryptopine Chloride

In the table on p. 193, some of the formulæ are collected together. In the first place, an examination of the structures of narceine, laudanosine and papaverine will show the step-by-step change from the open-chain grouping of the amino-chain in narceine to the closed and unsaturated pyridine ring in papaverine; and it will also reveal the identical distribution of the hydroxyl radicles in the three molecules, although the outward resemblance is masked to some extent by the substitution of a methylene ether radicle in narceine for the dimethoxyl grouping common to the others.

Comparison of narceine and hydrastine brings out the alliance between the two substances; for the carbonyl and carboxyl groups in the former compound become converted into the lactonic ring of hydrastine, at the same time as the open chain is contracted into the piperidine ring.

The main skeletons of laudanosine, glaucine, thebaine and morphine, are obviously identical, and the change from the one formula to another is accomplished by a preliminary closing of a ring between two benzene nuclei, followed by a second ring-formation by elimination of water between two hydroxyl groups.

The inter-relations between papaverine, berberine, and isocryptopine chloride can be seen by inspection of the formulæ on page 193.

It has not been thought necessary to do more than give these examples, for the resemblances between other analogously-constituted alkaloids can easily be detected when attention has been drawn to the matter.

CHAPTER VII

THE ANTHOCYANINS

1. *Introductory*

AN examination of plant pigments proves that they are, roughly divisible into two classes. On the one hand are the plastid pigments which are in some way intimately associated with the organized protoplasmic structure of the plant ; whilst on the other hand we have soluble pigments, existing in solution in the sap of cells. These soluble pigments are termed anthocyanins.[1]

In view of the number and variety of the tints exhibited by flowers, it may appear that the term anthocyanin is a very loose one covering a multitude of colouring materials whose only relation with each other lies in the fact that they occur naturally in the sap of plants ; but research has shown this idea to be erroneous. It seems practically established that the separate anthocyanins contain similar nuclei, no matter how much they may differ in colour from one another ; and the wide variations of tint in flowers are to be ascribed to slight alterations in constitution which leave the main anthocyanin skeleton intact. Thus the anthocyanins may be regarded as a chemical class in the same way as it is customary to speak of the proteins, the carbohydrates, or the fats.

Although 250 years have passed since Boyle[2] published an investigation of the colour changes which take place when extracts from flowers are treated with acids and alkalis, it is only quite recently that much progress has been made in the study of the anthocyanin group.[3] The unstable nature of the compounds and the difficulty of preparing them in a pure state

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[1] A complete account of the history of the anthocyanins as well as of their botanical significance is to be found in Miss Wheldale's book, *The Anthocyanin Pigments of Plants* (1916). For briefer accounts, see Everest, *Science Progress*, 1915, **9**, 597, and Willstätter, *Ber.*, 1914, **47**, 2831.

[2] Robert Boyle, *Experiments and Considerations Touching Colours*, 1664.

[3] A complete bibliography of the literature is to be found in Miss Wheldale's *Anthocyanin Pigments of Plants*, or in Perkin and Everest's *Natural Organic Colouring Matters*.

militated against research in this field. It was not until 1903 that an anthocyanin was first obtained in a crystalline condition by Griffiths.[1]

The next important stage in the history of the subject is marked by Grafe's discovery [2] that certain of the anthocyanins occurred in plants in the form of glucosides.

Meanwhile, on the botanical side of the problem a considerable amount of work had been carried out, chiefly dealing with the mode of formation of the anthocyanins in plants. Miss Wheldale [3] first suggested that anthocyanins might be formed from glucosides in the flavone or xanthone series by the action of oxidases; she indicated [4] that there are a certain number of anthocyanin types which give rise to a definite series of colour varieties.[5]

Having now surveyed the outlines of the anthocyanins' history from the chemical standpoint, it will be convenient, in the remainder of this chapter, to abandon the chronological method and deal with the present-day work in an order which will render the subject more readily comprehensible.

2. *The Methods of Extracting the Pigments from Flowers*

The choice of a suitable raw material from which to extract flower pigments is the first step which must be taken; and here two alternatives present themselves, for either fresh flowers or dried petals might be selected as the best source of the required product. The anthocyanins, under certain conditions, are unstable substances; and from this point of view it might be thought best to work up fresh flowers rather than to risk the chance of decomposition taking place during the drying process. As against this, there are certain practical arguments. In the first place, plants are in flower only during a short period of the year and in certain definite localities; so that the choice of fresh flowers as a source of anthocyanins would entail the necessity of carrying out the extraction of the pigment at fixed times and

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[1] Griffiths, *Chem. News*, 1904, **89**, 249; *Ber.*, 1903, **36**, 3959.

[2] Grafe, *Sitzber. k. Akad. Wien*, 1906, **115**, I., 975; 1909, **118**, I., 1033; 1911, **120**, I., 765.

[3] Wheldale, *Proc. Phil. Soc. Camb.*, 1909, **15**, 137.

[4] Wheldale, *Proc. Roy. Soc.*, 1909, **81**, B, 44.

[5] Nierenstein and Wheldale, *Ber.*, 1911, **44**, 3487.

places, and would demand the simultaneous collection of a very large number of flowers if any great quantity of raw material were required. Secondly, in fresh flowers the plant enzymes are still active, and their influence might make itself disagreeably marked in the course of the extraction. The substitution of dried petals for fresh flowers obviates both these difficulties, but on the other hand there is the possibility of a loss of anthocyanin owing to decomposition during the process of drying. Balancing one set of disadvantages against the other, it is found in practice better to employ the dried material than to use fresh flowers; and the extraction is generally carried out by using finely ground dried petals.

The solvent chosen for the removal of the pigment from the petals of flowers or the skins of berries varies, of course, according to the nature of the anthocyanin present. Water alone suffices to dissolve the colouring material of the cornflower [1]; hydrochloric acid in methyl alcohol solution is used for the rose,[2] the hollyhock,[3] the mallow,[4] the peony,[5] and the bilberry [6]; dilute alcohol is employed to remove the pigments from the larkspur [7] and the scarlet pelargonium [8]; whilst acetic acid is found to be the best solvent in the cases of the grape [9] and whortleberry.[10]

After the pigment has been obtained in solution it may be purified by one of three main methods [11]:—

1. Precipitation and crystallization of the chloride.
2. Purification by suitable reagents and crystallization of the chloride.
3. Separation in the form of a picrate and subsequent conversion into the chloride.

Under the first head come such cases as the precipitation of the chloride from alcoholic solution by means of ether. Examples

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[1] Willstätter and Everest, *Annalen*, 1913, **401**, 189.
[2] Willstätter and Nolan, *Annalen*, 1915, **408**, 1.
[3] Willstätter and Martin, *Annalen*, 1915, **408**, 110.
[4] Willstätter and Mieg, *Annalen*, 1915, **408**, 122.
[5] Willstätter and Nolan, *Annalen*, 1915, **408**, 136.
[6] Willstätter and Zollinger, *Annalen*, 1915, **408**, 86.
[7] Willstätter and Mieg, *Annalen*, 1915, **408**, 61.
[8] Willstätter and Bolton, *Annalen*, 1915, **408**, 42.
[9] Willstätter and Zollinger, *Annalen*, 1915, **408**, 86.
[10] Willstätter and Mallison, *Annalen*, 1915, **408**, 15.
[11] *Ibid.*, 1915, **408**, 160.

of the second category are to be found in the preparation of the cornflower pigment, which occurs as an alkali salt and can be purified by precipitating its aqueous solution with alcohol; and in the purification of the larkspur anthocyanin by heating it with dilute hydrochloric acid. In the picrate method the picrate is formed in the usual manner, purified, and then decomposed by a concentrated solution of hydrochloric acid in methyl alcohol.

3. *The Constitutions of Cyanin and Cyanidin*

The pigment extracted from the cornflower is termed cyanin; and it is generally prepared in the form of its chloride, which is found to have the composition $C_{27}H_{31}O_{16}Cl$.[1] When this substance is heated for a few minutes with 20 per cent. hydrochloric acid, it is hydrolysed, yielding two molecules of glucose and one molecule of a crystalline substance which has been named cyanidin chloride[2]:

$$\underset{\text{Cyanin chloride.}}{C_{27}H_{31}O_{16}Cl} + 2H_2O = \underset{\text{Cyanidin chloride.}}{C_{15}H_{11}O_6Cl} + \underset{\text{Glucose.}}{2C_6H_{12}O_6}$$

This reaction proves that cyanin is a diglucoside of the new body, cyanidin *; and, since glucose is colourless and cyanidin is coloured, this cyanidin forms the chromophoric portion of the pigment molecule.

The general structure of cyanidin has been established by its synthesis from quercetin,[3] and it may be well to give the complete synthetic process here, in order to show how cyanidin can actually be prepared from purely artificial materials.

In the Kostanecki synthesis[4] of quercetin (see scheme on p. 199), 2-hydroxy-4 : 6-dimethoxy-acetophenone (I.) is condensed with dimethoxyprotocatechuic aldehyde (II.) yielding 2′-hydroxy-4′ : 6′ : 3 : 4-tetramethoxychalkone (III.). On heating this for twenty-four hours with dilute hydrochloric acid, 1 : 3 : 3′ : 4-tetramethoxyflavonone (IV.) is produced. Treatment of this with amyl nitrite and hydrochloric acid converts

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[1] Willstätter and Nolan, *Annalen*, 1914, **408**, 1.

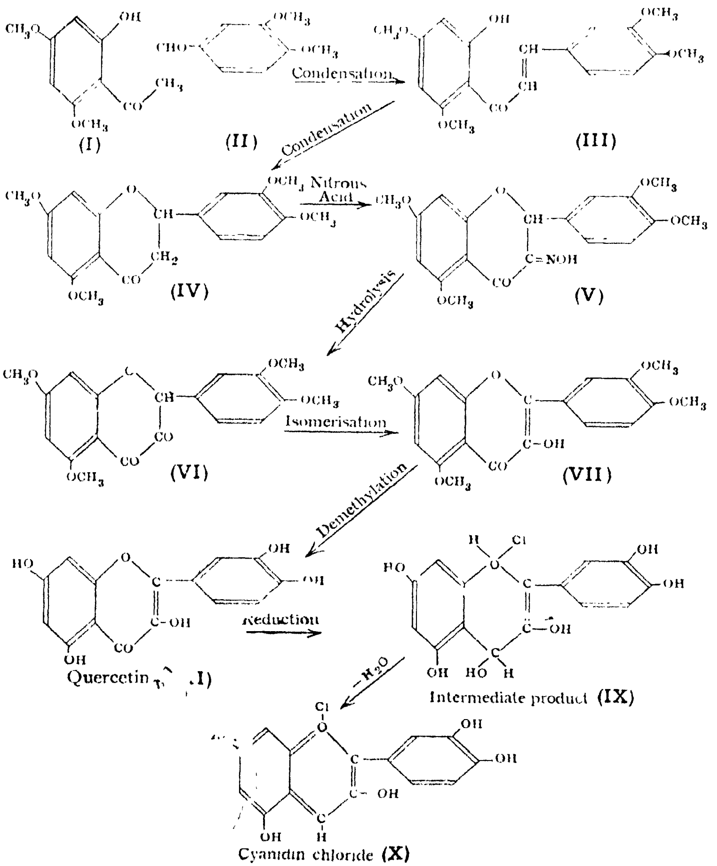
[2] Willstätter and Everest, *Annalen*, 1913, **401**, 1.

* From this is derived the class-name *anthocyanidins* to indicate the non-glucosidal portions of the anthocyanins.

[3] Willstätter and Mallison, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 769.

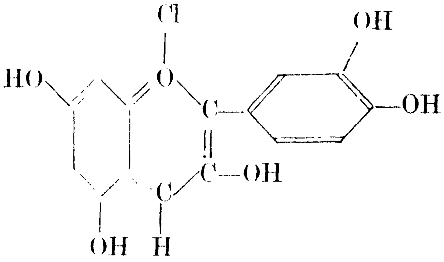
[4] Kostanecki and Tambor, *Ber.*, 1904, **37**, 793; Kostanecki, Lampe, and Tambor, *ibid.*, 1402.

it into the corresponding isonitroso-compound (V.), the methylene group next the carbonyl being attacked in the usual way. Hydrolysis of the isonitroso-compound splits off hydroxylamine, leaving a ketone (VI.); after which isomerization occurs by the production of the enolic form, resulting in the production of 1 : 3 : 3′ : 4′-tetramethoxyflavonol (VII.), which on demethylation with hydriodic acid yields quercetin (VIII.). When quercetin is reduced with sodium amalgam or magnesium in alcoholic solution containing hydrochloric acid and mercury, cyanidin chloride is formed, though the yield is very small. Apparently the reaction involves the formation of an intermediate product (IX.), which then loses a molecule of water, as shown in the scheme.



Another synthesis has been devised by Robertson and Robinson.[1]

An examination of the formula ascribed to cyanidin chloride



will show that it contains a peculiar heterocyclic nucleus: the pyrylium system which was discovered by Decker and Fellenberg.[2] The reason for assuming that this grouping is present lies in the consideration of the basic nature of the cyanidin molecule. Most of the oxonium salts, those of dimethylpyrone. for example, are susceptible to hydrolysis in aqueous solution; which points to the ordinary oxonium complex being weakly basic. Pyrylium compounds, on the other hand, are much more stable in solution than the commoner oxonium derivatives; and the behaviour of the cyanin salts in this respect tends to prove that they resemble pyrylium derivatives rather than such compounds as dimethylpyrone hydrochloride. The analysis of the cyanin salts also indicates that they are not akin to the normal oxonium hydrochloride, as they contain too little hydrogen to correspond with such a structure. On these grounds the pyrylium formula has been preferred.

From these facts it is clear that the anthocyanin cyanin is a diglucoside of cyanidin, which is a pyrylium derivative of the structure shown above

4. *The Properties of Cyanin and Cyani [illegible] hlorides*

The chloride of cyanin, when prepared in [illegible] usual manner, contains two and a half molecules of water of crystallization. Under the microscope, its rhombic leaflets appear tinted between grey-violet and brownish-yellow. In dilute solutions

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[1] Robertson and Robinson, *J.*, 1928, 1526.

[2] Decker and Fellenberg, *Annalen*, 1908, **364**, 1.

of sulphuric acid it appears red with a tinge of violet. It is very slightly soluble in cold water, alcohol, or dilute sulphuric acid ; but is easily soluble in hot water and moderately soluble in 7 per cent. acid. When sodium carbonate is added to its solution, the colour becomes first violet and then blue. Its behaviour when its aqueous solutions are diluted is peculiar. The colour of the solution weakens much more rapidly than might be anticipated and the solution may eventually become colourless. The tint of the anthocyanin can be restored either by evaporating the solution or by adding a large excess of acid. It therefore seems reasonable to suppose that the case is one of hydrolytic dissociation accompanied by intramolecular rearrangement. With ferric chloride, cyanin gives a blue tint in alcoholic solutions and a violet tinge in aqueous solutions [1] ; whilst with lead acetate it gives a characteristic lead salt.[2]

Turning now to cyanidin, it is found to crystallize with one molecule of water, which is retained with extraordinary tenacity. It is a brownish-red substance giving, when dissolved in dilute acids or alcohol, a red solution with a tinge of violet. Insoluble in water, it is readily soluble in alcohols ; very slightly soluble in dilute hydrochloric acid but comparatively soluble in 7 per cent. sulphuric acid. With sodium carbonate it gives the same colour change as cyanin, turning first to blue and then to violet. The hydrolytic dissociation of cyanidin is much more marked than that of its parent anthocyanin ; for when hot water is added to its alcoholic solution a violet precipitate is produced. The reaction with ferric chloride is slightly different also ; for in alcohol a stable blue coloration is produced by cyanidin ; whereas in aqueous alcoholic solution only an unstable violet tint is observed.[3] As in the case of cyanin, lead acetate yields a characteristic salt of cyanidin.[4]

The nature of the colourless modifications which are obtained by hydrolytic dissociation from both cyanin and cyanidin is not very clearly understood. In the case of cyanin chloride, it is found [5] that decolorization takes place when the chloride is heated for a short time in dilute alcohol at 80° C.

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[1] Willstätter and Mieg, *Annalen*, 1915, **408**, 124.

[2] Willstätter and Everest, *Annalen*, 1913, **401**, 225.

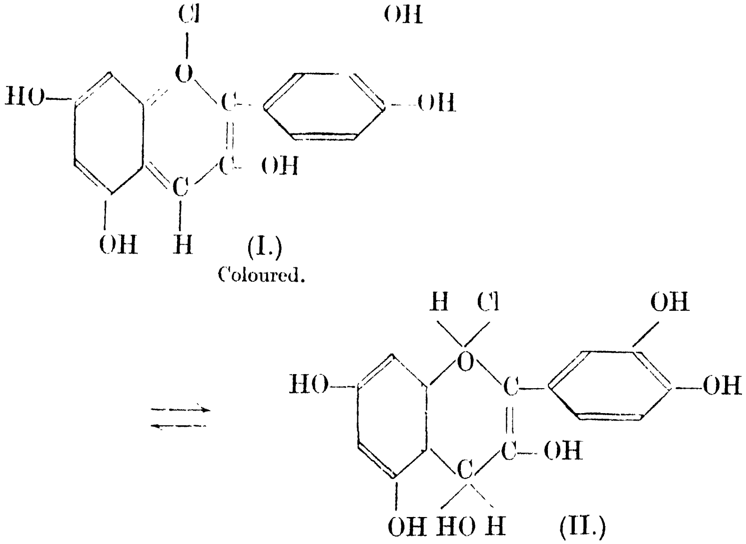
[3] Willstätter and Mieg, *Annalen*, 1915, **408**, 125.

[4] Willstätter and Everest, *Annalen*, 1913, **401**, 229.

[5] Everest, *Proc. Roy. Soc.*, 1914, **87**, B., 444.

The decolorized substance has properties resembling those of a yellow flavonol pigment; it is soluble in ether; colourless in acid solution, yellow in alkaline solution; from acid solutions it can be extracted with ether, from which it can be removed by shaking with alkali. On boiling with acids the colourless variety is reconverted into the ordinary coloured cyanidin salt.

Everest[1] suggests that cyanin chloride exists in solution as an equilibrium mixture of (I.)* and (II.), and that one set of conditions favours the stability of (I.), whilst under other conditions (II.) is the more stable form.



(I.)
Coloured.

(II.)
Colourless.

A distinction between anthocyanins and the corresponding anthocyanidins is found in the fact that amyl alcohol does not extract the former from acid solutions; but if the solution be heated so as to hydrolyse the anthocyanins to anthocyanidin, the latter passes into amyl alcohol readily.[2]

5. *The Synthesis of Pelargonidin*

The flowers of the scarlet pelargonium are found to contain an anthocyanin which has been named pelargonin. This

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[1] Everest, *Proc. Roy. Soc.*, 1914, **87**, B., 444.

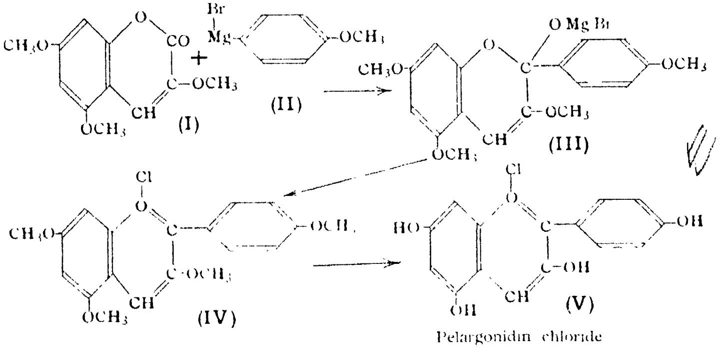
* The glucose molecules are omitted from the formula.

[2] Willstätter and Everest, *Annalen*, 1913, **401**, 205.

substance when isolated in the form of its chloride is shown to have the composition $C_{27}H_{31}O_{15}Cl$, and to contain, in addition, four molecules of water of crystallization.

On hydrolysis it proves to be a glucoside, and yields two molecules of glucose and one molecule of a substance pelargonidin chloride, akin to cyanidin chloride, and having the composition $C_{15}H_{11}O_5Cl$ with one molecule of water of crystallization.

Pelargonidin [1] has been synthesized in the following manner: 3 : 5 : 7-trimethoxycoumarin (I.) is allowed to interact with magnesium anisyl bromide (II.). When the intermediate compound (III.) is hydrolysed with hydrochloric acid it yields anisyltrimethoxyphenopyrylium chloride (IV.), which, after demethylation with hydriodic acid and treatment with hydrochloric acid, produces a substance (V.), indistinguishable chemically or spectroscopically from natural pelargonidin:



Pelargonidin chloride

Another synthesis has been devised by Robertson, Robinson, and Sugiura.[2]

6. *The Constitutions of Delphinin and Delphinidin*

The anthocyanin of the larkspur is termed delphinin [3] and with it a slightly more complex field is entered. A glance at the formula of delphinin chloride: $C_{41}H_{39}O_{21}Cl$, shows that it has a molecular weight of 902 as compared with 646 for cyanin

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[1] Willstätter and Zechmeister, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, **34**, 886.

[2] Robertson, Robinson, and Sugiura, *J.*, 1928, 1533.

[3] Willstätter and Mieg, *Annalen*, 1915, **408**, 61.

chloride; so it is evident that the former substance must contain some heavy radicle in addition to those found in cyanin or pelargonin.

Hydrolysis of delphinin proves the correctness of this. In addition to the products which might be expected (glucose and delphinidin) two molecules of *p*-hydroxybenzoic acid make their appearance; so that the equation for the reaction may be written thus–

$$\underset{\text{Delphinin chloride.}}{C_{41}H_{39}O_{21}Cl} + 4H_2O = \underset{\text{Glucose.}}{2C_6H_{12}O_6} + \underset{\substack{p\text{-Hydroxybenzoic}\\ \text{acid.}}}{2HO \,.\, C_6H_4 \,.\, COOH} + \underset{\substack{\text{Delphinidin}\\ \text{chloride.}}}{C_{15}H_{11}O_7Cl}$$

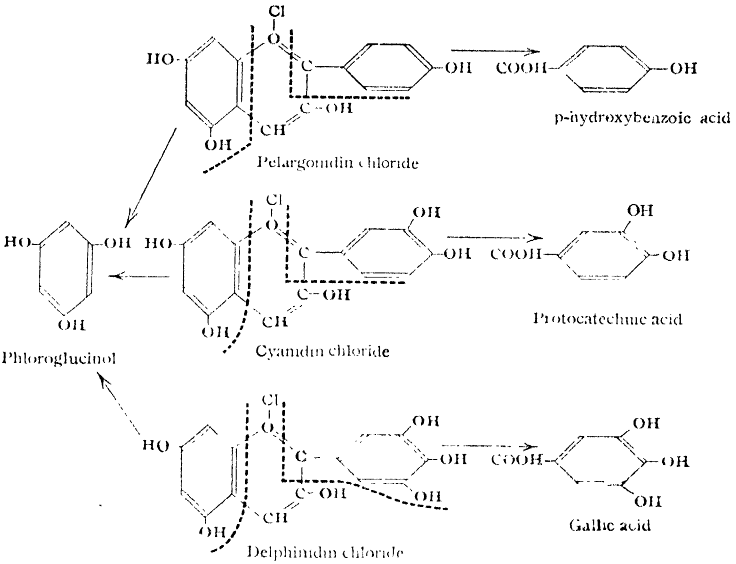
It appears from this that delphinin, like the other anthocyanins, is a glucoside; but that two of its hydroxyl radicles are esterified with *p*-hydroxybenzoic acid. Which of the hydroxyl groups are thus affected is not known definitely; but by analogy with populin (benzoylsalicin) it is assumed that the benzoylation takes place in the glucose chain and not in the delphinidin portion of the molecule.

The next stage in the deduction of delphinin's constitution is made by comparing the formulæ of pelargonidin, cyanidin, and delphinidin chlorides:—

Pelargonidin chloride	$C_{15}H_{11}O_5Cl$	or	$C_{15}H_7OCl(OH)_4$
Cyanidin chloride	$C_{15}H_{11}O_6Cl$	or	$C_{15}H_6OCl(OH)_5$
Delphinidin chloride	$C_{15}H_{11}O_7Cl$	or	$C_{15}H_5OCl(OH)_6$

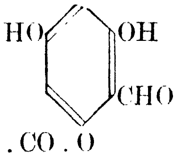
The comparison suggests that the difference between cyanidin and delphinidin may lie in the presence of an extra hydroxyl group in the delphinidin molecule.

Confirmation of this view is obtained when the results of heating the three compounds with alkali are considered. All three yield phloroglucinol; so that they contain a common grouping. In addition to the trihydric phenol, however, pelargonidin yields *p*-hydroxybenzoic acid; cyanidin produces protocatechuic acid; whilst delphinidin gives rise to gallic acid. From this it appears a reasonable deduction that the portion of the molecule which produces *p*-hydroxybenzoic acid in the case of pelargonidin is the same in nature as that which gives rise to gallic acid from delphinidin. A comparison between the two established formulæ and the one suggested for delphinidin will make the matter clear:



7. *A General Method of Synthesizing Anthocyanidins*

When phloroglucin-aldehyde is monobenzoylated by the Baumann-Schotten method,[1] it yields 2-benzoyloxy-4 : 6-dihydroxy-benzaldehyde :



This substance is condensed with acetylated derivatives of substituted ω-hydroxy-acetophenones by the use of hydrogen chloride in ethyl acetate (or alcoholic ethyl acetate) solution ; and the acetyl groups are removed by hydrolysis. The substances are then hydrolysed with aqueous-alcoholic sodium hydroxide to remove the benzoyl radicle ; and the anthocyanidins are produced by a final treatment with hydrochloric acid.

One example of the system will suffice. By condensing 2-benzoyloxy-4 : 6-dihydroxy-benzaldehyde (I.), with ω-4-diacetoxy-methoxy-acetophenone, (II.), the reaction yields 5-*O*-

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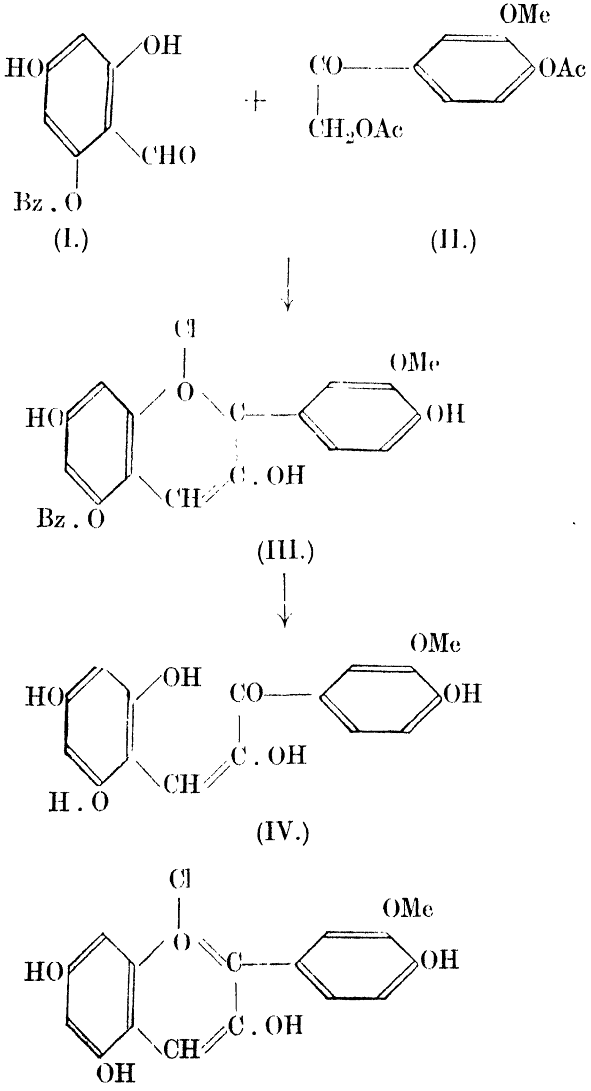
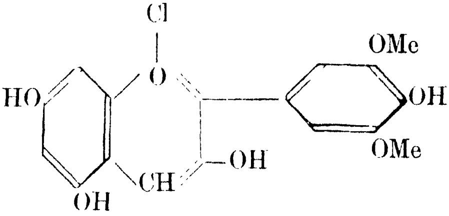
[1] Robinson and Struthers, *J.*, 1928, 1455.

benzoyl-peonidin chloride (III.). Alkaline hydrolysis removes the benzoyl group and simultaneously opens the pyrylium ring, yielding (IV.). Finally, by means of hydrochloric acid, the ring is reclosed, and peonidin chloride, (V.), is obtained.



(V.) Peonidin chloride.

By selecting the appropriate derivative of acetophenone, this method can be applied to the synthesis of various anthocyanidins.[1] Thus ω-3 : 4-triacetoxy-acetophenone yields cyanidin chloride; and ω-4-diacetoxy-acetophenone gives pelargonidine chloride. Malvidin chloride (syringidin chloride), which occurs naturally in the flowers of the wild mallow, has been produced by using ω-acetoxy-4-benzyloxy-3 : 5-dimethoxy-acetophenone :—

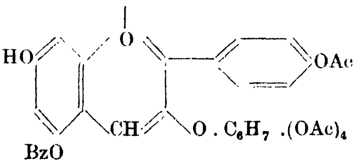


Malvidin chloride.

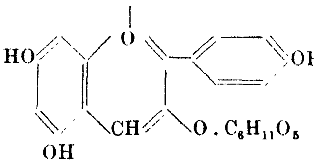
An actual synthesis[2] of a flower pigment has been accomplished in the case of callistephin chloride, which is derived from the summer aster.[3] By acting on a mixture of ω-hydroxy-4-acetoxy-acetophenone and *O*-tetra-acetyl-α-glucosidyl bromide with dry silver carbonate in benzene solution, ω-*O*-tetra-acetyl-β-glucosidoxy-4-acetoxy-acetophenone was obtained :—

$$(AcO)_4 \,.\, C_6H_7 \,.\, O \,.\, CH_2 \,.\, CO \,.\, C_6H_4 \,.\, OAc$$

When condensed with *O*-benzoyl-phloroglucin-aldehyde, it yielded 3-*O*-tetra-acetyl-β-glucosidoxy-7-hydroxy-5-benzoyloxy-4′-acetoxy-flavylium chloride (A); from which callistephin chloride (B) was obtained by hydrolysis with aqueous alkali and subsequent treatment with acid.



(A).



(B) Callistephin chloride.

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[1] Robinson and others, *J.*, 1928, 1526, 1533, 1537, 1541 ; 1930, 793.

[2] Robertson and Robinson, *J.*, 1926, 1713 ; 1927, 242, 1710.

[3] Willstätter and Burdick, *Annalen*, 1916, **412**, 149.

8. *Other Anthocyanins*

Mention must now be made of some other plant pigments which contain the skeletons we have already described.

Pelargonidin forms the basis of the anthocyanin of the flowers of the plant *Salvia coccinea*. This anthocyanin is called salvianin; and on hydrolysis it yields pelargonidin, two molecules of dextrose, and a considerable quantity of malonic acid. It is therefore more complex in its structure than the usual flower pigment.[1]

In the summer aster occurs an anthocyanin asterin, which hydrolyses into cyanidin and dextrose.[2]

The anthocyanin of the winter aster is chrysanthemin, derived from dextrose and cyanidin. Cyanidin also forms the foundation for the colours of *Zinnia elegans*, *Gaillardia bicolor*, *Helenium autumnale*, *Gladiolus Tulipa Gesneriana*, *Tropæolum majus*, *Rubes rubrum*, the raspberry, and the berry of the mountain ash.[3] The cherry contains keracyanin, built up from cyanidin, dextrose, and rhamnose; whilst the sloe owes its colour to prunicyanin, which is formed from cyanidin, rhamnose, and some as yet unidentified hexose.[4] The plum also contains a cyanidin glucoside.[4]

Peonin, the anthocyanin of the peony, belongs to the cyanidin series.[5] It is a diglucoside of peonidin. Another cyanidin derivative is idaein,[6] the anthocyanin of the whortleberry. It differs from the usual type of anthocyanin in that it is a galactoside and not a glucoside.

The poppy [7] contains two anthocyanins, one of them, mecocyanin, being a cyanidin derivative, whilst the other resembles the glucosides of delphinidin.

Turning to delphinidin derivatives, it is found that the pansy owes its colour to the anthocyanin violanin,[8] which on hydrolysis yields delphinidin, rhamnose, and some as yet unidentified

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[1] Willstätter and Bolton, *Annalen*, 1916, **412**, 113.

[2] Willstätter and Burdick, *Annalen*, 1916, **412**, 149.

[3] Willstätter and Bolton, *Annalen*, 1916, **412**, 136.

[4] Willstätter and Zollinger, *Annalen*, 1916, **412**, 164.

[5] Willstätter and Nolan, *Annalen*, 1915, **408**, 136.

[6] Willstätter and Mallison, *Annalen*, 1915, **408**, 15.

[7] Willstätter and Weil, *Annalen*, 1916, **412**, 231.

[8] *Ibid.*, 1916, **412**, 178.

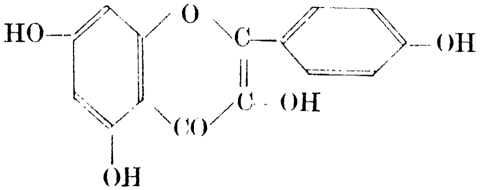
hexose, though these three products do not occur in equimolecular quantities in the reaction mixture. Monomethyl ethers of delphinidin are found in myrtillin,[1] the anthocyanin of bilberries, and petunin,[2] the anthocyanin of petunias. A dimethyl ether of delphinidin has been isolated from oenin,[3] the anthocyanin of grapes.

Finally, mention may be made of a glucoside ampelosin, which occurs in the wild vine. Its constitution has not yet been determined.

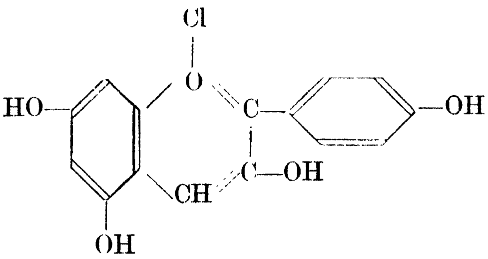
9. *The Anthocyanins and the Flavones*

It may be of interest to point out the similarity in structure which can be traced between the flower pigments and the natural dyes occurring in plants; for the close resemblance in the skeletons of the two classes may throw light in the future upon the mode in which both types are built up within the organism. Such a similarity can hardly be regarded as due to mere chance.

Taking kampherol as a flavone representative, and comparing it with pelargonidin chloride as a typical example of the anthocyanins, it will be seen that they bear a striking resemblance to one another in general structure :



Kampherol.



Pelargonidin chloride.

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[1] Willstätter and Zollinger, *Annalen*, 1915, **408**, 83.

[2] Willstätter and Burdick, *Annalen*, 1916, **412**, 217.

[3] Willstätter and Zollinger, *Annalen*, 1915, **408**, 83.

The only difference between them is to be found in the heterocyclic nucleus; the one is a true pyrone, whilst the other contains a —CH= group instead of the carbonyl radicle; and its structure is therefore more benzenoid in character. This difference is, of course, exhibited in their salts; the kampherol salts, being derived from a true pyrone, are easily hydrolysed even in the sap of plants; whilst the salts of anthocyanins are sufficiently stable to exist without decomposition in the vegetable structure.

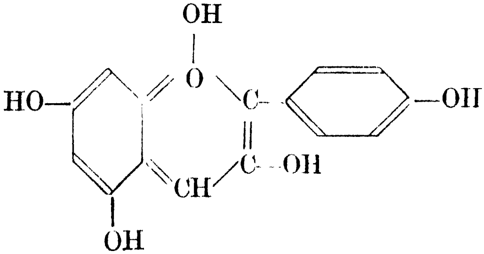
Compounds analogous to the anthocyanins have been synthesized,[1] by using the Perkin-Robinson [2] method for the synthesis of pyrylium salts from *o*-hydroxybenzaldehyde and compounds containing the $—CH_2 . CO—$ group.

10. *The Origin of Colour Variation in Plants*

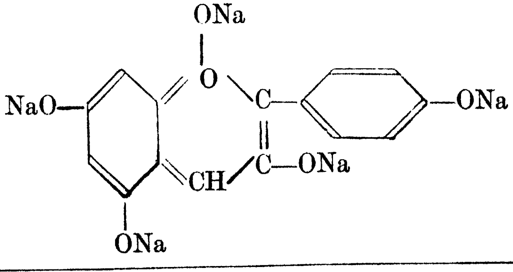
In view of the strong family resemblance between the various plant pigments, it may be interesting to indicate the manner in which such closely related compounds might give rise to such gradations of tint as are shown in the flowers.

An examination of the structure of pelargonidin (I.) will show that it is capable of yielding various types of derivatives: metallic salts like (II.), oxonium salts like (III.), and internal ethers like (IV.):—

(I.)



(II.)



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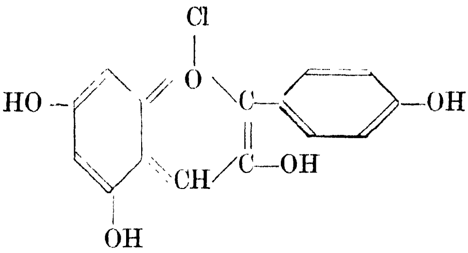
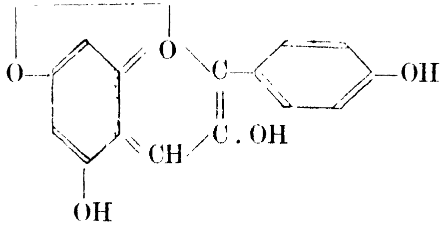
[1] Pratt and Robinson, *J.*, 1922, **121**, 1577.

[2] Perkin and Robinson, *P.*, 1907, **19**, 149.

(III.)

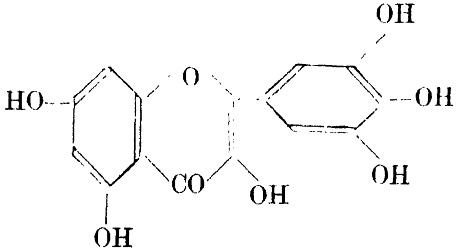


(IV.)



The importance of metallic derivatives of the anthocyanins has been emphasized by some work on the subject.[1] Reduction of a flavone derivative by means of a metal and a *mineral* acid leads to a production of a red compound; but when magnesium and an *organic* acid such as acetic acid is employed in presence of mercury, the colour of the product is found to diverge from the normal red tint. Thus when myricetin (I.) is reduced in this way, it yields green compounds which have the composition $C_{18}H_{11}O_8 . Mg . OAc, [Mg(OAc)_2]$. The reaction apparently proceeds in stages. In the first stage, the phenopyrylium derivative (II.) is formed; which then passes by elimination of acetic acid into (III.), which finally unites with magnesium acetate to produce (IV.).

(I.)



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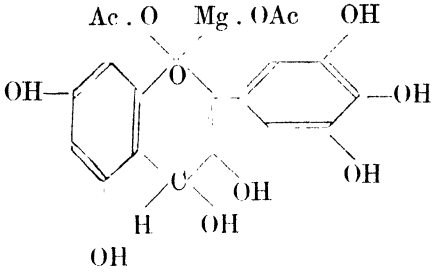
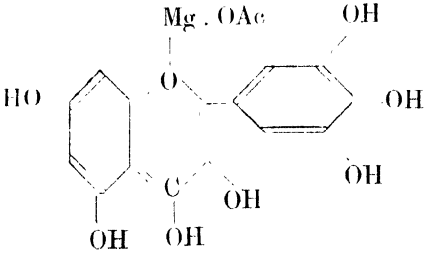
[1] Shibata, Shibata and Kasiwagi, *J. Amer. Chem. Soc.*, 1919, **41**, 208; compare Karrer and Widmer, *Helv. Chim. Acta*, 1927, **10**, 729.

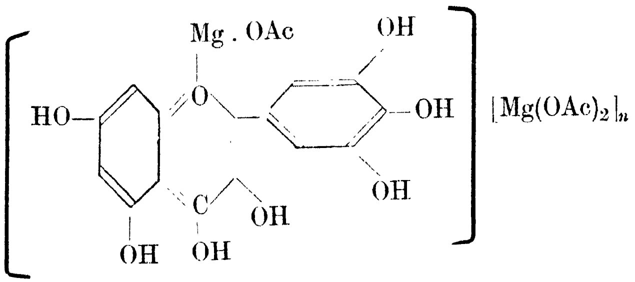
(II.)



(III.)



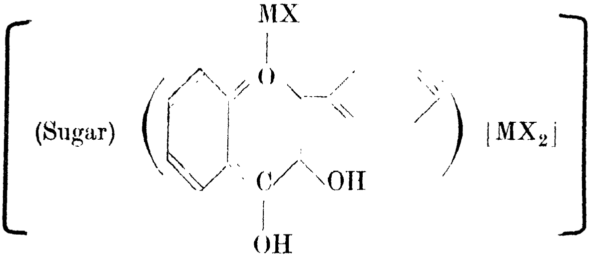
(IV.)



If, instead of myricetin itself, a rhamnoside derivative, myricitrin, is used, the resulting product is a deep blue substance containing four molecules of magnesium acetate.

The difference between the reaction-products when mineral and organic acids are employed has been traced to the fact that the radicle —Mg . Cl is replaced by a chlorine atom if hydrochloric acid is present in quantity; so that the end-product is the red oxonium chloride.

Basing themselves upon these results, Shibata, Shibata and Kasiwagi suggested that metallic complex salts of the type :—



are important factors in flower coloration and give rise to the "blue" anthocyanins. The metallic atoms which they contain (indicated by M in the formula) are probably calcium and magnesium. The "violet" and "red" pigments are assumed to be complex salts containing fewer hydroxyl groups than the "blue" ones; or to be mixtures of the "blue" compounds with a certain quantity of the red oxonium salts which have been formed from the "blue" derivatives by decomposition with acids.

The existence of these various types would be conditioned by the nature of the sap in the neighbourhood of the pigment; and as the sap must obviously be more highly concentrated the nearer we go to the evaporating surface of the petals, it is evident that variations in the structure of the pigment must be expected. Again, the sap in certain parts of the plant may be more alkaline than in others; and as the cyanidins are indicators, it is clear that their tint will be affected by this factor also.

CHAPTER VIII

THE CHLOROPHYLL PROBLEM

1. *Introductory*

THE chemical constitution of the green colouring matter of plants offers a problem which has taxed the ingenuity of many investigators. Not long ago our knowledge of the chlorophyll structure was so fragmentary and disconnected that the very name of the substance was omitted from standard textbooks. But since then the compound has been submitted to rigorous scrutiny, its reactions have been classified, its decomposition products brought into relation to each other ; and although our views on the exact nature of its structure are still fluid, the information at our disposal is sufficient to render a coherent account of it possible.[1]

In the present chapter an attempt will be made to link together the scattered data of the subject in a more or less connected scheme * ; and present to the reader a summary of the important information which has been acquired. In this branch of chemistry, theory in many cases has far outrun practice ; and constitutional formulæ have been proposed for some substances the true structures of which are possibly different from those assumed for them. Under these circumstances an endeavour will be made here to indicate as clearly as possible the points at which established facts end and pure hypotheses begin ; for it seems desirable to draw the line of demarcation as sharply as can be done. Some of the formulæ ascribed to certain compounds may be accurate, though yet

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[1] For a general account of Willstätter's researches, see *Ber.*, 1914, **47**, 2831.

* The reader is advised to make use of the table at the end of this volume in any difficulty which may arise as to the relations between certain chlorophyll derivatives.

unproved; but it would be doing the reader a poor service to leave him in doubt as to their actual present value, or to try to persuade him into an acceptance of constitutions which later work may prove to be erroneous.

A study of the literature on chlorophyll is beset with difficulties. In the first place, the nomenclature of the subject is to a large extent new and different from that with which the organic chemist is familiar; for instead of referring to acids in the usual terms, the investigators have christened them with a brand-new set of names, and as these titles have established themselves in the literature, it is hopeless to expect that they will be altered now. Secondly, chlorophyll contains within its molecule a complex and sensitive grouping capable of undergoing various intramolecular changes under the action of reagents; and these rearrangements form one of the most puzzling factors in the problem.

The extraction of chlorophyll from plants is a simple operation. The leaves are removed from their stems, dried and powdered. Alcohol is then poured over the powder and the mixture kept constantly stirred. After a longer or shorter time the chlorophyll passes into the liquid, from which it can be extracted. By this process a "crystalline chlorophyll" is obtained; whereas when ether is substituted for alcohol, an "amorphous chlorophyll" is found in solution.[1]

The composition of "amorphous chlorophyll" may be regarded provisionally as corresponding to $C_{55}H_{72}N_4O_5Mg$; but even here a word of caution is desirable. The lowest possible molecular weight of a substance such as this would reach nearly 900; and reflection will show that the exact analysis of so complex a compound must be difficult in the extreme.

The complication of the formula makes it obvious that our chief knowledge of chlorophyll must be gained through an acquaintance with its degradation products. Three main types of reaction might be employed to break down the chlorophyll molecule: oxidation, reduction, and hydrolysis. In practice, it has been found that most information is gained from a study of the last class; for oxidation and reduction

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[1] Willstätter and Benz, *Annalen*, 1908, **358**, 267; Willstätter and Oppé, *ibid.*, **1911**, **378**, **1**.

proved to be comparatively useless in so far as the production of immediate decomposition products is concerned.

Along with chlorophyll, two other colouring matters are found in leaves. The one, carotene, is coppery in colour and is identical with the substance which gives their colour to carrots. It is a hydrocarbon of the composition $C_{40}H_{56}$. The other colouring material, xanthophyll, is dark brown-red in tint; has the composition $C_{40}H_{56}O_2$; and seems to be an oxidation product of carotene.[1] It is suggested that in summer the green of chlorophyll masks the tints of carotene and xanthophyll; but when in autumn the chlorophyll decays, the reddish pigments become visible and give the leaves their autumn colouring.

It is interesting to note that the chlorophyll of brown algæ is identical with that derived from land-plants,[2] a fact which appears most unexpected from the tints of the organisms.

2. *Amorphous Chlorophyll and so-called "Crystalline Chlorophyll"*

As has been pointed out already, the extraction of chlorophyll from plants by means of ether yields an amorphous substance. Specimens of this amorphous product were obtained, under carefully regulated conditions, from about two hundred different kinds of plants; and, on examination, it was found that all the samples yielded on decomposition approximately the same amount—about 30 per cent.—of an alcohol named phytol.[3] This at once suggests that amorphous chlorophyll may be the phytyl ester of some unknown acid.

Confirmation of this view was obtained by hydrolysing amorphous chlorophyll with cold dilute potash. The products of the reaction are equimolecular quantities of methyl alcohol, phytyl alcohol, and the potassium salt of a tribasic acid, which is termed chlorophyllin.[4] It appears, then, that amorphous chlorophyll is a di-ester of this tribasic acid, chlorophyllin, in which one of the carboxyl groups is esterified with methyl alcohol, another with phytyl alcohol, whilst the third is occupied in some other manner.

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[1] Willstätter and Mieg, *Annalen*, 1907, **355**, 1.

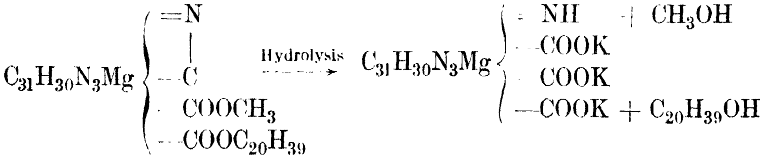
[2] Willstätter and Page, *Annalen*, 1914, **404**, 237.

[3] Willstätter, Hocheder, and Hug, *Annalen*, 1909, **371**, 1; Willstätter and Oppé, *Annalen*, 1911, **378**, 1.

[4] Willstätter and Stoll, *Annalen*, 1910, **378**, 18.

But three carboxyl radicles would imply the presence of six oxygen atoms in the chlorophyll molecule; whereas from the analytical results there appear to be only five. The possibility of internal anhydride formation is excluded by the fact that phytochlorin-*e* (a decomposition product of chlorophyll) contains the same grouping and does not form an amide with ammonia.[1] Since nitrogen atoms are found in the molecule, it might be assumed that the third acidic group is present as an amide; but in this case, ammonia would be found in the products of hydrolysis. The only feasible explanation is that the fifth oxygen atom of amorphous chlorophyll forms part of a lactam ring which is opened up on hydrolysis, setting free the third carboxyl group.*

Now since phytyl alcohol has the formula $C_{20}H_{39}OH$, it follows that on the above assumption we can express the hydrolysis reaction thus:



$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l} =N \\ \ \ | \\ -C \\ \cdot COOCH_3 \\ -COOC_{20}H_{39}\end{array}\right. \xrightarrow{\text{Hydrolysis}} C_{31}H_{30}N_3Mg\left\{\begin{array}{l} -NH \\ -COOK \\ -COOK \\ -COOK\end{array}\right. \begin{array}{l} +\ CH_3OH \\ \\ \\ +\ C_{20}H_{39}OH\end{array}$$

Amorphous chlorophyll. Chlorophyllin salt. Phytol.

The case of "crystalline chlorophyll" must now be examined. It also is found to be a di-ester: but instead of the phytyl radicle it contains an ethyl group; the second carboxyl radicle is esterified with methyl alcohol; whilst the third carboxyl resembles the corresponding one of amorphous chlorophyll. Thus, during the extraction of chlorophyll with alcohol, it is clear that the phytyl group has been replaced by an ethyl radicle. This process is traced to the action of an enzyme, chlorophyllase, which is found in plants. During prolonged processes of maceration with alcohol, the chlorophyllase from the

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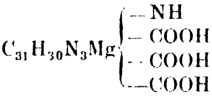
[1] Willstätter and Utzinger, *Annalen*, 1911, **382**, 129.

* It will be noted that at this point difficulties arise as to the exact hydrogen content of these bodies. When the lactam chlorophyll is converted into the acid chlorophyllin an atom of hydrogen is taken up by the imido group. Willstätter's formulæ take no account of this (*e.g.*, *Annalen*, 1911, **378**, 25). To avoid confusion, the present account takes as a starting-point the composition of chlorophyll-*a* as given by Willstätter in *Annalen*, 1912, **390**, 227; and it must be read accordingly.

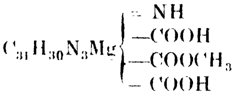
plant tissues substitutes ethyl for phytyl alcohol, and " crystalline chlorophyll " is the result.[1]

As " amorphous chlorophyll " is a crude term, it may now be replaced by something more scientific, if equally cumbrous. When one carboxyl radicle of the tribasic acid termed chlorophyllin is esterified with methyl alcohol, the product is called chlorophyllide. If now a second carboxyl group in chlorophyllide be esterified with phytyl alcohol, the new substance is termed phytyl chlorophyllide. " Crystalline chlorophyll " is obviously ethyl chlorophyllide. The following formulæ * show the relations between the four compounds :—



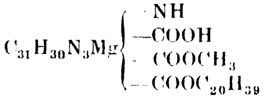
$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}-NH\\-COOH\\-COOH\\-COOH\end{array}\right.$$

Chlorophyllin.



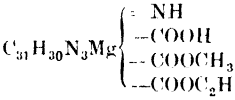
$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}-NH\\-COOH\\-COOCH_3\\-COOH\end{array}\right.$$

Chlorophyllide.



$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}-NH\\-COOH\\-COOCH_3\\-COOC_{20}H_{39}\end{array}\right.$$

Phytyl chlorophyllide
(Amorphous chorophyll).



$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}-NH\\-COOH\\-COOCH_3\\-COOC_2H_5\end{array}\right.$$

Ethyl chlorophyllide
(Crystalline chlorophyll).

These formulæ are given with all radicles free for the sake of clearness, but actually the amino-group and the neighbouring carboxyl probably form the lactam ring immediately. The evidence on this point is given in § 7.

3. *The Structure of Phytol*

Owing to the great difficulty involved in purifying the decomposition products of phytol, the investigation of its constitution has proved extremely hard ; and some erroneous data were given in the first paper on the subject [2] which have now been corrected.[3]

Phytol has the composition $C_{20}H_{39}.OH$. It is therefore a member of the ethylene or the polymethylene series. The results of oxidation prove it to be an ethylenic compound. It

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[1] Willstätter and Stoll, *Annalen*, 1910, **378,** 18.

* See footnote on p. 217.

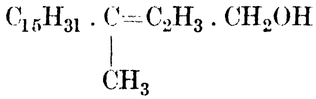
[2] Willstätter, Meyer, and Hüni, *Annalen*, 1910, **278,** 73.

[3] Willstätter, Schuppli, and Mayer, *Annalen*, 1919, **418,** 121.

occurs in two isomeric forms which differ from each other in the ease with which water is eliminated from the molecule. This points to its showing geometrical isomerism.

When oxidized, it is converted into an acid, phytenic acid, $C_{19}H_{37} . COOH$; and as this contains the same number of carbon atoms as phytol itself, the original phytol must be a primary alcohol, $C_{19}H_{37} . CH_2OH$.

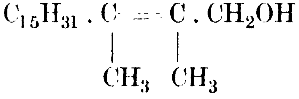
Oxidation with chromic acid produces a ketone, $C_{17}H_{34}O$, the reaction having evidently broken the phytol chain at the double bond. Since three carbon atoms are split off during this oxidation, we are justified in writing the phytol structure thus :



$$C_{15}H_{31} . \underset{\displaystyle CH_3}{\underset{|}{C}}{=}C_2H_3 . CH_2OH$$

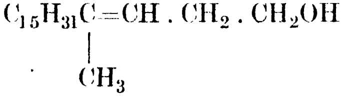
The methyl group attached to the ethylenic carbon atom is necessary in order to produce a ketone and not an acid upon oxidation.

Now the group $:C_2H_3—$ must have either of the structures $:C(CH_3)-$ or $:CH . CH_2—$; so that the formula for phytol must be :



$$C_{15}H_{31} . \underset{\displaystyle CH_3}{\underset{|}{C}} = \underset{\displaystyle CH_3}{\underset{|}{C}} . CH_2OH$$

or



$$C_{15}H_{31}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH . CH_2 . CH_2OH$$

Phytol.

(I.) (II.)

The alternative structure (II.) appears to be excluded, owing to the fact that phytenic acid forms a lactone, which is a reaction characteristic of acids containing methyl groups in the *a*- and *β*-positions and a double bond in the Δ^1-position, as is the case in the phytol formula given above.

4. *Chlorophyll-a and Chlorophyll-b*

Half a century ago Stokes[1] proved that the chlorophyll occurring in plants is a mixture of two substances differing in their spectra and solubilities in certain solvents ; but his paper remained almost unnoticed by later workers, and it

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[1] Stokes, *Proc. Roy. Soc.*, 1864, **13**, 144 ; compare Tswett, *Zeit. Biol.*, 1907, **5**, 6 ; *Ber. deutsch. bot. Ges.*, 1906, **24**, 316 ; 1907, **25**, 137 ; *Ber.*, 1908, **41**, 1352.

was not until 1912 that definite chemical corroboration of his statements was obtained.[1]

The newer researches on the subject started from a different standpoint. When chlorophyll was treated with certain reagents, it was found that it yielded a mixture of two substances: phytochlorin-*e* and phytorhodin-*g*. These compounds are found to occur among the degradation products of chlorophyll in the almost constant proportion of five molecules of phytochlorin-*e* to two molecules of phytorhodin-*g*. At first sight it appears easy to account for this by assuming that the chlorophyll skeleton contains five phytochlorin nuclei and two phytorhodin nuclei; so that in its decomposition it could give rise to the products in the required proportions. This explanation breaks down at once, however, when it is shown that the molecular weights of phytochlorin and phytorhodin are each approximately the same as that of chlorophyll itself, if we deduct from the latter the molecular weight of the phytyl radicle which does not occur in either the phytochlorin or the phytorhodin molecule. Clearly, if the molecular weight of phytochlorin-*e* is nearly the same as that of the non-phytyl part of the chlorophyll molecule, there is no room in the latter substance for five phytochlorin nuclei.

Evidently only one way can be found out of the difficulty. It is necessary to assume that chlorophyll is a mixture of two components, one of which on degradation produces phytochlorin-*e* whilst the other gives rise to phytorhodin-*g*. This view has actually been proved correct[2] by the separation of chlorophyll into two portions: chlorophyll-*a* and chlorophyll-*b*. By shaking a solution of chlorophyll in petroleum ether, with some water containing methyl alcohol, it is found that chlorophyll-*a* remains in the petroleum ether whilst the chlorophyll-*b* passes into the aqueous layer.

Chlorophyll-*a* is a bluish-black in tint; contains half a molecule of water of crystallization; and gives only phytochlorin-*e* when it is decomposed. Chlorophyll-*b* is greenish-black in colour; its crystals are anhydrous; and when it is broken down it yields only phytorhodin-*g*. On analysis, chlorophyll-*a* is found to be:

$$[C_{32}H_{30}ON_4Mg](COOCH_3)(COOC_{20}H_{39}) + \tfrac{1}{2}H_2O$$

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[1] Willstätter and Isler, *Annalen*, 1912, **390**, 269.

[2] *Ibid.*

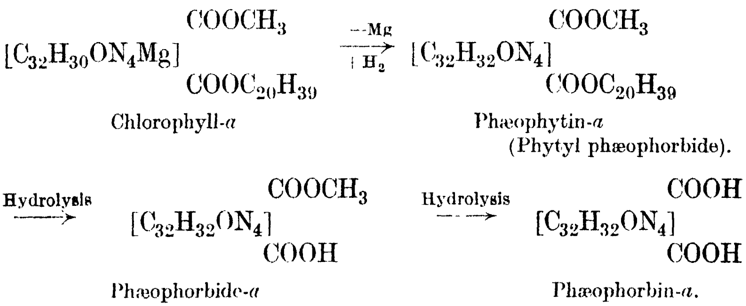
whilst chlorophyll-*b* gives results corresponding to:

$$[C_{32}H_{28}O_2N_4Mg](COOCH_3)(COOC_{20}H_{39})$$

5. *Phæophytins and Phæophorbides*

When chlorophyll-*a* or chlorophyll-*b* is treated with alcoholic oxalic acid, the magnesium atom of the molecule is removed and replaced by two hydrogen atoms.* In this reaction the ester groups of the molecule are left intact. The product of the reaction is clearly the methyl-phytyl ester of the hydrogen derivative of chlorophyll. It is termed a phæophytin; and the suffix "*a*" or "*b*" is used to indicate from which of the chlorophylls it is derived.[1]

Further treatment hydrolyses away the phytyl radicle, leaving a monomethyl ester, which is called a phæophorbide. Finally, removal of the methyl radicle leaves a dibasic acid, phæophorbin. The following scheme will make the matter clear:—



$$[C_{32}H_{30}ON_4Mg]\begin{array}{l}COOCH_3\\ \\ COOC_{20}H_{39}\end{array} \xrightarrow[+H_2]{-Mg} [C_{32}H_{32}ON_4]\begin{array}{l}COOCH_3\\ \\ COOC_{20}H_{39}\end{array}$$

Chlorophyll-*a* Phæophytin-*a* (Phytyl phæophorbide).

$$\xrightarrow{\text{Hydrolysis}} [C_{32}H_{32}ON_4]\begin{array}{l}COOCH_3\\ \\ COOH\end{array} \xrightarrow{\text{Hydrolysis}} [C_{32}H_{32}ON_4]\begin{array}{l}COOH\\ \\ COOH\end{array}$$

Phæophorbide-*a* Phæophorbin-*a*.

As has already been remarked, the nomenclature of the chlorophyll derivatives differs from that usually employed in organic chemistry; and therefore it may render the task of the reader easier if some indication be given at this point of the relations between the various groups of compounds with which it is necessary to deal in this chapter. The two main classes are the magnesium-containing derivatives and the

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* The reverse change (replacement of hydrogen by magnesium) can be carried out by heating the substance with magnesium oxide and caustic potash solution or by the action of the Grignard reagent (Willstätter and Forsén, *Annalen*, 1913, **396**, 180).

[1] Willstätter and Isler, *Annalen*, 1912, **390**, 269.

magnesium-free substances which are derived from the others by replacing the magnesium by two hydrogen atoms :—

MAGNESIUM DERIVATIVES.	CORRESPONDING COMPOUNDS WHEREIN THE MAGNESIUM ATOM IS REPLACED BY TWO HYDROGEN ATOMS.
* *Chlorophyllin* $\mathrm{MgR(COOH)_3}$	* *Phæophorbin*, *Phytochlorin* $\mathrm{H_2R(COOH)_3}$
* *Chlorophyllide* $\mathrm{MgR}\begin{cases}\mathrm{COOCH_3}\\ \mathrm{(COOH)_2}\end{cases}$	* *Phæophorbide* $\mathrm{H_2R}\begin{cases}\mathrm{COOCH_3}\\ \mathrm{(COOH)_2}\end{cases}$
* *Chlorophyll* $\mathrm{MgR}\begin{cases}\mathrm{COOCH_3}\\ \mathrm{COOC_{20}H_{39}}\\ \mathrm{COOH}\end{cases}$	* *Phæophytin* $\mathrm{H_2R}\begin{cases}\mathrm{COOCH_3}\\ \mathrm{COOC_{20}H_{39}}\\ \mathrm{COOH}\end{cases}$
Glaucophyllin, *Rhodophyllin* *Cyanophyllin*, *Erythrophyllin* $\mathrm{Mg\,.\,RH(COOH)_2}$	*Glaucoporphorin*, *Rhodoporphorin* *Cyanoporphorin*, *Erythroporphorin* $\mathrm{H_2RH(COOH)_2}$
Pyrrophyllin, *Phyllophyllin* $\mathrm{Mg\,.\,RH_2(COOH)}$	*Pyrroporphorin*, *Phylloporphorin* $\mathrm{H_2RH_2(COOH)}$
Ætiophyllin $\mathrm{MgRH_3}$	*Ætioporphorin* $\mathrm{H_2RH_3}$

Inspection of the above will show that the ætiophyllin and ætioporphorin are the parent substances of the two groups ; the other members are obtained from them by replacing hydrogen atoms by one, two, or three carboxyl radicles.

6. *The Decomposition of Chlorophyll by Alkali and by Acid*

The action of alkali upon chlorophyll is twofold. Under certain conditions, a change in composition takes place ; whilst under other conditions only rearrangements occur in the chlorophyll structure. In the present section, for the sake of clearness, the decompositions will be dealt with ; and a full treatment of the intramolecular rearrangements will be deferred to the next section.

It will be remembered that when chlorophyll-*a* is submitted to the action of alkali at ordinary temperatures, the first change noted is the hydrolysis of the phytyl radicle. Thereafter, the

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* Note that the third carboxyl group in these substances is masked by lactam formation. It has been shown free in the above formula merely for the sake of bringing out the analogies between the various compounds.

methyl group is displaced in turn; and, finally, the salt of a tribasic acid, chlorophyllin-*a*, is produced. If, now, the temperature be raised to 140° C., carbon dioxide is split off and a dicarboxylic acid, glaucophyllin, is formed. At 165° C. in presence of alkali, this undergoes rearrangement into rhodophyllin, which is also a dibasic acid. Treated with alkali at 200° C., rhodophyllin in its turn loses carbon dioxide and yields a monocarboxylic acid, pyrrophyllin.[1]

If hot alkali be allowed to act direct upon chlorophyllide-*a*, with no previous treatment in the cold, the decomposition takes a different but parallel course, owing to an intramolecular change occurring which produces iso-chlorophyllin-*a* instead of chlorophyllin-*a*. With alkali at 140° C. this isomeric substance yields cyanophyllin, isomeric with glaucophyllin. Cyanophyllin, when heated with alkali at 170° C., gives erythrophyllin. Finally, from erythrophyllin, alkali at 190° C. produces phyllophyllin.[2]

The table on page 224 will serve to bring out the parallelism between the various compounds formed in the latter stages of the two reactions.

Throughout these changes, the magnesium atom of chlorophyll retains its place in the molecule, as alkalis appear to have no power to displace it.

The action of acids upon chlorophyll, as was mentioned above, is to remove the magnesium from the molecule and replace it by two hydrogen atoms. Now it is clear that similar treatment might be given to the decomposition products of chlorophyll; and it is found that in their cases the same result follows. Thus for each magnesium-containing derivative there is a corresponding hydrogen compound.[3]

In this way we obtain from glaucophyllin the corresponding glaucoporphorin:

$$\left[C_{31}H_{32}N_4Mg\right]\begin{matrix}COOH\\COOH\end{matrix} \xrightarrow{\text{acid}} \left[C_{31}H_{34}N_4\right]\begin{matrix}COOH\\COOH\end{matrix}$$

Glaucophyllin. Glaucoporphorin.

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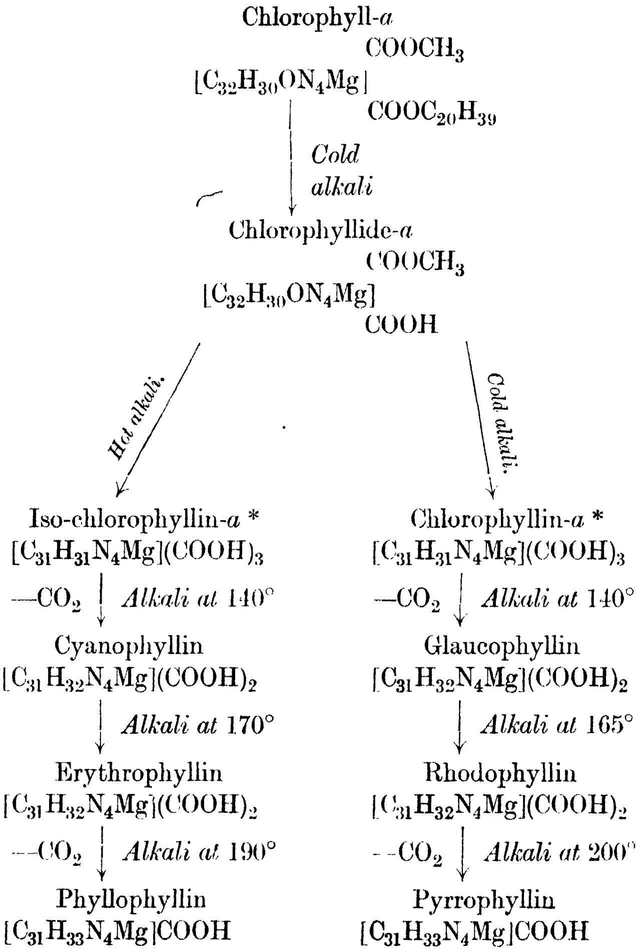
[1] Willstätter and Fritzsche, *Annalen*, 1909, **371**, 33; and Willstätter, *Ber.*, 1914, **47**, 2854.

[2] Willstätter, *Ber.*, 1914, **47**, 2854.

[3] Willstätter and Fritzsche, *Annalen*, 1909, **371**, 33.



and in a similar manner we get rhodoporphorin from rhodophyllin, pyrroporphorin from pyrrophyllin and phylloporphorin from phyllophyllin.†

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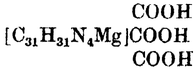
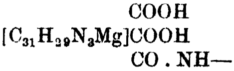
* As will be seen in the following section, chlorophyllin-*a* and iso-chlorophyllin-*a* probably contain lactam rings, so that their formulæ may be written either as



$$[C_{31}H_{31}N_4Mg]\begin{matrix}COOH\\COOH\\COOH\end{matrix}$$

or



$$[C_{31}H_{29}N_3Mg]\begin{matrix}COOH\\COOH\\CO\,.\,NH—\end{matrix}$$

† See the table at the end of this volume.

The final stage in the decomposition of chlorophyll requires more drastic reactions.[1] If the phyllins or porphorins are heated with soda-lime in a tube they lose carbon dioxide and are converted into substances containing no carboxyl radicles. When a phyllin is used as a starting-point, the substance produced is ætiophyllin, $C_{31}H_{34}N_4Mg$; whereas when a porphorin is treated with soda-lime it yields the corresponding magnesium-free compound ætioporphorin, $C_{31}H_{34}N_4$.

The decomposition of chlorophyll-*b* follows a slightly different course, some intermediate products being missing from the series, as can be seen from the table at the end of this volume.

7. *Intramolecular Changes in the Chlorophyll Nucleus*

When chlorophyll-*a* is treated with cold alkali, both the methyl and phytyl radicles are removed by the hydrolysis and a substance known as chlorophyllin-*a* results. On the other hand, if hot alkali solutions are employed, the end-product is an isomeric compound iso-chlorophyllin-*a*.[2] The actual progress of the reaction is marked by a peculiar colour-change. When the alkali acts on chlorophyll (or on a chlorophyllide) the green tint of the substance alters to a deep brown and then, after a few minutes, the brown coloration vanishes and is replaced by the original green. The brown tint corresponds to the presence of what has been termed the "brown phase" of chlorophyll.[3]

Taking these facts together, the only possible explanation of them must be found in some kind of intramolecular change occurring in the chlorophyll molecule under the action of the alkali: and Willstätter has suggested that this change involves the lactam group which was postulated as one of the radicles in the chlorophyll nucleus.[3]

He assumes that at least three of the nitrogen atoms of chlorophyll are capable of taking part in lactam rings. Then, as there are three carboxyl radicles also present in the molecule, it can be seen that a very considerable number of different lactams may be formed according to the choice which we

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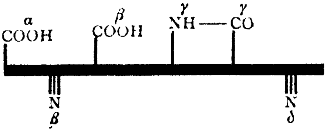
[1] Willstätter and Fischer, *Annalen*, 1913, **400**, 182.

[2] Willstätter, Fischer, and Forsén, *Annalen*, 1913, **400**, 147.

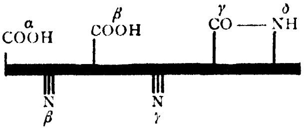
[3] Willstätter and Utzinger, *Annalen*, 1911, **382**, 129.

make of the carboxyl group and the nitrogen atom which are to build up the particular lactam in question.

Let us distinguish the three carboxyl radicles from one another by the letters, α, β, and γ; and let us attach the symbols, β, γ, and δ to the nitrogen atoms which Willstätter assumes to take part in the reactions. The remainder of the chlorophyll nucleus may be represented by a heavy line. On this scheme, it is clear that we might have various isomeric compounds formed, each of which would contain a different type of lactam ring. Thus the γ-nitrogen atom might be linked with the γ-carboxyl group, as in (I.); or the γ-carboxyl group might change its mode of linkage and attach itself to the δ-nitrogen atom as in (II.).



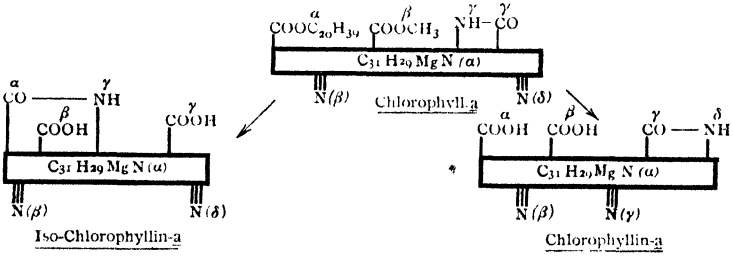
(I)



(II)

Now imagine that the compound (I.) is less stable than the compound (II.) owing to the difference in stability of the two lactam rings. It is clear that if the ring in (I.) be broken by any means it will not tend to re-form itself; but that, instead, the compound (II.) will be produced owing to the greater stability of its lactam ring.

Thus according to Willstätter's views, the formation of chlorophyllin-*a* and iso-chlorophyllin-*a* from chlorophyll may be represented in the following manner:—



This process of "allomerization," as Willstätter terms it, is obviously capable of application to the simpler chlorophyll derivatives as well as to chlorophyll itself; and when the complexity of the possible arrangements of the various carboxyl and imino radicles is taken into account it is no great wonder that three isomeric phytochlorins and an equal number of phytorhodins are known.

Both chlorophyll-*a* and chlorophyll-*b* give allomers simply on standing in alcoholic solution; which is sufficient to show how readily this intramolecular change takes place.

8. *The Magnesium Atom in the Chlorophyll Molecule*

The part played by the magnesium atom in the structure of chlorophyll cannot be ignored if a true picture of the substance is to be obtained; yet it must be admitted that in some respects the problem which it presents is a thorny one.

From the fact that the magnesium atom remains as part of the structure of ætiophyllin, $C_{31}H_{34}N_4Mg$, it is clear that the metal must be attached to carbon or nitrogen; since all the oxygen has disappeared in the process of degradation to which the original chlorophyll has been submitted.

Now in all the magnesium-carbon compounds with which we are acquainted, the magnesium is easily removed by the action of water; it certainly cannot withstand the attack of alkali. Further, the nitrogen-magnesium bond also appears to be a weak one, if we may judge from the behaviour of magnesium methyl iodide with pyrrol.[1] Clearly the affinity which holds the magnesium atom to the chlorophyll nucleus is no ordinary bond; and we are left to conjecture its nature.

Willstätter[2] regards the metallic atom as forming a complex with the basic groups of the molecule. This question of "complex" formation is one of the debatable points in modern organic chemistry; and the fact that chlorophyll appears to be the first instance of magnesium acting in this manner will possibly not recommmend the suggestion to some minds.* The problem is one which must be left to the judgment of the reader.

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[1] Hess and Wissing, *Ber.*, 1914, **47**, 1416.

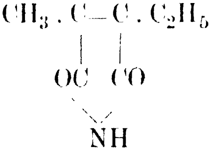
[2] Willstätter and Pfannenstiel, *Annalen*, 1908, **358**, 215; Willstätter and Fritzsche, *Annalen*, 1910, **371**, 46.

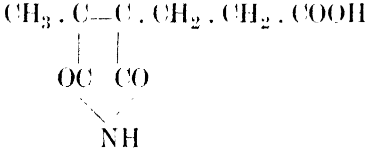
* The fact that the magnesium atom can be replaced by two hydrogen atoms without completely altering the character of the molecule makes the matter even more puzzling.

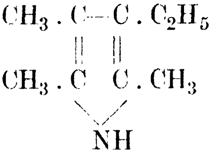
9. *The Structures of Ætiophyllin and Ætioporphorin*

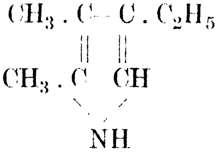
A consideration of the probable constitutions of the two ultimate degradation products in which the chlorophyll skeleton is retained leads us, as must frankly be admitted, into a region of almost pure hypothesis; but for the sake of completeness it is necessary to deal summarily with the subject.

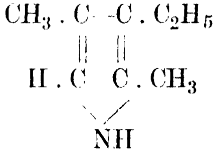
The actual facts at the disposal of the investigator are very few.[1] Oxidation of phylloporphorin produces more than one molecular quantity of methyl-ethyl-maleinimide (I.) along with one molecular quantity of hæmatic acid (II.). Reduction of porphorins leads to the formation of phyllopyrrol (III.), isohæmopyrrol (IV.), and cryptopyrrol (V.).


(I.)


(II.)


(III.)


(IV.)


(V.)

From these disjointed members it is necessary to piece together the complete skeleton of the substance.

Willstätter's suggestions are as follows. From the nature of the above degradation products he assumes that the original substance must have contained four pyrrol nuclei. Now since the composition of ætioporphorin, $C_{31}H_{36}N_4$, contains a markedly low percentage of hydrogen, he concludes that the pyrrols must be so united and substituted that eight hydrogen atoms are left out as compared with the case in which the pyrrol groups are joined by single linkages. This saving of hydrogen atoms he proposes to accomplish by utilizing double bonds or calling ring formation to his assistance. Next he assumes a

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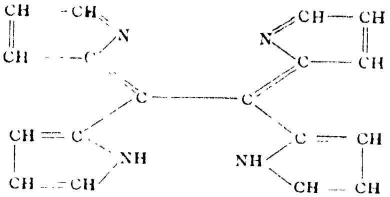
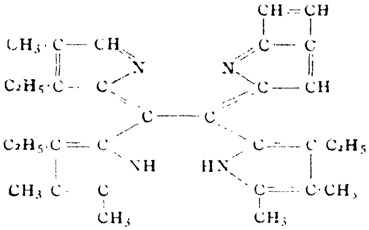
[1] Willstätter, *Ber.*, 1914, **47**, 2831.

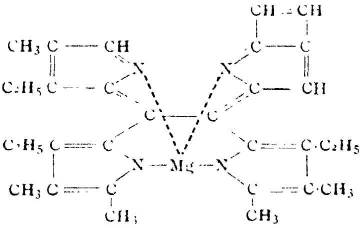
difference between pairs of pyrrol nuclei on the ground that two must be salt-forming radicles whilst the other two must be capable of complex formation. On this basis he suggests the following skeleton for the substance :



And from this, by substitution, he fills in the formulæ below for ætioporphorin and ætiophyllin :



Aetioporphorin



Aetiophyllin

10. *The Relations between Chlorophyll and Hæmin*

In the higher branches of the vegetable kingdom, chlorophyll plays a most important part in the vital economy of the organism ; whilst in animals an equally essential factor is the colouring matter of the blood. The parallel functions of the two compounds suggest that some similarity in nature might be traced between chlorophyll and hæmin ; and a survey of the chlorophyll problem would be incomplete without a brief reference to the colouring material of blood.

Examination of the blood pigment shows that it is composed of two portions : an albuminous substance called globin and a non-albuminous compound named hæmatin. It is with the latter that we are here concerned.

Both chlorophyll and hæmatin are metallic derivatives, the magnesium of chlorophyll finding its analogue in the iron of hæmatin. In each case the metallic atom displays an abnormal character ; and both compounds can be freed from their metallic portion by similar treatment. Finally, when analogous degradation methods are employed in the two cases, ætioporphorin is produced from both chlorophyll and hæmatin. These facts are sufficient to justify the assumption that the two substances are related to one another in a more than superficial degree.

When hæmatin is treated with hydrochloric acid it yields hæmin; and the reaction is supposed to take place by the replacement of a hydroxyl group by a chlorine atom:

$$R : Fe—OH \rightarrow R : Fe—Cl$$

Hæmin has been shown[1] to have the composition $C_{33}H_{32}O_4N_4FeCl$; which brings it into close resemblance with chlorophyllin. It will be seen that the divalent magnesium atom of chlorophyll is replaced by the divalent group: $=Fe—Cl$ in hæmin. Willstätter and Fischer[1] have brought forward a hæmin formula based to some extent upon their proposed structure for ætiophyllin. Küster,[2] on the other hand, rejects their suggestion and has put forward a formula of his own. It would require too much space to discuss the merits of either hypothesis, especially in view of the fact that both are quite possibly incorrect. In the present uncertain state of our knowledge, it is sufficient to indicate the general resemblance between chlorophyll and hæmin.

11. *Conclusion*

As chlorophyll is a more than usually complicated subject, it seems well in this place to summarize very briefly the undisputed information which has been acquired about its constitution; for without such a summary the reader may feel that he is in the position of the man who "could not see the wood for the trees."

Amorphous chlorophyll, extracted from leaves, is found to be a mixture of two compounds, chlorophyll-*a* and chlorophyll-*b*, both of which are methyl-phytyl esters. The compositions of the two compounds are:—

$$\left[C_{32}H_{30}ON_4Mg\right]\begin{array}{l}COOCH_3\\COOC_{20}H_{39}\end{array}+\tfrac{1}{2}H_2O, \qquad \left[C_{32}H_{28}O_2N_4Mg\right]\begin{array}{l}COOCH_3\\COOC_{20}H_{39}\end{array}$$

Chlorophyll-*a*. Chlorophyll-*b*.

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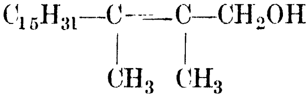
[1] Willstätter and Fischer, *Zeitsch. physiol. Chem.*, 1913, **87**, 423.

[2] Küster, *Zeitsch. physiol. Chem.*, 1913, **88**, 377.

Phytyl alcohol has been shown to have the following structure :—



$$C_{15}H_{31}-\underset{\displaystyle CH_3}{\underset{|}{C}}=\underset{\displaystyle CH_3}{\underset{|}{C}}-CH_2OH$$

When either of the chlorophylls is treated with acids, the magnesium atom is removed and its place is taken by two hydrogen atoms. The compounds thus formed are still methyl-phytyl esters; and they are termed phæophytins. After hydrolysis of the phytyl radicle, the residue is a methyl ester called a phæophorbide. The magnesium-free acids from which the esters are derived are named phæophorbins.

If either of the chlorophylls be acted on by cold dilute potash, the salt of a *tribasic* acid is formed, the acid itself being named a chlorophyllin. Hence, clearly, there is a third carboxyl radicle in the chlorophyll structure which is masked in some manner.

When the hydrolysis is carried out at higher temperatures in the case of chlorophyll-*a*, carbon dioxide is split off and two isomeric dicarboxylic acids, glaucophyllin and rhodophyllin, are formed; while by the use of still higher temperatures a further loss of carbon dioxide results in the production of a monobasic acid : pyrrophyllin.

Throughout these changes the magnesium atom is retained in the molecule; but by subsequent treatment with acids each of these decomposition products loses its magnesium, which is replaced by two atoms of hydrogen. In this way from glaucophyllin a substance named glaucoporphorin is obtained; and each of the other phyllins yields the corresponding magnesium-free porphorin. The decomposition of chlorophyll-*b* proceeds in an almost exactly similar manner, though certain of the intermediate compounds are missing in its series.

When the porphorins are heated with soda-lime, the last carboxyl group of the molecule is split off; and a substance, ætioporphorin, $C_{31}H_{34}N_4$, is formed. The phyllins, when subjected to the same treatment, give the corresponding magnesium derivative ætiophyllin, $C_{31}H_{34}N_4Mg$.

The action of cold alkali solutions upon either chlorophyll-*a* or chlorophyll-*b* results, as has been said, in the production of a tribasic acid. This is found to be a mixture of two acids;

so that from chlorophyll-*a* we get chlorophyllin-*a* and isochlorophyllin-*a*: and from chlorophyll-*b* two other isomeric chlorophyllin-*b* compounds are produced.

Further, when chlorophyll and its derivatives are treated with alkali they exhibit a peculiar colour change, turning from green to brown and back again—the so-called " brown phase " of chlorophyll.

The magnesium atom in the chlorophyll molecule is retained with a measure of affinity different from and greater than that which we are accustomed to find in organo-magnesium derivatives.

Finally, the nature of the ultimate degradation products of chlorophyll points to the probability that the chlorophyll molecule contains four pyrrol nuclei.

The foregoing summary contains all the important *facts* which have been established with regard to the structure of chlorophyll; and we must now deal with the theories which have been advanced to account for them.

The mystery of the third carboxyl group in the chlorophyll nucleus has suggested that this third carboxyl may be masked by lactam formation in which one of the nitrogen atoms of chlorophyll takes part. This view leads to the further hypothesis that, since there are three carboxyl groups and four nitrogen atoms present, a considerable number of possible lactam rings might be imagined, differing from one another in stability. Thus in one isomer it is assumed that the first carboxyl radicle forms a lactam with the first nitrogen atom; while in another isomer the first carboxyl reacts with, say, the second nitrogen atom to form a new lactam. On this hypothesis, the " brown phase " of chlorophyll represents the breaking of one lactam ring and the reclosing of the molecule into a more stable lactam grouping.

As to the structures proposed for ætiophyllin and ætioporphorin, their plausibility depends entirely upon the judgment of the reader; for it cannot be asserted that they have much solid basis; whilst as to the positions which the carboxyl groups of chlorophyll occupy in the ætiophyllin skeleton, not even the most random conjecture can be put forward with any justice.

CHAPTER IX

THE DEPSIDES

1. *Historical*

GALL-NUTS contain, in proportions varying up to 50 per cent., a material termed tannin, which can be extracted from the powdered nuts by means of organic solvents. Obtained in this way, it is a colourless, amorphous substance with an astringent taste. It is easily soluble in water, slightly soluble in alcohol, and almost insoluble in ether. From its aqueous solutions it is precipitated by mineral acids, common salt, or gelatine; and it can be removed from water by dipping animal membranes into the solution. It is optically active, and has an electrical conductivity, though of a low degree. With ferric chloride it produces a blue coloration, which is utilized in the manufacture of certain inks. On treatment with dilute acids, it gives a large yield of gallic acid, $(HO)_3C_6H_2 . COOH$.

As a result of extensive researches carried out in the middle of last century, Strecker[1] came to the conclusion that tannin was a compound containing three gallic acid nuclei and one glucose nucleus; and on these assumptions tannin would have the formula, $C_{27}H_{22}O_{17}$. The glucose portion of the molecule would account for the optical activity of tannin; whilst the presence of the gallic acid nuclei would explain the detection of this acid among the tannin hydrolysis products.

At a later date, the dehydration of gallic acid was attained by means of silver nitrate, arsenic acid,[2] and phosphorus oxychloride;[3] and the product was found to be a substance termed digallic acid, which is produced by the carboxyl group of one

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[1] Strecker, *Annalen*, 1852, **81**, 248; 1854, **90**, 328.

[2] Löwe, *Jahresbericht f. Chemie*, 1867, 446; 1868, 559.

[3] Schiff, *Ber.*, 1871, **4**, 232, 967; 1879, **12**, 33; *Annalen*, 1873, **170**, 143.

gallic acid molecule becoming esterified by a hydroxyl group belonging to a second gallic acid molecule:

$$(HO)_3C_6H_2—CO—O—C_6H_2(OH)_2—COOH$$

Schiff believed that this substance, with the simple formula $C_{14}H_{10}O_9$, was actually a synthetic form of tannin. This structure, of course, left out of account the optical rotatory power of natural tannin; but it must be borne in mind that at that date the analyses which had been made of tannin showed very marked differences in the percentage of sugar detected; and, in view of the amorphous character of the material, it seemed quite possible that the optically active substance was merely a variable impurity in the tannin preparations and not an indispensable constituent.

This conception of tannin lasted almost unchallenged for a quarter of a century; but in 1897, Walden [1] made a comparison between the properties of digallic acid and natural tannin, which proved beyond doubt that the two materials differed in absorption spectra, electrical conductivity, and behaviour towards arsenic acid. Attempts were made to resuscitate the digallic acid formula by assuming that natural tannin was a mixture of digallic acid with some other tannin-like material (leuco-tannin) possessing optical activity; but they are of no importance at the present day.

Thus in the early years of the present century, our knowledge of the tannin constitution was hardly more exact than it had been fifty years before. In the standard textbooks, the references to the subject, vague as they were, dealt with the material as a mixture.[2] The analytical method of investigation had failed to clear up the subject or even to settle whether tannin should be regarded as optically active *per se*. But now a new figure came upon the scene. Once again Emil Fischer was preparing his synthetic weapons for the attack upon yet another group of the naturally occurring compounds; and, for the last time, he was to bring clarity into a perplexing problem.

By the year 1906, Fischer's interest in the polypeptides was fading out. He had laid the foundations of the subject

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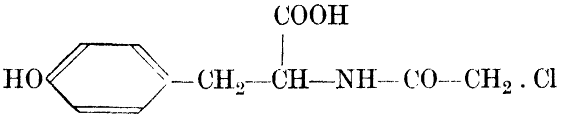
[1] Walden, *Ber.*, 1897, **30**, 3151; 1898, **31**, 3167.

[2] See, *inter alia*, Richter, *Organische Chemie*, vol. ii., p. 333 (1913).

firmly enough for other men to build upon; and it was time to turn his mind to some other field. For two years he was attracted by the problem of the Walden Inversion, which had come to his notice in connection with his researches upon the amino-acids; but this was, to him, merely an interlude between his self-appointed tasks in the great division of the natural products. He was already looking round him in search of a fresh field, when an investigation carried out in his own laboratory set him on the track for which he was seeking.

In the preparation of glycyl-tyrosyl-glycine, it had been necessary to obtain chloracetyl-tyrosine:



and then convert this into the acyl chloride. Now phosphorus chloride had the disadvantage that affected not only the carboxyl group but the phenolic hydroxyl radicle as well. Fischer therefore sought for some means of protecting the hydroxyl radicle by introducing a group which could be easily eliminated at a later stage in the synthesis; and this protective agent he discovered in the carbomethoxy radicle. By acting on phenols with chloroformic methyl ester, the phenolic hydrogen atom can be replaced by the group $—COOCH_3$; and, when it is necessary, the hydroxyl group can be regenerated by a mild hydrolytic action:

$$C_6H_5—OH + Cl.COOCH_3 = C_6H_5—O—COOCH_3 + HCl$$
$$C_6H_5—O—COOCH_3 + H_2O = C_6H_5—OH + CO_2 + CH_3OH$$

It will be recalled that Fischer had already, in his polypeptide syntheses, utilized chloroformic ester in the protection of amino-groups; but he had to abandon its use on account of the fact that the $-$ COOEt group could not be split off again in order to regenerate the original amino-radicle. This difficulty, obviously, does not make its appearance in the case of the phenols.

Tyrosine, with its reactive carboxyl radicle and its protectable hydroxyl group, gave Fischer the clue for which he had been searching. The polypeptide investigations had impressed on his mind the manner in which natural products may be built up by linking together in a chain a series of molecules, each of which contains an acidic and a basic radicle. Now, in the hydroxy-benzoic acids, he glimpsed the possibility of a fresh series of chain-compounds obtained by esterifying the carboxyl group of one acid molecule with the hydroxyl group belonging to a second ring :

$$HO\ C_6H_4-CO-O\ C_6H_4\ COOH$$

The occurrence of digallic acid in the decomposition products of tannin showed that chains of this description actually did occur in nature. Fischer had found his new subject for investigation ; and, as was his custom, he set about developing it in the broadest manner from the synthetic side.

2. *The Nature of the Depsides* [1]

As so often happened with Fischer's vast and intricate researches, his entry into a fresh field soon demanded the devising of a special nomenclature [2] for the compounds which his ingenuity evolved. Since the substances undoubtedly had a kinship with tannin, Fischer coined the term *depside* (from δέψειν, to tan) as a class-name for the whole group. The word had the additional advantage of a likeness to "peptide" ; and thus carried with it a suggestion of the similarity in the catenarian construction of the two types of compound. The remainder of the nomenclature followed on the lines of the polysaccharides and the polypeptides, being based upon the number of hydroxy-acid radicles united in the chain. When two hydroxy-acid radicles are coupled together, the compound is a *didepside.* Three coupled radicles compose a *tridepside* chain ; and four radicles, when united, make a *tetradepside.* The following formulæ will make the matter clear, as the dotted lines show the division between the radicles. The depsides chosen are assumed to be derived from a hydroxy-benzoic acid, $HO \,.\, C_6H_4 \,.\, COOH$.

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[1] Fischer's collected papers in this branch of chemistry have been republished under the title *Untersuchungen über Depside und Gerbstoffe* (1919). A summary of his work is to be found in his two lectures on the subject (*Ber.*, 1913, **46**, 3253 ; 1919, **52**, 809). The personal side of the matter is very well treated in Hoesch's *Emil Fischer : Sein Leben und sein Werk* (1921).

[2] Fischer and Freudenberg, *Annalen*, 1910, **372**, 32.

Example of a didepside :

$$HO\,.\,C_6H_4\,.\,CO-\vdots-O\,.\,C_6H_4\,.\,COOH$$

Example of a tridepside :

$$HO\,.\,C_6H_4\,.\,CO-\vdots-O\,.\,C_6H_4\,.\,CO-\vdots-O\,.\,C_6H_4\,.\,COOH$$

Example of a tetradepside :

$$HO\,.\,C_6H_4\,.\,CO-\vdots-O\,.\,C_6H_4\,.\,CO-\vdots-O.C_6H_4.CO-\vdots-O.C_6H_4.COOH$$

The terminology for individual compounds follows the lines already made familiar by the polypeptides. Thus the didepside shown above, if derived from *p*-hydroxybenzoic acid, would be termed *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid. The tridepside would be described as di-[*p*-hydroxybenzoyl]-*p*-hydroxybenzoic acid. The tetradepside would have the name : tri-[*p*-hydroxybenzoyl]-*p*-hydroxybenzoic acid.

3. *Some Factors which influence Depside Formation*

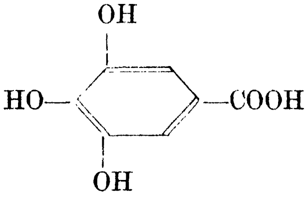
At the first glance, the depsides seem to furnish a close parallel to the polypeptides ; since in the syntheses of the two classes the analogous processes of amide-formation and esterification are used. Closer inspection reveals, however, that there are marked differences between them ; and that in almost every case the disadvantage lies with the depsides.

In the amino-acids from which the polypeptides are built up, the two interacting groups are markedly different in character, the acidity of the carboxyl radicle meeting its complement in the basic nature of the amino-group. In the depsides, however, the acidic carboxyl has to be forced into combination with the semi-acidic hydroxyl group of a phenol, which is not nearly so simple an operation as amide formation. It seems not improbable that this factor in itself is sufficient to account for the subordinate rôle in nature which is played by the depsides. There is not, in the depside molecule, that regular alternation of basic and acidic radicles which seems to make the almost infinite extension of the polypeptide chain a possibility.

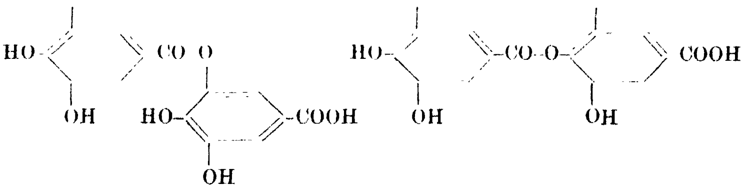
Again, in the polypeptides synthesized by Fischer, the structural difficulties were reduced to a minimum since each amino-acid molecule contained only one carboxyl and one amino-radicle. Among the depsides, however, the isomerism due to the phenyl nucleus introduces complications in more than one form.

In the first place, the simplest phenolic acid exists in three isomeric forms; and it was found that these acted quite differently in depside formation. Para-hydroxybenzoic acid underwent depside formation with comparative ease; the meta-acid showed less readiness in reaction; whilst the acid with the carboxyl and hydroxyl radicles in the ortho-positions could only be made to form depsides with difficulty. Evidently the simplicity of the syntheses is governed by the nature of the reagents to a very considerable extent.

Secondly, an even greater difficulty arises when the case of the polyhydroxy-benzoic acids is examined. Take gallic acid



as an example. Here there are two hydroxy-groups in the *meta*-position to the carboxyl group and the remaining hydroxyl is in the *para*-position. It is obvious that if two molecules of this substance interact, the carboxyl group of one molecule may attach itself either in the *meta*- or in the *para*-position to the carboxyl of the second molecule, leading to the production of a mixture * of the two compounds shown below:



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* A somewhat analogous difficulty in the polypeptide syntheses is found in the formation of mixtures of non-antipodic forms when *dl*-amino acids are employed.

In order to avoid the production of this mixture, which in the case of higher depsides would be difficult to resolve into its separate constituents, it is necessary to shield certain hydroxyl groups from the action of the acid, leaving open to its attack only one hydroxyl group in a known position in the structure. After the esterification is completed, these shielded hydroxy groups must then be brought back to their original condition.

A final difficulty, which presents itself in certain cases, is caused by the possibility of intramolecular rearrangements taking place; but this point can best be dealt with later in the present chapter.

4. *The Synthesis of Depsides*

From what was mentioned in the foregoing section, it will be clear that in the synthesis of the depsides there are three processes involved: (*a*) the protection of those hydroxyl groups which are not to be attacked by the carboxyl radicle; (*b*) the coupling reaction; and (*c*) the regeneration of the shielded hydroxyl groups. It will be convenient to deal with these in turn.

(*a*) *The Protection of Hydroxyl Groups.*—In this problem three factors have to be taken into account. The shielding group must be easily introduced; it must be readily removed; and, if possible, it should improve (or not deteriorate) the power of crystallization of the substance under examination. The first two factors limit the choice, so far as depsides are concerned, to acyl radicles such as acetyl, benzoyl, and the carbomethoxy group. The molecular weight of depsides being so high, the introduction of a heavy radicle like benzoyl is not advantageous; so the final selection is limited to the acetyl and carbomethoxy groups; and in the final depside syntheses the acetyl radicle was found to yield better crystalline derivatives than the carbomethoxy group.

It is comforting to lesser chemists to find that even Fischer could take the wrong track on at least one occasion. A study of the literature of the subject had convinced him[1] that the removal of the acetyl group from phenols required strong reagents such as boiling alkali; and as such reagents would naturally tend to hydrolyse the depside junctions, he avoided the acetylation method of shielding until quite far on in his researches. When driven back to it by force of circumstances, he found that

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[1] Hoesch, *Emil Fischer*, p. 456; Fischer, *Ber.*, 1919, **52**, 809.

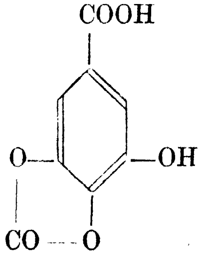
he had been misled; and in his later work he adopted the introduction of acetyl groups as the simplest and most satisfactory method of protection for his hydroxyl radicles.

In practice the acetylation of the phenolic acids was carried out by shaking the acid with acetic anhydride in presence of zinc chloride, dimethylaniline, or pyridine. This leads to complete acetylation; and thereafter one of the hydroxyls can be freed again by hydrolysis with potassium carbonate solution. The identity of the particular hydroxyl group set free is established by converting it into a methyl ether by means of diazomethane, hydrolysing away the remaining acetyl radicles and identifying the ether thus produced.

For example, gallic acid is first converted into triacetyl-gallic acid. By controlled hydrolysis, this is changed into 3, 5-diacetyl-gallic acid, which is then ready for depside synthesis, owing to its single free hydroxyl group. The identity of the 3, 5-diacetyl compound is established by methylating the free hydroxyl with diazomethane and hydrolysing the two acetyl radicles, when the product is found to be 4-methoxy-3, 5-dihydroxy-benzoic acid.

The second protection method consists in shaking the phenolic acid in cold alkaline solution with chloro-formic methyl ester and acidifying after the reaction has run its course. Here, as in the foregoing case of acetylation, all the hydroxyl groups are attacked by the reagent; and in order to free one of them for depside synthesis a partial hydrolysis with alkali or ammonia is necessary.

A third protection method was used by Fischer in the case of polyhydroxy-compounds having two hydroxyls in the *ortho*-position. Carbonyl chloride was allowed to act upon the polyphenol, with the result that a ring was formed at the two *ortho*-positions. Gallic acid, for example, yields the compound shown below:

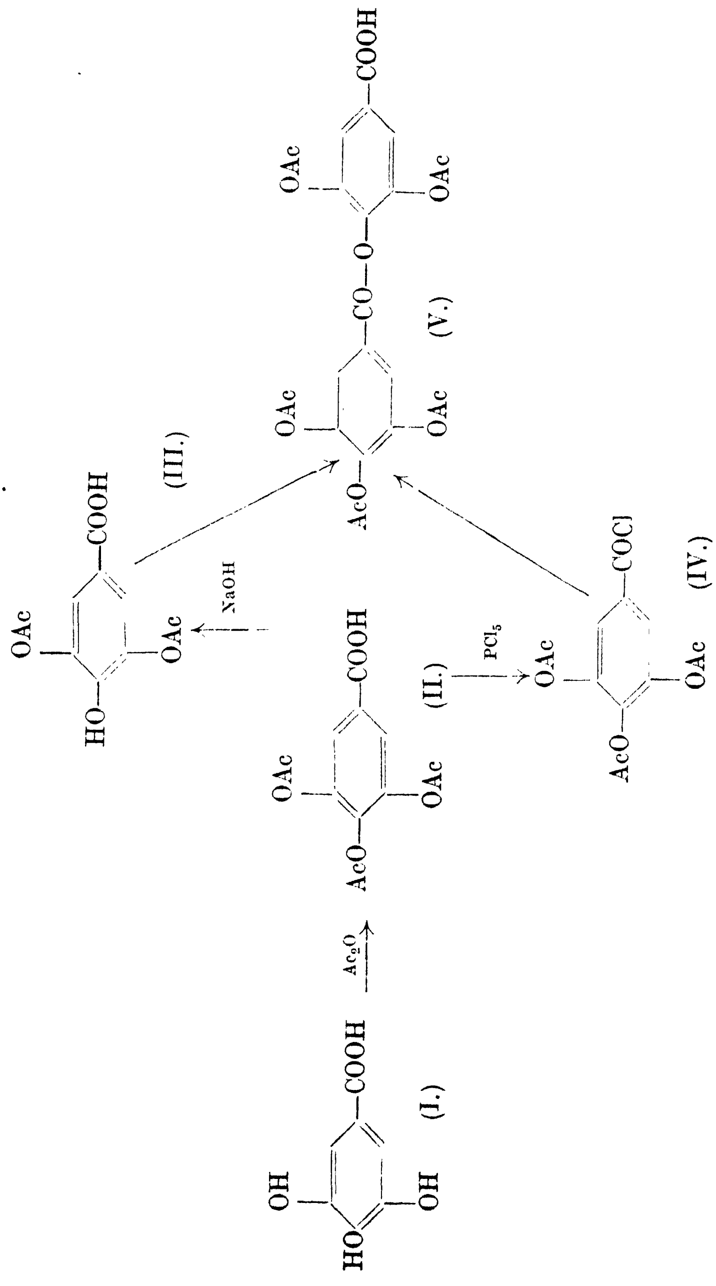


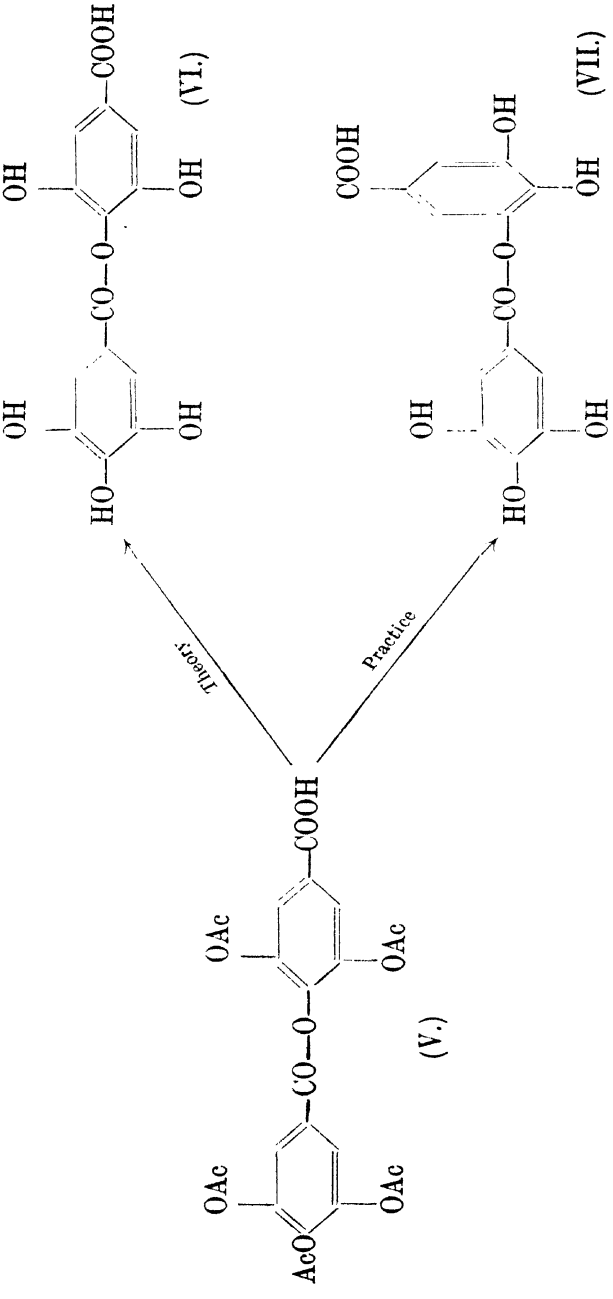
(*b*) *The Coupling of Nuclei.*—It will be recalled that in the polypeptide work, Fischer employed by preference the acyl chlorides as reagents to act upon the amino-group of the amino-acids during the process of chain-formation. In the field of the depsides the catenation was brought about in an analogous manner by the action of acyl chlorides upon the phenolic acids. The chlorides were readily obtained by the action of phosphorus pentachloride upon the carboxyl group after the hydroxyl radicles of the molecule had been protected as has already been described. The interaction between acyl group and phenolic hydroxyl took place readily in acetone solution in presence of alkali, dimethylamine, or aluminium chloride; and by subsequent addition of dilute mineral acid, the depside was precipitated.

(*c*) *The Regeneration of the Hydroxyl Group.*—After the completion of the coupling, the protective acetyl groups are easily removed by the action of alkali, even at ordinary temperatures. Ammonia is also a reagent sufficient for the purpose; and if the temperature be raised, sodium acetate will effect the de-acetylation rapidly. By using different quantities of alkali, the hydrolysis can be stopped at fixed stages instead of being run through to completion in one operation. For the removal of the carbomethoxy-group, normal alkali solutions are used in most cases; sometimes sodium carbonate solution can be employed with advantage; and in certain cases ammonia in presence of pyridine has proved a satisfactory agent.

At this point, it seems of interest to trace the steps in the synthesis of a didepside: digallic acid. For the sake of clearness, the acetyl group is represented by the symbol Ac in the formulæ.

Gallic acid (I.) is first converted into triacetyl-gallic acid (II.). Partial hydrolysis yields 3, 5-diacetyl-gallic acid (III.), which is the phenolic compound to be used in the synthesis. The triacetyl-gallic acid (II.) is treated with phosphorus pentachloride, yielding triacetyl-galloyl chloride (IV.). The diacetyl-compound (III.) and the chloride (IV.) are then allowed to interact, with the production of the pentacetyl-digallic acid (V.), from which a didepside, digallic acid, is obtained by hydrolysis of the five acetyl groups by means of alkali.

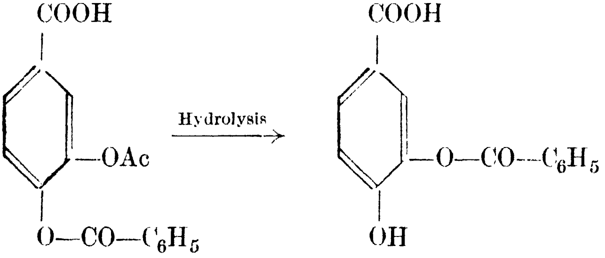

(I.)
Ac_2O
(II.)
NaOH
(III.)
PCl_5
(IV.)
(V.)


(V.)
Theory
Practice
(VI.)
(VII.)
OAc
AcO
COOH
CO—O
OH
HO

5. *Intramolecular Change in the Depsides*

The example of depside formation given in the foregoing section was chosen to illustrate a further point which raised difficulties in the depside field. As can be seen from the formulæ, there can, apparently, be no doubt as to the constitution of the pentacetyl derivative (V.); and the natural assumption would be that, on removing the five acetyl groups by hydrolysis, the didepside (VI.) would be produced. In actual practice, however, this substance is not formed; but, instead, the end-product of the hydrolysis is the compound with the constitution (VII.). Instead of the expected *para*-digallic acid, a *meta*-digallic acid is formed.

The explanation of this apparently mysterious phenomenon was found by Fischer in a wandering of the galloyl radicle from the *para-* into the *meta*-position during the hydrolysis of the acetyl groups. This wandering is not confined to the galloyl radicle; for when the benzoyl group is substituted for the galloyl nucleus, it also wanders in precisely the same way. Further, when *p*-benzoyl-acetyl-protocatechuic acid (VIII.) is hydrolysed, the removal of the acetyl group is accompanied by a similar wandering of the benzoyl radicle, so that *m*-benzoyl-protocatechuic acid (IX.) is the end-product:



(VIII.) (IX.)

From these and other results, it appears that the phenomenon is a general one in this series of compounds.

The wandering of radicles from one atom to another is, of course, nothing new in organic chemistry. The shift of acyl groups from the oxygen to the carbon atom in acetoacetic ester syntheses will occur to the mind of the reader at once. Among other examples might be mentioned the production of N-benzoylaminophenol by the reduction of O-benzoyl-*o*-nitrophenol;[1] and the conversion of O-carbethoxy-*o*-aminophenol into N-carbethoxy-*o*-aminophenol.[2] What makes the Fischer change so remarkable is that the wandering takes place between two hydroxyl groups, the only difference between which is their structural position in respect to the carboxyl radicle.

No explanation has yet been found for this peculiar intramolecular rearrangement, which Fischer likens to the equally unexplained case of the benzoyl derivatives of dulcitol and its acetone-derivative.[3]

6. *The Moss Acids*

Up to the present time, the lichens are the solitary abundant natural source of depsides. If Schwendener's views be correct, the lichens are produced by a symbiosis of fungi and algæ; and possibly this peculiar origin may account for the presence in their tissues of the depside group, which is so conspicuously scarce in the rest of nature.

Among the so-called moss acids, four have attracted more attention than the rest: orsellinic acid, $C_8H_8O_4$; the two isomeric acids, lecanoric and gyrophoric acid, $C_{16}H_{14}O_7$; and evernic acid, $C_{17}H_{16}O_7$. At the time Fischer began his work on these compounds, lecanoric and gyrophoric acid were believed to be built up from two molecules of orsellinic acid, since on careful hydrolysis this acid was obtained from them. Evernic acid was assumed to be some sort of ester-anhydride formed from one molecule of orsellinic acid and one molecule of its methyl ether, everninic acid. Fischer set himself to test these views by synthesis of the compounds, with the results which will be described in the present section.

In the first place, the structure of orsellinic acid had to be determined. This compound gives a purple-violet tint with ferric chloride and easily decomposes into carbon dioxide and orcinol. The ferric chloride coloration resembles that of salicylic acid; the production of orcinol gives the skeleton

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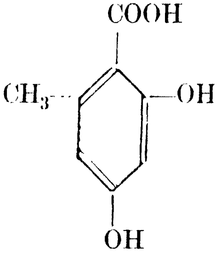
[1] Böttcher, *Ber.*, 1883, **16**, 629.

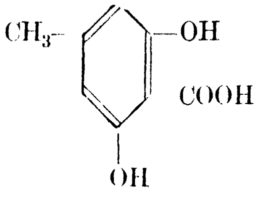
[2] Ransom, *Ber.*, 1898, **31**, 1055; 1900, **33**, 199.

[3] Fischer, Bergmann, and Lipschitz, *Ber.*, 1918, **51**, 45; Fischer, *ibid.*, 1915, **48**, 271; Fischer and Bergmann, *ibid.*, 1916, **49**, 290.

of the molecule ; so that orsellinic acid appears to be either (I.) or (II.) :

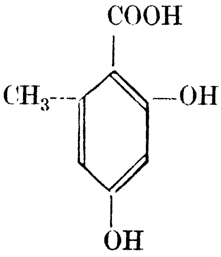


(I.)

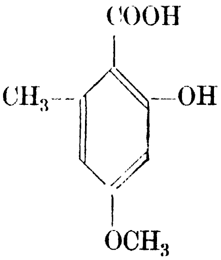


(II.)

Now everninic acid is a methyl ether of orsellinic acid. The structure (I.) permits the existence of two isomeric methyl ethers ; whereas since (II.) is a symmetrical molecule, only one methyl ether could be obtained from it. In practice, a second methyl ether, isomeric with everninic acid, has been prepared by acting on orsellinic acid with diazomethane and removing one of the methyl groups from the dimethyl ether thus produced. The existence of this second methyl ether establishes that orsellinic acid has the asymmetrical formula



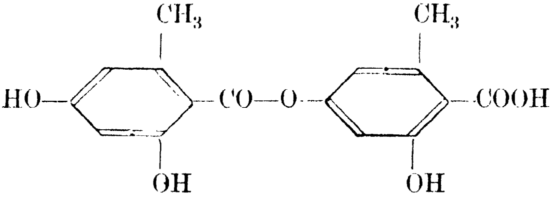
Orsellinic acid.



Everninic acid.

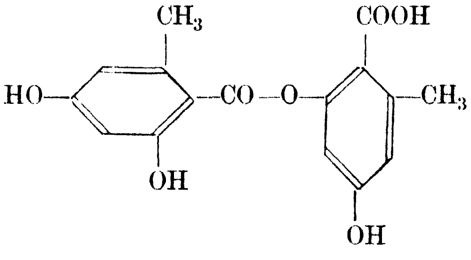
With regard to the structure of everninic acid, Fischer adduced the following evidence in favour of the formula shown above. In the first place, with ferric chloride it gives a strong reddish-violet tint like that of salicylic acid. Secondly, methylation of the phenolic acids with diazomethane takes place more readily in the *para*-position than in the *ortho*-position to the carboxyl group ; and the partial methylation of orsellinic acid, when only one hydroxyl is affected, yields everninic acid. Thirdly, similar reasoning suggests that when a carbomethoxy-derivative of orsellinic acid is formed, the carbomethoxy-group occupies the *para*-position. Methylation of the remaining hydroxyl and removal of the carbomethoxy-group leads to the isomer of everninic acid, which is what would be expected.

Fischer's next step was to condense dicarbomethoxy-orsellinic acid chloride with orsellinic acid. Since the choice is between condensation in the *ortho-* or the *para*-position, the well-known preference for *para*-condensation leads to the formation of the didepside structure shown below, after removal of the carbomethoxy-groups. On comparing this synthetic substance with natural lecanoric acid, the two were found to be identical, so that the structure of lecanoric acid is :



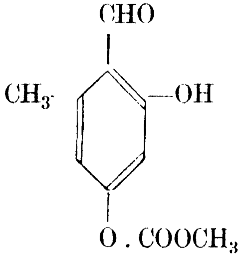
Lecanoric acid.

It will be remembered that an isomer of lecanoric acid exists, to which the name gyrophoric acid has been given ; and as it also is reported to yield orsellinic acid on hydrolysis, it seemed possible that it might be the corresponding didepside



which would arise from a *ortho*-condensation of the two orsellinic acid nuclei.

This compound was synthesized in the following manner. The monocarbomethoxy-orcyl aldehyde shown below



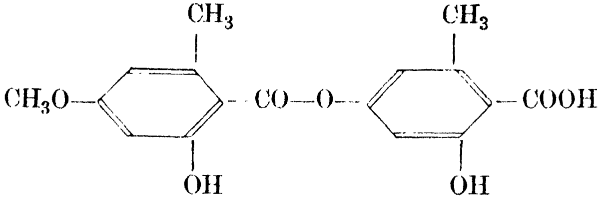
was coupled with the chloride of dicarbomethoxy-orsellinic acid in the usual way; and the aldehyde radicle was then oxidized to a carboxyl group by means of potassium permanganate. On splitting off the carbomethoxy-groups with ammonia, the *ortho*-didepside shown above was formed; but its properties were found to be entirely different from those of natural gyrophoric acid. This definitely establishes that gyrophoric acid is not a didepside at all, since it corresponds to neither of the only two possible structures for a diorsellinic acid.

The problem of the evernic acid constitution still remains to be considered. In this case, synthesis was not necessary, as the question could be cleared up more easily by another method.

On subjecting lecanoric acid and evernic acid to total methylation, Fischer found that the end-products were identical. Since lecanoric acid is a *para*-compound, this proves that evernic acid also is a *para*-didepside derivative, differing from lecanoric acid only in that it has a methoxy-group instead of one of the hydroxyl radicles of lecanoric acid.

Now the hydrolysis of evernic acid yields orsellinic acid and everninic acid. But, as we have seen earlier in this section, everninic acid has no free hydroxyl group in the *para*-position to the carboxyl; for this point is occupied by a methoxy radicle. Since this precludes *para*-coupling with everninic acid acting as a phenol, it is clear that in evernic acid, the acidic part of the molecule must be the everninic nucleus; while the phenolic portion is furnished by orsellinic acid, which has a free hydroxyl radicle in the required *para*-position. The formula for evernic acid must therefore be :

Evernic acid.



Everninic nucleus. *Orsellinic nucleus.*

7. *The Analysis of Tannin*

By 1913, Fischer's syntheses had resulted in the production of no fewer than twenty-eight didepsides, two tridepsides, and a pair of tetradepsides; and from the study of these substances he had gained clear ideas of the general properties of the depside class. To an ordinary investigator, a piece of research on this scale would have been an end in itself; but for Fischer it was a mere preliminary step towards the solution of a greater problem. In his depside researches he was clearing the ground on the road to the real objective which he had set before himself in this branch of chemistry: the elucidation of the constitution of tannin.

The scantiness of our accurate knowledge of tannin at this period has already been indicated in the first section of this chapter. It was not even known with certainty whether glucose did or did not form an integral part of the tannin molecule. Thus at the conclusion of the preliminary work on the depside syntheses, Fischer had to start from the foundation and subject tannin to analysis, in order to settle the question of its main constituents.

First, however, it was necessary to prepare pure samples of tannin, which was done by various methods.[1] Extraction of tannin from an alkaline solution by means of acetic ester proved in the end the most satisfactory process. But even after rigorous purification in this way, the tannin obtained could not be crystallized; so that definite proof of purity was lacking. However, since the same material was obtained from various samples of

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[1] Fischer and Freudenberg, *Ber.*, 1912, **45**, 919; see also Paniker and Stiasny, *J.*, 1911, **99**, 1819.

commercial tannin derived from different sources, it seemed most probable that the purified substance was homogeneous.

It should be noted that this mode of extraction would free the tannin from any substance containing a free carboxyl group; so the possibility of tannin being a glucoside of gallic acid * is straightway eliminated from consideration.

Fischer's next step was to study the hydrolysis of this most carefully purified tannin, by heating it for seventy hours with 5 per cent. sulphuric acid at 100° C. The results of a large number of tests and control-experiments led him to the conclusion that the tannin molecule on hydrolysis yields ten molecules of gallic acid and one molecule of glucose. No phenolic acid except gallic acid was detected among the hydrolysis products.

At this point, the tannin riddle appeared to be simpler than had been feared. Since glucose contains only five hydroxyl groups, it was evident that it could unite directly with only five acyl radicles. The ten gallic acid nuclei must therefore be so grouped as to present to glucose only five acyl radicles; which is the same thing as saying that some, at least, of them must be joined to one another in depside form. The simplest mode of combination would be to arrange them into five digallic acid chains; and on Fischer's view, tannin was simply glucose with its five hydroxyl groups esterified by five molecules of digallic acid. Thus at the end of his career, Fischer had come into a field upon which converged two of his earlier lines of research: the investigation of the sugars and the study of the depsides. It seemed a most favourable augury of ultimate success.

All that was now necessary to strengthen his hypothesis was to prove the presence of digallic acid among the fission products of tannin. But here, strangely enough, only complete failure awaited him. It seems that any agent which breaks the junction between digallic acid and glucose will simultaneously rupture the bond between the two nuclei of digallic acid itself; so that hydrolysis ends in a total disintegration of the complex molecule into its simplest constituents.

Herzig and his collaborators [1] had methylated tannin by

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* This is confirmed by Fischer's synthesis of β-glucosido-gallic acid (*Ber.*, 1912, **45**, 3773), which was found to be non-identical with tannin.

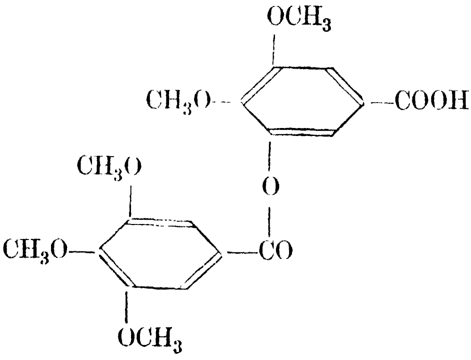
[1] Herzig and others, *Ber.*, 1905, **38**, 989; *Monatsh.*, 1909, **30**, 543.

means of diazomethane; and on hydrolysis their product yielded trimethyl-gallic acid and the unsymmetrical *meta-para*-dimethyl-gallic acid. This last fact shows that in the tannin molecule *meta*-digallic acid is the esterifier of the glucose hydroxyl radicles.

Since the analytical method had failed to establish the tannin constitution in which he believed, Fischer turned once more to his well-tried weapon of synthesis.

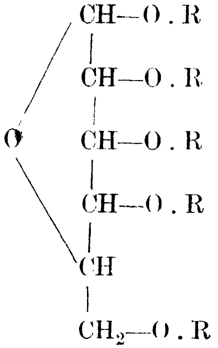
8. *The Penta-(m-digalloyl)-glucoses*

In the field of tannin syntheses, Fischer's first long step was the preparation of a completely methylated *m*-digallic acid:

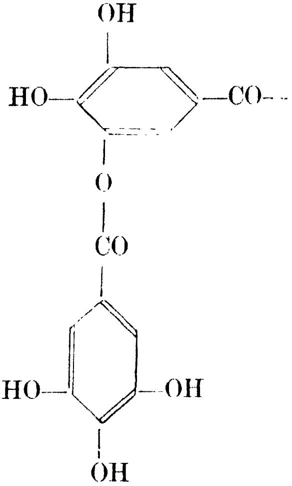


which he obtained by acting with trimethyl-galloyl chloride upon the *meta-para*-dimethyl ether of gallic acid. This methylated acid was then used for the complete esterification of the five hydroxyl groups of glucose, producing a substance known as penta-(pentamethyl-*m*-digalloyl)-glucose, two forms of which are known, corresponding to the α- and β-forms of glucose. This substance was expected to be identical with the compound which is formed when tannin itself is methylated with diazomethane.

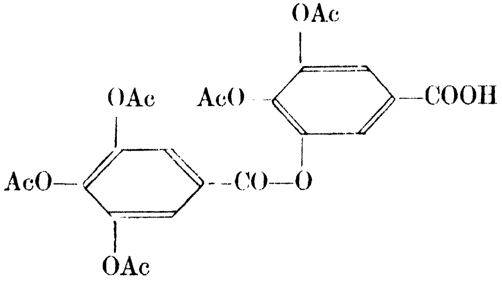
It may seem surprising that Fischer did not at once take up the synthesis of the parent substance instead of devoting time to the synthesis of the pentamethyl derivative. The reason lies in the fact that in this case the carbomethoxy method of shielding the hydroxyl radicles had been a failure, since it led to uncrystallizable compounds. But in a short time the acetylation method of protection came to its own in Fischer's laboratory; and by its help he was enabled to prepare the parent penta-(*m*-digalloyl)-glucoses which he surmised might be identical with natural tannin. The structure of these synthetic substances is shown below.



where R represents the group



On paper, at least, this synthesis is simple enough. *Meta*-digallic acid, the synthesis of which has already been described in the fourth and fifth sections of this chapter, was completely acetylated by treatment with acetic anhydride, yielding pentacetyl-*m*-digallic acid:



This was then converted into the corresponding acyl chloride by treatment with phosphorus pentachloride in presence of chloroform. This acyl chloride in slight excess was mixed with the proper quantity of glucose (either α- or β-variety) suspended in dry chloroform to which some dry quinoline had been added; and the mixture was mechanically shaken for two days. After standing for two days more, the mixture was diluted with more chloroform; the quinoline was removed by means of very dilute sulphuric acid; the residue was washed with water; and the chloroform was removed by distillation under reduced pressure.

Final purification was attained by repeatedly dissolving the solid material in chloroform and precipitating it therefrom with methyl alcohol. The ultimate product was a light colourless powder which was easily electrified by rubbing. The yield was surprisingly large for so complex a substance, being 87 per cent. of the theoretical in the case of the α-glucose derivative, and no less than 95 per cent. of the theoretical yield in the case of the β-derivative. A combustion of the material gave good results; and an estimation of the acetyl groups was also very close to the theoretical value; so that there can be no doubt as to the identity of the synthetic product.

The last stage in the synthesis consisted in freeing the compounds from their twenty-five acetyl groups. The acetyl derivatives were dissolved in acetone, cooled to zero, and then treated with sodium hydroxide solution. A hydrogen atmosphere was employed, to avoid any accidental oxidation by the air. After the completion of the hydrolysis, sulphuric acid was added; and the penta-[digalloyl]-glucose was extracted by shaking with ethyl acetate. On evaporating off the ethyl acetate, a syrup was left behind, which eventually solidified to a pale yellow-brown solid. This solid was dissolved in absolute alcohol and an alcoholic solution of potassium acetate was added. The potassium salt was thus precipitated as a thick, almost colourless precipitate. After further treatment with alcohol, this potassium salt was decomposed with sulphuric acid and the free penta-[digalloyl]-glucose was extracted by means of acetic ester. It proved to be a pale brown, amorphous substance. The yield was 80 per cent. of the theoretical.

A combustion showed good concordance * between theory

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* It should be noted that with substances of so complex a nature combustion results alone can hardly differentiate between two derivatives which are of nearly the same molecular weight.

and practice; but although chemically the substance was quite pure, it was physically non-homogeneous, since part of it was less soluble in cold water than the remainder. This rather extraordinary state of affairs seems to find its explanation in the semi-colloidal character of the material.

9. *Penta-(m-digalloyl)-β-glucose and Chinese Tannin*

On collating the properties of his synthetic products and those of certain natural tannins, Fischer detected the closest approximation in the case of Chinese tannin. Since this forms the crux of the whole problem, some space must be devoted to it here; and the chief resemblances between Chinese tannin on the one hand and penta-(*m*-digalloyl)-β-glucose on the other must be described in some detail.

(1) The depside derivative and Chinese tannin both show all the normal tannin reactions with gelatine, alkaloid salts, potassium acetate, and arsenic acid. No differences between them were noticeable in any of these respects.

(2) So far as organic solvents go, there is no noticeable difference in the solubilities of the two materials. In aqueous solution, the synthetic product is much less soluble; but this may well be due to a difference in colloidal state between the two substances.

(3) In organic solvents, the optical rotatory powers of the two materials are approximately the same, differing less from each other than the rotatory powers of two samples of a natural tannin derived from the same source. In aqueous solution, the differences are greater; and the synthetic material has a lower rotation than the natural tannin. Here again, however, the colloidal character may be playing a part.

(4) On hydrolysis with dilute sulphuric acid, natural tannin and the synthetic product give like quantities of glucose and gallic acid.

(5) Methylation of both bodies with diazomethane yields very similar products, having very similar optical rotatory power in various solvents.

(6) On acetylation with acetic anhydride and pyridine, both substances are completely acetylated. Estimation of the acetyl radicles in the natural compound gave exactly the same value

as in the case of the synthetic material. The optical rotations of the two acetyl-derivatives are close to each other ; and neither substance gives a coloration with ferric chloride. On hydrolysis, both the natural and the synthetic substances are regenerated intact.

(7) The compositions of corresponding compounds in the two series are identical so far as elementary analysis goes.

From the foregoing, it is self-evident that there is a very close kinship between Fischer's depside derivative and Chinese tannin ; and to that extent Fischer's hypothesis as to the nature of tannin is fully justified. If we were to go beyond this, we should be pressing the point further than Fischer himself thought justifiable ; for his own conclusion on the subject was couched in the most moderate terms. "On the other hand, there can be no question of a definite identification, since all the materials in question are amorphous and thus lack the surest tokens of homogeneity. Even the synthetic products, as I have repeatedly stated, are not homogeneous, since they are for the most part mixtures of stereoisomers."

10. *Compounds of High Molecular Weight*

One of the by-products of the depside investigations deserves mention here, if only under the guise of a chemical curiosity. Among the natural products there are many compounds of very high molecular weight, such as chlorophyll, hæmine, the proteins, and the celluloses ; but our knowledge of their structures is only sketchy, and even their molecular weights are not known with exactitude. In most cases the colloidal character of the material hinders any accurate molecular weight determination ; and inferences can be drawn only from the percentages of certain elements in the compounds. Thus, for example, by making assumptions as to the number of iron atoms in the molecule of oxyhæmoglobin, it is possible from the composition of the compound to make a guess that its molecular weight lies in the neighbourhood of 16,000 ; but even this is hardly more than a random shot.

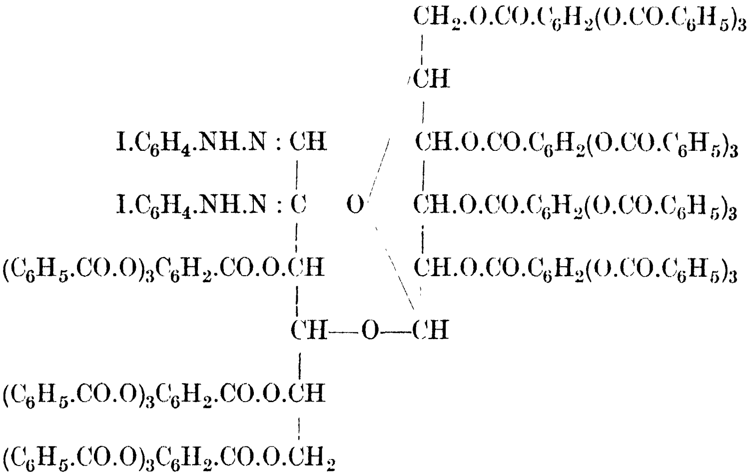
It will be remembered that in the course of his work on the polypeptides, Fischer synthesized the octadecapeptide, *l*-leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine, which has the formula $C_{48}H_{81}O_{19}N_{18}$ and a molecular weight of 1213. Now in the depside series it is possible to reach much higher stages if the depside radicles be coupled with sugar nuclei as in Fischer's attempted synthesis of tannin ; and in such cases the constitution of the final product is established by the steps in the synthetic process. Fischer thought it worth while to produce one or two of these extremely complex materials.

For this purpose, he chose as his basic reagent tribenzoyl-gallic acid, $(C_6H_5 . CO . O)_3C_6H_2 . COOH$, since this substance has the double advantage of being readily obtainable in quantity and yielding a crystalline, easily-purifiable chloride. Its molecular weight, 482, is already a high one ; so that by esterifying the acid with a sugar, a very massive molecule can be obtained.

Mannitol was the first sugar chosen for this purpose ; and the neutral ester obtained from it had a molecular weight of 2967. Compounds of this type, however, presented the difficulty that the combustion results did not serve to differentiate sharply enough between a fully acylated derivative and one containing fewer acyl radicles ; so that a definite proof of the constitution of the materials was lacking ; and as the substances are amorphous, no indisputable proof of homogeneity could be adduced.

To get round this, Fischer hit upon the idea of introducing into the molecule a definite number of halogen atoms, so that a halogen estimation would reveal the proportion of the halogen to the remainder of the structure and thus yield a gauge of the number of acyl groups present. This method was tested by esterifying the glucoside of tribromophenol with tribenzoyl-gallic acid, whereby tetra-(tribenzoyl-galloyl)-tribromophenol-glucoside was formed. From a bromine estimation, the number of tribenzoyl-galloyl groups in the molecule could be determined ; and the molecular weight was thus found to be 2349.

Fischer's final attack on the subject yielded a still more striking result. Maltose was treated with *p*-iodo-phenyl-hydrazine and *p*-iodo-phenyl-maltosazone was produced. This was coupled with tribenzoyl-galloyl chloride in presence of quinoline ; and the result was a hepta-(tribenzoyl-galloyl)-*p*-iodo-phenyl-maltosazone. The number of acyl radicles in the molecule was determined by an estimation of the iodine percentage, which gave such sharp results that no doubt was left as to the homogeneity of the material. Assuming the structure of maltose to be one of the alternatives accepted at present, the formula of this new gigantic molecule can be represented thus :



Hepta-(tribenzoyl-galloyl)-*p*-iodophenyl-maltosazone.

This formula corresponds to $C_{220}H_{142}O_{58}N_4I_2$, and the compound has a molecular weight of 4021. It is over three times as heavy as Fischer's most complex polypeptide and is by far the most massive molecule yet synthesized with a known structure.

The compound is an amorphous, clear-yellow powder, very slightly soluble in alcohol and ligroin, easily soluble in acetone, chloroform, and benzene. It begins to decompose at about 145° C., and at 160° C. it is converted into a red liquid. An attempt was made to determine its molecular weight cryoscopically, with bromoform as a solvent ; but great difficulty was found in removing the last traces of the solvents with which the material had been purified, since these were hard to drive out of the amorphous body. The molecular weight results gave an average of 3503 instead of 4021. When the experimental difficulties of purification are taken into account, this seems a very good result, and it certainly shows that the freezing-point method is not completely at fault even in extreme cases like this, since it at least enables us to say that the substance is monomolecular.

11. *Conclusion*

The foregoing survey of the depside field has necessarily been a restricted one, owing to the exigencies of space; but even so, enough has been said to call attention to some of the interesting problems which Fischer's work suggests. A really fruitful research is marked by the manner in which it raises questions extending far beyond the original subject-matter; and when judged by this criterion, the work on the depsides has been more than usually fertile. Fischer[1] himself has pointed to some of these associated problems; and a summary of his views can be given here.

From the alcoholic nature of the sugars, it is obvious that they can form esters with the organic acids; and the acetylation and benzoylation of the sugar group members is well-known. Fischer's work, however, gave a great extension to our knowledge in the matter; and this extension brings with it some fresh ideas. Hitherto, the esters detected in living tissues have been in the main derived from the simple alcohols or from glycerine. The living organism in general shows a remarkable aversion to the presence of free acid, except in certain restricted regions such as the rind of fruits or the stomachs of animals; and as a result, there is a biochemical striving towards neutralization. Sometimes this takes the form of salt-formation; more commonly amide-formation is observed; and, in the fats, esterification is used to rid the organism of the irritant carboxyl radicle.

Fischer pointed out that hitherto attention has been concentrated upon the esters of simple alcohols or the glycerides; but his work in the depside field opened up wider prospects. Not merely the phenolic acids but all hydroxy-acids of the fatty series are evidently capable of esterifying the sugars; and sensitive esters of this type might quite well escape notice owing to the readiness with which they can be hydrolysed. He suggested that such esters might be sought in those sweet fruits which contain notable quantities of glycollic acid and its congeners. Further, the unequal distribution of the acids between the rind and the inner tissues of certain fruits seems to suggest a further field of investigation for the future.

To these problems raised by Fischer, another may be added.

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[1] Fischer, *Ber.*, 1913, **46**, 3253.

How does it come about that the depsides occur so plentifully in one particular type of plant-life? The rarity of the depsides in general, as compared with the profusion of the proteins in nature, can perhaps be accounted for on lines already suggested on an earlier page. Amide-formation depends upon the combination of dissimilar groups, whilst in the esterification of a phenolic acid two groups of a much less unlike character are being linked together. But this serves only to make the case of the natural depsides still more strange; for it is difficult to see why, when they do occur, the plant should produce such relatively enormous yields as are indicated by the high percentage of tannin in galls. Nor does it account for the limitation of the sources of the natural depsides. In this last connection, one point may be suggestive. Every one knows that mosses grow best in dimly-lit localities; whereas the ordinary plant flourishes only in a good light. Now the normal plant is engaged in building up cellulose, whereas the moss synthesizes a large proportion of depside which is not found in the normal vegetable. Is it beyond the bounds of possibility that there is some connection between these facts; and that photochemical action plays its part in the problem?

These speculations, and others which will doubtless occur to the reader, serve to indicate the wide range of problems which are raised by the existence and distribution of the depsides. Undoubtedly this class of substances will provide many subjects of investigation to any one who can take a view which is not bounded by chemical formulæ.

CHAPTER X.

SOME THEORIES OF THE NATURAL SYNTHESES OF VITAL PRODUCTS *

1. *Introductory*

WHEN we survey that portion of organic chemistry which deals with compounds derived from natural sources, it is impossible to overlook the fact that, although many of these substances can be synthesized in our laboratories, the methods which we employ there differ entirely from those which are utilized in the natural production of the same substances by physiological or phytological means.

The first great difference between the lines of syntheses is found in the ranges of temperature employed in the two cases. In the plant or in the animal body, the reactions which build up extremely complicated products take place, obviously, within very narrow temperature limits; whilst in our laboratories the temperature conditions may vary from one another by as much as 300° C. Not only so, but we press into our service reagents of such instability and reactive power that it is impossible to conceive their coming into existence at all in the animal or vegetable kingdom.

It may be argued that this is only natural. After all, our object in laboratory practice is to obtain the best yield in the shortest time; and a resort to natural methods may be regarded with the same distaste as might be shown by a traveller from London to Inverness at the suggestion that he should tear

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* When this chapter was under consideration, Professor Collie, at my request, sent me a communication embodying some of his views on the subject; and these appeared to me to necessitate the re-writing of the major part of the chapter on the basis of his notes. To avoid continual reference to this private communication and at the same time to indicate his share in the matter, I have placed a † at the beginning of each paragraph which is derived from his notes.—A.W.S.

up his first-class railway ticket and perform his journey on foot. But on the other side there is something to be said also. Very little is as yet known about vital syntheses; and it is quite possible that the methods adopted by the living machine, when we come to understand them, may be simpler and more efficient than our present-day laboratory reactions. Even if this view proves to be erroneous, there can be no doubt that attempts to throw light upon plant and animal methods will broaden our outlook upon organic chemistry as a whole; for at present organic chemists, almost without exception, leave this branch of the subject severely alone.

† One reason for this abstention is perhaps to be found in the manner in which our chemical literature is compiled. In the textbooks of the subject, the naturally occurring substances are not grouped according to their place of origin but are arranged under the headings of alcohols, acids, etc., and are scattered about the literature merely to fill up gaps in long lists of artificially prepared compounds.[1] Organic chemistry of to-day is not properly organic chemistry at all, but has swollen into a chemistry of thousands of carbon compounds which do not occur in nature. Many of these synthetic compounds are the result of the immense industry of chemists who have been misled by the idea that a new compound must necessarily be interesting; and also of the very narrow outlook of certain other chemists who think that a graphic formula is the be-all and end-all of the science.

† Of course the chief reason why in textbooks we find so little information about " how " and " why " certain compounds are produced in plants and animals is because we do not know the answers to the questions involved. In the plant, for example, there appears to be no step-by-step process for making more and more complex materials, as we do in the laboratory. Carbon dioxide, water, and nitrogen, combined or otherwise, are absorbed by the green plant in sunlight. The first substances which can be isolated from the reaction products are sugars, the next ones are the highly complex starches, celluloses, and proteins. All the organic compounds such as acids, esters, fats, colouring

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[1] Haas and Hill's *Chemistry of Plant Products* gives an excellent survey of the " organic " field, and should be consulted by any one who desires to go further into the subject.

matters, and alkaloids are most probably formed by a down-grade process: a decomposition of the starches, celluloses, and proteins. The chemist in his laboratory seeks to make these compounds by syntheses from simpler bodies; the plant appears to produce them by a reverse operation from stored-up material of an extremely complex molecular structure.

† Some of these down-grade processes can be followed to a certain extent in the laboratory. Celluloses, starches, and proteins can be hydrolysed, oxidized, or otherwise decomposed. But our methods, as a rule, are too violent; and the fine grades of reaction which take place slowly at ordinary temperatures in plants have, up to the present, defied imitation in the laboratory.

† Nevertheless we must not lose sight of the fact that although natural reactions often *seem* to operate in a way quite different from laboratory reactions, yet both sets must obey the same laws. Therefore, if we find that in the synthetic processes of our laboratories certain lines are followed under conditions which could exist in plants, we are not far wrong in assuming that, in the down-grade processes of nature, the same general direction will be taken in the formation of products.

† Another point arises here. All reactions which are likely to be employed in vital syntheses are reversible; and hence if they be carried out in glass test-tubes they must come to an equilibrium point, except in those cases wherein gaseous products are formed. How, then, does the plant succeed in producing its high yields of certain substances which, in a test-tube, would be formed only in minor quantities from the same reagents? When we examine the living plant, we are at once struck by the wonderful mechanism of the natural chemical laboratory which we find there. It is a system of test-tubes made of cellulose and differing from ordinary test-tubes in that the walls are constructed from semi-permeable membranes. Each cellulose test-tube is immersed in a solution differing from that which is contained within the cellulose vessel. The membrane acts not only as a container, as the glass test-tube does, but in addition it behaves as a filter, a concentrator, or a separator. Thus during the progress of a down-grade reaction in which a complex molecule is broken up into constituent parts, the cellulose wall permits a certain product to accumulate in one part of the plant whilst a mixture of other compounds

may be withdrawn to a different region. In this way the ordinary equilibrium stage of the reaction is evaded; and much higher yields may thus be attained.

† But what starts this down-grade process? Once the plant has synthesized its starches, etc., why are these substances not stable, as they are when we place them in bottles in a chemical museum? To answer this question we must know how the plant grows; and what is meant by a living material as opposed to dead matter. The differences between the two are much too marked to allow of dispute.

† When a crystal grows in a solution, we may regard the process as the first glimmering of individual life in that particular substance. Infinitely more complex is the growth of protoplasm from carbon, hydrogen, nitrogen, and oxygen; the smallest particle of protoplasm is inconceivably greater than the atoms from which it has been built up. Still more complex is the growth of a plant from the seed. In all these cases a directive agency seems to be at work. Whether further investigation will or will not show that all these phenomena can be explained by purely chemical and physical laws, time alone can show; but it is quite certain that at present the only scientific course is to admit that we do not know. The chemical reactions which take place in the living plant are in certain respects so different from those which go on in the laboratory that we are forced to recognize the action of some subtle agency which, up to the present, we have been unable to imitate.

† Let us return to the degradation of the starches, celluloses, and proteins. The plant, under the action of sunlight, has stored these substances in its body and has grown to its full size. The directive force begins to get exhausted; the plant is growing old; most of its starches are now used up; and the celluloses and proteins are beginning to undergo more and more rapid decomposition. The down-grade process has set in with increasing velocity. The plant is still alive, but the system is losing instead of gaining energy. Fermentations have begun; but fermentations will only explain a part of the process, for they are catalytic reactions which would, normally, reach their equilibrium stages whether the plant were young or old. The enzymes causing them are chemical reagents which enable part of the stored-up energy in the plant to be set free again; but the

actual disturbance of equilibrium is due to the separation and segregation of the reaction products by the semi-permeable membranes.

It seems not impossible that the later stages in the life-history of a plant are brought about by some change in the nature of its cell-walls, akin, perhaps, to the ossification of arteries which sets in within the animal body under somewhat similar conditions. If, at this stage, the cells ceased to act as semi-permeable membranes, the whole machinery of the plant would become choked with by-products, and the natural changes which are necessary in living matter would gradually come to an end.

† During the growing phase of the plant, starches, cellulose, proteins, and enzymes are produced ; but as the plant ages, the growing energy lessens, the enzymes get the upper hand and prey upon the substance of the plant. They are the parasites which finally kill their parent.

† Considering the importance of the ferments in the scheme of nature, it is extraordinary to notice how very briefly they are referred to in most textbooks of organic chemistry ; [1] and the textbook reflects to a great extent the outlook of the average organic chemist. It is hardly to be wondered at if the new generation of organic chemists, trained by such methods, becomes imbued with an almost superstitious reverence for the deluge of organic compounds which have been spawned in thousands in chemical laboratories for, apparently, no useful purpose whatever.

2. *The General Course of Vital Syntheses and Degradations*

† When the action of the living machine is considered in its broadest aspects, there seems to be no doubt that it can be regarded as divisible into two opposed processes. In the first group come the synthetic reactions by means of which the products assimilated by the plant or animal are converted into extremely complicated celluloses and proteins ; whilst in the second class are placed those decompositions and changes which convert the celluloses and proteins into simpler substances.

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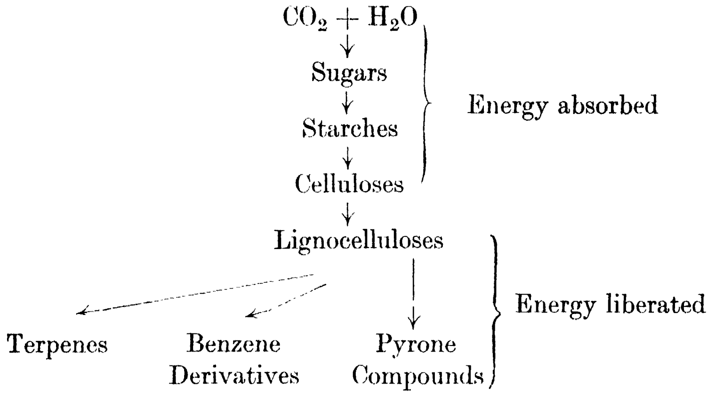
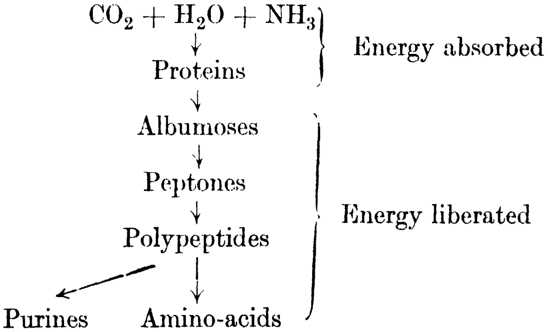
[1] Haas and Hill, in their *Chemistry of Plant Products*, give a very good summary of the nature of enzymes and their action in plants. See also Bayliss, *Nature of Enzyme Action*.

The first series of reactions are probably carried on with the absorption of external energy; the second group comprises reactions which liberate this energy once more. It may be convenient at this point to give a table indicating the course of vital action in the two cases:—





In the cellulose synthesis, the reactions lead to the formation of long chains built up from sugar molecules; for hydrolysis of cellulose yields simple carbohydrate derivatives almost unaltered. In this case—after the initial production of formaldehyde—the reactions are obviously quite uncomplicated and appear to be simple polymerization and dehydration.

The transformation of the celluloses into lignocelluloses is evidently more complex, as the latter compounds appear to contain cyclic nuclei of various types; and from them the aromatic and heterocyclic substances formed in plants may be produced by a series of degradation reactions.

Turning to the proteins the same holds good in general. The first stage must be the formation of simple amino-compounds which have not yet been isolated and proved to take part in the synthesis. From these, by dehydration, the proteins are formed. After this, fermentation yields simpler substances which are classed as albumoses. Further degradation yields peptones, which are closely akin to the albumoses; and finally the material breaks down into polypeptides and simple amino-acids.

3. *Possible Reactions in Vital Syntheses*

In attempting to deduce the actual processes which lead to the formation of natural products, we are faced by two facts. In the first place, we are able to rule out as impossible such reactions as depend upon high temperatures and violent reagents; but, in the second place, we are not entitled to assume that, because up to the present we have not succeeded in making a reaction "go" at ordinary temperatures, it is therefore impossible for such a reaction to proceed effectively under these conditions. The safest course is obviously to confine ourselves as far as possible to reactions involving mild reagents and capable of proceeding economically at ordinary temperatures; though at the same time we need not exclude other reactions entirely.

Limiting ourselves thus, the choice before us is by no means so restricted as might at first be expected. Polymerization, condensation, hydrolysis, hydration and other addition reactions, dehydration, oxidation, reduction, and intramolecular change are all reactions which are known to be capable of taking place at ordinary temperatures.

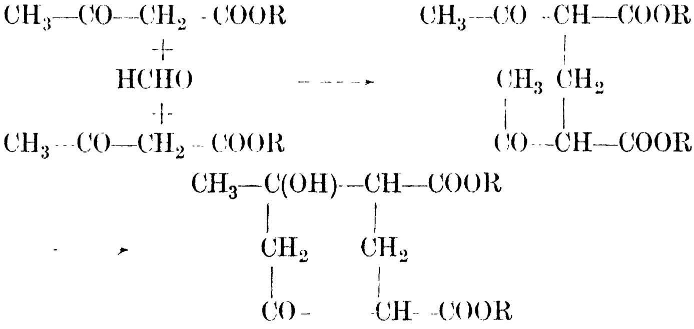
With regard to polymerization the data are too numerous to need reference in detail. The polymerization of aldehydes, the production of truxillic acid from cinnamic acid under the action of light, the conversion of ethylene into higher hydrocarbons and the synthesis of rubber from isoprene are too well known to render it necessary to discuss them.

When we come to condensation the matter demands a more careful scrutiny; for various types of reaction are involved, each of which has its particular application to the problem before us.[1]

The aldol condensation [2] can be carried out with the help of traces of foreign materials; and it is noteworthy that among these catalysts are to be found salts such as the acetates, carbonates, and bicarbonates of the alkalis, all of which might be found in the saps of plants.* Now the aldol condensation not only provides a means whereby carbon chains may be formed from shorter groups:

$$CH_3 . CHO + CH_3 . CHO = CH_3—CH(OH)—CH_2—CHO$$

but in addition it also gives rise to carbocyclic derivatives: [3]



The benzoin condensation might also be reckoned as a probable vital reaction, for, although it is usual to employ heat in the laboratory, it seems evident that this condensation proceeds at ordinary temperatures at a slower rate.

The second class of condensation under consideration includes those reactions in which ammonia molecules or their substitution products take part. Of these, apart from amide formation the most important is the production of amino-alcohols from aldehydes:

$$R—CH:O + NH_3 = R—CH(OH)—NH_2$$

An intramolecular application of this reaction, in which an

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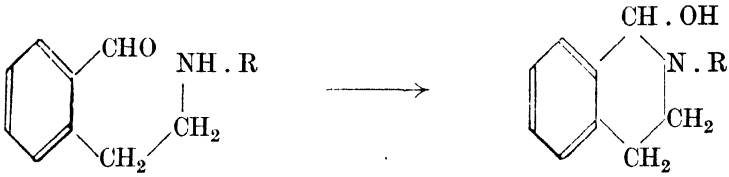
[1] See Baeyer, *Ber.*, 1870, **3**, 63.

[2] See Robinson's suggestions on this point (*J.*, 1917, **111**, 876); compare Raper, *J.*, 1907, **91**, 1831.

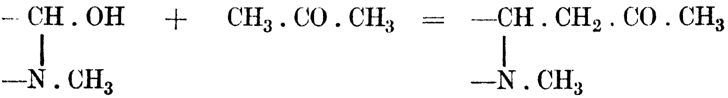
* The actual catalyst may be the hydroxyl ion.

[3] Rabe, *Annalen*, 1908, **360**, 265.

amino-aldehyde is employed, leads to ring-formation and the production of an amino-alcohol of the following type:—

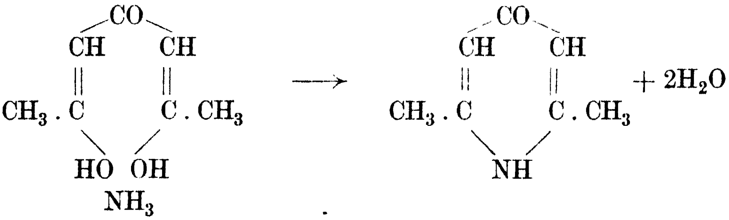


And, as Robinson[1] has shown, these amino-alcohols react readily in aqueous solutions with ketones, producing new derivatives by the elimination of water:



$$\begin{array}{l} -\mathrm{CH.OH} \\ \quad | \\ -\mathrm{N.CH_3} \end{array} + \mathrm{CH_3.CO.CH_3} = \begin{array}{l} -\mathrm{CH.CH_2.CO.CH_3} \\ \quad | \\ -\mathrm{N.CH_3} \end{array}$$

Different in nature is the ring-formation produced when such substances as diacetylacetone are treated with ammonia.[2] Here one molecule of ammonia interacts simultaneously with two hydroxyl radicles—the ketone enolizing—in order to produce a derivative of pyridine:



Turning to the question of hydrolysis, it is unnecessary to dwell at length upon the ordinary reactions. Attention must be drawn, however, to the fact that the same reagents may produce different end-products according to the conditions employed. Thus acetoacetic ester derivatives may yield either a ketone or an acid in addition to acetic acid, in the ordinary acetoacetic ester synthesis.

The most important reagents in this field, however, are the enzymes; and it may be worth while to deal with their action

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[1] Robinson, *J.*, 1917, **111**, 876.

[2] Collie, *J.*, 1907, **91**, 1806.

in more detail. For the hydrolysis of the proteins, two classes of enzyme are known, which are termed proteolytic. The pepsin group attack albumins only in weak acid solutions, converting them into albumoses and peptones, which are soluble albuminous compounds of complicated structure. The trypsin group, on the other hand, act only in neutral or weakly alkaline solution. A third class of enzymes, the labenzymes, have the faculty of coagulating protein compounds and are therefore termed coagulating enzymes. To some extent a fourth type of enzyme might be included in this section, since its reaction resembles those of the proteolytic class in so far that it depends upon the hydrolysis of the amide group. This last type has the faculty of breaking down urea and uric acid derivatives. The lipolytic enzymes are utilized to break down fats, from which they liberate glycerine. They appear to react best in acid solution.

Several enzymes are known which can be employed to hydrolyse such materials as starch; and the progress of the hydrolysis depends upon the enzyme chosen. Thus when diastase acts upon starch it converts it into soluble material and breaks it down eventually to simple carbohydrates, the end-product being maltose, $C_{12}H_{22}O_{11}$. The application of maltase carries the process a stage further, two molecules of glucose being formed. Cane-sugar is broken down by invertase to glucose and fructose.

In all these cases, of course, the enzyme acts merely as a catalytic agent and has no influence upon the equilibrium point. Thus, as has been mentioned in a previous chapter, chlorophyllase may be employed either to hydrolyse a phytyl ester or to replace the phytyl radicle by an ethyl group.

Under the head of addition reactions it is only necessary to mention one or two processes. Among the unsaturated compounds, and especially in the terpene group, water can be added on to double bonds at ordinary temperatures when acids are present.[1] Apparently the reaction takes place in two stages: a molecule of acid first attaching itself to the double linkage in order to form an ester which is then hydrolysed, leaving an alcohol.

Under ordinary conditions also, ammonia has the faculty

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[1] Wallach, *Annalen*, 1908, **360**, 102.

of attacking certain ethylenic linkages. Thus mesityl oxide takes up a molecule of ammonia to form diacetonamine :

$$(CH_3)_2C:CH.CO.CH_3 + NH_3 = (CH_3)_2C(NH_2).CH_2.CO.CH_3$$

Dehydration is a reaction capable of almost endless applications in the field of vital chemistry. Saturated compounds may be converted into unsaturated derivatives ; carbon chains may be formed, as in the mesityl oxide and phorone syntheses ; benzene derivatives and heterocyclic substances such as pyrones can be prepared without exceeding ordinary temperatures. Indeed, it seems probable, though not yet proved, that a large proportion of vital syntheses depend upon successive dehydrations and rehydrations, by means of which the structure of the molecule can be altered.

As to oxidation and reduction, no doubt can be entertained as to the prominent part taken by them in vital reactions. As far as oxidation goes, we are acquainted with numerous enzymes (oxidases) which act as agents in the reactions of living tissue ; and though the nature of the corresponding reducing enzymes, the reductases, has not been fully studied, there seems to be no question about their existence. Apart from enzyme action, numerous cases of spontaneous oxidation are known to the organic chemist, such as the formation of indigo from indoxyl and the production of oxyhæmoglobin from hæmoglobin.

Intramolecular change is a branch of the subject which it is hardly necessary to treat in detail ; but the pinacone change, the Beckmann rearrangement, and the benzilic acid change may be mentioned, since they may serve to throw light upon vital reactions. The most important of all is the keto-enol rearrangement ; but this will be fully described in a later section.

In Volume I. of this book we have already encountered some examples of an intramolecular rearrangement which is of the greatest importance from the point of view of natural terpene syntheses : the formation of cyclic compounds from open-chain di-olefinic derivatives. The cases of citronellal and isopulegol ; rhodinal and menthone ; citral and cyclo-citral ; and the conversion of geraniol, nerol, and linalool into terpineol, are examples of the type to which we refer. These changes take place either spontaneously or under the influence of alkali or acid ; and it seems not improbable that some such rearrangement leads to the production of terpenes in nature.

Among natural products, methylamine derivatives occur ; and it appears probable that these are formed by the action of formaldehyde :—

$$2NH_3 + 3CH_2O = 2NH_2 . CH_3 + CO_2 + H_2O$$

In laboratory practice the reaction takes place even at the temperature of a water-bath ; so that it evidently can be carried out, though slowly, under ordinary conditions.

Photochemical effects must, of course, play a very striking part in vital processes, especially in the vegetable kingdom. Of these, the most important from the theoretical standpoint is the discovery by Cotton [1] that the dextro- and lævo- forms of tartaric acid absorb *d*-circularly polarized light to different extents ; which implies that such light will decompose them at different rates. Now since light is circularly polarized by the surface of the sea, we have a natural method whereby the production of unequal quantities of asymmetric material can be attained ; and once the balance between the two isomers is thus disturbed, the general production of optically active compounds becomes possible. It may be that these experiments indicate the manner in which optically active substances first made their appearance on the earth's surface.

4. *The Production of Carbohydrates*

Since the carbohydrates form so large a proportion of plant tissues and so important a group of animal foodstuffs, it is natural that much speculation has been directed to the question of how these materials come into existence as a result of biochemical syntheses. As to the source from which the carbon is drawn, there is no dispute : the living plant is believed to obtain it from the surrounding atmosphere in the form of carbon dioxide or carbonic acid.

Strangely enough, the next stage in the process is the one which has given rise to most controversy, and even at the present day there is much dispute as to the exact mechanism involved in the

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[1] Cotton, *Ann. Chim. Phys.*, 1896, VII., **8**, 373.

changes which undoubtedly take place.[1] It will suffice here to indicate some of the suggestions which have been put forward.

The simplest hypothesis rests on the assumption that water and carbon dioxide may undergo a process of mutual oxidation and reduction.

$$H_2CO_3 + 2H_2O \rightleftharpoons H\,.\,CHO + 2H_2O_2$$

If, now, an enzyme were present in the plant which has the power of decomposing hydrogen peroxide,[2] the reaction's main course would be from left to right in the equation above, and a steady production of formaldehyde would occur in the leaf. The energy required to furnish driving-power in the reaction must be drawn originally from solar radiation; but the immediate cause of the transformation might possibly be found in the electrical conditions on the leaf-surface.[3] Unfortunately for this view, the presence of hydrogen peroxide in leaves [4] has not been confirmed.[4]

Another hypothesis [5] depends upon the assumption that hydroxylamine plays a part in the process. This hydroxylamine is supposed to be present in the leaf as a result of the reduction of nitrates absorbed by the plant as part of its nutriment. The reactions postulated are as follows:

$$\begin{aligned} CO_2 + NH_2OH &= H\,.\,CHO + HNO_2 \\ 2CO_2 + 2NH_2OH &= CH_2(OH)\,.\,CHO + 2NHO_2 \end{aligned}$$

These products have actually been detected in the leaves of the elder. Now the glycollic aldehyde formed in the second reaction is assumed to be reduced to acetaldehyde; and a further stage of carbon dioxide absorption ensues, yielding lactaldehyde:

$$CH_3\,.\,CHO + CO_2 + NH_2OH = CH_3\,.\,CH(OH)\,.\,CHO + HNO_2$$

These materials exist in the leaves of the poplar. Obviously processes of this sort might be utilized to explain the production of complex carbohydrate structures.

[1] See Jörgensen and Stiles, *Carbon Assimilation*; Meldola, *J.*, 1906, **89,** 745; Moore, *J.*, 1921, **119,** 1555; Haas and Hill, *The Chemistry of Plant Products.*

[2] Loew, *Ber.*, 1902, **35,** 2487.

[3] Gibson, *Ann. Botany*, 1908, **22,** 117.

[4] Molisch, *Biochem. Z.*, 1921, **125,** 257.

[5] Mazé, *Compt. rend.*, 1921, **172,** 173.

Willstätter and Stoll,[1] from a study of chlorophyll, arrived at the following conclusions. Chlorophyll acts not only as a sensitizer in photochemical reaction, but it plays a direct part in the break-down of carbonic acid. A stage in the process is the formation of a labile addition-product of chlorophyll which may be built up either from carbonic acid itself or from one of its derivatives. According to Willstätter and Stoll, the action of light is to loosen the bonds of the carbonic acid molecule and thus bring about isomeric change into per-formic acid or formaldehyde peroxide. By enzymatic action, these compounds then lose some of their oxygen. Whether formaldehyde is the actual product of the process is left in doubt; for even the detection of formaldehyde in the leaf is not sufficient to show that it is an intermediate-product in assimilation, since it might also occur as a result of reactions totally unconnected with the reduction of carbonic acid.

Somewhat similar views of the mechanism were put forward by Spoehr and McGee,[2] whose results indicate that the leaf contains something which chemically absorbs carbon dioxide and which they believe to be a protein.

An hypothesis which inverts the usually accepted sequence of things is due to Wo. Ostwald,[3] who suggests that the photochemical reaction is one of photo-autoxidation instead of photo-reduction. He assumes that the first stage in the process takes the form of the production of a compound of a protein with carbon dioxide. This is accompanied by the autoxidation of a lipoid with the formation of a lipoid peroxide which is sparingly soluble in water.[4] Interaction of the protein-carbon dioxide compound and the lipoid peroxide in presence of water is supposed to lead to the production of formaldehyde and oxygen; and the lipoid-peroxide is regenerated by autoxidation. The whole process is supposed to take place at a protein-lipoid boundary surface. On Ostwald's hypothesis the part played by chlorophyll is simply that of a promoter in the autoxidation of the lipoid.

Turning to purely photochemical experiments, the evidence

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[1] Willstätter and Stoll, *Untersuchungen über die Assimilation der Kohlensäure* (1918).

[2] Spoehr and McGee, *Science*, 1924, **59**, 513.

[3] Wo. Ostwald, *Kolloid-Z.*, 1923, **33**, 356.

[4] Compare Gallagher, *Biochem. J.*, 1923, **17**, 515; 1924, **18**, 29, 39

proves somewhat confusing. Usher and Priestley[1] reported that by exposing a saturated solution of carbon dioxide in a quartz tube to the action of ultra-violet light they obtained an easily recognizable quantity of formaldehyde, mostly in the polymerized form. Berthelot and Gaudechon,[2] on the other hand, were unable to detect formaldehyde as an end-product of the action of ultra-violet light on carbonic acid except when hydrogen was present. This was supported by the work of Stoklasa.[3] Baly, Heilbron and Barker[4] state that formaldehyde may be produced from carbon dioxide and water by purely photochemical means. According to their results, formaldehyde is formed in aqueous solutions of carbon dioxide under the influence of light of short wave-length ($\lambda = 200\mu\mu$) as well as by visible light in presence of visibly coloured substances which have the power of forming labile additive compounds with carbonic acid. Spoehr[5] has been unable to confirm these results.

If it be assumed that formaldehyde is the primary product in the course of carbohydrate syntheses, two questions present themselves immediately. (1) Can the plant tolerate formaldehyde? (2) How is formaldehyde converted into its higher polymerides?

With regard to the first question, formaldehyde is undoubtedly a poison for some of the lower plant organisms; but it can be assimilated by others[6]—*e.g.*, the Tropæolum majus[7]—without injury. And in any case, if the polymerization of the aldehyde proceeds at a velocity comparable to that of its synthesis, there is no need to assume that at any moment there will be more than a trace of the poison present in the plant-organism. This is justified by the fact that it was only with great difficulty that the presence of any formaldehyde in the leaf could be established,[8] which indicates that the aldehyde must be polymerized almost immediately after its formation.

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[1] Usher and Priestley, *Proc. Roy. Soc.*, 1911, **84**, *B*, 101.

[2] Berthelot and Gaudechon, *Compt. rend.*, 1910, **150**, 1690.

[3] Stoklasa, *Monatsh.*, 1911, **32**, 53; *Biochem. Z.*, 1912, **41**, 333.

[4] Baly, Heilbron and Barker, *J.*, 1921, **119**, 1025.

[5] Spoehr, *J. Amer. Chem. Soc.*, 1923, **45**, 1184; compare Baly, Heilbron and Barker, *Nature*, 1923, 112, 323.

[6] Sabalitschka and Riesenberg, *Biochem. Z.*, 1924, **144**, 545, 551; **145**, 373.

[7] Jacoby, *Biochem. Z.*, 1922, **128**, 119.

[8] Gibson, *Ann. Botany*, 1908, **22**, 117.

It is now necessary to consider the second problem and see what sort of mechanism can be suggested for the conversion of formaldehyde into its higher polymers. In earlier days it was believed that cane-sugar was the first recognizable carbohydrate produced by carbon assimilation in the plant;[1] but more recent investigations[2] lead to the conclusion that sucrose alone is detectable in the non-green parts of variegated leaves, whilst in the green parts monoses were discovered. Further, when full-grown leaves of pelargonium were entirely depleted of sugar by keeping the plants in the dark and were subsequently exposed to light, the first sugars identified were monoses; and it was only later that sucrose and starch were formed. From this it seems that monoses are really the first products, and that the appearance of sucrose is a secondary stage in the process.

The polymerization of formaldehyde to fructose was long ago shown to be brought about by the action of calcium hydroxide in dilute solutions;[3] and Baly, Heilbron and Barker, by acting on a solution of carbonic acid with ultra-violet light, obtained a product which was examined by Irvine and Francis[4] and found to contain about 10 per cent. of a hexose.

These results, though interesting in themselves, have little bearing on the actual production of the carbohydrates in the living plant; for the laboratory-produced sugars are racemic, whereas the products of biochemical action are optically active. This fact differentiates the two processes in a decisive manner since it shows that in the phytological production of the sugars an asymmetric agent comes into play at some stage in the action.

Two possible explanations suggest themselves for the occurrence of the active sugars. In the first place, the agent which stimulates the polymerization of the formaldehyde may itself be asymmetrical (an enzyme); and thus one enantiomorph may be formed in greater quantity than the other: or possibly the racemic sugar is produced by direct methods and is then

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[1] Brown and Morris, *J.*, 1893, **62**, 604.

[2] Weevers, *Proc. K. Akad. Wetensch. Amsterdam*, 1924, **27**, 46.

[3] Loew, *J. pr. Chem.*, 1886, **33**, 321; Fischer and Passmore, *Ber.*, 1889, **22**, 359.

[4] Irvine and Francis, *J. Ind. Eng. Chem.*, 1924, **16**, 1019.

acted upon by a selective enzyme such as are common in plants, with the result that one antipode is more rapidly decomposed than the other. In either way a preponderance of one active form would result. It must be frankly admitted that even in this simple problem we can only say that we do not know the true solution.

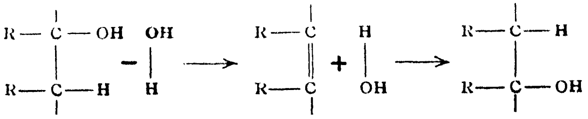
With the production of sugars of the hexose type, however, the main difficulties are ended : for by the action of enzymes these can be converted into much more complex materials, the polysaccharides ;[1] and even higher complexes such as dextrin can be produced from the hexoses by catalytic means. As to the further stages by which cellulose and its analogues are formed, we can only admit our ignorance ; though the fact that these substances can be reduced to simpler materials by catalytic action certainly suggests that they are probably built up by a similar process.

5. *Collie's Theory of Enzyme Action*

† During the break-down of certain carbohydrate derivatives under the action of enzymes, an important step in the reaction is evidently the accumulation of hydrogen atoms at one end of the chain and the gathering of oxygen atoms at another point. Only on this assumption can we explain the conversion of the radicle (I.) into the grouping (II.) which evidently takes place during alcoholic fermentation :—

$$\underset{\text{(I.)}}{CH_2OH{-}CH\,.\,OH{-}} \qquad \underset{\text{(II.)}}{CH_3{-}CH_2{-}}$$

Now if the sugar molecule be regarded as being built up from a chain of carbon atoms united with water molecules, such a transformation can readily be represented by a mere change in orientation of the hydrogen and hydroxyl radicles, which might be produced by dehydration and rehydration :—



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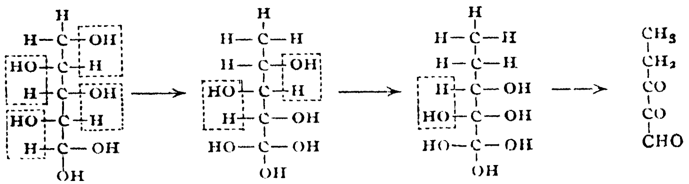
[1] Hill, *J.*, 1898, 73, 634 ; see also Bayliss, *The Nature of Enzyme Action*.

† In the case of a pentose, distinguishing the inverting groups by the dotted lines, we should get the following picture :—



† Take the case of a hexose as an illustration of the next step in the argument. At one end of the chain is the weakly basic hydroxyl group, whilst at the other end lies the aldehyde radicle, which, in its ortho-form, is weakly acidic. It is therefore reasonable to assume that the main chain of the sugar is subjected to electrical strain. Now if this electrical condition can be interfered with, changes might be expected to occur in the molecule ; and it is possible that the enzymes work in this manner. The enzyme molecule is probably built up from amino-acids somewhat in the same manner as a protein ; so that it contains, like the sugar, a basic group (—NH_2) and an acidic radicle (—COOH). From what we know of their molecular complexity, the enzyme molecules must be immensely greater than the molecules of simple carbohydrates ; and it is therefore probable that one molecule of enzyme may react simultaneously with hundreds of carbohydrate molecules. The basic and acidic groups of the sugar will come into contact with the acidic and basic portions of the enzyme *provided that these groups occupy suitable positions in space* ; * the system is then short-circuited ; and what might be termed " molecular electrolysis " results ; the energy of the sugar molecule is set free as heat ; and, by the rearrangement of the hydrogen and hydroxyl groups of the sugar, new compounds are formed which are no longer capable of combining with the amphoteric enzyme. The latter may then be recharged by induction or by the presence of ions in the solution, as is the case with many colloids.

The following diagram represents the various steps in the process :—

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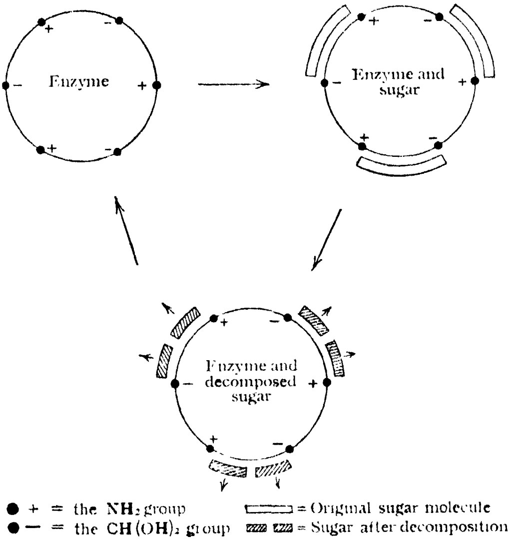
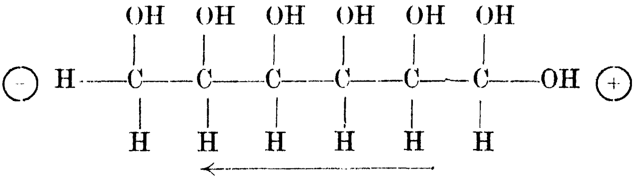
* This serves to explain the selective power of enzymes.



In its elements the Collie theory bears a strong resemblance to Ehrlich's side-chain theory of toxins and anti-toxins, the two groups at the points attacked being analogous to Ehrlich's receptors, whilst the corresponding points in the enzyme are akin to Ehrlich's haptophore groups.

With slight modification, Collie's theory would furnish a mechanism for the polymerization of formaldehyde to optically active sugars.

† Another possibility must not be left out of account. When we examine the structural formula of a sugar in its ortho-form the similarity between it and one of the usual diagrams to illustrate electrolysis strikes the eye at once :



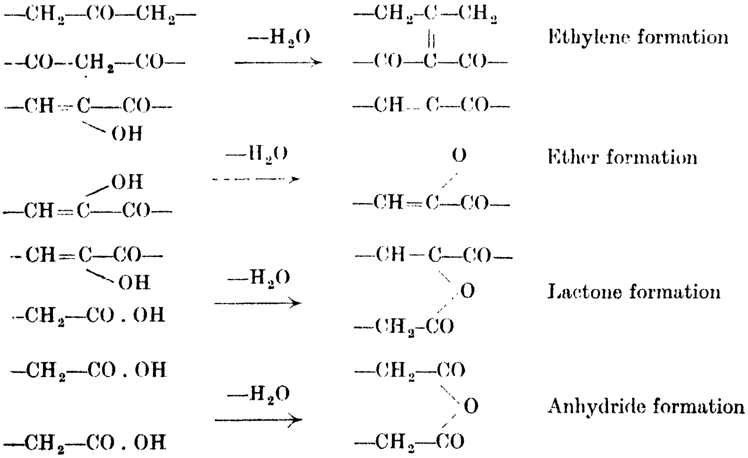
$$\begin{array}{ccccccccccccccc} & & & \multicolumn{11}{c}{\longrightarrow} & \\ & & OH & & OH & & OH & & OH & & OH & & OH & & \\ & & | & & | & & | & & | & & | & & | & & \\ \ominus & H- & C & - & C & - & C & - & C & - & C & - & C & -OH & \oplus \\ & & | & & | & & | & & | & & | & & | & & \\ & & H & & H & & H & & H & & H & & H & & \\ & & & \multicolumn{11}{c}{\longleftarrow} & \end{array}$$

Now if we imagine a pair of terminals inserted in the molecule as shown by the + and — signs, it is clear that the hydrogen atoms would be drawn to the left, whilst the hydroxyl groups would move to the right. This would give us the same accumulation of hydrogen atoms at one end and hydroxyl groups at the other. Collie's conception of the action of enzymes allows us to picture the necessary electrical terminal inserted into the molecular structure of the sugar; and it may be noted that these terminals do not necessarily attack the two ends of the chain; they might quite as easily be supposed to be inserted at any point in the molecular structure which is spatially suitable for this entry; and in this way the selective action of different enzymes may be accounted for.

6. *The Polyketide Group*

Since the addition of water to some molecules and the removal of it from others are two of the most important reactions in the chemistry of vital processes, it is worth while to examine the known behaviour of certain atomic groupings which show a marked inclination towards these two reactions.

It may be recalled that the polyketides * have the general formula $H . (CH_2 . CO)_n . OH$. The higher members of the series therefore contain the carboxyl radicle, —COOH, and also the grouping —CO—CH_2—CO—, which is capable of enolization into —C(OH) : CH—CO— . From these three groupings water can be removed in four different ways, as shown in the formulæ below.



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* See Vol. I. A general account of the polyketide reactions is given by Collie, *J.*, 1907, **91**, 1806.

It is hardly necessary to point out that the last three reactions are easily reversible, since the addition of water to anhydrides, lactones, and ethers of this special type is familiar. The first reaction is also a reversible one in a number of well-known cases, among which the break-down of pulegone into acetone and methyl-cyclohexanone may be quoted.

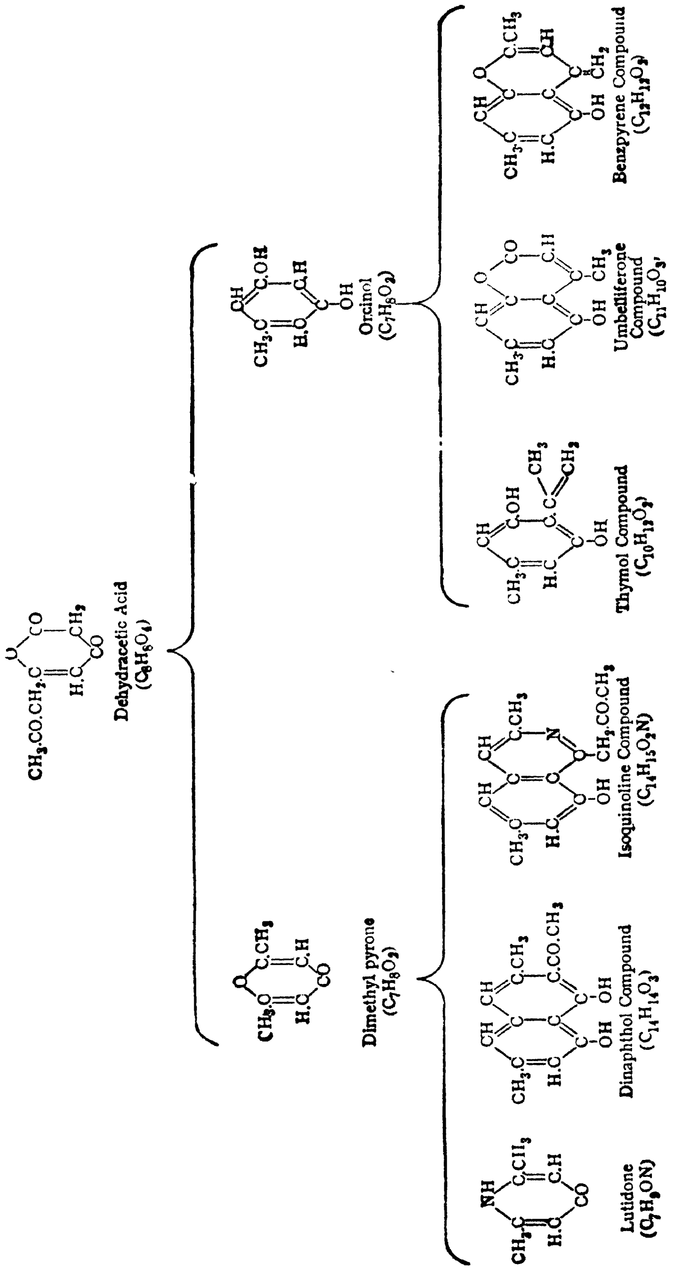
The higher members of the polyketide group have another property which deserves mention here: the ease with which they lose carbon dioxide and yield ketones. The production of acetone from acetoacetic acid is the simplest instance of this; and triacetic acid acts in the same way, giving acetylacetone:

$$CH_3.CO.CH_2.CO.CH_2.COOH = CH_3.CO.CH_2.CO.CH_3 + CO_2$$

Finally, they react readily with ammonia, yielding amino-derivatives like β-amino-crotonic acid or imino-compounds of the pyridine group.

From this it is obvious that the polyketides form one of the most reactive classes known to organic chemistry; and a glance at the table on p. 281 will give some idea of the number and variety of compounds, akin to natural products, which can be obtained from a single polyketide derivative, dehydracetic acid.

In the following sections of this chapter, an attempt will be made to show how it is possible to link up genetically the polyketide group with a large number of the more important groups of natural products such as the carbohydrates, the benzene series, the anthocyanins and other plant pigments, the alkaloidal series, and the fats. It seems advisable to call the attention of the reader to the remarkable way in which the polyketide skeleton can be traced in detail through so many of the natural products, even of complex character; and throughout the remainder of the chapter it should be borne in mind that the raw material of the plant is cellulose, since from its degradation are obtained all the more important plant products. The connection between the carbohydrates and the polyketides is therefore of the greatest importance; and it will be dealt with in the next section.

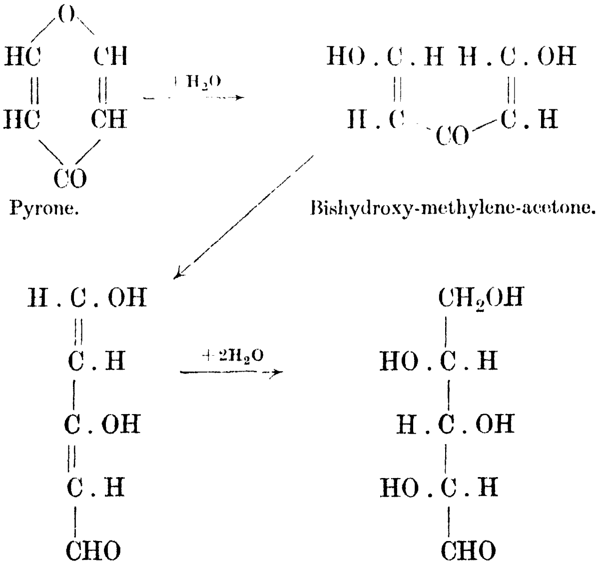

Dehydracetic Acid ($C_8H_8O_4$)
Dimethyl pyrone ($C_7H_8O_2$)
Orcinol ($C_7H_8O_2$)
Lutidone (C_7H_9ON)
Dinaphthol Compound ($C_{14}H_{14}O_3$)
Isoquinoline Compound ($C_{14}H_{15}O_2N$)
Thymol Compound ($C_{10}H_{12}O_2$)
Umbelliferone Compound ($C_{11}H_{10}O_3$)
Benzpyrene Compound ($C_{12}H_{12}O_2$)

7. *The Relations between the Carbohydrates and the Polyketides*

† When a carbohydrate is compared with a polyketide having the same number of carbon atoms, it is clear that since both structures are built up from straight carbon chains, the main difference between them must lie in the oxygen and hydrogen atoms of their formulæ. On comparing, for example, a hexose with the triketide, triacetic acid, it becomes clear that the two formulæ differ from each other by the elements of a round number of water molecules :

$$C_6H_{12}O_6 - H\,.\,(CH_2\,.\,CO)_3\,.\,OH = 2H_2O$$

Now consider the polyketide derivative pyrone. This is acted upon by metallic alcoholates with the formation of derivatives of bishydroxy-methylene-acetone.[1] The proper conditions for carrying out a similar reaction with a water molecule instead of one of sodium ethylate have not yet been discovered ; but the point is not without theoretical interest, as it suggests a means whereby sugars may be converted into polyketides and *vice versa.* Taking pyrone as an example, the following stages would be involved :—



Pyrone.

Bishydroxy-methylene-acetone.

A pentose.

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[1] Willstätter and Pummerer, *Ber.*, 1905, **38**, 1461.

A reverse series of reactions would lead from the carbohydrates to the polyketides and thence to all the classes of compounds which were enumerated in the last section.

A simpler, though less probable, way of formulating the conversion of a carbohydrate into a polyketide, and *vice versa,* is shown in the following formulæ. For the sake of clearness, the hydrogen atoms and hydroxyl groups involved in the first dehydration reaction are printed in heavy type. Starting with say, glucose:

$$CH_2\mathbf{OH}—C\mathbf{H}(OH)—CH(\mathbf{OH})—C\mathbf{H}(OH)—CH(\mathbf{OH})—C\mathbf{H}:O$$

removal of three molecules of water would lead to the production of the following structure:

$$CH_2 \quad C(OH)——CH \quad C(OH)——CH \quad C:O$$

which is the enolic form of:

$$CH_3——CO——CH_2——CO——CH \quad C:O$$

and from this the polyketide could be obtained by the addition of an extra molecule of water:

$$CH_3——CO——CH_2——CO——CH_2——COOH$$

Now, though it must be frankly confessed that up to the present our laboratory methods have failed to bring about either of these conversions,* there are numerous facts tending to show that many plant products are derived from polyketide chains; and since the carbohydrates form the most obvious source of polyketide derivatives it seems not unwarranted to assume that reactions similar to the above do take place in plants. If we do not make this assumption, we require so many different postulates in devising syntheses of vital products that the matter becomes extremely complicated; whereas by granting the possibility of polyketide production it may be rendered very simple.

8. *The Carbohydrates, Polyketides, and Benzene Series*

† The aromatic series is strongly represented among plant products; and it seems evident that the source of the vegetable

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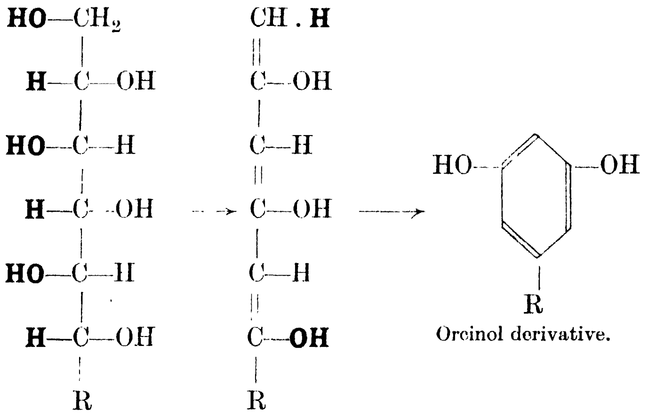
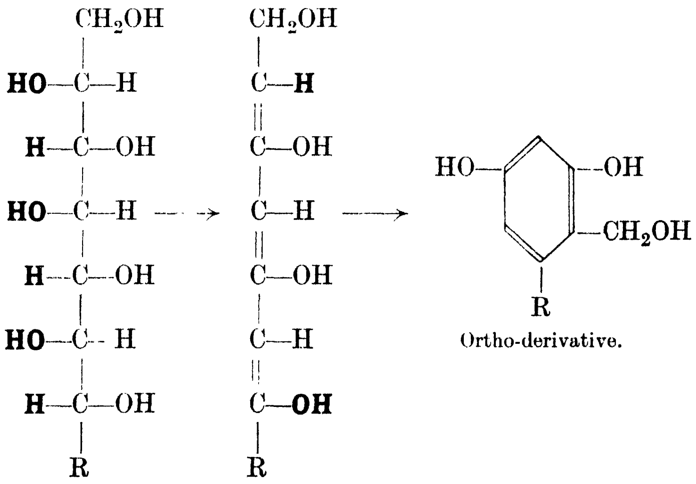
*** One great difficulty in the way is the ease with which open-chain derivatives of the polyketide series are hydrolysed in presence of alkali or acid.**

benzene compounds must be sought in the carbohydrates of the plant. The formulæ below indicate how benzene derivatives might be produced direct from the carbohydrates by means of simple dehydration followed by intramolecular rearrangement. Only two examples are given, as they are intended as illustrations and not as a complete list of possible changes. The groups involved in the dehydrations are printed in heavy type.



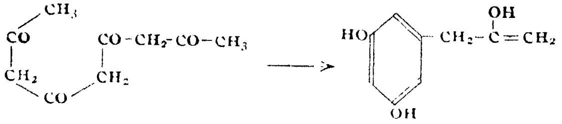
Orcinol derivative.



Ortho-derivative.

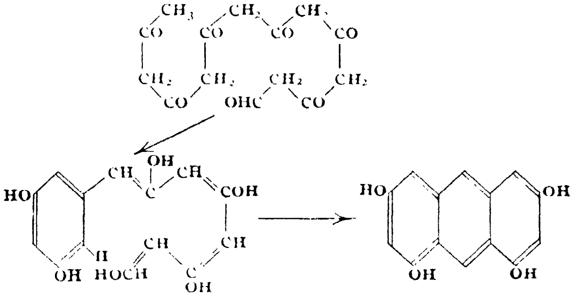
† If the production of polyketides from the carbohydrates be assumed in order to simplify the formulæ, the following

scheme shows how unsaturated side chains attached to benzene nuclei could be formed by dehydration and rearrangement :—



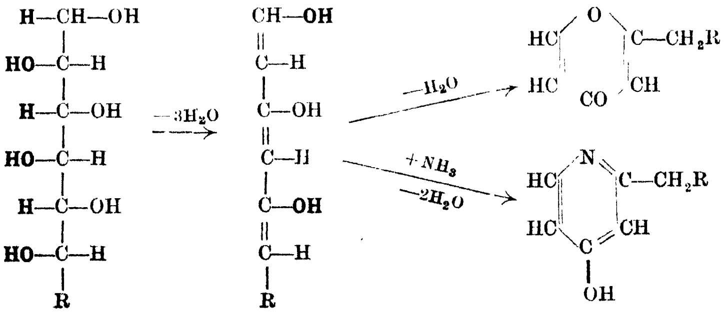
from which, by enzymatic reduction, an analogue of anethol would be formed.

† The production of anthracene derivatives could be accounted for in a similar manner :—



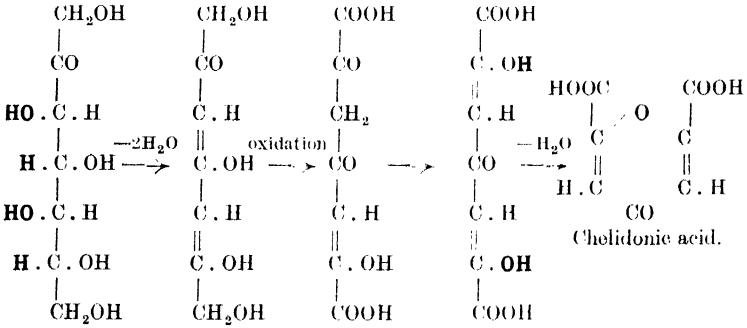
9. *The Formation of Pyrones and Pyridines from Carbohydrates*

The relations between the polyketides on the one hand and the pyrone and pyridine derivatives on the other have already been explained ; so two examples will be sufficient to indicate the possibility of a direct passage from the carbohydrate series to the two heterocyclic groups. As before, the atoms involved in the dehydrations are printed in heavy type.



10. *The Genesis of Some Plant Pigments*

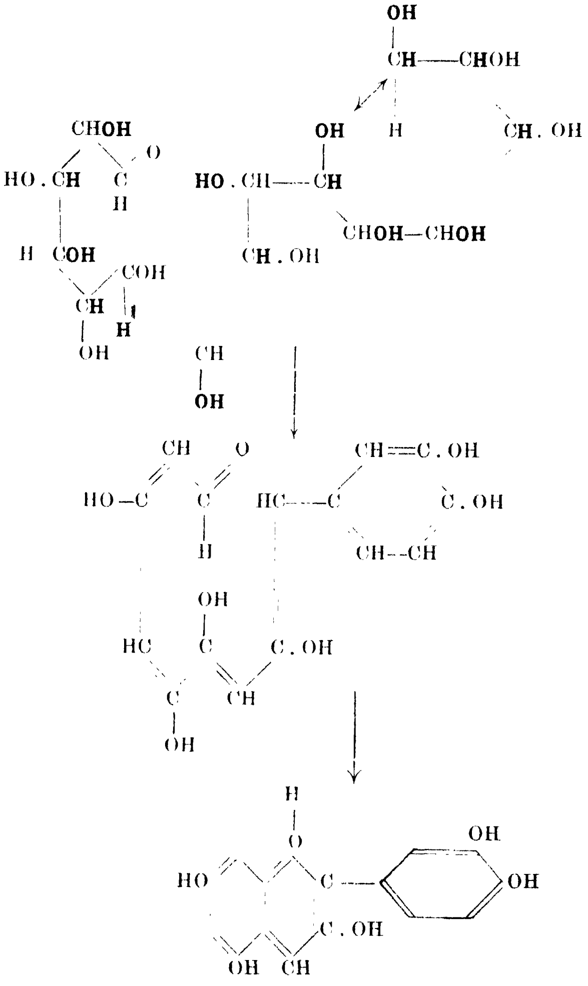
The fact that many of the important plant colouring materials belong to the pyrone group suggests that they may be derived from polyketide chains and hence, indirectly, from the celluloses. In the simpler colouring matters the connection is almost obvious from an inspection of the formulæ ; and one example will suffice. Chelidonic acid may be chosen, and its possible derivation from a heptose accounted for by the usual processes of dehydration and oxidation :



The benzo-pyrone group can be accounted for in a similar manner.

In the case of the anthocyanins, the reaction may be traced directly back to a carbohydrate chain without requiring the intermediate formation of a polyketide derivative at all. An examination of the formula of cyanidin, $C_{15}H_{12}O_6$, shows that it might be derived from a carbohydrate having the composition $C_{15}H_{30}O_{15}$ by the abstraction of nine molecules of water ; and from cyanidin the corresponding anthocyanin is produced by the action of glucose. From the cyanidin, also, quercetin may be formed by oxidation ; so that such a synthesis would open the way to the flavone series as well.

The following formulæ show how, by simple dehydration, it is possible to imagine the production of cyanidin from a carbohydrate of the structure $CH_2OH . (CH . OH)_{13} . CHO$. In order to make the steps clearer, the atoms eliminated by dehydration are printed in heavy type :



Cyanidin.

It is unnecessary to give further examples, as the reader can easily work them out for himself if he is interested in the point.

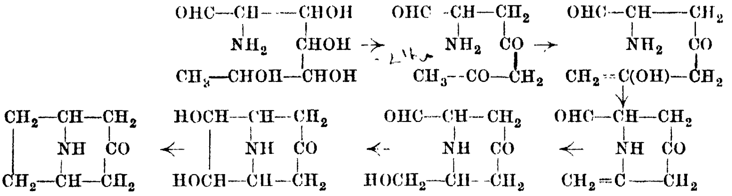
11. *The Alkaloidal Skeletons*

With regard to the formation of the alkaloids, two views are possible. In the first place, the alkaloidal skeleton may be supposed to come into existence directly by the action of ammonia upon a long carbon chain derived from the celluloses; or, secondly, we may assume that the celluloses and proteins break down into smaller molecules which then take part in piece-meal syntheses of the larger alkaloid groupings. In either case, it will be seen that the production of alkaloids is to be regarded as a down-grade reaction.

The formation of tropinone furnishes a case to which both methods are applicable; so it may be given here as an example.

Let us assume that among the degradation products of cellulose a methyl-hexose-amine is produced. This will have the composition $C_7H_{15}O_5N$. Now nor-tropinone (*i.e.* tropinone without the methyl radicle attached to the nitrogen atom) has the composition $C_7H_{11}ON$. The difference between the two formulæ is H_4O_4; from which it is clear that dehydration alone will not suffice to pass from the one compound to the other; reduction to the extent of four hydrogen atoms is also necessary.

The steps in the conversion may be represented as follows:—



All the dehydrations and rehydrations involved in the process have not been indicated in the formulæ, as by this time the reader is probably sufficiently expert in appreciating the method to dispense with some of the steps. The last stage shown above consists in a reduction of the dihydric alcohol to a hydrocarbon grouping, which accounts for the four extra hydrogen atoms already mentioned. Having thus reached nor-tropinone, methylation with formaldehyde would account for the production of tropinone itself.

Of course the order in the above series of changes might be varied, some of them coming earlier than is shown. The methylation of the nitrogen atom, for example, might take place much sooner than has been assumed.

Robinson [1] has put forward a series of suggestions as to the manner in which many of the familiar alkaloidal skeletons may be produced by using comparatively simple reactions; and

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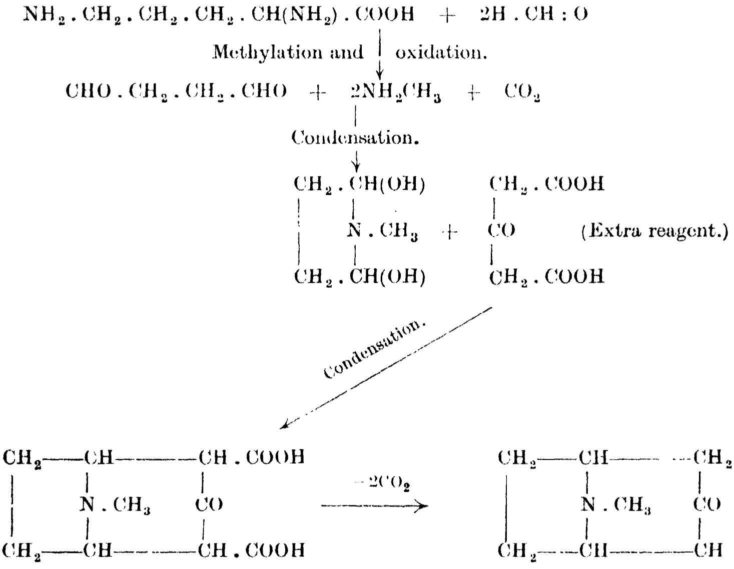
[1] Robinson, *J.*, 1917, **111**, 876.

his paper should be studied by all who are interested in the question. Unfortunately, it would lose by condensation, so cannot be dealt with here. In it examples are given of possible lines of syntheses in the pyrrolidine, piperidine, quinoline, and isoquinoline groups of alkaloids. Two reactions only are demanded as essential to the formation of the skeletons: the aldol condensation and the similar reaction between carbinolamines [containing the grouping $R_2 : C(OH) . N : R_2$] and compounds containing the radicle : CH . CO.

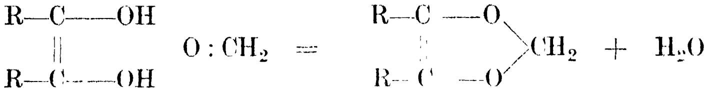
As an example of the method, we may choose the synthesis of tropinone—



Robinson's synthesis of tropinone has shown that reactions of the type required by his views can actually take place in practice under ordinary conditions.

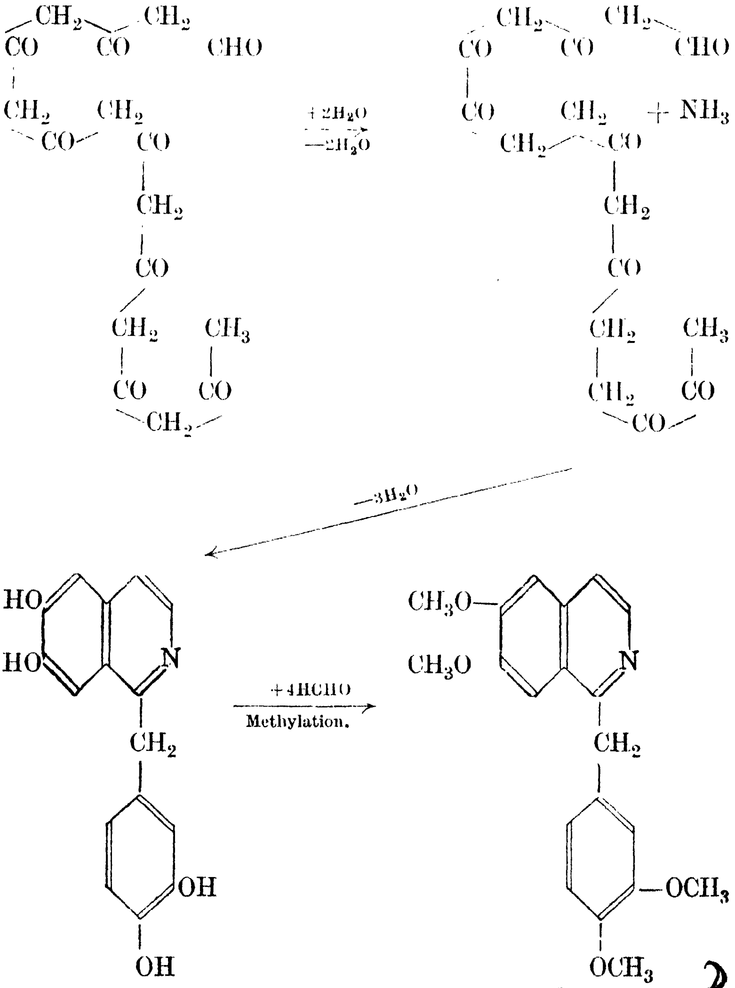
† Returning to the idea that the cellulose chain, *viâ* the polyketides, affords a source of alkaloid material, an example may be given of the course which the synthesis of papaverine might be expected to take. It must be pointed out that by the usual process of dehydration and rehydration, it is possible to pass from the grouping $R . CO . CH_2 . CO—$ to the arrangement $R . CH_2 . CO . CO—$; and also that the formation of methoxyl :

$$R—OH + 2CH_2O = R—O—CH_3 + H.COOH$$



$$\begin{matrix} R—C—OH \\ \| \\ R—C—OH \end{matrix} \quad O:CH_2 = \begin{matrix} R—C—O \\ \| \\ R—C—O \end{matrix} \!\!> CH_2 + H_2O$$

radicles and methylene-ether groups may be supposed to take place by the action of formaldehyde. The steps in the papaverine synthesis are shown below.

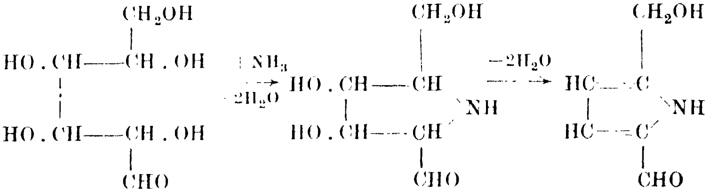


Papaverine.

12. *The Natural Syntheses of Pyrrol Derivatives*

The importance of the pyrrol compounds from the standpoint of natural processes has already been indicated in an earlier chapter. The assimilative machinery of plants is bound up with chlorophyll; whilst hæmine plays an analogous part in animals: and both these substances are built up on a basis of pyrrol rings. In addition to them, numerous other pyrrol derivatives are known to occur in the products of vegetable and animal metabolism: the pyrrolidine alkaloids and the bile acids are cases in point. It is therefore desirable to indicate here how these substances may be produced by vital reactions.

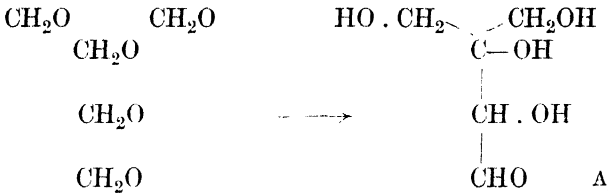
The carbohydrates probably form one source from which materials are drawn for pyrrol syntheses; whilst the nitrogen may be supplied either from ammonia or indirectly from the proteins. Assuming the presence of a sugar and ammonia, the synthesis of a pyrrol derivative may be accounted for by two dehydration reactions thus—



From a pentose, of course, a pyrrol with a single aldehydic side chain would be produced.

13. *Branched Chains and Terpene Compounds*

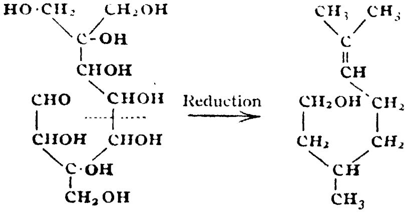
Hitherto we have confined our attention to carbohydrates in which the carbon atoms form a straight chain, but it seems desirable to indicate how forked chains may come into existence, as compounds of this type occur naturally along with straight-chain substances. The formation of apiose may be taken as an example. Its composition is $C_5H_{10}O_5$, and it might obviously be produced by the aldol condensation of five molecules of formaldehyde in the following manner:—



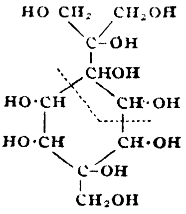
Apiose.

It seems difficult to imagine how apiose can be synthesized naturally in any other way.

But if this be granted, it becomes clear that terpene skeletons might be produced by an extension of the same series of condensations. Two possibilities are open. In the first place, two apiose nuclei may condense together giving the substance (I.) which by reduction may be transformed into an olefinic terpene derivative (II.); and from this, by intramolecular change similar to the geraniol-terpineol rearrangement, a terpene derivative might be formed. Or, alternatively, ten molecules of formaldehyde might condense together to produce a doubly-linked apiose chain (III.) from which terpenes might be formed by reduction.



(I) (II)



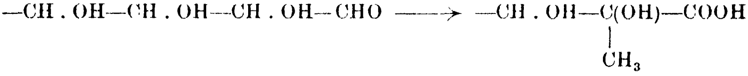
(III)

The particular terpene derivative formed would depend on the stage of oxidation of the original open-chain compound in the second case and also upon the position of the double bonds in the open chain.

Another possible line of synthesis of the terpenes is suggested by the production of a thymol derivative from the condensation products of orcinol and aceto-acetic ester. Since the orcinol and the aceto-acetic ester are both obtainable from polyketide chains, and hence possibly from carbohydrates; and since the thymol compound thus produced may be supposed to be reducible to a terpene, this line of thought leads also from the carbohydrates to the terpene group.

Finally it may be pointed out that a terpene $C_{10}H_{16}$ could be derived from a carbohydrate $C_{14}H_{28}O_{14}$ by the removal of four molecules of carbon dioxide and six molecules of water. In this case it would be necessary to assume as an intermediate compound one of those unsaturated acids which tend to lose their carboxyl radicles spontaneously.

Other reactions which might lead to the formation of a forked chain are the condensation of formaldehyde with a straight sugar chain and subsequent dehydration of the aldol thus produced ; or the peculiar rearrangements in the sugar group observed by Kiliani,[1] whereby, under the action of lime-water, the group (I.) is transformed into (II.) :



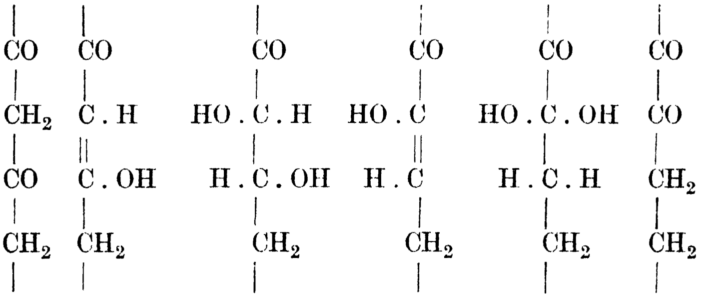
$$\text{—CH.OH—CH.OH—CH.OH—CHO} \longrightarrow \text{—CH.OH—}\underset{\substack{|\\ CH_3}}{C}\text{(OH)—COOH}$$

(I.) (II.)

or the analogous benzilic acid change.

14. *The Formation of Fats.*

For the production of fats in the animal body the carbohydrates absorbed as food form the most probable source. We have already seen that sugars may be converted into polyketide chains by dehydration, so it is not necessary to give these steps. We may commence with the polyketide chain shown in (I.) as an example :—



(I.) (II.) (III.) (IV.) (V.) (VI.)

† If we take as our starting-point the group (I.) and convert it into the enolic form (II.), we can then add a molecule of water on to the double bond to form (III.). This substance

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[1] Kiliani, *Ber.*, 1884, **17**, 1302 ; 1905, **38**, 2668 ; 1908, **41**, 158, 469.

could then be dehydrated to produce (IV.), to which water might be again attached, giving (V.), in which two hydroxyl groups are attached to the same carbon atom. This compound would lose a molecule of water, leaving (VI.).

† A comparison of the formulæ (I.) and (VI.) shows that the whole process implies a wandering of the hydrogen atoms to the lower end of the chain, and a corresponding migration of the oxygen atoms to the other. This purely theoretical series of actions could then be repeated, and the final result would be a loss of carbon dioxide from one end of the chain, and a building up of an aliphatic chain at the other end. Some such process may take place in the living organism during the formation of oils or fats,* and the liberation of carbon dioxide in respiration would be explicable in the same way.

Evidence in favour of this conception of the formation of fats from carbohydrates is obtained when the results of the reverse process are examined. In the disease pentosuria, the body fats are broken down and converted into sugars. Now, if this process involved the decomposition of the fat, with subsequent assimilation in the organism, then a synthesis of the pentose and, finally, its excretion, we should expect to find that the inactive fat had been converted into an *optically active* sugar owing to the intervention of the asymmetric components of the body tissues, etc. On the other hand, if the fat is converted direct into the sugar by the converse of the process sketched above—*i.e.* if the process involves a mere passage from Stage VI. to Stage I.—then, owing to the continual formation of enolic forms and consequent loss of asymmetry, the products of the fatty decomposition would not be active. In actual practice it is found that the arabinose excreted by patients suffering from pentosuria is the racemic form [1] of the compound; and this notwithstanding the fact that the organism is quite capable, even in that state, of decomposing *l*-arabinose if this sugar be given in food. It seems evident, therefore, that the arabinose excreted by such patients cannot have passed through the ordinary channels, but must have been produced directly from fat by some simple reaction such as is shown above. Further, the occurrence of aceto-acetic acid and acetone along with sugar in the urine of patients suffering from diabetes proves

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* Or wax in the case of bees.

[1] Neuberg, *Ber.*, 1900, **33**, 2243.

that polyketide derivatives make their appearance during the disease.

15. *Syntheses and Degradations of the Proteins*

In the foregoing sections we have dealt very fully with the carbohydrates and their possible mutations; so that it will be necessary to devote only a small space to the proteins, that second great class of up-grade products of the vital machinery. Fischer's researches on the polypeptides leave little doubt that the protein molecules contain long chains of amino-acids coupled together in the form of amides; and it remains to suggest methods whereby such substances could be synthesized from simple materials within the living organism.

As in the case of the carbohydrates, our knowledge of the initial steps in the process is incomplete. Nitrates appear to be assimilated by the plant and reduced to nitrites; but uncertainty exists as to the further fate of the nitrite when it has been formed. The most suggestive experiments on the subject appear to be those of Baudisch.[1] On exposing potassium nitrate to diffused daylight, he found that it was reduced to potassium nitrite. Under the same conditions, potassium nitrite, when mixed with formaldehyde or methyl alcohol, became converted into hyponitrite and then, by the action of more methyl alcohol, was changed into the potassium salt of formohydroxamic acid:

$$CH_3OH + KNO_2 = HO . CH : N . OK + H_2O.$$

Prolonged exposure to light resulted in a further reduction, ammonia being formed.

According to Baudisch, ammonia in plants is oxidized by oxidases or by ultra-violet light, and the resulting product combines with formaldehyde to form aci-nitromethane which, being a reactive substance, takes part in vegetable syntheses.

If we assume the presence of ammonia and carbohydrates, however, the further reactions may be formulated in other ways. Since unripe plants contain a high percentage of amides, we may postulate that the first step in the synthesis of the proteins is the production of an amide. We are then faced with a certain difficulty; for it is clear that an inversion of some kind must take place in order to convert the group (I.)

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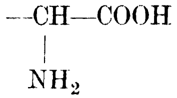
[1] Baudisch, *Ber.*, 1911, **44**, 1009.

into the group (II.), which entails the transference of the nitrogen atom from one carbon atom to the next

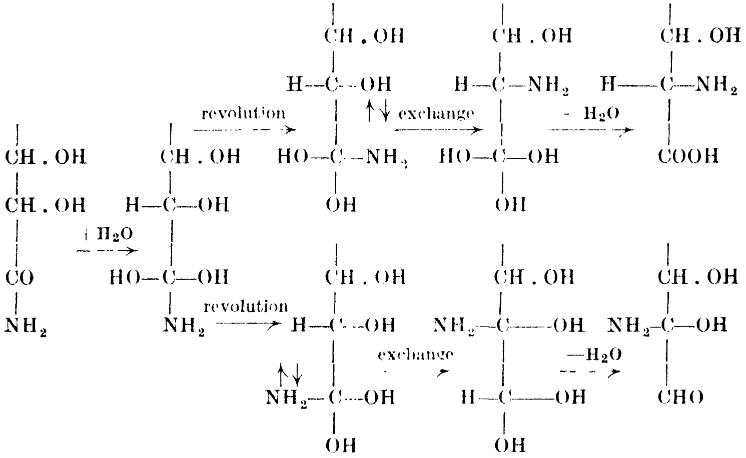
$$-CH_2-CO-NH_2$$



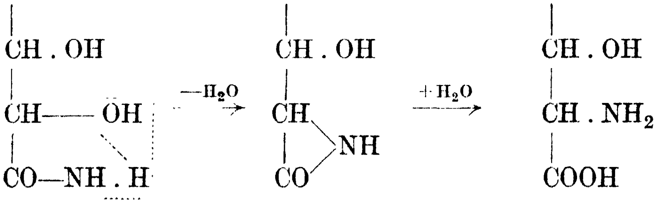
$$-\underset{\displaystyle NH_2}{CH}-COOH$$

(I.) (II.)

† Such transferences are quite possible on lines with which we are already familiar. The following symbols show the application of the pinacone rearrangement to the problem :—

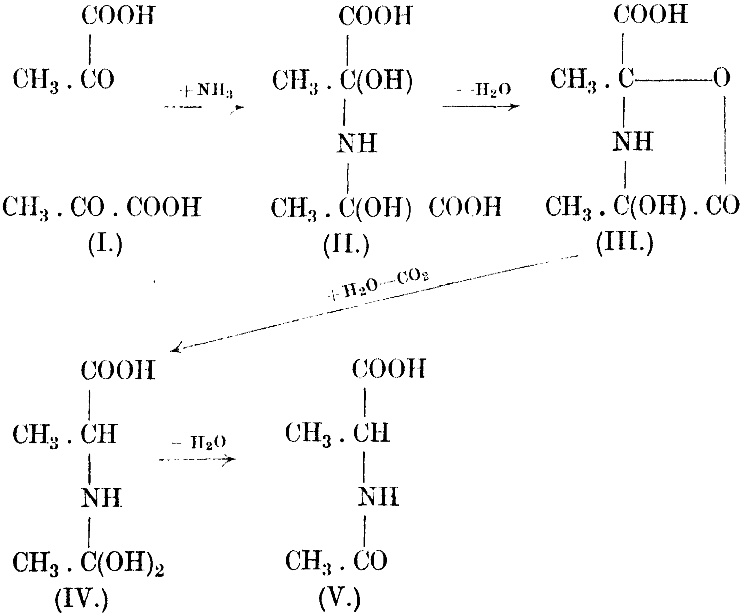


Another method by which the transference of the nitrogen atom to the neighbouring carbon might be accomplished is by the temporary production of a three-membered ring which, as soon as formed, might open up again in a new place. In this way the reaction is reduced to the simple subtraction and readdition of a molecule of water—



The production of the original amide radicle may be attributed to the formation and partial hydrolysis of a cyanhydrin of the sugar; for hydrocyanic acid is known to be formed in plants in quantities sufficient to yield the required cyanhydrins.

Much more probable than either of the above suggestions is the following, which is based upon an observation of de Jong [1] in the case of pyruvic acid. When ammonium pyruvate is mixed with pyruvic acid the reaction takes the following course. In the first place the two pyruvic molecules (I.) react with ammonia from the ammonium salt to form an imino-compound (II.). This substance then loses water, and forms the lactone (III.). A molecule of water is then taken up and carbon dioxide is split off, yielding the substance (IV.), which immediately eliminates another molecule of water, producing *a*-acetyl-amino-propionic acid (V.):



$$\begin{array}{c} COOH \\ | \\ CH_3 . CO \\ \\ \\ CH_3 . CO . COOH \\ (I.) \end{array} \xrightarrow{+NH_3} \begin{array}{c} COOH \\ | \\ CH_3 . C(OH) \\ | \\ NH \\ | \\ CH_3 . C(OH)\ COOH \\ (II.) \end{array} \xrightarrow{-H_2O} \begin{array}{c} COOH \\ | \\ CH_3 . C\text{———}O \\ | \\ NH \\ | \\ CH_3 . C(OH) . CO \\ (III.) \end{array}$$

$$\xrightarrow{+H_2O-CO_2} \begin{array}{c} COOH \\ | \\ CH_3 . CH \\ | \\ NH \\ | \\ CH_3 . C(OH)_2 \\ (IV.) \end{array} \xrightarrow{-H_2O} \begin{array}{c} COOH \\ | \\ CH_3 . CH \\ | \\ NH \\ | \\ CH_3 . CO \\ (V.) \end{array}$$

Now it will be seen that this reaction leads to the formation of the type of amino-acid most common among the protein derivatives—the α-amino-acid; for the acetyl group could easily be hydrolysed away by enzyme action.

The application of this to more complex cases is not difficult. It will be remembered that in the section dealing with the

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[1] De Jong, *Rec. trav. chim.*, 1900, **19**, 259; 1904, **23**, **131**.

formation of fats it was pointed out that a very simple process would lead from the carbohydrates of the type R—CH . OH—CH . OH—CH . OH—CH . OH—CHO to derivatives of the structure $R—CH_2—CH_2—CO—CO—COOH$. Oxidation of the latter would yield homologues of pyruvic acid, the number of carbon atoms in the group R depending upon the length of the carbohydrate chain which serves as a raw material. Once these pyruvic acid derivatives have been produced, there is no reason why they should not undergo de Jong's reaction and form the corresponding α-amino-acids; and in this way the raw materials for polypeptide and protein syntheses might be produced.[1]

In connection with the protein syntheses, another point of interest arises, though it must be classed as a purely speculative one. If two molecules of formaldehyde could be induced to condense together in the following manner, keten would be formed; and from this, by polymerization, chains of polyketides might be formed:

$$H_2C:O + H_2C:O = H_2O + CH_2:C:O$$

Now, similarly, we might devise a synthesis in the nitrogen group:

$$NH_3 + (HO)_2C:O = 2H_2O + NH:C:O$$

This compound is, of course, isomeric with cyanic acid.

† For present purposes, however, our interest in it arises from the fact that it is obviously the nitrogen analogue of keten:

$$CH_2:C:O \qquad NH:C:O$$

and, from this similarity, we may term the compound aziketen. Now just as keten can polymerize to long chains which then add on water to form polyketides, so aziketen should polymerize and hydrate in order to produce the simplest type of polypeptide—

$$NH_2—CO—NH—CO—NH—CO—NH—COOH$$

† It is at this point desirable to bring the matter into touch with actual practice. If we examine the formula of uric acid, it requires no great stretch of imagination to recognize that the purine compounds are derivatives of this type of polypeptide, probably produced from the open-chain compound by reduction accompanied by ring formation:

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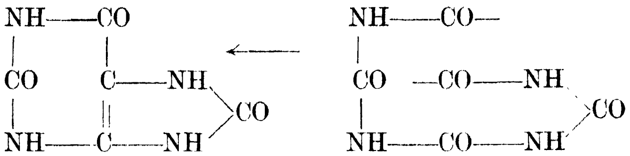
[1] For other suggestions see Haas and Hill, *Chemistry of Plant Products* (1917), pp. 333 ff.



Thus the break-down of the sugars into the various aromatic and pyrone derivatives would find its analogue in the formation of the uric acid derivatives from the proteins.

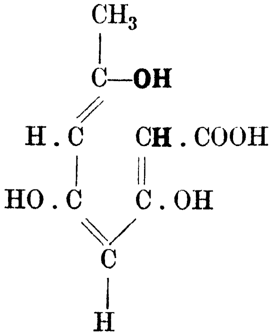
† Another suggestion as to the production of purine derivatives by vital processes may be put forward. In the break-down of proteins, amino-acids of the type $R—CH(NH_2)—COOH$ are formed. Now in the oxidation of these, it is possible that the hydrocarbon chain R is burned away first, leaving behind the potential —NH . CO— portions, which may then unite to form uric acid and its derivatives.

16. *The Carbohydrates and the Depsides*

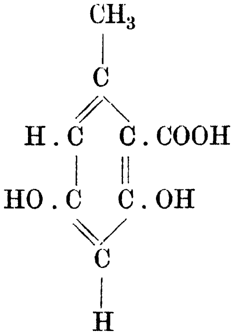
The application of Collie's views to the formation of natural depsides can be illustrated by the case of the moss acids. Here the fundamental skeleton is to be found in orsellinic acid; and the starting-point would be an acid derived from a methyl-heptose (I.). Removal of three molecules of water, as indicated by the heavy type of this formula, would produce the polyketide derivative (II.), which is obviously an enolic derivative of the straight-chain tetracetic acid. A further loss of one molecule of water by elimination of the atoms shown in heavy type would yield orsellinic acid (III.).

$$CH_3.\mathbf{CH}(OH).CH(\mathbf{OH}).\mathbf{CH}(OH).CH(\mathbf{OH}).\mathbf{CH}(OH)\ CH(\mathbf{OH}).COOH$$

(I.)



(II.)



(III.) Orsellinic acid.

The production of orsellinic acid would lead on to the syntheses of the remaining moss acids. By esterifying the carboxyl group of one molecule of orsellinic acid with a hydroxyl group belonging to another molecule, lecanoric acid would be formed. The methylation of one hydroxyl group of orsellinic acid would yield everninic acid ; and a combination of the remaining hydroxyl radicle of this with a second molecule of orsellinic acid would produce evernic acid.

It is thus evident that Collie's ideas are capable of accounting for the changes necessary to convert a carbohydrate into the principal moss depside derivatives.

17. *Conclusion*

In this chapter an attempt has been made to sketch certain methods by which natural products may possibly come into existence in the organism, but it cannot be too strongly emphasized that they are intended merely as suggestions and not as dogmatic attempts to settle the problems involved. If they have brought to the notice of the reader the questions which arise in this branch of chemistry and have inspired any desire to go further into the matter, they have amply fulfilled the object for which they were written. We are at present far from a definite knowledge of how the vital machine carries out its work ; but if the ideas collected in the present chapter induce the reader to speculate for himself on the subject, he will find a most fascinating field open to him.

One point which certainly comes into prominence in the foregoing pages is the fact that, by a series of hypothetical dehydrations and rehydrations, it is easy to see how very different types of grouping might be produced. A system which is capable of accounting for the production of such widely varying materials as benzene derivatives, pyrrols, pyridine derivatives, pyrones, anthocyanins, depsides, fats and alkaloids has evidently something more than mere plausibility behind it. We are not yet able to carry out these changes in the laboratory, except in the case of the polyketide derivatives ; but it will be surprising if sooner or later some experimental evidence is not found to bear out much that has been advanced in the preceding sections.

† Should the reader wish to pursue speculations in this

field the following questions may serve to guide his attention to some hitherto unsolved problems. The fatty acids of the acetic series are quite common in nature, whilst their hydroxy-derivatives—with the exception of lactic acid—are hardly represented at all. Why should this be so? Why do all the important sugars and starches contain a chain of five or six *or a multiple of five or six* carbon atoms? Why are the majority of the amino-acids obtained from the proteins the α-amino-acids? Why are the ortho- and meta-derivatives so strongly represented among naturally occurring benzene derivatives, whilst the majority of the terpenes are derived from *para*-cymene?

† In such broad generalities there must surely be some simple solution. The curious thing is—not that the answers to these questions are omitted from the ordinary text-books, but rather that the questions do not appear to have suggested themselves to the writers at all.

CHAPTER XI

SOME CASES OF ISOMERISM IN CYCLIC COMPOUNDS

1. *The Space Models of Hexamethylene*

WHEN a six-membered ring is built up from the tetrahedral models used for stereochemical demonstration, it is found that, without undue strain, it is impossible to force all the six atoms into one plane. As Sachse [1] pointed out, two strainless arrangements are possible, photographs of which are given in Plate I.

Examination of these illustrations will show that a plane drawn through the atoms, 2, 3, 5, 6, will not contain the atoms 1 and 4 in either model. Further, in Type A, the atoms 1 and 4 lie on the same side of the plane containing 2, 3, 5, 6; whilst in Type B, the atoms 1 and 4 lie on opposite sides of this plane.

If the structures were perfectly rigid, a number of results would follow:—

(1) There should be two isomeric hexamethylenes, one corresponding to Type A, the other having the configuration of Type B.

(2) Every mono-substitution-product of hexamethylene should occur in two forms, since in either of the models there are two distinct sets of hydrogen atoms: the group 2, 3, 5, 6, in one plane, and the pair 1, 4, which are not in this plane.

(3) *Cis*-hexahydrophthalic acid should be capable of resolution into optical antipodes if the configuration of any of its molecules is of the Type B.

In practice, hexamethylene itself and all its mono-substitution-products are found to be homogeneous; and the attempt to resolve *cis*-hexahydrophthalic acid into its antipodes proved a failure.[2] These facts suggest that neither Type A nor Type B can represent hexamethylene correctly.

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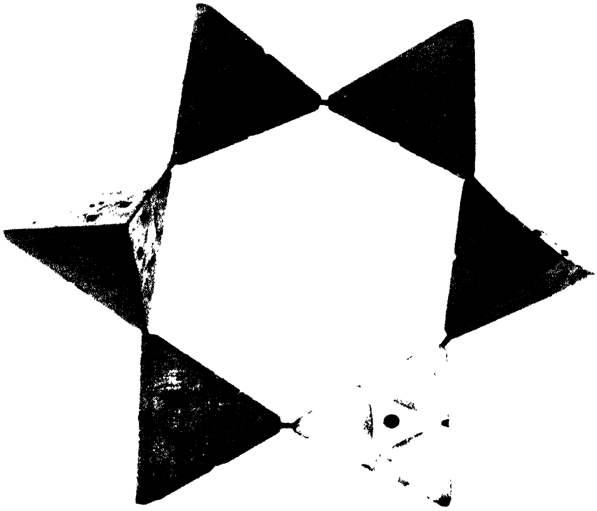
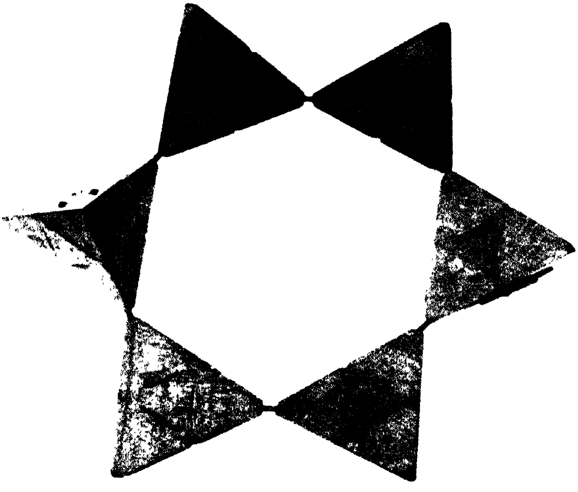
[1] Sachse, *Ber.*, 1890, **23**, 1363; *Z. physikal. Chem.*, 1892, **10**, 203.

[2] Werner and Conrad, *Ber.*, 1899, **32**, 3046.



TYPE A.



TYPE B.

THE TWO SPACE-MODELS OF HEXAMETHYLENE

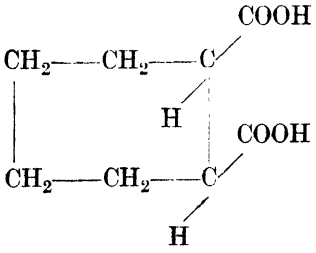
A possible explanation of the state of affairs is found when slight pressure is applied to the atom 1 in either model. It is then found that very little effort forces the model from the Type A configuration into the Type B form, and *vice versa.* If the same holds good in the molecule itself, then it is easy to see that a labile system of this sort would evade the difficulties set forth above.

This, however, would not apply to the solid state; and from an X-ray examination of the crystal-structure of benzene hexahalides, $C_6H_6X_6$, Hendricks and Bilicke[1] arrived at the conclusion that so far as hexamethylene goes, the spatial arrangement of the atoms in hexamethylene is more complex than is suggested by the simple tetrahedral models.

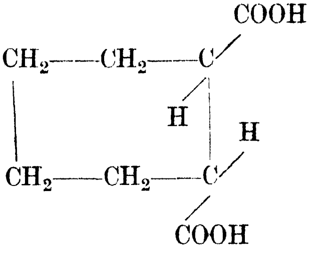
2. *Mohr's Views on Fused Rings*

It was pointed out by Mohr[2] that although the simple hexamethylene ring can escape the production of isomerism by a simple distortion, the conditions are altered when a second ring is fused on to the primary one in such a manner that two adjacent atoms are common to both cyclic systems. In this case, the model can still undergo distortion; but more force is required to change the one configuration into the other; and in one special type, an isomerism is possible which cannot be eliminated by any simple twisting.

A preliminary consideration of the isomeric hexahydrophthalic acids will make the matter quite simple. These acids occur in two stereoisomeric forms, in one of which the two carboxyl groups lie on the same side of the ring, whilst in the isomeric configuration, the carboxyls lie on opposite sides of the ring:—



Cis-form



Trans-form

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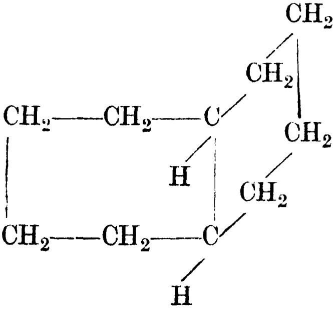
[1] Hendricks and Bilicke, *J. Amer. Chem. Soc.*, 1926, **48**, 3007.

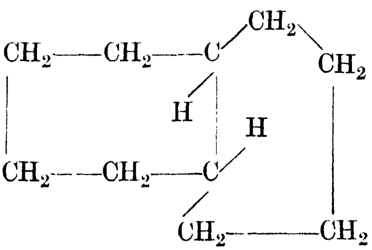
[2] Mohr, *J. pr. Chem.*, 1928, **98**, 315.

Inspection will show that no twisting of the molecule will suffice to convert the one variety into the other, so long as the bonds remain intact.

Now imagine that in each model the carboxyl groups are removed and that, in their places, the two ends of a $—CH_2 . CH_2 . CH_2 . CH_2—$ chain are inserted, yielding decalins, $C_{10}H_{18}$. The *cis-trans* peculiarities will remain; and the result will be two models which can be represented by the following formulæ :—



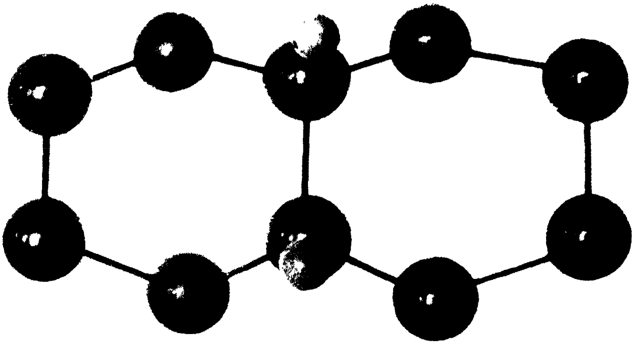
Cis-form



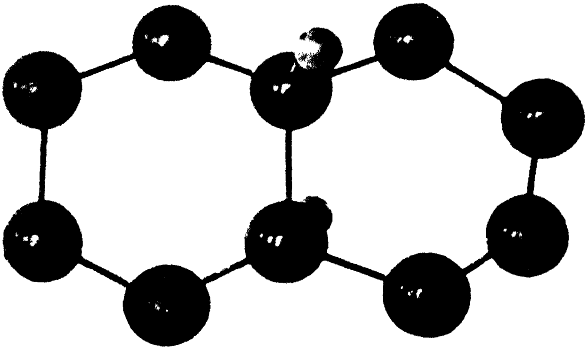
Trans-form

Photographs of these two structures are shown in Plate II. The hydrogen atoms of the methylene groups have been omitted from the model for the sake of clarity. From an inspection of the illustration it will be clear that no twisting of the model can alter the relative positions of the two rings, since these depend upon the points of attachment of the cyclic groupings to the two central carbon atoms of the system: an arrangement which could be altered only by actual rupture of the bonds concerned.

On building up the model, it is found that the system is practically strainless, owing to the manner in which the atoms arrange themselves in three dimensions. (See Plate II.) Mohr regards it as strange that rings of this description do not occur among the natural products, since bicyclic systems of this kind could evidently be formed from open chains with very little expenditure of energy. Yet among the naturally-occurring cyclic substances the tendency is to form rings of types which entail far greater strains, such as :—

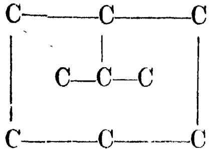
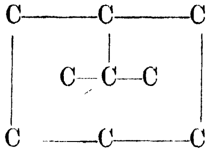
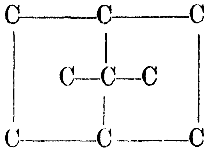


CIS-FORM.



TRANS-FORM.

SPACE-MODELS SHOWING THE ISOMERISM IN
REDUCED NAPHTHALENE RINGS

This is, however, hardly a fair presentation of the facts. All the evidence suggests that the terpenes, for example, are built up by the combination of isoprene molecules or analogous units; and in the passage from an open chain to a cyclic structure it is clear that two influences may be working against each other: the effort to form a stable, saturated arrangement, on the one hand, and the difficulty involved in overcoming the strain of ring-closure on the other. The result produced will be due to a balancing of these factors and can hardly be paralleled by the direct formation of saturated rings, as Mohr's statement seems to imply.

A more interesting problem arises when the space formulæ of the decalins are examined. Two forms are obviously capable of existence in the model: the *cis*-form and the *trans*-form. The model suggested that these isomeric forms should be quite stable; and Mohr's ideas opened the way into a fresh field of research.

3. *The Decalins and their Analogues*

The early history of the reduced naphthalene derivatives becomes quite clear in the light of Mohr's suggestions; but while the investigation of these compounds was actually in progress, a considerable amount of misunderstanding occurred, owing to the lack of the true key to the problem.

In 1905, Leroux[1] obtained a decahydro-β-naphthol $C_{10}H_{17}.OH$, by repeated hydrogenation of β-naphthol below 200° C. This material melted at 75° C. Two years later, Ipatieff[2] prepared a decahydro-β-naphthol which apparently had the melting-point 99°–100° C. When a specimen of Ipatieff's compound was examined by Mascarelli and Recusani,[3] it was found to be a mixture of two isomerides, melting at 75° and 105° C.

Now the complete hydrogenation of β-naphthol results

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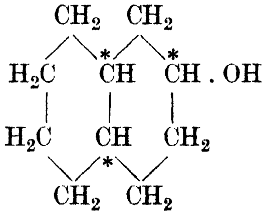
[1] Leroux, *Compt. rend.*, 1905, **140**, 590.

[2] Ipatieff, *Ber.*, 1907, **40**, 1281.

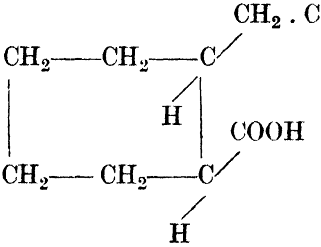
[3] Mascarelli and Recusani, *Gazzetta*, 1912, **42**, II, 35.

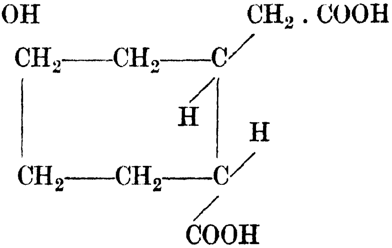
in the production of asymmetric carbon atoms marked with asterisks in the formula :



and Mascarelli and Recusani naturally adopted the obvious explanation and accounted for the isomerism by postulating the existence of several racemic compounds, two of which were assumed to correspond to the components in Ipatieff's mixture.

Fresh facts came to light in the course of an investigation of the anhydride-formation of dicarboxylic acids.[1] When homophthalic acid (*o*-carboxy-phenylacetic acid) is hydrogenated in glacial acetic acid solution in presence of platinum black, it yields a mixture of the *cis*- and *trans*-forms of *o*-carboxy-cyclohexane-acetic acid :—





As was anticipated, the *cis*-acid was transformed into the corresponding *cis*-anhydride by heating it with acetic anhydride, M.P. 57° C. But from the *trans*-acid, a second anhydride was obtained, with the M.P. 80°–81° C. When either isomer is heated to 220° C. for a time, an equilibrium mixture is obtained which contains 25 per cent. of the *cis*-anhydride and 75 per cent. of the *trans*-anhydride.

By this time, Mohr's views had been published ; and the two anhydrides were recognised as *cis-trans* isomerides in accordance with his theory, since the anhydride bridge forms the necessary second ring in the molecular structure.

Attention now reverted to the reduction-products of β-

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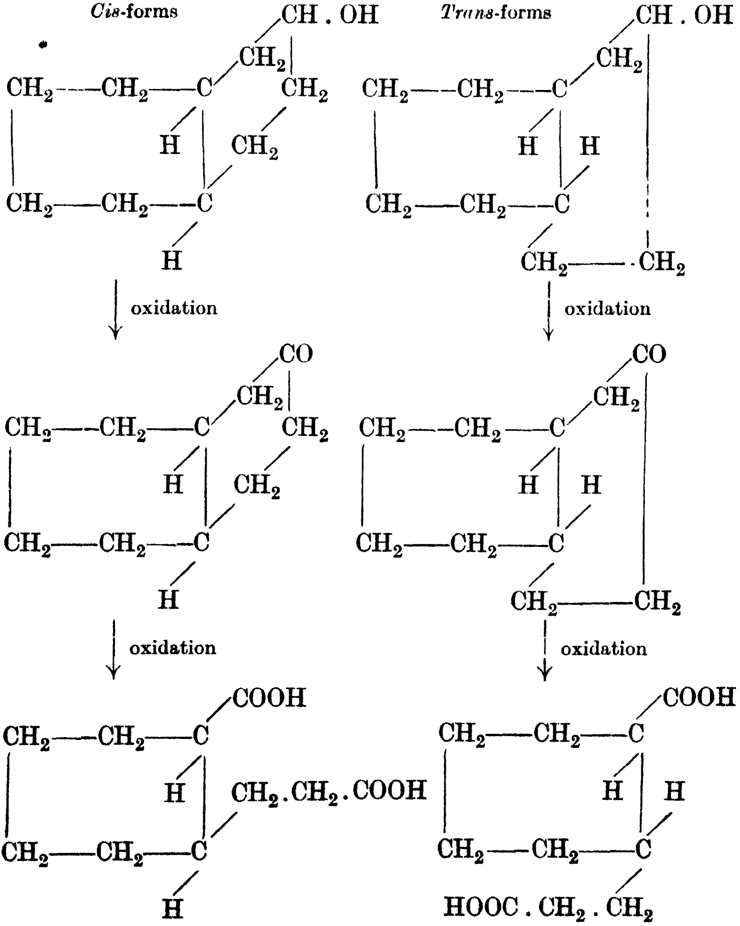
[1] Windaus, Hückel, and Reverey, *Ber.*, 1923, 56, [*B*], 91.

naphthol.[1] On oxidizing these isomeric decahydro-β-naphthols, it was found that two isomeric ketones were obtained. This disproved the original assumption that the isomerism had its origin in the asymmetry of the groups —CH . OH— since this asymmetry is destroyed by the conversion of the secondary alcohol radicle into the carbonyl group. On Mohr's theory, the isomerism of the ketones is simply accounted for by assuming the existence of *cis*- and *trans*-forms; and the production, on further oxidation, of the corresponding pair of isomeric acids is also easily explicable :—



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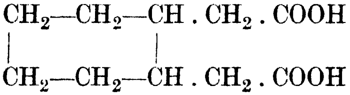
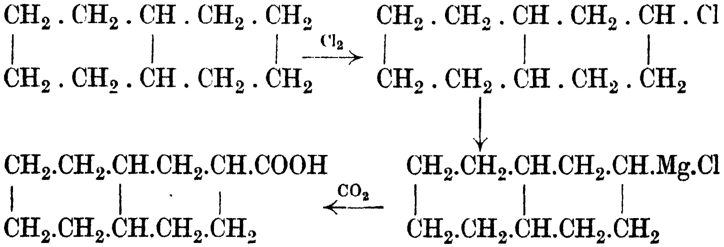
[1] Hückel, *Nach. K. Ges. Wiss. Göttingen*, 1923, 43.

The final oxidation to the acids produces also a second pair of isomers which are obviously *cis*- and *trans*-forms of the acid



$$\begin{array}{l} CH_2—CH_2—CH\,.\,CH_2\,.\,COOH \\ |\qquad\qquad\quad | \\ CH_2—CH_2—CH\,.\,CH_2\,.\,COOH \end{array}$$

The isomeric decahydronaphthalenes themselves have been obtained from the ketones formulated above by first forming the semi-carbazone and acting on this with sodium and alcohol,[1] or by the catalytic reduction of naphthalene itself.[2] The *cis*-compound has a B.P. of 193°/768 mm., whilst the *trans*-compound boils at 185°/756 mm. It is curious to note that reduction with a platinum catalyst leads to the production of about 90 per cent. *cis*- and 10 per cent. *trans*-form, whilst when a nickel catalyst is employed the product is mainly the *trans*-isomer. From these results it is obvious that commercial decalin is a mixture of the two stereoisomers; and this has been definitely established[3] by chlorinating decalin and then treating a Grignard reagent prepared from the chlorinated product with carbon dioxide to form the corresponding carboxylic acids, which were then identified by comparison with the acids obtained by a similar process from each stereoisomer of decahydronaphthalene separately.



$$\begin{array}{ccc} \begin{array}{l} CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH_2 \\ |\qquad\qquad\quad |\qquad\qquad\quad | \\ CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH_2 \end{array} & \xrightarrow{Cl_2} & \begin{array}{l} CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH\,.\,Cl \\ |\qquad\qquad\quad |\qquad\qquad\quad | \\ CH_2\,.\,CH_2\,.\,CH\,.\,CH_2\,.\,CH_2 \end{array} \\ & & \downarrow \\ \begin{array}{l} CH_2.CH_2.CH.CH_2.CH.COOH \\ |\qquad\quad |\qquad\quad | \\ CH_2.CH_2.CH.CH_2.CH_2 \end{array} & \xleftarrow{CO_2} & \begin{array}{l} CH_2.CH_2.CH.CH_2.CH.Mg.Cl \\ |\qquad\quad |\qquad\quad | \\ CH_2.CH_2.CH.CH_2.CH_2 \end{array} \end{array}$$

Among the substitution-products of the decanaphthalenes which have been studied up to the present, reference may be made to the decahydro-β-naphthoamides. Four of these are theoretically possible; and out of this number two have been isolated by Borsche and Lange,[4] and a third by Kay and Stuart.[5]

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[1] Eisenlohr and Polenske, *Ber.*, 1924, **57**, [*B*], 1639.

[2] Willstätter and Seitz, *Ber.*, 1924, **57**, [*B*], 683; Hückel, *Annalen*, **1925**, **441**, 1; *Ber.*, 1925, **58**, [*B*], 1449; Hückel and others, *Annalen*, 1926, **451**, 109.

[3] Borsche and Lange, *Annalen*, 1923, **434**, 219.

[4] *Ibid.*, 1923, **434**, 219.

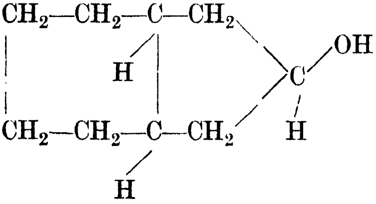
[5] Kay and Stuart, *J.*, 1926, 3038.

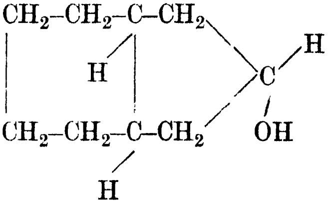
In the case of the β-hydroxy- and β-amino-decahydronaphthalenes, all four isomers have been obtained.[1]

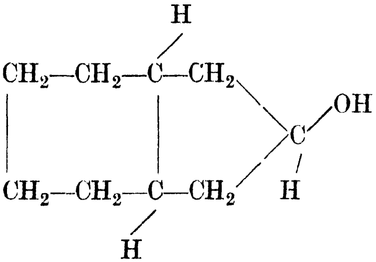
4. *Other Ring-Systems*

It is evident that this type of isomerism may show itself in other cases wherein two rings have a couple of atoms in common; and already several examples have been detected.

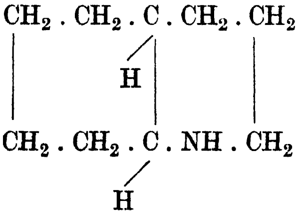
Three forms of hexahydro-β-hydrindol have been isolated,[2] two being *meso*-forms and the third a racemic variety.

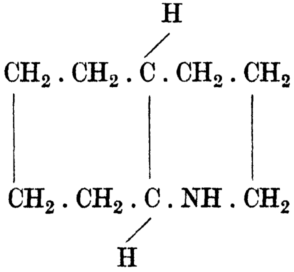






By hydrogenating quinoline by means of platinum black in a solution of acetic acid containing hydrochloric acid, the product was found to contain 65 per cent. of a new isomeride of decahydroquinoline.[3] The two possible configurations obviously are those shown below:





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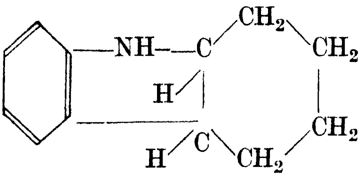
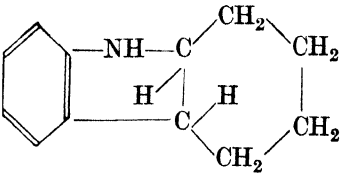
[1] Hückel and others, *Annalen*, 1926, **451**, 109.

[2] Hückel and Friedrich, *Annalen*, 1926, **451**, 132.

[3] Hückel and Stepf, *Annalen*, 1927, **453**, 163.

An interesting case is provided by hexahydrocarbazole,[1] for here there are three ring-systems fused together. When tetrahydrocarbazole is reduced with tin and hydrochloric acid, a yield of 1 per cent. to 2 per cent. of a previously unknown hexahydro-derivative was isolated. The two isomerides may be formulated thus :—





The foregoing facts seem ample to establish the correctness of Mohr's speculations.

[1] Gurney, Perkin, and Plant, *J.*, 1927, 2676.

CHAPTER XII

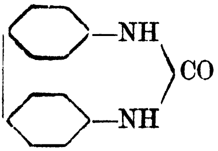
THE DIPHENYL PROBLEM

1. *The Kaufler Hypothesis*

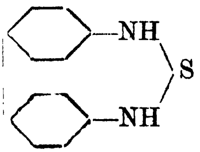
IN science, even erroneous hypotheses may have their uses; and the history of the diphenyl isomerism furnishes one of the best examples of this fact. Here was a case in which a number of isolated data were brought together under a single head by means of a simple hypothesis; and then, when further work showed that the hypothesis was untenable, investigators were stimulated to check the original evidence in its favour; and finally, it was found that mistakes had been made in many cases. Without the incentive provided by the hypothesis, these erroneous statements would never have been checked as a whole; and the reference books might easily have misled later workers who had need of the particular compounds which were misdescribed.

It is an ungrateful task to chronicle honest errors; and the first stage in the history of the diphenyl problem need not be dealt with in any great detail. One or two examples will be quite sufficient.

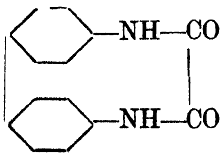
By acting on benzidine with reagents such as carbonyl chloride, various compounds were obtained to which the following formulæ were ascribed :—



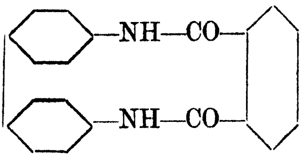
I. Carbonyl-benzidine[1]



II. Thiocarbo-benzidine[2]



III. Oxalyl-benzidine[3]



IV. Phthalyl-benzidine[4]

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[1] Michler and Zimmermann, *Ber.*, 1881, **14**, 2178.

[2] Borodine, *Jahresbericht*, 1860, 356.

[3] Schiff and Vanni, *Annalen*, 1890, **258**, 363.

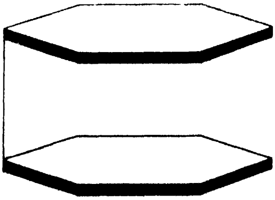
[4] Kolber, *Ber.*, 1904, **37**, 2882.

In each of these cases, it will be noticed, the reagent is assumed to have attacked the two amino-groups simultaneously. Now if the benzidine molecule be represented by :—

$$NH_2 — C_6H_4 — C_6H_4 — NH_2$$

the amino-groups should be far apart in space and therefore unlikely to react simultaneously with, say, carbonyl chloride.

This peculiarity suggested to Kaufler[1] the idea that in the diphenyl molecule the two rings might lie in planes * in such a way that the positions para to the points of junction would be adjacent in space :—



In this diagram, the two rings are supposed to be lying in planes perpendicular to the plane of the paper ; and the heavily-printed lines indicate the sides of the hexagons which are nearest to the reader.

When Kaufler's views were put forward, Baeyer's Strain Theory was still supposed to represent facts fairly well ; for nothing higher than nonomethylene had been obtained among the simpler cyclic compounds, and it was supposed that there were great difficulties in the way of a synthesis of rings containing a large number of atoms. With these ideas in the air, it was natural that Kaufler's suggestion should receive a certain support, since it seemed to offer a means of accounting for the stable existence of the eleven- and fourteen-membered rings shown in the formulæ above. Further, when applied to the benzidine change, it suggested a simple explanation of the mysterious para-coupling which is the marked feature of that rearrangement.

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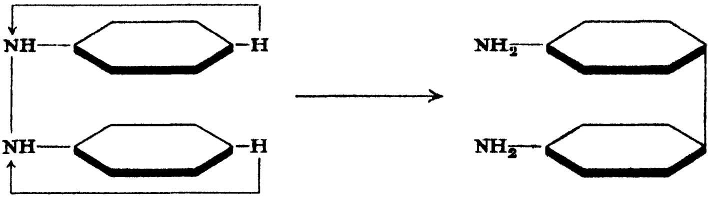
[1] Kaufler, *Annalen*, 1907, **351**, 151 ; *Ber.*, 1907, **40**, 3250.

* Kaufler's actual statement was that the planes of the rings were inclined at an angle to each other, but his diagrams showed them lying parallel.



For a time, the Kaufler hypothesis held the field ; and various pieces of research were fitted to it. Only one of these need be mentioned here. Since on Kaufler's assumptions the two amino-groups of benzidine are adjacent in space, it seemed possible that they could be made to react with the carbonyl groups of α-diketones so as to form cyclic compounds thus :—

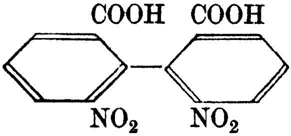
$$\begin{array}{l} C_6H_4{-}NH_2 \\ | \\ C_6H_4{-}NH_2 \end{array} + \begin{array}{l} O : C{-}CH_3 \\ \quad\;\; | \\ O : C{-}CH_3 \end{array} = \begin{array}{l} C_6H_4{-}N : C{-}CH_3 \\ | \qquad\qquad\;\; | \\ C_6H_4{-}N : C{-}CH_3 \end{array} + 2H_2O$$

Condensation of benzidine with diacetyl and with dibenzil was found to be practicable ; and it was assumed that the products were of the type shown above.

It was in connection with these compounds that the Kaufler hypothesis sustained an initial shock. Further investigation [1] established that their constitutions were not of the type which Kaufler's ideas suggested. But in the meanwhile light was thrown on the subject from a fresh direction by the study of the diphenic acids.

2. *Substitution-products of the Diphenic Acids*

By oxidizing the nitration-products of phenanthraquinone and also by direct nitration of diphenic acid, Schultz [2] obtained a dinitrodiphenic acid. As a result of an examination of this acid, Schmidt and Kämpf [3] came to the conclusion that it was 2 : 2′-dinitro-diphenic acid :—



The synthesis of the acid had not been carried out, however, and as a rigid proof of its constitution was required in the course of

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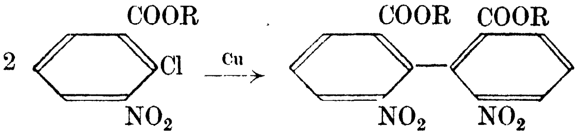
[1] Ferriss and Turner, *J.*, 1920, **117**, 1140.
[2] Schultz, *Annalen*, 1880, **203**, 95.
[3] Schmidt and Kämpf, *Ber.*, 1903, **36**, 3745.

a research by Kenner and Stubbings, these workers [1] proposed to prepare it in the following manner.

By oxidizing 2-chloro-3-nitrotoluene with dilute nitric acid, 2-chloro-3-nitrobenzoic acid was obtained; and on treating the ester of this last compound with copper powder, the ester of 6 : 6′-dinitro-diphenic acid was produced.

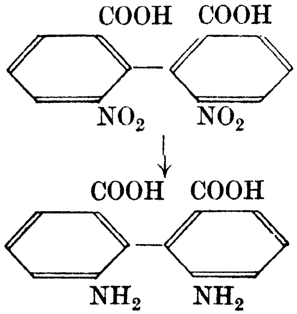


On hydrolysis, this ester yielded a surprise; for the acid derived from it melted at 263° C. without decomposition, whereas Schultz's acid melted at 297° C. and Schmidt's acid melted at 303° C. with decomposition.

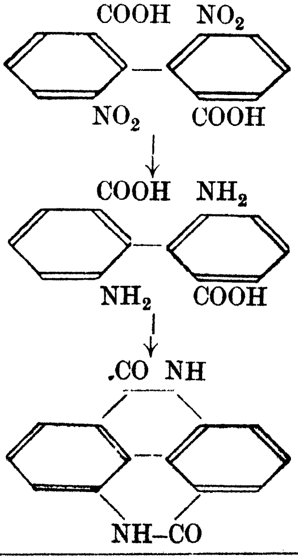
On reduction, Schultz's acid yields the corresponding diamino-acid; whereas Kenner's compound produces an internal di-lactam with extraordinary readiness, so much so that an attempt to isolate the intermediate diamino-compound failed.

Kenner and Stubbings suggested that 6 : 6′-dinitrodiphenic acid existed in two forms which they believed were stereoisomers; and on this basis they explained the phenomena thus :—

Schultz's Series.



Kenner and Stubbing's Series.



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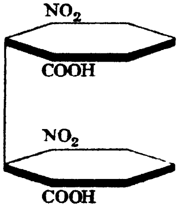
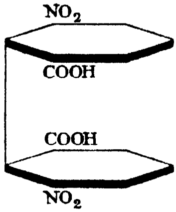
[1] **Kenner and Stubbings, *J.*, 1921, 119, 593.**

As Christie and Kenner [1] pointed out, there are at least three possible explanations for the behaviour of these diphenic acid derivatives. In the first place, both benzene rings may lie in one plane and there may be a hindrance to their free rotation about the bond which unites them. In these conditions, the isomerism would be akin to the *cis*-trans isomerism of maleic and fumaric acids, and no question of optical activity could arise. Secondly, the Kaufler hypothesis may be invoked; in which case the two isomeric acids would be represented thus:—

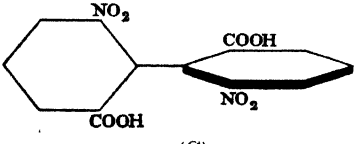


(A)

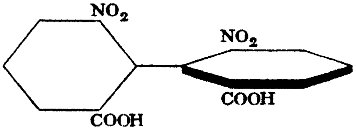


(B)

In this case, the *cis*-compound (A) possesses a plane of symmetry; whilst the *trans*-isomer (B) cannot be superposed on its mirror-image, and ought therefore to be capable of resolution into its antipodes. Finally, the two benzene rings may have a common axis, but the plane containing one ring may be perpendicular to the plane containing the second ring:—



(C)



(D)

In (C) the left-hand ring is supposed to lie in the plane of the paper, whilst the right-hand ring is assumed to lie in a plane inclined to the first at some angle other * than 90°. In this case the two nitro-groups and the two carboxyl radicles will lie at the corners of an irregular tetrahedron; and as an arrangement of this sort is not superposable upon its mirror-image, optical activity

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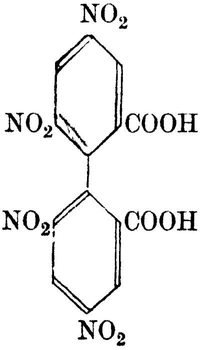
[1] Christie and Kenner, *J.*, 1922, **121**, 614.

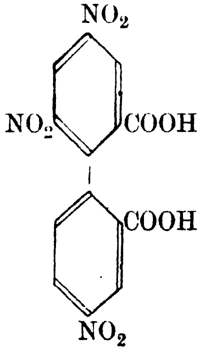
* If the two planes were perpendicular to each other, only one form of 6 : 6′-diphenic acid would be possible, since one model would be convertible into the other by mere rotation.

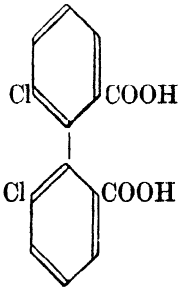
might be possible. There is a fourth possibility for the arrangement of the two rings, in which the model has neither an axis nor a plane of symmetry; but as it would demand more isomers than are known, it is unnecessary to consider it.

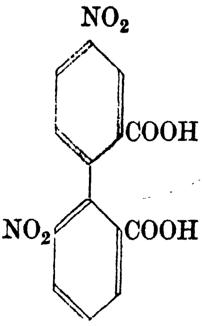
Christie and Kenner[1] found that Kenner's 6 : 6′-dinitrodiphenic acid yielded two brucine salts having different rotatory powers; so that the Kenner acid is clearly a mixture of two antipodic forms. This eliminated the possibility that the two benzene rings lie in one plane; and proved conclusively that either the Kaufler configuration or else the models suggested by Kenner and Christie must be relied on to account for the experimental results.

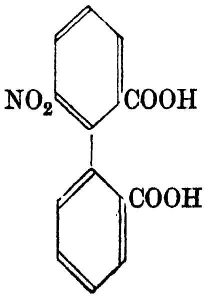
Further investigation extended this field of optical activity; and it was found that the following five acids[2] also existed in active forms :—











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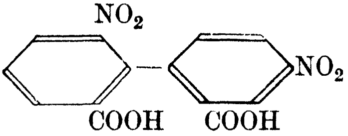
[1] Christie and Kenner, *J.*, 1922, **121**, 614.

[2] *Ibid.*, 1922, **121**, 614; 1923, **123**, 779; Christie, James, and Kenner, *ibid.*, 1948; Christie, Holderness and Kenner, *J.*, 1926, 671; Bell and Kenyon, *Chem. and Ind.*, 1926, **45**, 864.

At this point it may be well to forestall a possible criticism. It might be suggested that the benzene molecule is not necessarily a plane arrangement and that the optical activity observed by Christie and Kenner might have its origin in the asymmetry of a single benzene nucleus. This criticism can hardly be maintained in view of the failure of numerous attempts to resolve substituted benzenes into optically active components.[1]

The series of diphenyl acids had not yet yielded all its surprises with the discoveries which have just been described. A repetition[2] of the work of Schmidt and Kämpf on Schultz's dinitro-diphenic acid led to the discovery that instead of the 2 : 2′-dinitro-diphenyl which Schmidt and Kämpf believed they had obtained on driving off carbon dioxide, the actual product is 2 : 4′-dinitro-diphenyl. Thus Schultz's acid is not 6 : 6′-dinitro-diphenic acid, but is 4 : 6′-dinitro-diphenic acid with the structure shown below :—



Thus Schultz's acid and the acid of Christie and Kenner are not stereoisomers but simply structure-isomers, differing from each other in the position of a nitro-group.

Like the 6 : 6′-dinitro-diphenic acid of Christie and Kenner, Schultz's acid has been shown to exist in active forms.[3]

3. *The Collapse of the Kaufler Hypothesis*

While this work was proceeding on the substituted diphenic acids, the original evidence upon which Kaufler had based his ideas was being subjected to revision, with the surprising result that all the data were found to be erroneous.[4]

The examples given in the first section of this chapter will be sufficient for the sake of illustration. The compound

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[1] Le Bel, *Bull. Soc. chim.*, 1882, [2], **38**, 98 ; Lewkowitsch, *J.*, 1888, **53**, 791 ; V. Meyer and Lühn, *Ber.*, 1895, **28**, 2795 ; Jones and Kewley, *Proc. Camb. Phil. Soc.*, 1904, **12**, 122.

[2] Christie, Holderness, and Kenner, *J.*, 1926, 671.

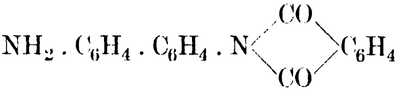
[3] *Ibid.*, 1926, 671.

[4] Le Fèvre and Turner, *J.*, 1926, 2476 ; *J.*, 1928, 963 ; Dennett and Turner, *J.*, 1926, 1759 ; Le Fèvre, Moir, and Turner, *J.*, 1927, 2330 ; Brady and McHugh, *J.*, 1923, **123**, 2047 ; Le Fèvre, *J.*, 1929, 733.

supposed to be carbonyl-benzidine (I.), turned out to be (I.a); the thio-carbo-benzidine (II.) was shown to have the structure (II.a); the oxalyl derivative to which the formula (III.) had been ascribed, was proved to have a free amino-group; and the phthalyl compound has the constitution (IV.a) and not (IV.).

$[NH_2 . C_6H_4 . C_6H_4 . NH]_2CO$ (I.a)

$NH_2 . C_6H_4 . C_6H_4 . N : C : S$ (II.a)



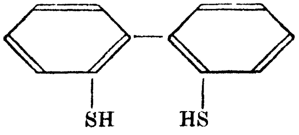
$$NH_2 . C_6H_4 . C_6H_4 . N\begin{matrix} CO \\ CO \end{matrix}C_6H_4$$

(IV.a)

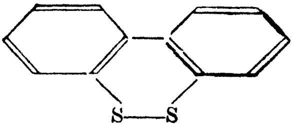
In none of these cases, as can be seen, do the two amino-groups of the benzidine molecule come into reaction simultaneously; and thus the phenomena which the Kaufler hypothesis was intended to explain do not exist in actual practice.

Williams and Weissberger[1] from an examination of the electrical moments of various diphenyl derivatives, inferred that in 4 : 4′-dichloro-diphenyl and 4 : 4′-dinitro-diphenyl, the rings are co-axial and cannot be inclined at an angle to each other; but in benzidine the molecule may have "a collapsed or folded structure." They are cautious to add, however, that their data are insufficient to establish the general truth of these conclusions.

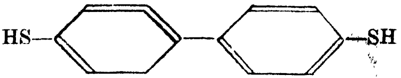
One of the most convincing pieces of evidence against the Kaufler hypothesis has been brought forward by Barber and Smiles.[2] By oxidizing 2 : 2′-dithioldiphenyl (I.), they obtained the diphenylene disulphide (II.).



(I.)



(II.)



(III.)

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[1] Williams and Weissberger, *J. Amer. Chem. Soc.*, 1928, **50**, 2332; compare Adkins, Steinbring, and Pickering, *ibid.*, 1924, **46**, 1917; Kühn and Albrecht, *Annalen*, 1927, **455**, 272.

[2] Barber and Smiles, *J.*, 1928, 1141.

Now obviously on the Kaufler hypothesis, the 4 : 4′-positions must be as near together in space as the 2 : 2′-positions ; and therefore 4 : 4′-dithiol-diphenyl (III.) should also give a disulphide on oxidation, if Kaufler's views be accurate. In practice, however, neither the 4 : 4′-dithiol-diphenyl nor the 3 : 3′-dithiol-diphenyl yield any such result. This seems absolutely convincing evidence on the subject.

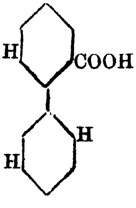
The net result of all this is perfectly plain. There is no evidence left which can be regarded as establishing the Kaufler hypothesis. All the evidence on which the hypothesis was first reared, turns out to be erroneous. And any fresh evidence which has real chemical value tells directly against Kaufler's views.

4. *Optical Activity in the Diphenyl Series*

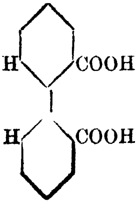
Though the Kaufler hypothesis is now out of court, it has left behind it the peculiar problem of optical activity among the substituted diphenic acids ; and at this stage it is desirable to consider the conditions under which this optical activity has been found to exist.

The first point which suggests itself is the relationship between structure and the occurrence of optical activity. Here the experimental material is sufficient to give a clue to the essential feature in the problem. The formulæ of ten acids are shown below, with the benzene rings printed as simple hexagons to avoid complicating the pictures. The five formulæ in the top line represent acids which have shown no sign of any capacity for resolution into optical antipodes ; whilst the five formulæ in the lower lines represent acids which have been demonstrated to be racemic.

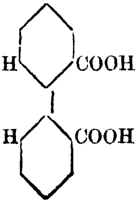
No resolution was attained with these acids :—



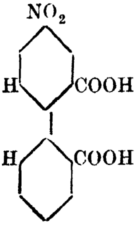
(I.)



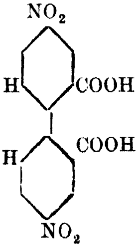
(II.)



(III.)

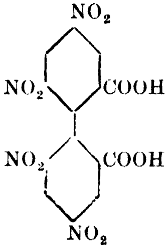


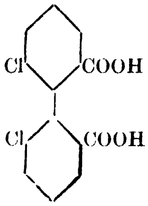
(IV.)

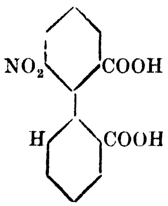


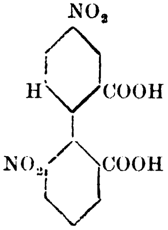
(V.)

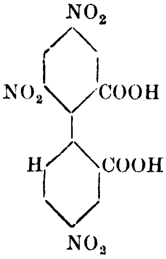
These acids are capable of resolution :—


(VI.)

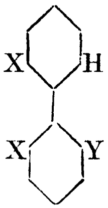

(VII.)


(VIII.)


(IX.)

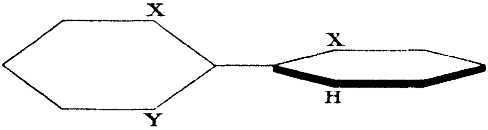

(X.)

Inspection of these two sets of formulæ reveals at a glance the difference between them. Taking the four positions which are ortho to the bond uniting the two phenyl nuclei, it is clear that optical activity does not occur unless *three out of the four* are occupied by substituents. If this condition be fulfilled, it is not necessary to have four *different* substituents attached to the diphenyl nucleus ; it is sufficient if the two substituents in the same benzene ring are different from each other. Thus diphenic acid, (II.), has not been resolved ; and, as the formula shows, it does not fulfil the condition about the three ortho-positions being filled by substituents. The dichloro-diphenic acid, (VII.), has been proved to exist in active forms ; and in it the four ortho-hydrogens of diphenic acid have been replaced by substituents. Further, in (VII.) the diphenyl nucleus carries a pair of unlike substituents in each ring ; but there are not four different substituents in all, so that the case is not parallel to that of the asymmetric carbon atom. Evidently a compound having the structure :—



would fulfil the conditions required for the production of optical activity.

At this point it becomes clear that the two benzene rings in the active compounds cannot lie in the same plane; because if they did so, the compound corresponding to the above formula would be symmetrical and hence unable to display optical activity. The hypothesis put forward by Christie and Kenner offers the easiest way out of the difficulty. If it be assumed that the planes of the two benzene rings are at right angles to each other,* then the following diagram will represent the conditions in the active molecules:—



Here the left-hand benzene ring is assumed to lie in the plane of the paper, whilst the right-hand one lies in a plane perpendicular to the paper. This model is not superposable on its mirror-image.

This model in itself is not sufficient, however; for if there be free rotation about the bond joining the two nuclei, the two rings could swing into a co-planar configuration and symmetry would be established which would extinguish the optical activity of the compounds. In the above diagram, for example, if the right-hand ring were turned through 90°, it would fall into the plane of the paper and hence the model would become a plane figure.

To evade this objection, it is necessary to postulate that the free rotation of the rings around their common axis is inhibited by some factor or other, so that they can never become co-planar.

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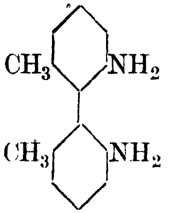
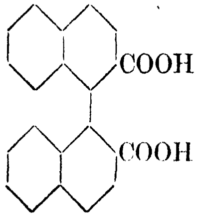
* This is the simplest assumption, though angles of inclination other than 90° are not excluded.

Various guesses [1] have been put forward as to the nature of the influence which prevents free rotation of the two nuclei. One of them depends upon a supposed "electrical repulsion" between the atoms in the four ortho-positions; but it is difficult to see why this should break down in the case of diphenic acid itself, since the two similar carboxyl groups in it ought surely to exert a considerable mutual repulsion if there is anything in the idea at all.

A much more satisfactory explanation is obtained by going back to the purely mechanical idea of steric hindrance and taking into account the bulk of the substituent groups. When the model is built up from the usual tetrahedra, it is found that two bulky ortho-substituents in the one ring will interfere with the free rotation of the second ring, owing to collisions between them and the third ortho-substituent. If two of the groups are small, then free rotation is possible. This agrees with the case of the inactive diphenic acids, for there the two ortho hydrogen atoms are not bulky enough to prevent the free rotation of the two rings about their common axis.

After the publication of this suggestion by Mills, other diphenyl derivatives [2] were obtained in optically active forms :—





both of these fulfil the requirements of Mills's hypothesis.

Further support is lent to the steric hindrance view by negative results.[3] For example, in the three formulæ shown below, it is clear that the substituents are not in positions which would

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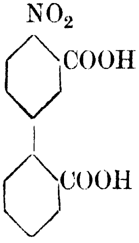
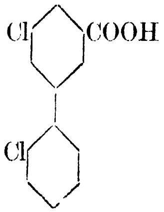
[1] Turner and Le Fèvre, *Chem. and Ind.*, 1926, **45**, 831; Mills, *ibid.*, 883, 905; Bell and Kenyon, *ibid.*, 864; *J.*, 1926, 3045.

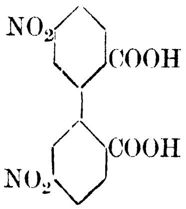
[2] Meisenheimer, *Ber.*, 1927, **60**, [*B*], 1245; Kühn and Albrecht, *Annalen*, 1928, **464**, 91, **465**, 282; Kenner and Turner, *J.*, 1928, 2340; Kühn and Goldfinger, *Annalen*, 1929, **470**, 18; Mascarelli, *Gazzetta*, 1928, **58**, 627; Stanley and Adams, *Rec. trav. chim.*, 1929, **48**, 1035.

[3] McAllister and Kenner, *J.*, 1928, 1913; Kühn and Albrecht, *Annalen*, 1927, **455**, 272; Hyde and Adams, *J. Amer. Chem. Soc.*, 1928, **50**, 2499; Pufahl, *Ber.*, 1929, **62**, [*B*], 2817.

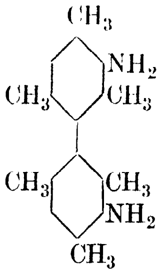
enable them sterically to hinder free rotation; and in practice these acids have not been resolved into active isomers.





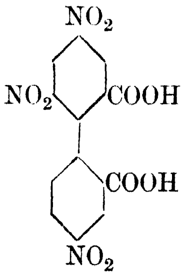


The electrical character of the groups seems to play a very minor part—if any—in the phenomenon. This is shown by the fact that 3 : 3′-diamino-dimesityl

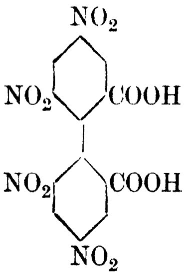


has been proved to be optically active,[1] although difference in "polarity" between the ortho-substituents is non-existent.

The effect of blocking the fourth ortho-position with a substituent[2] can be seen in the influence this exerts upon racemization:—



Racemized



Not racemized.

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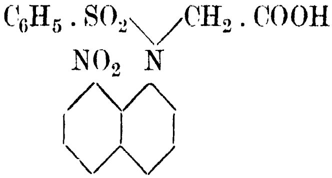
[1] Moyer and Adams, *J. Amer. Chem. Soc.*, 1929, **51**, 630.

[2] Kühn and Albrecht, *Annalen*, 1927, **458**, 221.

Even outside the diphenyl series, similar conditions seem to hold good, for the *peri*-naphthalene derivative :



has been resolved,[1] though its activity proved to be slight. Here the free rotation of the benzene-sulphonyl-glycyl group is apparently hindered by the presence of the nitro-group.

Further, Stanley and Adams[2] have succeeded in resolving 2, 2′-dihydroxy-3, 3′-dicarboxy-1, 1′-dinaphthyl into its optical isomers, a result which shows that the phenomenon persists even in the dinaphthyl series.

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[1] Mills and Elliott, *J.*, 1928, 1291.

[2] Stanley and Adams, *Rec. trav. chim.*, 1929, **48**, 1035.

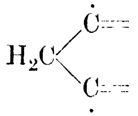
CHAPTER XIII

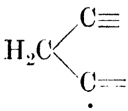
NEW ORGANO-ALKALI COMPOUNDS

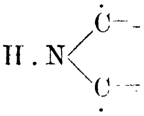
1. *Introductory*

Among the most familiar phenomena of organic chemistry is the displacement of a hydrogen atom by sodium. Acetylene, acetic acid, malonic ester, cyanacetic ester, cyclopentadiene, biuret, and pyrrol—to name only a few compounds—contain replaceable hydrogen atoms. In these cases, it appears that the property depends upon the accumulation of residual affinity in the immediate neighbourhood of the replaceable hydrogen; for one or other of the following groupings is always present:

$$H.C\equiv \qquad\qquad H.O.\dot{C}=$$







Where a choice is possible, the sodium atom on entering the molecule, appears to attach itself by preference to a non-carbon atom.

On the other hand, many of the polyvalent metals are known to form alkyl derivatives which contain no structures similar to those shown above; for in their case there is a direct attachment of alkyl and aryl radicles to the metallic atom, as in zinc methyl, $Zn(CH_3)_2$, and mercury diphenyl, $Hg(C_6H_5)_2$. It is, however, only in quite recent times that a study has been made of the simple alkyl and aryl derivatives of lithium, sodium, and potassium; for the experimental difficulties which stood in the way were found to be considerable.

As far back as 1858, Wanklyn[1] observed that metallic

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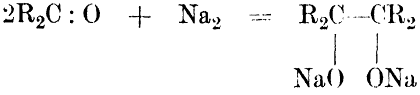
[1] Wanklyn, *Annalen*, 1858, **107**, 125; **108**, 168; 1859, **111**, 234; 1866, **140**, 211.

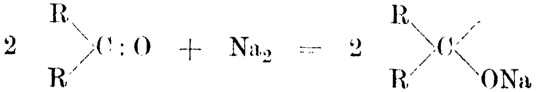
sodium dissolves in zinc ethyl with the formation of a double compound. A year later, Buckton [1] studied the action of sodium upon the mercury alkyl derivatives ; but owing to the readiness with which the products were oxidized, he was unable to obtain definite results. The work of Schorigin [2] brought some fresh points to light ; but still the experimental difficulties stood in the way of fuller knowledge. It was left to later investigators with improved technique to clear up the field.[3]

A very similar delay is found, as will be seen later, in the history of the metal-ketyls, which are prepared by the action of sodium upon certain ketones. When the alkali metals act upon ketonic compounds, the reaction is found to follow one of the three following courses. (1) An alkali compound may be formed, with the evolution of hydrogen. This takes place when the ketone is capable of enolization ; and it is not confined to cases in which the group $—CO—CH_2—CO—$ is present ; for acetone itself has been found to react with sodium in the form $CH_2 : C(OH) . CH_3$. Reactions of this type may lead to very complex products ; for condensations may set in, and there may be reduction due to the liberated hydrogen. (2) The alkali metal may be taken up by the ketone without elimination of hydrogen, yielding reaction-products from two molecules of the ketone :



$$2R_2C : O + Na_2 = \begin{array}{c}R_2C—CR_2\\ \vert \quad\ \ \vert\\ NaO\ \ ONa\end{array}$$

Finally, (3) the alkali metal may attack a single molecule of the ketone, without the evolution of hydrogen, forming a metal-ketyl containing a trivalent carbon atom :



Cases (2) and (3) are observed only when the ketone is incapable of enolization. Our present knowledge is not sufficient to

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[1] Buckton, *Annalen*, 1859, **112**, 222.

[2] Schorigin, *Ber.*, 1908, **41**, 2711 ; 1910, **43**, 1931.

[3] The fullest account of this work, including details not published elsewhere, is to be found in Schlenk's article in Houben-Weyl's *Die Methoden der organischen Chemie*, Band IV., pp. 957 ff. (1924). In the journals, see Schlenk and his collaborators, *Ber.*, 1914, **47**, 473 ; 483, 1664 ; 1916, **49**, 608 ; 1917, **50**, 262 ; 1922, **55**, 2285.

enable us to predict whether a non-enolizable ketone will yield by preference reaction (2) or reaction (3).

2. *The Alkali-alkyls*

When metallic lithium or sodium acts upon an alkyl derivative of mercury, the reaction [1] takes the following course :

$$HgR_2 + Na_2 = 2Na . R + Hg$$

In practice,[2] however, the matter is by no means simple, as special precautions have to be observed owing to the great sensitiveness of the alkali-alkyls.

For example, in the case of sodium methyl, $CH_3 . Na$, metallic sodium in a finely-divided state is covered with absolutely dry ligroin in a special apparatus through which thoroughly-dried nitrogen is passed to exclude all traces of air and moisture. The proper quantity of mercury methyl is then added, and the apparatus is sealed off from contact with the air. After the mixture has stood for some days at a temperature of 65° C., a small amount of a white powder separates out and the particles of sodium become covered with a yellowish crust. At the same time, the liberated mercury forms an amalgam with the unaffected sodium. In order to separate the powdery sodium methyl from the amalgam, the apparatus is placed in a freezing-mixture, which has the effect of loosening the deposit of alkyl derivative from the surface of the sodium particles ; and thereafter by decantation and filtration in a special apparatus a separation of the two materials is attained.

In the preparation of lithium methyl, $Li . CH_3$, advantage is taken of the fact that it is insoluble in a mixture of petroleum ether and petroleum benzine, whereas lithium ethyl is soluble. A solution of lithium ethyl in petroleum benzine is mixed with a solution of mercury dimethyl in petroleum ether, and the lithium methyl formed by double decomposition is precipitated :

$$\underset{\text{Soluble.}}{2Li . C_2H_5} + \underset{\text{Soluble.}}{Hg(CH_3)_2} = \underset{\text{Insoluble.}}{2Li . CH_3} + \underset{\text{Soluble.}}{Hg(CH_3)_2}$$

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[1] Buckton, *Annalen*, 1859, **112**, 222 ; Acree, *J. Amer. Chem. Soc.*, 1903, **29**, 590 ; Schorigin, *Ber.*, 1908, **41**, 2711 ; 1910, **43**, 1931 ; Schlenk and Holtz, *Ber.*, 1917, **50**, 262.

[2] See Schlenk's article in Houben-Weyl's *Methoden der organischen Chemie*, IV., p. 959 (1924).

Here also, of course, all the operations are conducted in a dry nitrogen atmosphere.

Sodium methyl is generally obtained in an impure state, contaminated with some coloured material. Lithium ethyl has been prepared quite pure. It forms transparent crystals melting in a nitrogen atmosphere at 95° C. In the absence of air it can be distilled without much decomposition. It is soluble in benzene and the low-boiling hydrocarbons. Ether decomposes it readily according to the following equation:

$$Li . C_2H_5 + (C_2H_5)_2O = C_2H_5OLi + C_2H_4 + C_2H_6$$

Phenol acts upon sodium methyl with the production of sodium phenate.

In order to observe the reactions of the sodium alkyls it is not necessary to isolate them in a pure state. By mixing together metallic sodium, the proper mercury alkyl, and the third substance upon which the sodium alkyl is to act, it is possible to obtain the same end-product as would be produced by the direct action of the sodium alkyl upon the third substance. In this way [1] from benzophenone, sodium, and mercury diethyl, it was found that diphenyl-ethyl-carbinol, $(C_6H_5)_2C(Et) . OH$, was formed. Benzoic ester with sodium and mercury diethyl gave diethyl-phenyl-carbinol, $C_6H_5 . C(Et)_2 . OH$. The action of carbon dioxide upon a mixture of sodium and mercury di-isoamyl yielded isobutyl-acetic acid, $(CH_3)_2CH . CH_2 . CH_2 . COOH$. When benzene or its homologues are used as solvents in these reactions, complications arise, for the hydrocarbons themselves are attacked during the process. It is noteworthy that homologues of benzene are more susceptible in the side-chain than in the nucleus. Thus when toluene is used as a solvent in the reaction between sodium, carbon dioxide, and mercury diethyl, a certain quantity of phenyl-acetic acid is produced. Sodium ethyl reacts with carbon monoxide [2] to yield various products, among which is a ketone.

In view of further facts which will be mentioned later in this chapter, it should be noted that the alkali-alkyls when pure are colourless substances.

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[1] Schorigin, *Ber.*, 1908, **41**, 2711.

[2] Wanklyn, *Annalen*, 1866, **140**, 211; Schlubach, *Ber.*, 1919, **52**, 1910

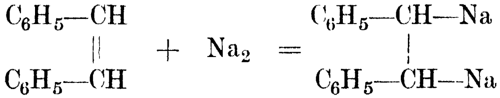
3. *The Alkali-aryls*

The aryl derivatives of the alkali metals have been obtained by four different methods: (1) by the action of mercury aryl derivatives upon metallic sodium; (2) by the double decomposition of an alkali-alkyl with a mercury-aryl derivative; (3) by the addition of metallic atoms to ethylenic linkages; and (4) by the union of alkali metals with free radicles of the triphenylmethyl type.

The applications of the first two methods to the preparation of lithium phenyl are illustrated by the following equations :—

$$Hg(CH_3)_2 + Li_2 = 2Li\,.\,CH_3 + Hg$$
$$Hg(C_6H_5)_2 + 2Li\,.\,C_2H_5 = 2Li\,.\,C_6H_5 + Hg(C_2H_5)_2$$

In the third method, the process employed is as follows.[1] The ethylene derivative, such as stilbene or tetraphenyl-ethylene, is dissolved in dry ether and mixed with sodium in a sealed tube from which air has been excluded. After having been shaken for a time which varies from hours to days, the liquid becomes coloured; and eventually the sodium derivative separates out in the form of a fine powder, which is isolated with special precautions. In the case of stilbene, the addition takes place as shown below :



$$\begin{array}{r} C_6H_5\text{—}CH \\ \| \\ C_6H_5\text{—}CH \end{array} + Na_2 = \begin{array}{l} C_6H_5\text{—}CH\text{—}Na \\ \qquad\quad | \\ C_6H_5\text{—}CH\text{—}Na \end{array}$$

The fourth method [2] consists in allowing an ethereal solution of the triarylmethyl to act upon sodium powder. Rather unexpectedly, triphenylmethyl itself is the only member of the series which up to the present has been found to react with difficulty; its homologues readily react thus :

$$2R_3C + Na_2 = 2R_3C\,.\,Na$$

When sodium amalgam is used instead of metallic sodium, triphenylmethyl gives the normal reaction smoothly.

It seems of interest to point out certain factors which have a bearing upon the production of alkali-aryls by the third and fourth methods.

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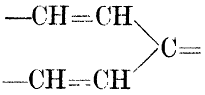
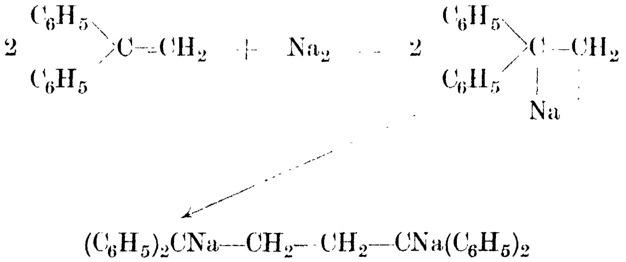
[1] Schlenk and Appenrodt, *Ber.*, 1914, **47**, 473.

[2] Schlenk and Marcus, *Ber.*, 1914, **47**, 1664.

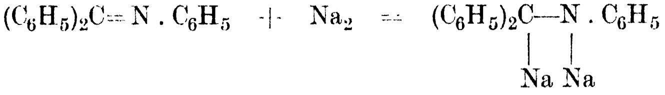
In order that sodium may act upon a double linkage, one of two conditions must be fulfilled. The carbon atoms united by the ethylenic bond must be joined directly to benzene nuclei, as in stilbene or anthracene ; or else the grouping



must be present in the structure of the reacting molecule. For example, diphenyl-ethylene reacts as shown below, only the carbon atom carrying the two phenyl groups being attacked :

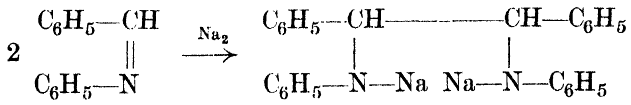


It is noteworthy that when these conditions are fulfilled, the carbon-nitrogen double bond is attacked by sodium ; but there it is essential to have two phenyl radicles attached to the carbon atom. Thus benzophenone-anil yields a disodium derivative :



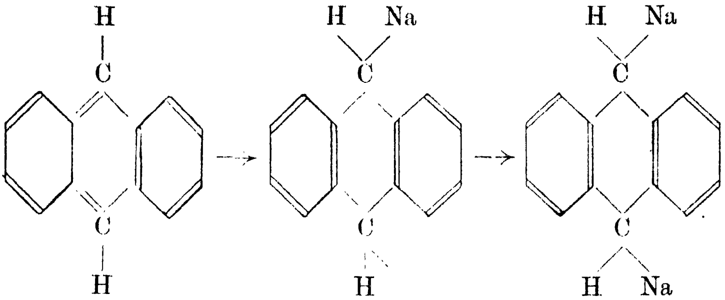
$$(C_6H_5)_2C{=}N\,.\,C_6H_5 + Na_2 = (C_6H_5)_2\underset{\displaystyle Na}{\underset{|}{C}}{-}\underset{\displaystyle Na}{\underset{|}{N}}\,.\,C_6H_5$$

whereas the anil of benzaldehyde takes up one atom of sodium at the nitrogen atom and then two molecules of this product unite together, as in the case of diphenyl-ethylene which was mentioned above.



$$2\begin{array}{c}C_6H_5{-}CH\\ \|\\ C_6H_5{-}N\end{array} \xrightarrow{Na_2} \begin{array}{ccc}C_6H_5{-}CH & \text{———————} & CH{-}C_6H_5\\ | & & |\\ C_6H_5{-}N{-}Na & & Na{-}N{-}C_6H_5\end{array}$$

The case of anthracene is interesting on account of the fact that the addition-reaction proceeds in two stages which are marked by colour-changes in the solution.



Initially colourless, the solution first turns deep-blue when one sodium atom is attached; and with the entry of the second sodium atom it goes violet.*

Turning now to the fourth method of preparing the alkali-aryls, it has already been pointed out that only in the case of triphenylmethyl itself was any difficulty encountered in the application of the general method. The source of trouble lies in the fact that, in presence of metallic sodium, triphenylmethyl is readily isomerized into the hydrocarbon [1] discovered by Ullmann and Borsum, $(C_6H_5)_3C—C_6H_4—CH(C_6H_5)_2$; and this naturally lowers the yield of alkali-aryl which it is possible to obtain. By substituting sodium amalgam for metallic sodium this is avoided; and if that be done, then there is no need to make a separate preparation of the triphenylmethyl, since it becomes unnecessary. Triphenyl-chloro-methane is used as a starting-point. On treatment with sodium amalgam, the chlorine atom is removed by the mercury of the amalgam and its place is taken by a sodium atom. The sodium triphenylmethyl thus produced reacts with the remaining triphenyl-chloro-methane to form triphenylmethyl which, with the excess of sodium, then gives the sodium triaryl:

$$\begin{aligned} 2(C_6H_5)_3C\,.\,Cl + Hg + Na_2 &= HgCl_2 + 2Na\,.\,C(C_6H_5)_3 \\ (C_6H_5)_3C\,.\,Cl + Na\,.\,C(C_6H_5)_3 &= NaCl + 2C(C_6H_5)_3 \\ Na_2 + 2C(C_6H_5)_3 &= 2Na\,.\,C(C_6H_5)_3 \end{aligned}$$

Only a brief survey of the properties of the alkali-aryls

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* This colour change is hard to explain on ordinary views of the relations between colour and constitution. Compare the case of the disodium derivative of benzophenone on p. 342.

[1] Ullmann and Borsum, *Ber.*, **1902, 35, 2877.**

can be given here ; but it will be found that they present certain peculiarities of considerable interest.

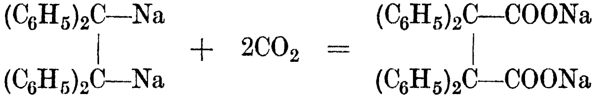
Lithium phenyl, $Li.C_6H_5$, resembles the alkali-alkyls in being a white crystalline powder. It reacts violently with water. When burned in air, it shows a *yellow* flame, quite unlike the usual flame-colour of lithium.

When the metallic atom is not directly attached to the phenyl nucleus, a complete change in properties is observed. Sodium benzyl, $Na.CH_2.C_6H_5$, is strongly coloured red ; sodium diphenylmethyl, $Na.CH(C_6H_5)_2$, and sodium triphenylmethyl, $Na.C(C_6H_5)_3$, are also deeply coloured compounds. Now an examination of electrical conductivity in ethereal solution proves that the colourless alkali derivatives are non-electrolytes, whereas the coloured * alkali-aryls conduct the current. This cannot fail to recall to mind the behaviour of triphenylmethyl and the carbonium salts.

The disodium derivatives, obtained by acting upon double bonds with metallic sodium, are reactive like the simpler materials. In presence of air, they regenerate the original compounds from which they were prepared,

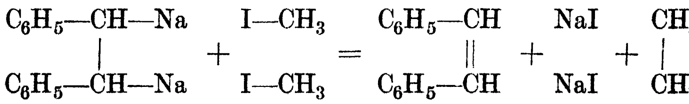
$$(C_6H_5)_2CNa{-}CNa(C_6H_5)_2 + O_2 = Na_2O_2 + (C_6H_5)_2C{:}C(C_6H_5)_2$$

though in some cases further decomposition ensues. Water hydrolyses them instantly, with the production of an alkali hydroxide and regeneration of the original material. Carbon dioxide acts with the formation of the salts of carboxylic acids



$$\begin{array}{l} (C_6H_5)_2C{-}Na \\ \quad\quad\;\; | \\ (C_6H_5)_2C{-}Na \end{array} + 2CO_2 = \begin{array}{l} (C_6H_5)_2C{-}COONa \\ \quad\quad\;\; | \\ (C_6H_5)_2C{-}COONa \end{array}$$

A rather curious result is observed when alkyl halides interact with these disodium derivatives. Instead of a replacement of sodium atoms by alkyl groups—which might be expected—a regeneration of the original compound is observed, accompanied by the production of a new hydrocarbon.



$$\begin{array}{l} C_6H_5{-}CH{-}Na \\ \quad\quad\;\; | \\ C_6H_5{-}CH{-}Na \end{array} + \begin{array}{l} I{-}CH_3 \\ \\ I{-}CH_3 \end{array} = \begin{array}{l} C_6H_5{-}CH \\ \quad\quad\;\; \| \\ C_6H_5{-}CH \end{array} + \begin{array}{l} NaI \\ \\ NaI \end{array} + \begin{array}{l} CH_3 \\ \;\; | \\ CH_3 \end{array}$$

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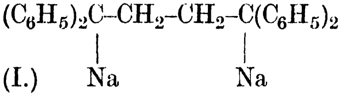
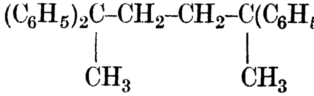
* The *colourless* alkali phenyls are not electrolytes.

In the case of the abnormal disodium derivatives which have the sodium atoms in the 1, 4- instead of the 1, 2-positions, methyl iodide acts normally by replacing the sodium atoms by methyl radicles. Thus the disodium derivative (I.), obtained from diphenyl-ethylene, gives rise to 2, 2, 5, 5-tetraphenylhexane (II.).



(I.)

$$(C_6H_5)_2\underset{\displaystyle Na}{\underset{|}{C}}-CH_2-CH_2-\underset{\displaystyle Na}{\underset{|}{C}}(C_6H_5)_2$$



(II.)

$$(C_6H_5)_2\underset{\displaystyle CH_3}{\underset{|}{C}}-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{|}{C}}(C_6H_5)_2$$

The reactions of the sodium triaryls[1] are of special interest. There appears to be a close parallelism between sodium triphenylmethyl and the Grignard reagent, though the sodium compound is much more active than the magnesium derivative. It should be noted that sodium triphenylmethyl is very readily converted into triphenylmethane. When the sodium derivative acts upon any substance containing a hydroxyl radicle, triphenylmethane is formed; and thus sodium triphenylmethyl, like the Grignard reagent, is a sensitive reagent for the detection of enolic hydroxyl groups. Ammonia acts in a similar manner on sodium triphenylmethyl:

$$(C_6H_5)_3C—Na + NH_3 = (C_6H_5)_3C—H + NH_2Na$$

A few illustrations will bring to light the close resemblance between the Grignard reactions and those of sodium triphenylmethyl. When carbon dioxide acts on sodium triphenylmethyl, the sodium salt of triphenyl-acetic acid, $(C_6H_5)_3C\,.\,COONa$, is formed. With sulphur dioxide, an exactly analogous reaction leads to the production of a sulphinate, $(C_6H_5)_3C\,.\,SO_2\,.\,Na$. Alkyl halides replace the sodium atom of the sodium triphenylmethyl by an alkyl radicle. When an aldehyde cannot yield a hydroxyl group by enolization, it reacts normally with sodium triphenylmethyl. For instance, formaldehyde yields $(C_6H_5)_3C.CH_2OH$, and benzaldehyde gives $(C_6H_5)_3C.CHOH.C_6H_5$. If the aldehyde, however, can be isomerized into an enolic variety, then triphenylmethane is formed. A similar state of affairs is found with the esters. When there is a hydrogen atom attached to the carbon atom carrying the carbethoxy-group,

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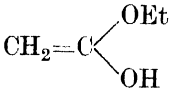
[1] Schlenk and others, *Ber.*, 1914, **47**, 1664; 1916, **49**, 608; 1922, **55**, 2285; Schlubach, *Ber.*, 1919, **52**, 1910.

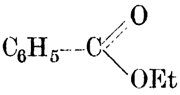
the reaction proceeds with the formation of triphenylmethane. For instance, acetic ester behaves as if it had the structure (I.); whereas benzoic ester (II.) obviously cannot furnish an enolic form, and the product in its case is β-benzopinacoline, $(C_6H_5)_3C\,.\,CO\,.\,C_6H_5$.

(I.)



$$CH_2{=}C\begin{matrix}\diagup OEt\\ \diagdown OH\end{matrix}$$

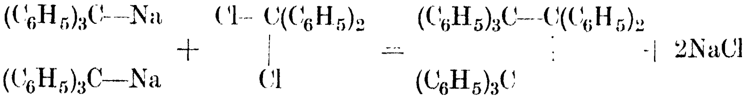
(II.)



$$C_6H_5{-}C\begin{matrix}\diagup\!\!\diagup O\\ \diagdown OEt\end{matrix}$$

This benzopinacoline is formed also by the action of sodium triphenylmethyl upon benzoyl chloride, the reaction being a simple elimination of sodium chloride.

Two peculiar reactions of sodium triphenylmethyl deserve special attention. When it reacts with benzophenone chloride, a mixture of triphenylmethyl and pentaphenylethyl is formed:



$$\begin{array}{l}(C_6H_5)_3C{-}Na\\ (C_6H_5)_3C{-}Na\end{array} + \begin{array}{c}Cl{-}C(C_6H_5)_2\\ |\\ Cl\end{array} = \begin{array}{l}(C_6H_5)_3C{-}C(C_6H_5)_2\\ \qquad\qquad :\\ (C_6H_5)_3C\end{array} + 2NaCl$$

It appears as if octaphenyl-propane were formed and then dissociated into the two radicles, each of which contains trivalent carbon.

The most interesting product obtained from sodium triphenylmethyl is prepared as follows.[1] Sodium triphenylmethyl is mixed in ethereal solution with tetramethyl ammonium chloride. Excess of ammonium salt is removed by solution in pyridine and precipitation with ether. Red crystals are obtained, which have a composition corresponding to the formula $(C_6H_5)_3C{-}N(CH_3)_4$. The compound, as can be seen by inspection, has *five* alkyl groups attached to a nitrogen atom. On testing the material's conducting power in pyridine solution, it was found to be an electrolyte. Thus for the first time a compound has been obtained in which an aryl radicle acts as the anion of an ammonium derivative.

By parallel methods, the compound $(C_6H_5)_2N{-}N(CH_3)_4$ has been prepared from potassium diphenylamine and tetramethylammonium chloride; and this diphenylamino-tetramethylammonium also yields ions in pyridine solution.

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[1] Schlenk and Holtz, *Ber.*, 1916, **49**, 608; compare Kraus and Kawamura, *J. Amer. Chem. Soc.*, 1923, **45**, 2756.

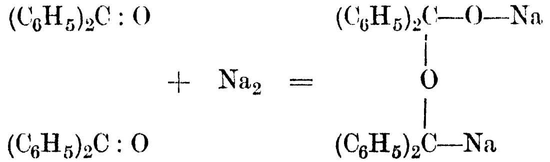
The facts described in the foregoing pages give some idea of the interesting points presented by these alkali-aryl derivatives; and very little thought will show that they suggest some problems which will have to be taken into account in framing the ultimate theory of valency.

4. *The Metal-ketyls*

During an investigation of the action of sodium upon certain aldehydes and ketones dissolved in indifferent solvents, Beckmann and Paul[1] observed that diaryl ketones (such as benzophenone) yielded results which were surprising in more ways than one. In the first place, the reaction which occurred did not lead to any evolution of hydrogen; secondly, the products were strongly coloured; and, thirdly, they were extraordinarily sensitive materials with respect to oxygen or moisture.

The dark-blue product which was thus prepared from benzophenone had a composition corresponding to one molecule of the ketone combined with one atom of sodium.* When acted upon by water it yielded, according to the conditions, either a mixture of benzophenone and benzohydrol, $C_6H_5—CH(OH)—C_6H_5$, or else a mixture of these two products along with benzopinacoline, $(C_6H_5)_2C(OH)—(HO)C(C_6H_5)_2$. On treatment with carbon dioxide, a yellow powder was obtained which, when decomposed by water, gave benzophenone and sodium benzilate, $(C_6H_5)_2C(OH) . COONa$.

Beckmann and Paul assumed that the blue compound was formed according to the following equation:



$$\begin{array}{l}(C_6H_5)_2C:O\\ \\ \\ \\(C_6H_5)_2C:O\end{array} \quad + \quad Na_2 \quad = \quad \begin{array}{l}(C_6H_5)_2C—O—Na\\ \qquad\quad |\\ \qquad\quad O\\ \qquad\quad |\\(C_6H_5)_2C—Na\end{array}$$

In view of the strangeness of these results, it is surprising that no further work was carried out in this field for a number of years; but apparently the difficulties arising out of the great

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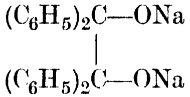
[1] Beckmann and Paul, *Annalen*, 1891, **266**, 1.

* This result, of course, does not enable us to determine whether the material is composed of one molecule of ketone plus one atom of sodium or of two molecules of ketone united to two sodium atoms.

reactivity of the substances prevented the matter being examined, until in 1903, Acree[1] repeated the experiments. To account for the results, he proposed the following formula for the blue compound :



$$\begin{array}{c}(C_6H_5)_2C—ONa\\ |\\ (C_6H_5)_2C—ONa\end{array}$$

At first sight, this structure gives no reason for the marked colour of the compound, for according to all normal rules a sodium derivative of this description should be colourless.

There the matter rested, however, until Schlenk and Weickel[2] approached the field with fresh ideas. In order to obtain a better crystalline material, they chose for their investigation not benzophenone, but di-diphenyl ketone, $(C_6H_5 . C_6H_4)_2C : O$.

Schlenk and Weickel attempted to determine the molecular weight of the sodium derivative in order to see whether its molecule contained one or two sodium atoms ; but in this they were unsuccessful, since according to them the coloured solutions contain colloidal or highly complex forms of the material, so that the results of ordinary molecular weight determinations are of no value. At a later date, Schlenk and Thal[3] surmounted this difficulty in a very ingenious manner. A solution of the ketone was placed in an air-free, nitrogen-filled boiling-point apparatus and the boiling-point was carefully determined. Pieces of pure metallic potassium were then added to the solution, and the boiling-point of the now coloured liquid was determined. No change in boiling-point was found, which, of course, proves that the same number of molecules is present in both cases. This excludes the possibility of the formation of compounds having formulæ like those of Beckmann-Paul or Acree, since in those cases the number of molecules in solution would be lessened after the reaction, owing to two ketone molecules uniting to form a single molecule of the sodium derivative. Thus although the actual molecular weight of the solid sodium derivative remains unknown, the Schlenk-Thal experiments prove that the reaction initially consists in the union of one atom of alkali metal with one molecule of ketone.

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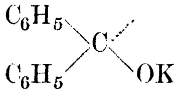
[1] Acree, *Am. Chem. J.*, 1903, **29**, 604.

[2] Schlenk and Weickel, *Ber.*, 1911, **44**, 1182.

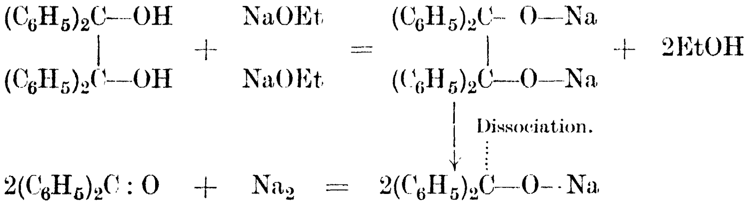
[3] Schlenk and Thal, *Ber.*, 1913, **46**, 2840.

A further experiment of Schlenk and Thal served to clear up the whole matter, although at the first glance it seems rather to confuse the problem. When benzopinacone is suspended in benzene and treated with an alcoholic solution of sodium ethylate, the same sodium derivative is formed as is obtained by the action of sodium upon benzophenone. This appears to support the Acree formula; but the Acree formula will not agree with the boiling-point phenomena. How can these results all be brought into concord?

Schlenk and Thal suggested the simplest explanation by assuming that the coloured materials are really free radicles containing trivalent carbon atoms. On that assumption, the sodium derivative of benzophenone will have the formula



and the production of this substance from benzopinacone and benzophenone can be expressed as shown below:



$$\begin{array}{l}(C_6H_5)_2C{-}OH\\ \quad |\\ (C_6H_5)_2C{-}OH\end{array} + \begin{array}{l}NaOEt\\ \\ NaOEt\end{array} = \begin{array}{l}(C_6H_5)_2C{-}O{-}Na\\ \quad |\\ (C_6H_5)_2C{-}O{-}Na\end{array} + 2EtOH$$

$$\downarrow \text{Dissociation.}$$

$$2(C_6H_5)_2C:O + Na_2 = 2(C_6H_5)_2C{-}O{-}Na$$

This explanation is now accepted* as the most probable solution of the problem; and these alkali derivatives of the diaryl ketones (and certain other substances to be mentioned later), which contain a trivalent carbon atom carrying the group —ONa in addition to two hydrocarbon radicles, are termed *metal-ketyls*.

Although the direct action of sodium furnishes satisfactory yields of metal-ketyls from certain ketones, it gives poor results in other cases; and with these last compounds a different method is generally employed. The most soluble of all the known metal-ketyls is potassium phenyl-diphenyl ketyl, $C_6H_5 . C_6H_4{-}C(OK){-}C_6H_5$. When an ethereal solution of this is mixed with dimethyl-pyrone, also dissolved in ether, a double

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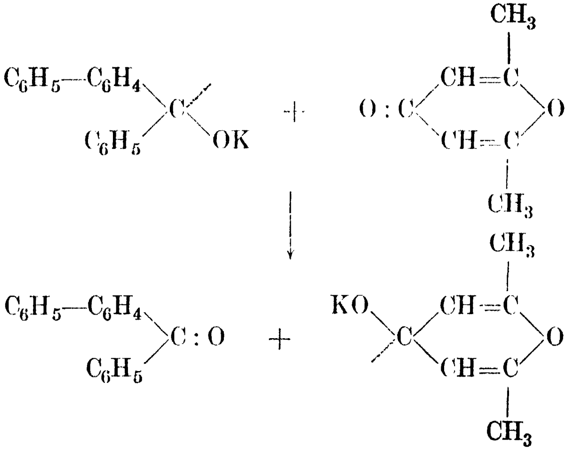
* Compare, however, Schmidlin, *Das Triphenylmethyl* (1914), pp. 186 ff.

decomposition occurs which yields phenyl-diphenyl ketone and the potassium ketyl of dimethyl-pyrone :



The bright red potassium ketyl of dimethyl-pyrone is precipitated, leaving the solution colourless.

A large number of potassium ketyls have been prepared by either of the foregoing methods ; and it may be convenient to gather them together in a table. The first column gives the name of the ketone from which the ketyl was prepared ; in the second column, the composition of the ketyl is placed ; whilst the third column contains notes of the ketyls' tints.

Ketone.	*Ketyl.*	*Colour.*
Dimethyl-pyrone . . .	$C_7H_8O_2K$	Bright cinnabar-red
β-Benzopinacoline . . .	$C_{26}H_{20}OK$	Deep red
Phthalophenone	$C_{20}H_{14}OK$	Dark red
N-Methyl-isatin	$C_9H_7O_2K$	Deep blue
O-Methyl-isatin	$C_9H_7O_2K$	Deep violet
m-Dibenzoyl-benzene . .	$C_{20}H_{14}O_2K$	Dark red
p-Dibenzoyl-benzene . .	$C_{20}H_{14}O_2K_2$ *	Deep red
Furil	$C_{10}H_6O_4K$	Black
Phenanthrenequinone . .	$C_{14}H_8O_2K$	Dark brown

In addition to the simple ketyls given in the table above, some others remain to be described, since their composition

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* This dipotassium derivative might be regarded as having either a normal quinonoid structure or as possessing two trivalent carbon atoms in the para-position with regard to each other. In view of the fact that it ignites spontaneously when exposed to air, the latter formulation seems the more probable of the two.

has some complexity. From chromone, a compound is obtained which appears to contain one molecule of the ketyl $C_9H_6O_2K$ combined with one molecule of chromone itself, $C_9H_6O_2$. Somewhat similar results were obtained with *p*-benzoquinone. In one case a compound was obtained which had the composition corresponding to one molecule of ketyl plus one molecule of quinone, ($C_6H_4O_2K+C_6H_4O_2$). The results varied so much from experiment to experiment, however, that too much reliance need not be placed on this. It appears possible that something akin to quinhydrone formation may be taking place in these cases.

The behaviour of *o*-benzoquinone is peculiar. On treating an ethereal solution of potassium phenyl-diphenyl ketyl with this quinone a dark-green precipitate is formed, which later changes to a white material. On examination, this last substance is found to be the potassium derivative of catechol. If the method be reversed, so that the ketyl is added to the quinone—thus avoiding the presence of an excess of potassium—the solution turns intensely red-violet in tint. This phenomenon has not yet been completely cleared up, owing to the difficulty of isolating the extremely unstable substances involved.

Before leaving this section of the subject, mention must be made of one or two other investigations in an allied field. By the action of potassium upon benzil in dry benzene solution with the usual precautions, Staudinger and Binkert[1] obtained two products. With one molecule of potassium, a deep blue-violet solution was produced; whilst the addition of a second molecule of potassium yielded a deep-red solution from which a dark-red precipitate was thrown down. The action of oxygen on the precipitate produced mainly potassium benzoate with 20–30 per cent. of benzilic acid. It was suggested that the precipitate was the potassium derivative of dihydroxy-stilbene, $KO—C(C_6H_5):(C_6H_5)C—OK$; and that the substance containing half the quantity of potassium was a quinhydrone type.

Wieland[2] has prepared a compound which appears to be a phenyl ether corresponding in type to the metal-ketyls. When

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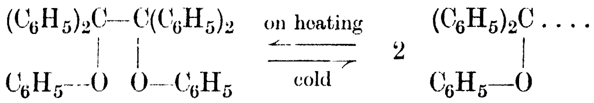
[1] Staudinger and Binkert, *Helv. Chim. Acta*, 1922, **5**, 703; Scheuing and Hensle, *Annalen*, 1924, **440**, 172.

[2] Wieland, *Ber.*, 1911, **44**, 2550.

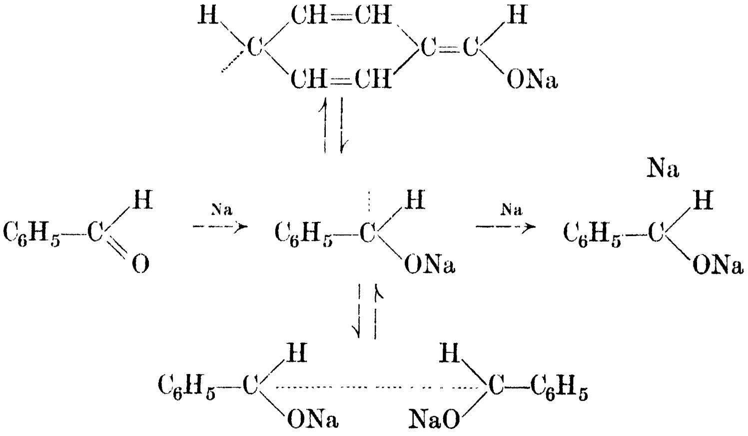
triphenylmethyl peroxide, $(C_6H_5)_3C—O—O—C(C_6H_5)_3$, is dissolved in hot naphthalene it is dissociated into the two free radicles $(C_6H_5)_3C—O$. These undergo rearrangement in part into the form $(C_6H_5)_2C—O—C_6H_5$; and by the union of these two, the compound (I.) shown below is produced :



(I.) Colourless. Red. (II.)

The present point of interest in the matter is that the solution in hot naphthalene is red in colour, which may reasonably be ascribed to the presence of the trivalent carbon derivative (II.) by dissociation, as indicated in the foregoing formulæ.

Benzaldehyde and the ethyl and phenyl esters of benzoic acid have been found to react with sodium, yielding highly-coloured reactive materials.[1] In order to account for the properties of the mono- and disodium derivatives of benzaldehyde, Blicke has put forward the following scheme, which brings the materials into parallel with compounds of the triphenylmethyl series :



A somewhat similar series of changes is assumed to account for

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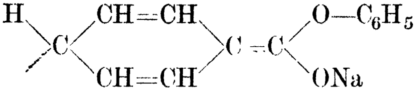
[1] Church, *Annalen*, 1863, **128**, 295 ; Frey, *Ber.*, 1895, **28**, 2520 ; Wahl, *Compt. rend.*, 1908, **147**, 73 ; Scheibler and others, *Ber.*, 1920, **53**, 390 ff. ; *Annalen*, 1923, **434**, 268 ; Lachman, *J. Amer. Chem. Soc.*, 1923, **45**, 708 ; Blicke, *ibid.*, 1924, **46**, 2560 ; 1925, **47**, 229.

the action of sodium upon phenyl benzoate, the quinonoid material in this case being regarded as having the structure:



It can be seen from the above formulæ that Blicke assumes the trivalency of one of the benzenoid carbon atoms, whereas Schlenk postulated trivalency in an extra-cyclic carbon atom.

Some account must now be given of the reactions of these interesting materials.[1] It must be remembered that, just like the alkali-alkyls and alkali-aryls, the metal-ketyls must be handled entirely in a nitrogen atmosphere, since the least trace of air or moisture would lead to their decomposition. In order to simplify the formulæ, we shall replace the symbol C_6H_5—C_6H_4— by —R, so that $(C_6H_5 . C_6H_4)_2CO$ becomes R_2CO.

When the sodium derivative of di-diphenyl-ketone is dissolved in ether, it yields a deep-green solution. Admission of oxygen leads to an immediate decolorization and a voluminous precipitate is deposited, which on examination is found to be a mixture of sodium peroxide with the original ketone. This agrees well with Schlenk's hypothesis as to the constitution of the ketyls.

Iodine reacts with the metal-ketyls, yielding an alkali iodide and regenerating the original ketone.

The action of methyl iodide is rather peculiar. When it is added to an ethereal solution of sodium di-diphenyl ketyl, the green solution changes its colour to yellow; and a precipitation of sodium iodide and the original ketone takes place. If the ethereal solution be now shaken with water, it goes colourless. On separating off the water and evaporating the ethereal solution, a residue is obtained which proves to be di-diphenyl-methyl carbinol, $R_2C(CH_3) . OH$.

With water, the sodium derivative of di-diphenyl ketone yields di-diphenyl carbinol, $R_2CH . OH$, and the original ketone. Nothing corresponding to a pinacone was detected.

Like the alkali-triaryls, the metal-ketyls have the power of combining with an atom of sodium by utilizing their free

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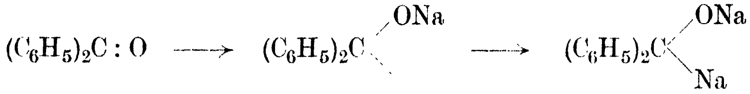
[1] Schlenk and Weickel, *Ber.*, 1911, **44**, 1182; Schlenk and Thal, *Ber.*, **1913**, **46**, 2840.

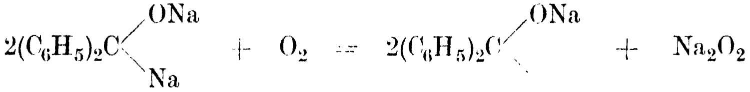
valency.[1] When excess of sodium powder is added to an ethereal solution of benzophenone, the deep blue colour of the mono-sodium derivative is first produced; but on standing, it changes to a dark-violet * tint:



$$(C_6H_5)_2C:O \longrightarrow (C_6H_5)_2C{<}\begin{smallmatrix}ONa\\ \cdot\end{smallmatrix} \longrightarrow (C_6H_5)_2C{<}\begin{smallmatrix}ONa\\ Na\end{smallmatrix}$$

Colourless. Blue. Violet.

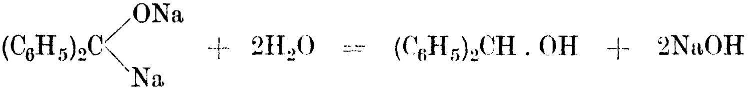
These disodium derivatives are, like the mono-sodium compounds, extremely sensitive to the action of oxygen or moisture. Oxygen converts them first into metal-ketyls; and finally the original ketone is regenerated:



$$2(C_6H_5)_2C{<}\begin{smallmatrix}ONa\\ Na\end{smallmatrix} + O_2 = 2(C_6H_5)_2C{<}\begin{smallmatrix}ONa\\ \cdot\end{smallmatrix} + Na_2O_2$$

$$2(C_6H_5)_2C{<}\begin{smallmatrix}ONa\\ \cdot\end{smallmatrix} + O_2 = 2(C_6H_5)_2C:O + Na_2O_2$$

Water decomposes them smoothly with the formation of secondary alcohols:



$$(C_6H_5)_2C{<}\begin{smallmatrix}ONa\\ Na\end{smallmatrix} + 2H_2O = (C_6H_5)_2CH.OH + 2NaOH$$

Carbon dioxide decomposes the disodium derivatives with the production of acids of the benzilic series:

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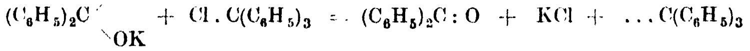
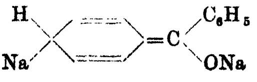
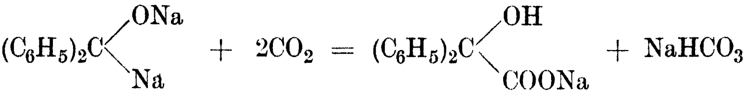
[1] Schlenk, *Houben-Weyl's Methoden der organischen Chemie*, Vol. IV., p. 977; Schlenk and others, *Ber.*, 1914, **47**, 486. When a metal-ketyl is treated with triphenyl-chloro-methane, triphenylmethyl is formed, and the original ketone is regenerated:



$$(C_6H_5)_2C{<}\begin{smallmatrix}\cdot\\ OK\end{smallmatrix} + Cl.C(C_6H_5)_3 = (C_6H_5)_2C:O + KCl + \ldots C(C_6H_5)_3$$

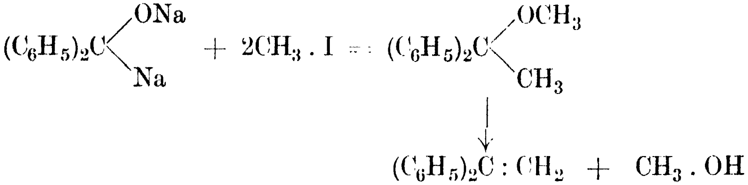
* Compare the similar colour-changes in the formation of the mono- and di-sodium derivatives of anthracene (p. 330). The coloration of $(C_6H_5)_2C(ONa)Na$ seems difficult to explain on ordinary assumptions. It would certainly be more easily accounted for by a formula such as





$$(C_6H_5)_2C\begin{cases}ONa\\Na\end{cases} + 2CO_2 = (C_6H_5)_2C\begin{cases}OH\\COONa\end{cases} + NaHCO_3$$

The action of alkyl halides is peculiar. Labile ethers of tertiary alcohols are formed first, which then decompose readily to yield ethylenic derivatives :

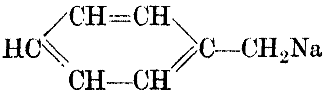


$$(C_6H_5)_2C\begin{cases}ONa\\Na\end{cases} + 2CH_3 . I = (C_6H_5)_2C\begin{cases}OCH_3\\CH_3\end{cases}$$
$$\downarrow$$
$$(C_6H_5)_2C : CH_2 + CH_3 . OH$$

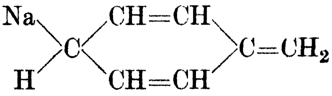
5. *Conclusion*

The facts described in earlier sections of this chapter suggest a number of problems which will doubtless be cleared up in due course by further investigation.

It is perhaps too early as yet to come to any definite conclusion with regard to the structure of the metal-ketyls ; but the evidence at present available seems to favour Blicke's views rather than Schlenk's. In the first place, lithium phenyl is colourless ; which proves that the mere direct linking of an alkali atom to carbon does not produce colour, even when a phenyl nucleus is present in the molecule. In marked distinction to this we have sodium benzyl, which is a strongly coloured compound. Since colour in the benzene series is generally associated with a quinonoid structure, it is hard to see why a substance of the type (I.) should be coloured at all ; but if intramolecular rearrangement be assumed, then, with the structure (II.), the sodium derivative would be markedly tinted :



(I.)

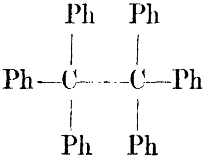


(II.)

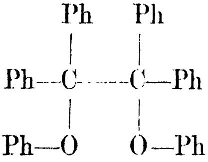
This formula for sodium benzyl, it will be noted, involves no trivalency of carbon and therefore leaves the parallelism with the simpler metal alkyls in existence. The colourlessness of lithium phenyl would be accounted for by the fact that no such quinonoid structure can be composed for it.

If this structure (II.) be accepted for sodium benzyl, however, it seems possible—on the analogy with triphenylmethyl—that in some of its reactions sodium benzyl should give rise to a hydrocarbon with the structure $C_6H_5 . CH_2 . C_6H_4 . CH_3$, which would be a parallel to the Ullmann and Borsum hydrocarbon $(C_6H_5)_3C . C_6H_4 . CH(C_6H_5)_2$, which is formed in certain conditions from triphenylmethyl. Further experiment will probably settle this question.

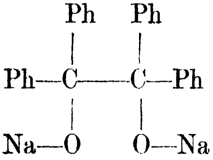
The increase in the number of substances containing trivalent carbon atoms offers some prospect of discovering the conditions which govern the dissociation of carbon compounds by the rupture of single bonds and the formation of free radicles.[1] At the present time it is known that substances of the following types can be split apart at the central bond. For the sake of simplicity the phenyl group may be printed as Ph.



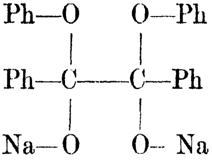
$$\begin{array}{ccccc} & \mathrm{Ph} & & \mathrm{Ph} & \\ & | & & | & \\ \mathrm{Ph-} & \mathrm{C} & \cdots & \mathrm{C} & \mathrm{-Ph} \\ & | & & | & \\ & \mathrm{Ph} & & \mathrm{Ph} & \end{array}$$



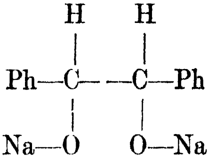
$$\begin{array}{ccccc} & \mathrm{Ph} & & \mathrm{Ph} & \\ & | & & | & \\ \mathrm{Ph-} & \mathrm{C} & \cdots & \mathrm{C} & \mathrm{-Ph} \\ & | & & | & \\ \mathrm{Ph-} & \mathrm{O} & & \mathrm{O} & \mathrm{-Ph} \end{array}$$



$$\begin{array}{ccccc} & \mathrm{Ph} & & \mathrm{Ph} & \\ & | & & | & \\ \mathrm{Ph-} & \mathrm{C} & - & \mathrm{C} & \mathrm{-Ph} \\ & | & & | & \\ \mathrm{Na-} & \mathrm{O} & & \mathrm{O} & \mathrm{-Na} \end{array}$$



$$\begin{array}{ccccc} \mathrm{Ph-} & \mathrm{O} & & \mathrm{O} & \mathrm{-Ph} \\ & | & & | & \\ \mathrm{Ph-} & \mathrm{C} & - & \mathrm{C} & \mathrm{-Ph} \\ & | & & | & \\ \mathrm{Na-} & \mathrm{O} & & \mathrm{O} & \mathrm{-Na} \end{array}$$



$$\begin{array}{ccccc} & \mathrm{H} & & \mathrm{H} & \\ & | & & | & \\ \mathrm{Ph-} & \mathrm{C} & - \; - & \mathrm{C} & \mathrm{-Ph} \\ & | & & | & \\ \mathrm{Na-} & \mathrm{O} & & \mathrm{O} & \mathrm{-Na} \end{array}$$

Examination of these formulæ seems to dispose of the older idea that the production of a trivalent carbon atom necessitated a large accumulation of highly unsaturated groups on that atom; for the trivalent atom in C_6H_5—CH(ONa)— is certainly not overloaded with centres of residual affinity. It will be of considerable interest to see how further research in this field will develop; for it bids fair to give us some clearer ideas about the whole problem of abnormal valency.

[1] Compare Kraus, *J. Amer. Chem. Soc.*, 1924, **46**, 2196.

CHAPTER XIV

OTHER CASES OF ABNORMAL VALENCY

A.—INTRODUCTORY

In view of the interest excited by the triphenylmethyl problem from 1900 onwards, it seems strange that no one at that time appears to have thought of examining other compounds which show some structural analogy with hexaphenyl-ethane.

$(C_6H_5)_3C.C(C_6H_5)_3$	$(C_6H_5)_2N.N(C_6H_5)_2$	$C_6H_5.O.O.C_6H_5$
$(C_6H_5)_3Pb.Pb(C_6H_5)_3$	$(C_6H_5)_2As.As(C_6H_5)_2$	$C_6H_5.S.S.C_6H_5$

In each of the formulæ shown above there is a symmetrical structure; all the formulæ contain a central single bond in the molecule; and the various substances represent the highest possible phenyl-substitution product of their type.

Tetraphenylhydrazine was already known at the time when triphenylmethyl was arousing interest by its peculiar nature; yet no one seems to have been struck by the analogy between it and hexaphenyl-ethane; and it was quite accidentally, in 1906, that the close correspondence between the two series was first brought out in practice. It has since been shown that, just as the free radicle triphenylmethyl can exist in solution, so can the corresponding diphenylhydrazyl grouping $(C_6H_5)_2N$ appear in the free state; and if carbon is to be considered as a trivalent element in certain circumstances, we cannot deny the possibility of divalent nitrogen derivatives. Between the two series a strong resemblance undoubtedly exists, though the bond N—N is much less readily ruptured than the single linkage between the central carbon atoms of Gomberg's hydrocarbon.

With regard to the analogous phenyl derivatives of the divalent elements, it is found that experimental evidence points to the possibility of aryl peroxides yielding dissociation products;[1] whilst apparently diphenyl disulphide can, under certain circumstances, give rise to a free radicle. There are indications that derivatives of monovalent mercury may be capable of existence. In the following sections of this chapter the behaviour of these compounds will be briefly surveyed.

B.—TRIVALENT TIN

In its organic compounds, tin shows a kinship with both zinc and carbon. A polymeric form of tin dimethyl has been obtained,[2] which is spontaneously inflammable in air, like zinc dimethyl. On the other hand, alkyl derivatives of quadrivalent tin have been known for some time; and the optical activity of asymmetric tin compounds furnishes a parallel to the case of the optically active carbon derivatives. These cases, however, do not go outside our normal ideas of the valency of tin, since the compounds might be regarded as being derived from $SnCl_2$ or $SnCl_4$.

The case of trimethyl-tin,[3] however, shows the metallic atom in possession of a valency different from that manifested in the chlorides or hydrides; and apparently we have here to deal with another example of abnormal valency.

The free trimethyl-tin group, $(CH_3)_3Sn$, is quantitatively obtained by the reduction of trimethyl-tin halides with metallic sodium in liquid ammonia solution:

$$(CH_3)_3Sn . Br + Na = NaBr + (CH_3)_3Sn$$

Trimethyl-tin is a white solid melting at 23° C. It boils in an inert atmosphere at 182° C., with some decomposition. When distilled in air, its vapour flashes, owing to combination with oxygen. In boiling benzene, the molecular weight of trimethyl-tin at low concentrations is 171, whilst at high concentrations it is 352. As the calculated value for $(CH_3)_3Sn$ is 164, this suggests that in concentrated solution the material is present as

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[1] Pummerer and Cherbuliez, *Ber.*, 1914, **47**, 2957.

[2] Kraus and Greer, *J. Amer. Chem. Soc.*, 1925, **47**, 2568.

[3] Rügheimer, *Annalen*, 1910, **364**, 5; Kraus, *Rec. trav. chim.*, 1923, **42**, 588; *J. Amer. Chem. Soc.*, 1924, **46**, 2196; Kraus and Callis, *ibid.*, 1923, **45**, 2624; Kraus and Greer, *ibid.*, 1923, **45**, 3078; Kraus and Sessions, *ibid.*, 1925, **47**, 2361.

$(CH_3)_3Sn—Sn(CH_3)_3$ and dissociates into trimethyl-tin as the solution is diluted.

In liquid ammonia solution, trimethyl-tin combines direct with sodium, yielding sodium trimethyl-tin, $Na . Sn(CH_3)_3$, which is also obtainable by the action of sodium upon tetramethyl-tin in liquid ammonia :

$$Na + Sn(CH_3)_4 + NH_3 = Na . Sn(CH_3)_3 + NaNH_2 + CH_4$$

This sodium derivative combines with oxygen to form $[(CH_3)_3Sn]_2O$ and with sulphur to yield the corresponding sulphide. By acting on the sodium derivative with a triethyl-tin halide, the compound $(CH_3)_3Sn—Sn(C_2H_5)_3$ has been prepared. With chlorine, trimethyl-tin gives trimethyl stannonium chloride, $(CH_3)_3Sn . Cl$.

The trimethyl-tin radicle is of considerable interest, since in its case all possible complexities of constitution due to the presence of phenyl nuclei are excluded and the dissociation indicated by the molecular weight determinations is evidently a simple one.

C.—TRIVALENT LEAD

When to an ethereal solution of magnesium *p*-2-xylyl bromide, finely-powdered lead dichloride is added in the proportion required by the equation :

$$3PbCl_2 + 6Br.Mg.C_8H_9 = 2Pb(C_8H_9)_3 + Pb + 3MgCl_2 + 3MgBr_2$$

a greenish-yellow crystalline material can be isolated from the reaction-mixture.[1] The molecular weight of the substance, determined by the cryoscopic method in benzene solution, corresponds to the formula $(C_8H_9)_3Pb . Pb(C_8H_9)_3$; and the body appears to be the lead analogue of hexaphenyl-ethane.

It does not oxidize in air under ordinary conditions, wherein it differs from its carbon analogue ; but with bromine it yields $Br . Pb(C_8H_9)_3$, just as triphenylmethyl gives triphenyl-bromomethane.

The lead derivative is quite stable up to a temperature of 220° ; but in solution it appears to be remarkably photosensitive, being readily decomposed by the action of light. By the

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[1] Krause and Schmitz, *Ber.*, 1919, **52** (B), 2165.

Grignard reaction, it yields lead tetra-*p*-2-xylyl, which is only decomposed at temperatures above 270°.

Attempts to prepare the corresponding simpler derivatives (such as lead triphenyl) by the same method were not successful, the tetra-aryl compounds being obtained instead.

D.—DIVALENT AND QUADRIVALENT NITROGEN

1. *The Tetra-aryl-hydrazines*

Tetraphenyl-hydrazine can be prepared either by the action of iodine upon the sodium derivative of diphenylamine [1] or by the oxidation of diphenylamine in an organic solvent by means of lead oxide or potassium permanganate.[2] Obtained by any of these methods, it is a colourless solid melting at 144° C.

As a class the tetra-aryl-hydrazines are stable substances when in the solid state, though they are easily affected by light and are rapidly changed when dissolved in various solvents. Nascent hydrogen converts them with ease into two molecules of the diarylamine from which they were originally produced.

Their most peculiar behaviour is observed when they are treated with acid. In their ordinary form they possess no basic properties; for anhydrous mineral acids give no normal (colourless) salts. On the other hand, when they are acted on by acids, even in organic solvents, they exhibit intense colours,* green, blue, or violet.[2] The coloured derivatives can be isolated in an impure condition; and when they are treated with alkali they regenerate the parent hydrazines. They must therefore be regarded as salt-like addition products of the undecomposed hydrazines.[3]

These coloured products are extremely labile and soon decompose under ordinary conditions, yielding a mixture of several different compounds.[4] Thus in presence of acids, tetraphenyl-hydrazine gives diphenylamine, *p*-chloro-anilido-

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[1] Chattaway and Ingle, *J.*, 1895, **67**, 1090.

* Similar colours are obtained with halogens, thionyl chloride, ferric chloride, aluminium chloride, zinc chloride, and the pentachlorides of phosphorus and antimony.

[2] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499.

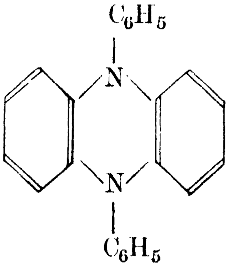
[3] Wieland, *Die Hydrazine*, 1913, p. 63.

[4] Wieland, *Annalen*, 1911, **381**, 200; 1912, **392**, 169; *Ber.*, 1907, **40**, 4262; 1908, **41**, 3478.

triphenylamine (I.), diphenylbenzidine (II.), and a perazine-derivative (III.):

$Cl.C_6H_4.NH.C_6H_4.N(C_6H_5)_2$ (I.)

$C_6H_5.NH.C_6H_4.C_6H_4.NH.C_6H_5$ (II.)



(III.)

The presence of acids is not essential to ensure the breakdown of the tetra-aryl-hydrazines; for with some of them it is only necessary to heat the substance itself in benzene or toluene solution, whereupon decomposition takes place and follows a course similar to that traced when acids are present, though naturally, with slight variations due to the absence of acidic radicles.[1]

The influence of solvents upon the hydrazines manifests itself in another manner. As has been mentioned, the hydrazines are colourless in the solid state; but when they are dissolved in organic solvents and then heated, a marked colour makes its appearance,* which disappears again if the substance be cooled immediately. Colours also make their appearance when the hydrazines are bombarded with cathode rays and kept cool with liquid air.[2] As soon as the bombardment ceases, the substance reverts to its original colourless condition.†

When treated with nitrogen peroxide in toluene solution at 90° C., tetraphenyl-hydrazine reacts and produces nitroso-

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[1] Wieland and Lecher, *Ber.*, 1912, **45**, 2600.

* Cryoscopic molecular weight determinations prove that the substance $[(CH_3)_2N . C_6H_4]_2N . N[C_6H_4N(CH_3)_2]_2$ is dissociated to an extent of 10 per cent. in benzene solution and 21 per cent. in a solution of nitrobenzene (Wieland, *Ber.*, 1915, **48**, 1078).

[2] Wieland, *Annalen*, 1911, **381**, 200.

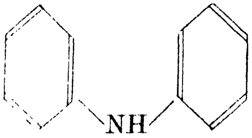
† Exactly similar results are obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

diphenylamine (I.); whilst with triphenylmethyl it yields triphenylmethyl-diphenylamine * (II.):

$$\underset{\text{(I.)}}{(C_6H_5)_2N{-}N:O} \qquad \underset{\text{(II.)}}{(C_6H_5)_3C{-}N(C_6H_5)_2}$$

Alkali metals act on the tetra-aryl-hydrazine with greater or less readiness, producing compounds of the type $R_2:N.Na$, the reaction being similar to that observed in the case of triphenylmethyl.[1]

In conclusion, it must be pointed out that in one case at least the general synthetic method for preparing tetra-aryl-hydrazines breaks down. When carbazole—



is oxidized with the usual reagents, it does not behave like diphenylamine,[2] though it contains the diphenylamine skeleton. Apparently the presence of the pyrrol ring in the compound has some influence upon the reaction; and it is suggested that the extra valency of the nitrogen atom is in this case absorbed by that portion of the molecule.

Results somewhat similar to those in the tetra-aryl-hydrazines have been obtained by Goldschmidt[3] in the series of hexa-substituted tetrazanes, which appear to dissociate thus:

$$R_2N{-}NR{-}NR{-}NR_2 \rightleftharpoons 2(R_2N{-}NR{-})$$

2. *Wieland's Hypothesis of Divalent Nitrogen*

In order to explain the reactions described in the foregoing section, Wieland[4] proposes to regard the tetra-alkyl-hydrazines as analogues of the triphenylmethyl series; so that under certain conditions he assumes a depolymerization of the sub-

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* Exactly similar results are obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

[1] Schlenk and Marcus, *Ber.*, 1914; **47**, 1664.

[2] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499.

[3] Goldschmidt, *Annalen*, 1924, **437**, 194.

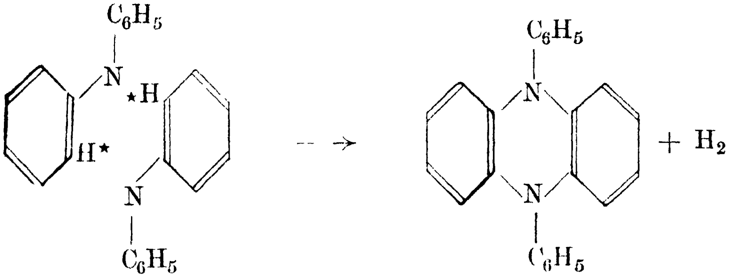
[4] Wieland, *Annalen*, 1911, **381**, 200; 1912, **392**, 127; 193, **401**, 233.

stituted hydrazine which parallels the formation of triphenylmethyl from hexaphenyl-ethane :

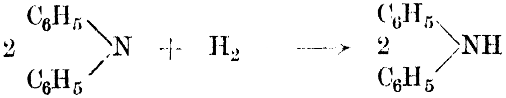
$$(C_6H_5)_2N—N(C_6H_5)_2 \longrightarrow 2\,N(C_6H_5)_2$$
$$(C_6H_5)_3C—C(C_6H_5)_3 \longrightarrow 2\,C(C_6H_5)_3$$

The colours observed when tetraphenyl-hydrazine derivatives are treated with acids or with reagents such as stannic chloride are thus brought into line with those which are obtained in the triphenylcarbinol series under similar conditions.

The formation of a dihydrophenazine derivative and diphenylamine is explained by the mutual oxidation and reduction of four free radicles in the following manner. In the first place, two of them unite with the elimination of two hydrogen atoms (marked with an asterisk) to form diphenyl-dihydrophenazine :

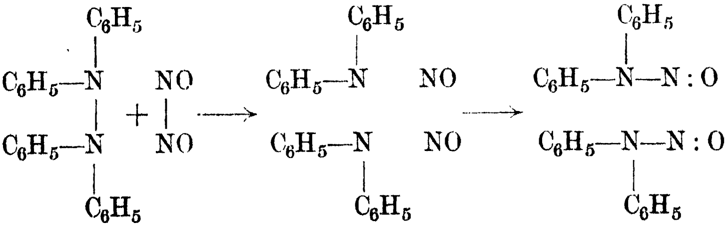


These two hydrogen atoms, thus set free, then reduce the two other free radicles to form two molecules of diphenylamine :



$$2\,\begin{matrix}C_6H_5\diagdown\\ \quad N\\ C_6H_5\diagup\end{matrix} + H_2 \longrightarrow 2\,\begin{matrix}C_6H_5\diagdown\\ \quad NH\\ C_6H_5\diagup\end{matrix}$$

The production of nitroso-diphenylamine, on this hypothesis, may be represented thus :

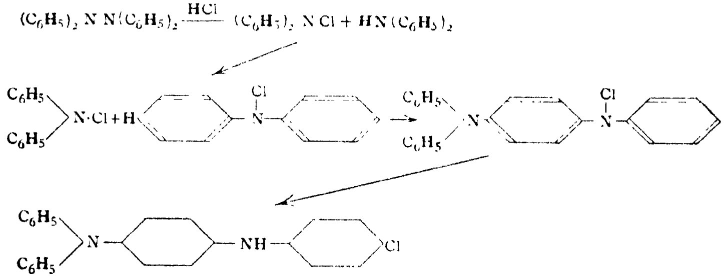


$$\begin{array}{c}C_6H_5\\|\\C_6H_5—N\\|\\C_6H_5—N\\|\\C_6H_5\end{array} + \begin{array}{c}NO\\|\\NO\end{array} \longrightarrow \begin{array}{c}C_6H_5\\|\\C_6H_5—N\\ \\C_6H_5—N\\|\\C_6H_5\end{array}\quad\begin{array}{c}NO\\ \\NO\end{array} \longrightarrow \begin{array}{c}C_6H_5\\|\\C_6H_5—N—N:O\\ \\C_6H_5—N—N:O\\|\\C_6H_5\end{array}$$

and the reaction with triphenylmethyl is simply a union of the two free radicles to form triphenylmethyl-diphenylamine :

$$(C_6H_5)_3C + N(C_6H_5)_2 \longrightarrow (C_6H_5)_3C{-}N(C_6H_5)_2$$

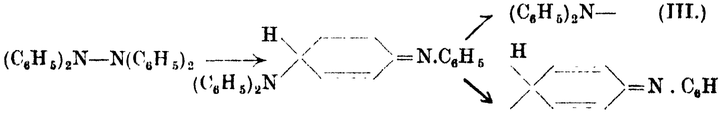
To account for the formation of *p*-chloro-anilido-triphenylamine, Wieland assumes that the first action of acids upon tetraphenyl-hydrazine is to decompose it into one molecule of diphenylamine and one molecule of chloro-diphenylamine, two molecules of which then interact as shown below :



3. *An Application of the Quinonoid Hypothesis*

The parallelism between the tetraphenyl-hydrazine derivatives and the triphenylmethyl group is so close that it seems not unwarrantable to extend to the former the ideas which have been used to account for the behaviour of the trivalent carbon compounds.

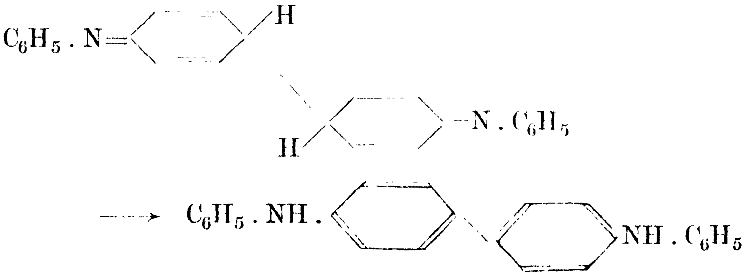
In the triphenylmethyl group, it was assumed that hexaphenyl-ethane was capable of intramolecular change resulting in a quinonoid structure. An analogous change in tetraphenyl-hydrazine would result in the formation of a compound of the type (II.) which, if we follow out the parallel, would dissociate into a benzenoid portion (III.) and a quinonoid part (IV.) :



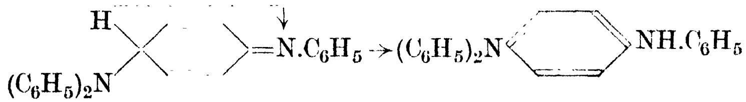
(I.) (II.) (III.) (IV.)

The presence of the quinonoid structure here would account for the appearance of colour when colourless tetraphenyl-hydrazine is heated in solution, and also for the readiness with which the substance is affected by light.

To account for the production of diphenylbenzidine from the hydrazine, it is only necessary to assume that two molecules of (IV.) join together and then rearrange themselves into the benzenoid form—



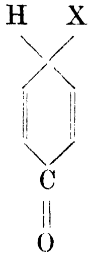
To explain the production of *p*-chloro-anilido-triphenylamine, it may be assumed that in acid solution the radicle $(C_6H_5)_2N$ is attacked by a chlorine ion, giving chloro-diphenylamine, after which the reactions would take place according to Wieland's suggestion. The occurrence of the parent substance, anilido-triphenylamine, which is noticed when tetraphenyl-hydrazine is heated in benzene solution, can be even more simply explained by a wandering of a hydrogen atom; thus recalling the formation of Ullmann and Borsum's hydrocarbon in the case of triphenylmethyl:



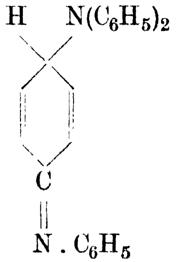
Anilido-triphenylamine.

The interaction with triphenylmethyl and with nitrogen peroxide is easily accounted for by assuming that these two reagents combine directly with the free benzenoid radicles (III.).

In order to make clear the formation of the perazine derivative it must be pointed out that along with one molecule of this substance, the reaction gives rise simultaneously to two molecules of diphenylamine. Now an examination of the quinonoid structure proposed for tetraphenyl-hydrazine suggests a resemblance to the quinole constitution :

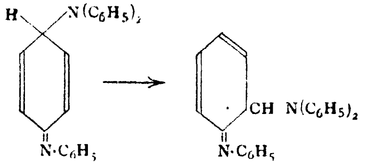


Quinole.

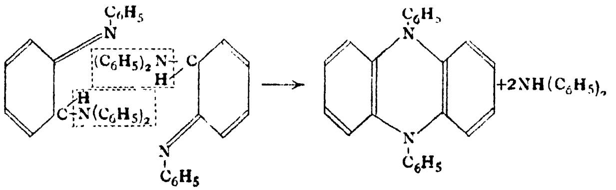


Tetraphenyl-hydrazine.

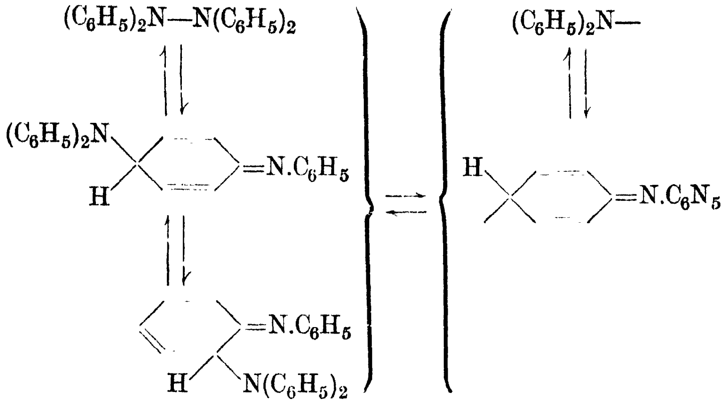
and just as some quinoles exhibit a wandering of the group X to the nucleus, so we may assume a similar wandering to take place in tetraphenyl-hydrazine, giving rise to a compound of the following structure :



Two molecules of this would combine directly to produce a perazine and at the same time eliminate two molecules of diphenylamine (as shown by the dotted line) for each molecule of perazine produced :



Thus in order to account satisfactorily for the various reactions of tetraphenyl-hydrazine, it is necessary to assume the following series of equilibria :—



4. *The Hexa-aryl-tetrazanes*

Goldschmidt[1] studied the oxidation of tri-aryl-hydrazines and detected the formation of tri-aryl-tetrazyls of the type R_2N—NR—, in which one of the nitrogen atoms is divalent.

When triphenyl-hydrazine, $(C_6N_5)_2N$. NH . C_6H_5, is oxidized in methyl ether solution with lead oxide at —60° C., the solution turns deep blue, and an almost colourless set of crystals is obtained which were shown to be hexaphenyl-tetrazane: $(C_6H_5)_2N$. $N(C_6H_5)$. $(C_6H_5)N$. $N(C_6H_5)_2$. On redissolving the crystals, a blue solution is obtained which contains the free radicle triphenyl-hydrazyl; but after standing for a time, the colour alters to reddish-brown owing to the formation of diphenylamine and quinone-anil-phenyl-hydrazone.

The presence of a derivative of divalent nitrogen is proved by the following facts. Nitric oxide acts on the solution, yielding N-nitroso-triphenyl-hydrazine, $(C_6H_5)_2N$. N(NO) . C_6H_5. Triphenylmethyl also attacks the free radicle. These two reactions furnish a perfect analogy with those occurring in the case of the di-aryl-hydrazyls and put the matter beyond doubt. Further, just as in the hydrazyls, the colour of the tetrazyl solutions deviates from Beer's dilution law.

The most interesting of these new free radicles is *αα*-diphenyl-*β*-picryl-hydrazyl: $(C_6H_5)_2N$. N . $C_6H_2(NO_2)_3$. It is stable in

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[1] Goldschmidt and others, *Ber.*, 1920, **53**, 44; 1922, **55**, 616; *Annalen*, 1924, **437**, 194.

the free state, forming crystals with a remarkable colour-similarity to those of potassium permanganate. Its solutions also have the tint of permanganate solutions. It can be boiled in toluene solution for some minutes without decomposition; and even in glacial acetic acid it remains relatively stable. Curiously enough, it does not react with nitric oxide in chloroform solution, though nitrogen peroxide readily attacks it. Hydroquinone reduces the hydrazyl to the corresponding hydrazine; and the colour-change caused by the reduction is so sharp that it can be employed for the estimation of the free radicle by titration of the hydrazyl with a hydroquinone solution of known strength.

5. *Derivatives containing Quadrivalent Nitrogen*

The oxidation of diphenyl-hydroxylamine with silver hydroxide yields a compound[1] which appears to have the formula shown below:

$$(C_6H_5)_2 : N . OH \xrightarrow{Ag_2O} (C_6H_5)_2 : N : O$$

Owing to its analogy in structure with nitrogen peroxide, this substance is termed diphenyl-nitrogen oxide. It is a crystalline compound, deep red in tint; and its vapour resembles that of nitrogen peroxide. It liberates iodine from potassium iodide:

$$(C_6H_5)_2 : N : O + 3HI = (C_6H_5)_2 : NH + 3I + H_2O$$

With bromine it gives a halogen derivative of diphenylamine containing two bromine atoms attached to one phenyl nucleus and one bromine atom in the other. With nitrogen peroxide and triphenylmethyl it reacts readily. Concentrated mineral acids react with almost explosive violence upon the new compound.

The molecular weight determined cryoscopically in benzene corresponds to the monomolecular formula; and this apparently remains unaltered even in a mixture of ether and carbon dioxide, for at —60° C. the substance can be recrystallized from ether and still retain its red colour.

One point of interest in connection with the compound is that its discovery throws considerable doubt upon a structure suggested for nitrogen peroxide: for it is clear that diphenyl-

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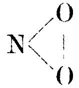
[1] Wieland and Offenbächer, *Ber.*, 1914, **46**, 2111.

nitrogen oxide resembles nitrogen oxide closely; and this tends to support the formula (II.) as against (III.).

$(C_6H_5)_2{=}N{=}O$ (I.)

$O{=}N{=}O$ (II.)



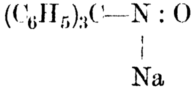
(III.)

The formation of $Br_3C_6H_2{-}NH{-}C_6H_4Br$ by the action of bromine upon the substance may point to the existence of a quinonoid grouping in the molecule; and it is possible that the case may be one of trivalent carbon instead of an example of quadrivalent nitrogen. Too little is known of the subject at present to make it worth while to speculate further.

The action of nitric oxide upon sodium triphenylmethyl takes place in stages. When the gas is passed into a solution of the sodium derivative, a colour-change from red-brown to faint bluish-red is observed, and a fine precipitate of the latter tint is thrown down. Further action of nitric oxide decolorizes both the solution and the precipitate; and the end-product is a yellowish-white body. On the basis of analyses, Schlenk regards the first formed compound as either (I.) or (II.). The first formula contains a divalent, the second a quadrivalent nitrogen atom.

(I.) $(C_6H_5)_3C{-}N{-}ONa$

(II.)

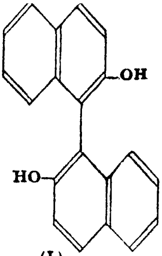


$(C_6H_5)_3C{-}\underset{\displaystyle Na}{\underset{|}{N}}{:}O$

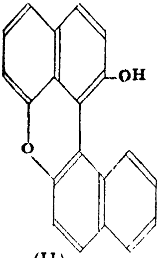
The final product is the sodium derivative of triphenylmethyl-nitroso-hydroxylamine: $(C_6H_5)_3C{-}N(NO){-}ONa$.

E.—Monovalent Oxygen

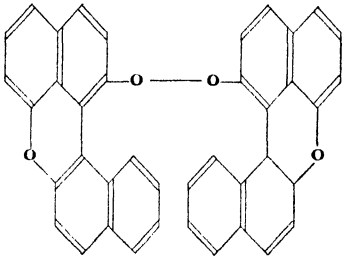
When β-dinaphthol (I.) is oxidized with silver hydroxide, it yields a substance termed hydroxy-naphthylene oxide, to which the formula (II.) is ascribed. By treating this with potassium ferricyanide or indigo white, dehydroxy-dinaphthylene oxide is formed, which is supposed to have the structure (III.) or (IIIa.). This body, when dissolved in various solvents, shows colour phenomena akin to those observed in the triphenylmethyl series; and, partly on this ground, it is assumed to dissociate into radicles[1] which have either of the structures (IV.) and (V.).



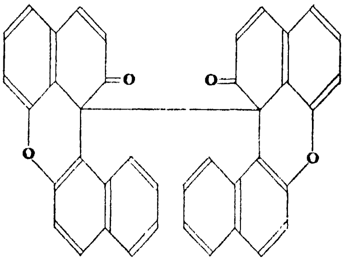
(I)



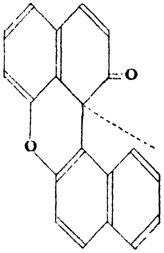
(II)



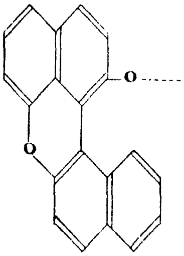
III



IIIa



(IV)



(V)

The supposed free radicle reacts readily with oxygen (though less rapidly than triphenylmethyl) forming an ochreous peroxide. Iodine also acts upon it more slowly than might have been anticipated. Hydrochloric acid decomposes it. Triphenylmethyl, cyclopentadiene, and pinene add themselves on to the radicle. Nitrogen peroxide forms an additive compound in ethereal or benzene solution, but does not attack the radicle to any extent in chloroform solution. When the substance is

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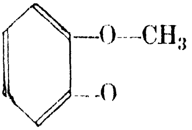
[1] Pummerer and Frankfurter, *Ber.*, 1914, **46**, 1472; compare Pummerer and Cherbuliez, *Ber.*, 1914, **46**, 2957.

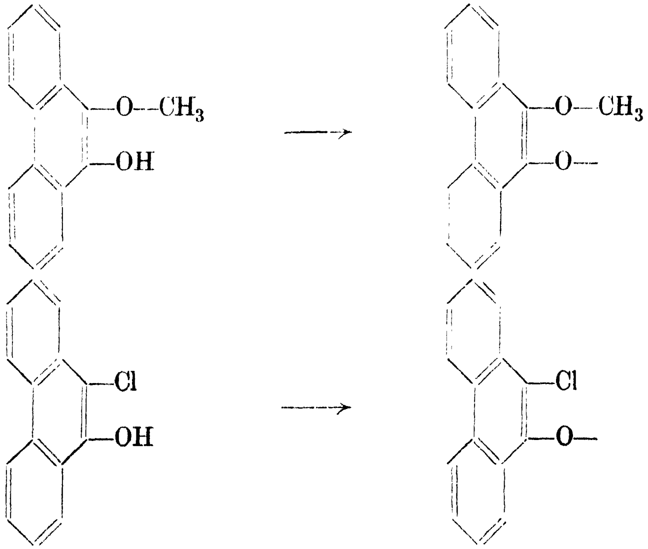
boiled in benzene solution it undergoes decomposition, yielding hydroxy-dinaphthylene oxide and dinaphthylene dioxide.

It will be seen from the above data that the compound is extremely complicated ; its reactions have not been fully studied ; and it may be well to refrain from laying too much stress upon its structure till its properties have been more thoroughly investigated.

Goldschmidt,[1] by oxidizing guaiacol with lead oxide, obtained a green solution which was immediately decolorized by hydroquinone or triphenylmethyl. He ascribed his results to the presence of the free radicle



More definite results [2] were obtained by him in the phenanthrene series during oxidations with potassium ferricyanide. The radicles shown below were formed, and the dissociation of the bimolecular saturated compound was found to reach 37 per cent. in the first case and 62 per cent. in the second case :



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[1] Goldschmidt and Schmidt, *Ber.*, 1922, **55**, 3197.

[2] Goldschmidt and Steigerwald, *Annalen*, 1924, **348**, 202.

F.—MONOVALENT SULPHUR

The oxidation of phenyl mercaptan yields phenyl disulphide,

$$C_6H_5—S—S—C_6H_5$$

This substance in the solid state is colourless, but when it is dissolved in any indifferent solvent, the solution shows a faint yellow tinge, and the colour is intensified by raising the temperature. On cooling, the solution regains its original tint. This change in colour cannot be attributed to dissociation, according to Lecher,[1] since the solutions do not deviate from Beer's Law when examined in a colorimeter; so that the case is not parallel to that of triphenylmethyl in this respect.

Further, in the case of *p*-dimethylanilido-disulphide:

$$(CH_3)_2N—C_6H_4—S—S—C_6H_4—N(CH_3)_2$$

an analogous colour change is observed when the solid substance is heated and cooled.

To explain these phenomena, Lecher suggests that the bond between the sulphur atoms is not broken but is merely weakened; and that the weakening of the valency and the development of colour are parallel changes.

Evidence of this weakening of the bond between the sulphur atoms was sought for in various reactions. For example, at ordinary temperatures or even at 80° C. sodium has little effect upon phenyl disulphide; but at 125° C. it reacts to produce sodium mercaptide:

$$C_6H_5—S—S—C_6H_5 + 2Na = 2C_6H_5—S—Na$$

The weakness of the bond between the sulphur atoms is also indicated by the interaction of *p*-dimethylanilido-disulphide and triphenylmethyl, which gives rise to 1-dimethylamidophenyl-4-triphenylmethyl disulphide—

$$\begin{aligned}(CH_3)_2N\,.\,C_6H_4—S—S—C_6H_4\,.\,N(CH_3)_2 &+ 2(C_6H_5)_3C\\ &= 2(CH_3)_2N\,.\,C_6H_4\,.\,S\,.\,C(C_6H_5)_3\end{aligned}$$

These reactions suggest that under certain conditions it might be possible to obtain derivatives of monovalent sulphur; and though no actual isolation of such compounds has yet been achieved, their existence has been rendered probable by

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[1] Lecher, *Ber.*, 1915, **48**, 524.

the following evidence.[1] Phenyl-triphenylmethyl sulphide can be obtained by the action of triphenyl-chloro-methane upon sodium phenyl mercaptide :

$$C_6H_5 . S . Na + Cl . C(C_6H_5)_3 = C_6H_5 . S . C(C_6H_5)_3 + NaCl$$

Now this sulphide becomes strongly yellow when heated in ethyl benzoate solution ; and an examination of the spectrum proves that triphenylmethyl is present. By shaking the solution in the air, the triphenylmethyl is oxidized, the solution becomes colourless ; and by further shaking in an indifferent atmosphere the yellow colour of triphenylmethyl reappears owing to a further decomposition of sulphide. The only way in which this reaction can reasonably be expressed is as follows :—

$$C_6H_5—S—C(C_6H_5)_3 = C_6H_5 . S + C(C_6H_5)_3$$

Further evidence[2] is found in the examination of mercury phenyl mercaptide, $C_6H_5 . S . Hg . S . C_6H_5$. It was observed by Dreher and Otto,[3] that this body, when heated, breaks up into mercury and phenyl disulphide ; and this suggests that heat loosens the bond between the sulphur and mercury atoms. On Lecher's view, the weakening of the valency force ought to be accompanied by a development of colour as the temperature rises. This actually proves to be the case. Whether dry or in solution, the mercaptide is colourless at ordinary temperatures but becomes yellow when heated, though no mercury separates from it under the experimental conditions employed.

Lecher suggests that the Dreher-Otto reaction is a reversible one which may take one of the two following courses :—

$$\begin{array}{lrcl}
\text{(I.)} & (C_6H_5 . S)_2Hg & \rightleftharpoons & C_6H_5 . S . S . C_6H_5 + Hg \\
\text{(II.)} & (C_6H_5 . S)_2Hg & \leftrightharpoons & 2C_6H_5 . S + Hg \\
 & 2C_6H_5 . S & \rightleftharpoons & C_6H_5 . S . S . C_6H_5
\end{array}$$

If it can be proved that the reaction includes the two equilibria shown in (II.), the existence of monovalent sulphur would be established ; but at present the subject is not beyond dispute ; and we must wait for further evidence before classing monovalent

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[1] Lecher, *Ber.*, 1915, **48**, 524 ; 1920, **55**, 577.

[2] *Ibid.*, 1915, **48**, 1425 ; 1920, **53**, 577.

[3] Dreher and Otto, *Annalen*, 1870, **154**, 178.

sulphur compounds along with the better-established cases of trivalent and divalent nitrogen.

G.—MONOVALENT MERCURY

If a liquid ammonia solution of methyl mercury chloride, $CH_3 . Hg . Cl$, is electrolysed with a small cathode, a highly attenuated opaque mass collects around the cathode.[1] When the mass is collected and allowed to warm up to near ordinary temperature it suddenly undergoes decomposition with the evolution of heat. The reaction appears to correspond to the following equation :—

$$2CH_3 . Hg = Hg + Hg(CH_3)_2$$

Other compounds containing other alkyl radicles and acidic groups behave similarly.

The material is black, like a finely divided metal ; and it is a good conductor of electricity. It does not amalgamate with mercury to any marked extent.

It is suggested by Kraus that this compound contains monovalent mercury ; and this is possibly the case. On the other hand, it is not improbable that it is actually $CH_3 . Hg . Hg . CH_3$; which might be formed at the small cathode just as persulphates are formed from sulphates under similar conditions at the anode. Further research will probably decide which of these views is correct.

H.—STABILITY AND CONSTITUTION

Though our knowledge of the free alkyl groups is rapidly extending, it is as yet too meagre to permit of any large generalizations being made about the factors which influence dissociation. One or two points, however, seem worthy of note.

In the group of substances allied to triphenylmethyl, the effect of replacing phenyl radicles by other radicles has been examined by various investigators.[2] From their results it is possible to draw the following inferences. In the first place,

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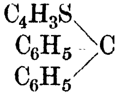
[1] Kraus, *J. Amer. Chem. Soc.*, 1913, **35**, 1732.

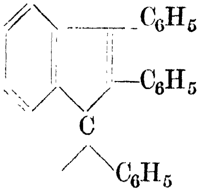
[2] Kohler, *J. Amer. Chem. Soc.*, 1918, **40**, 228; Ziegler and Ochs, *Ber.*, 1922, **55**, 2257; *Annalen*, 1923, **434**, 34; Ziegler and Schnell, *ibid.*, 1924, **437**, 252; Conant and Sloan, *J. Amer. Chem. Soc.*, 1923, **45**, 2466; Conant and Small, *ibid.*, 1925, **47**, 3068; Gray and Marvel, *ibid.*, 2796; Gomberg and Jickling, *ibid.*, 1913, **35**, 446.

the presence of more than two phenyl groups attached to the trivalent carbon atom is shown to be unnecessary by the existence of Gomberg and Jickling's diphenyl-thienyl-methyl:



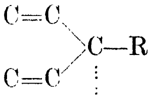
$$\left.\begin{array}{r}C_4H_3S\\C_6H_5\\C_6H_5\end{array}\right\rangle C$$

This is confirmed by the fact that Kohler has obtained 1, 2, 3-triphenyl-indyl:



wherein the trivalent carbon is directly attached to only two phenyl rings.

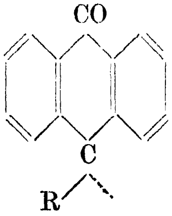
Inspection of this formula shows that it contains the group



$$\left.\begin{array}{r}C{=}C\\C{=}C\end{array}\right\rangle C{-}R$$

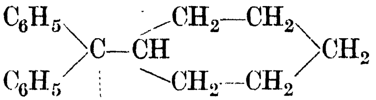
wherein the trivalent atom is distinguished by the dotted line. In 1, 2, 3-triphenyl-indyl, both the double bonds form part of a cyclic structure; but the same grouping occurs in triphenylmethyl itself, though in its case the double bonds belong to different rings; so that the grouping C : C—C—C : C is evidently the important factor and not the indene ring.

That R may be an aliphatic radicle has been shown by Conant and Small, who prepared derivatives of the following type:



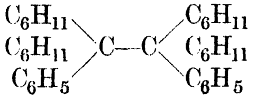
in which R represents normal hexyl or cyclohexyl.

Ziegler and Schnell have obtained the free radicle



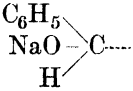
which establishes the fact that a cyclohexyl group has no inhibitive influence upon dissociation.

When, however, a second cyclohexyl group is substituted for one of the two phenyl radicles in the above formula, it was observed by Gray and Marvel that no dissociation could be detected, and that the compound behaved simply as if it had the formula :



In this structure there is no grouping C : C—C—C : C ; from which it appears reasonable to infer that that particular grouping is essential to dissociation, so far as this group of compounds is concerned.

Among the metal-ketyls and their allies, the simplest case is that of the sodium derivative of benzaldehyde :



What part the phenyl group plays in this structure is as yet undetermined. If it acts merely as a radicle incapable of yielding a hydrogen atom to the remainder of the molecule, so that enolization is prevented, then a compound of the structure $(CH_3)_3C\,.\,CHO$ should also give rise to a sodium derivative containing trivalent carbon. Possibly the pinacoline change may take its rise in some kindred phenomenon. If, on the other hand, the unsaturated character of the group attached to the aldehyde radicle is the dominant factor, then the compound $CH_3—C \equiv C—CHO$ might be made to yield a trivalent carbon atom when acted upon by sodium. It would be interesting to know the results in these two cases.

In the case of the divalent nitrogen compounds, a study has been made[1] of the constitutional factor's influence upon

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[1] Goldschmidt and others, *Ber.*, 1922, **55**, 616 ; *Annalen*, 1924, **437**, 194.

dissociation, with the following results. When the hexa-aryl tetrazanes of the formula $Ar_2N . N(Ar) . (Ar)N . NAr_2$ are compared with diacyl-tetra-aryl tetrazanes of the structure $R . CO . N(Ar) . N(Ar) . (Ar)N . (Ar)N . CO . R$, it is found that the acylated derivatives are less dissociated than the parent type. The influence of substitution is further noticeable in the following " order of dissociation," wherein the groups producing the least dissociation are placed at the botton of the list :

↑ Increasing Dissociation

Diacetyl-tetra (*p*-dimethylamino-phenyl)
Dibenzoyl-tetratolyl
Diacetyl-tetratolyl
Dibenzoyl-tetraphenyl
Diacetyl-tetraphenyl

I.—CONCLUSION

The abnormal compounds described in the present chapter, as well as their allies among the metal-ketyls and the triphenyl-methyl series, cannot fail to suggest problems affecting the very bases of structural chemistry. Once the conception of free radicles is admitted, the long-tried dogma of the quadrivalence of carbon comes into the scales for a final test. It is doubtful if all the older ideas will be suddenly thrown aside. Much more probably we shall simply incorporate the idea of free radicles in our thinking and shall not trouble ourselves too much over the incompleteness of our valency scheme. But the chemistry of free radicles, as it extends, is certain to have a marked influence upon our conception of valency. During the present generation, there has been a gradual process of facing fresh facts with regard to the chemical bonds, so far as organic chemistry is concerned. This first manifested itself in a preoccupation with residual affinity and partial valencies ; then it showed itself in the attempt to bring electronic ideas to bear upon the carbon compounds ; and finally, in recent times, the atomic theory of G. N. Lewis seems to have given us something much more definite and satisfactory than anything which preceded it. It is much too soon, as yet, to consider ourselves on firm ground ; but when the further implications of the Lewis theory have been worked out and applied to unsaturated compounds in general, it seems not unlikely that we shall have a much clearer idea of a good many problems than we have at present.

The case of the free radicles is of especial interest from the standpoint of Lewis's theory, since in the triphenylmethyl derivatives carbon acts as an ionogenic element, and thus we have a bridge built between the behaviour of the normal non-iogenic carbon derivatives on the one hand and the ionizable molecules of salts upon the other hand. Lewis's theory, with its inclusive sweep, seems to offer most interesting possibilities in this region of chemistry.

CHAPTER XV

STRUCTURAL FORMULÆ AND THEIR FAILINGS

AN unbiassed survey of the fields covered by organic chemistry cannot fail to reveal to any critical mind the fact that our structural formulæ are becoming less and less able to cope with the strain which modern research is placing upon them. It is true that for work-a-day purposes they still answer admirably; and from the point of view of teaching it is doubtful if anything better could be devised. But when we go into the matter beyond the mere surface, things are not so satisfactory as they may appear to the superficial observer. In the present chapter an attempt will be made to indicate briefly some points in the problem.

In the first place, it will be well to inquire as to the exact nature of our present-day formulæ. According to Kekulé,[1] structural formulæ were "decomposition" formulæ:—

"Rational formulæ are decomposition formulæ, and in the present state of chemical science can be nothing more. These formulæ give us pictures of the chemical nature of substances; because the manner of writing them indicates the atomic groups which remain unattacked in certain reactions. . . . Every formula which expresses definite metamorphoses of a compound is *rational*; that one of the different rational formulæ is the *most rational*, which expresses the greatest number of the metamorphoses."

Couper,[2] on the other hand, put the case as follows:—

"Gerhardt . . . is led to think it necessary to restrict chemical science to the arrangement of bodies according to their decompositions, and to deny the possibility of our comprehending their molecular constitution. Can such a view tend

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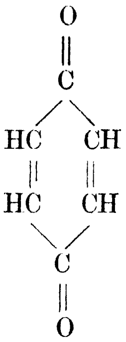
[1] Kekulé, *Annalen*, 1858, **106**, 149.

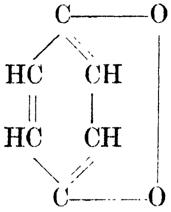
[2] Couper, *Phil. Mag.*, 1858, IV., **16**, 107.

to the advancement of science ? Would it not be only rational, in accepting this veto, to renounce chemical research altogether ? "

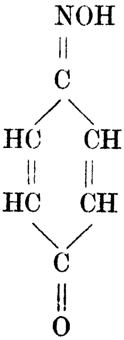
Thus, on the one side, we have Kekulé maintaining that graphic formulæ are mere shorthand symbols by means of which we can easily and compactly express the results of our chemical experiments ; whilst, on the other side, Couper claims that these ciphers give us the key to the actual mode of linkage of the atoms within the molecule. Let us take each of these views in turn and see how far they can be brought into agreement with modern conditions.

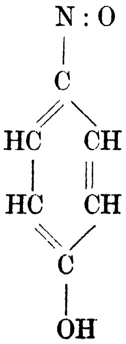
Regarded as pure reaction-formulæ, it must be admitted that our present symbols fail at too many points for our intellectual satisfaction. If quinone be chosen as an example, we find that its formula is written in either of two ways :





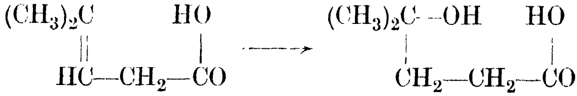
each of which is a representation of its method of reacting with a certain reagent. But neither of these formulæ allows us to foresee the fact that quinone monoxime will react as if it were nitroso-phenol :





The number of facts of this type which have accumulated in recent years is considerable, and the result of this increase in knowledge has been remarkable. Instead of attempting to bring their formulæ into harmony with the facts, organic chemists have been content to drag behind them a lengthening chain of implications, which they read into a formula; *e.g.*, we do not distinguish in our formulæ between the two carbonyl groups of acetone and ethyl acetate, but we mentally interpret the two symbols differently. Thus, at the present time, it is quite conceivable that a student may be well acquainted with the meaning of all the ordinary chemical symbols, but may be hopelessly at sea with regard to the behaviour of a given compound; though to a more experienced chemist this is implicitly expressed in the formula which misleads the beginner.

A concrete example will serve to bring out the amount of unexpressed material which we read into the ordinary formula. Let us consider the reactions of the unsaturated monobasic acids in presence of dilute sulphuric acid. In the first place, we assume that an addition of water to the double bond occurs:



$$\begin{array}{ccccc}(\mathrm{CH_3})_2\mathrm{C} & & & & \mathrm{HO}\\ \| & & & & | \\ \mathrm{HC} & - & \mathrm{CH_2} & - & \mathrm{CO}\end{array} \longrightarrow \begin{array}{ccccc}(\mathrm{CH_3})_2\mathrm{C{-}OH} & & & & \mathrm{HO}\\ | & & & & | \\ \mathrm{CH_2} & - & \mathrm{CH_2} & - & \mathrm{CO}\end{array}$$

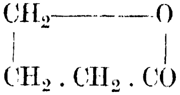
Now, we know from general experience that when one hydroxyl group lies in the 1,6-position to another in the same chain, water is usually eliminated with ease; so we should infer that the next step in the process would be such an abstraction of a water molecule:

$$\begin{array}{ccccc}(\mathrm{CH_3})_2\mathrm{C{-}OH} & & & & \mathrm{HO}\\ | & & & & | \\ \mathrm{CH_2} & - & \mathrm{CH_2} & - & \mathrm{CO}\end{array} \longrightarrow \begin{array}{ccccc}(\mathrm{CH_3})_2\mathrm{C} & - & - & - & \mathrm{O}\\ | & & & & | \\ \mathrm{CH} & - & \mathrm{CH_2} & - & \mathrm{CO}\end{array}$$

The formation of this compound is actually what does take place, so that in this case our inferences are justified; but let us apply the same series of ideas to another instance. Take the case of vinyl-acetic acid (I.), which contains the double bond in exactly the same position as in the other substance. Applying our experience as before, we should infer that the final product on heating with dilute sulphuric acid would be the lactone (II.). In practice no such substance is formed, the product being the new unsaturated acid (III.).

$$CH_2 : CH . CH_2 . COOH$$

(I.)



$$\begin{array}{l} CH_2 \text{———} O \\ | \qquad\qquad\quad | \\ CH_2 . CH_2 . CO \end{array}$$

(II.)

$$CH_3 . CH : CH . COOH$$

(III.)

But this does not bring us to the end of the possible reactions of this class of substances; for if we take the case in which two methyl groups are attached to a different carbon atom we find that the reaction follows yet another course:

$$CH_2 : CH . C(CH_3)_2 . COOH$$

$$\searrow$$

$$CH_3 . CHOH . C(CH_3)_2 . COOH$$

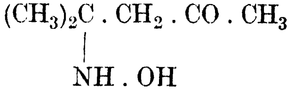
$$\searrow$$

$$CH_3 . CH : C(CH_3)_2 + CO_2 + H_2O$$

Thus, our formulæ have ceased to be true reaction formulæ, and may merely serve to mislead us if we attempt to draw any general conclusions from them.

Let us now turn to Couper's view of formulæ, *viz.*, that they are to be regarded as true representations of the intimate structure of molecules. Here we appear to be upon safer grounds; but again we meet with drawbacks. If a formula represents the actual mode of linkage of the atoms in a molecule, how can we be certain of our results when we apply chemical reagents to the compound? Quinone, when treated with hydroxylamine, behaves as if it contained a carbonyl radicle; but if we employ phosphorus pentachloride as our reagent it acts as if quinone contained a benzene nucleus, since *p*-dichlorobenzene results. In this case, what is the true structure of quinone? If it be regarded as an equilibrium mixture of two compounds or as existing in two vibration-phases, what becomes of our "intimate structure of the molecule"?

Evidently, from Couper's point of view, the outside reagent is a disturbing factor not allowed for in our formulæ. An example is furnished by the action of hydroxylamine upon mesityl oxide.[1] If the reaction is allowed to take place in a methyl alcoholic solution in presence of sodium methylate, the chief product is the substance formed by the addition of hydroxylamine to the double bond :



$$(CH_3)_2\underset{\substack{|\\ NH\,.\,OH}}{C}\,.\,CH_2\,.\,CO\,.\,CH_3$$

But if, on the other hand, after exactly neutralizing hydroxylamine hydrochloride with sodium carbonate we allow it to act upon an alcoholic solution of mesityl oxide, we get the usual carbonyl group reaction, and mesityl oxime is formed :

$$(CH_3)_2C : CH\,.\,C(NOH)\,.\,CH_3$$

Thus in *alkaline* solution the ethylenic bond is stimulated into activity, while in *neutral* solution the carbonyl radicle appears the more reactive of the two.

From this it becomes clear that in order to ascertain the true " intimate structure of the molecule " we must find some way of determining it apart from extraneous materials. How is this possible ?

The recent developments in the study of physical properties of compounds indicates a means whereby the constitution of a body might be guessed without the necessity of applying disturbing reagents to it. At present our methods are not sufficiently advanced to permit us to establish molecular structure definitely by physical means alone ; but even to-day we can accomplish a good deal with the help of absorption spectra, magnetic rotation, refractive index, magnetic susceptibility, electric absorption, optical rotatory power and dispersion ; and there seems to be little reason to despair of further progress.

It is at this point that we encounter the difficulty which has been responsible for wrecking a considerable amount of work in recent years. On the one hand, as we have seen, stand our " chemical " formulæ which give us—incompletely enough, it must be confessed—a picture of the reactions of substances. On the other side, physical methods are showing us glimpses of the " intimate structure of molecules." Now

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[1] Harries and Lellmann, *Ber.*, 1897, **30**, 230, 2726 ; Harries and Jablonski, *ibid.*, 1898, **31**, 1371 ; Harries, *Annalen*, 1904, **330**, 191.

a great mistake appears to have been made in assuming that both these things could be expressed by the same formulæ. Our old reaction-formulæ, though unable to cope with the difficulties in their own special field, have been imported willy-nilly into the problem of molecular structure, because we had nothing better to utilize there. The result has been something like the state of affairs which would reign in arithmetic if we insisted on using a mixture of Roman and Arabic notations in our calculations.

There is another region wherein our modern formulæ are failing to meet the demands made upon them: the field of the unsaturated compounds. For present purposes, an unsaturated compound may be defined as a molecule which, without total disruption of its original structure, is capable of uniting with one or more fresh molecules. Now when this matter is considered in its broadest aspects, it is evident that what we term unsaturation is a specific and not a general property. We represent the unsaturation of an ethylenic linkage and of a carbonyl radicle by the same symbol, a double bond; and as far as the action of nascent hydrogen is concerned, this is quite accurate, for both the ethylenic linkage and the carbonyl group will attach to themselves two atoms of hydrogen. But when we use bromine instead of hydrogen, we find that only the ethylenic linkage reacts; for the carbonyl radicle remains unaffected by the reagent.

It is especially in this region of unsaturation that we find the limitations of our structural formulæ most clearly marked. When we write a double bond between two atoms, we do not always mean the same thing. The double bonds in the cases of diphenyl-ethylene, ethylene, and fulvene certainly do not resemble one another chemically: in the first case the double bond is not attacked by bromine, which is taken up easily by the double bond of ethylene; but while the fulvene series are oxidized by air, ethylenic substances are not. Thus we have an increase in unsaturation (or reactivity as regards bromine and oxygen) as we go from diphenyl-ethylene through ethylene to the fulvenes; yet we symbolize all three unions between the carbon atoms of the double bonds in exactly the same way. It is perfectly evident that the amount of reactivity is different in these three cases, and therefore the "chemical affinity," which gives rise to the reactions, must be different also.

But it is not only in the case of the double bond that we can trace this alteration in value of valencies; we can discover it in the case of single bonds as well. It is well known that in bromo-benzene, the bromine atom is held to the carbon atom of the nucleus more firmly than in aliphatic bromine derivatives. But if we nitrate the benzene ring, the bromine in the aromatic bromine derivative becomes as labile as that in the aliphatic one. This increase in reactivity can be due only to some change in the force which holds together the carbon and bromine atoms; in other words, the "valency-force" uniting bromine to carbon is stronger in bromobenzene than in nitro-bromobenzene.* Flürscheim [1] has carried out some experiments by means of which he showed that this variation in the value of the single bond is quite a general property.†

From this point of view, investigations of the reactivities of certain atoms and groups in molecules are of the greatest importance. A considerable amount of work [2] in this direction has already been carried out; but a vast field lies open to research in this branch of the subject.

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* When the above paragraph was written in 1908, I was under the impression that this had long been common knowledge. Dr. Flürscheim desires me to mention, however, that he published a paper on the point in 1906 (*Ber.*, **38**, 2016).—A. W. S.

[1] Flürscheim, *J. pr. Chem.*, II., 1902, **66**, 329; see also Werner, *Ber.*, 1906, **39**, 1278.

† An interesting paper by Tschitschibabin (*J. pr. Chem.*, 1912, **86**, 381) on "The Valency of Carbon Atoms in So-called 'Unsaturated' Compounds" may be brought to the notice of the reader in this connection.

[2] See among others, Clarke, *Trans.*, 1911, **99**, 1432; 1912, **101**, 1788; Harper and Macbeth, *J.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824; Petrenko-Kritschenko, *J. pr. Chem.*, 1900, [2], **61**, 431; Petrenko-Kritschenko and Kantscheff, *Ber.*, 1906, **39**, 1452; Senter, *J.*, 1909, **95**, 1827; *J.*, 1910, **97**, 1623; Stewart, *J.*, 1905, **87**, 185, 410.

CHAPTER XVI

SOME APPLICATIONS OF ELECTRONICS TO ORGANIC CHEMISTRY

1. *Introductory*

THE first quarter of the twentieth century will doubtless be noted in the history of chemistry as the period when our ideas of valency changed their form and drew nearer than ever before to the underlying reality. Up to that period, modern chemistry had always suffered from a lack of unity. In early days, the vitalistic ideas demanded a segregation of naturally-synthesized organic compounds from the remainder of the subject; and the science was arbitrarily divided into " organic " chemistry and " inorganic " chemistry. This cleavage had hardly been healed by the work of Wöhler when a fresh line of fission made its appearance. The multiplicity of the carbon derivatives and their difference from the metallic salts soon led to a separation of the two classes from one another; and thus once again chemistry became a kind of dual monarchy. The constitutional formulæ of Kekulé at first seemed to offer the hope that all chemical compounds might eventually be brought back under a single head, since his symbols could be made to fit the simpler inorganic compounds like sulphuric acid. Before much time had been wasted in this attempt, however, a fresh line of division appeared with the ionic theory of solution; and compounds came to be classified as electrolytes or non-electrolytes, a method of demarcation which cut clean across the earlier grouping, since it included the organic acids and their salts along with the inorganic salts and acids.

At this period, a contest became focussed upon the two modes of regarding chemical affinity. In the ionic reactions, the processes were obviously electrical in their nature and were associated with the occurrence of definite electrical units. All the simpler salts, bases, and acids could be regarded as being held together by purely "polar" forces, since in their reactions the governing factors appeared to be charges of positive and negative electricity. But, on the other hand, the far more numerous organic compounds refused to be explained on a "polar" basis. So far as could be ascertained, the reactions of organic chemistry differed completely in nature from the rudimentary processes which served to account for the behaviour of ionizable materials.

At this stage, little hope of ultimate harmony appeared likely. The extreme ionists seemed to wish for a return to the rigid "polar" ideas of Berzelius, extending the idea of ions throughout the whole range of the carbon compounds; but as few of them had any thorough knowledge of the complexities of organic chemistry, their arguments failed to convince the specialists in that branch of the science. The more enthusiastic exponents of Kekulé's "non-polar" ideas, on the other hand. held the firm belief that the intimate constitution of the ferrocyanides, for example, could be expressed satisfactorily by "non-polar" bonds; and the fact that such symbolism perforce omitted from its scope the ionic character of the substances, seemed to have little weight in their minds.

The unfortunate pretensions of the extremists in both schools did much to hinder progress. Instead of trying to find some common ground upon which both sides could meet and co-operate, each group endeavoured to annex the field properly belonging to the other. To Ostwald, who did not believe in the real existence of atoms, structural chemistry could appear only in the guise of fantastic nonsense; and he calmly proposed to throw overboard the whole graphic symbolism and replace it by a series of purely mathematical expressions which he believed would serve as well, if not better.* The extremists in the other camp were hardly wiser; and some of the attempts to write graphic formulæ for complicated inorganic compounds proved too much for even confirmed "constitutionalists."

Sir J. J. Thomson's work on electrons marked the opening of a fresh avenue in chemistry; but unfortunately the initial

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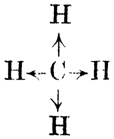
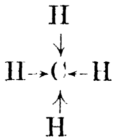
* He prudently left the task of discovering these mathematical expressions "to younger colleagues" and refrained from adventuring into the field himself.

hypotheses put forward by him and others had incorporated in them an element based on " direction." For example, methane might be represented as being formed by four electrons leaving the carbon atom and fixing themselves on the hydrogen atoms, or by an electron leaving each of the hydrogen atoms and coming to rest on the central carbon atom :



$$\begin{array}{c} H \\ \uparrow \\ H \leftarrow C \rightarrow H \\ \downarrow \\ H \end{array}$$



$$\begin{array}{c} H \\ \downarrow \\ H \rightarrow C \leftarrow H \\ \uparrow \\ H \end{array}$$

Thus methane should exist in two " electromeric " forms ; whereas only a single methane is known in practice. In more complex compounds the number of possible " electromers " rose to very high figures ; and the only way of reconciling theory and practice was to assume that most of the arrangements were unstable systems incapable of real existence.

A further step in advance was marked by Sir Ernest Rutherford's proof that the atom consisted of a positive nucleus surrounded by a group of neutralizing electrons ; and Moseley's researches brought out the relationship between the number of positive charges on the nucleus and the atomic number of the element.

2. *The Theory of G. N. Lewis*

It was not until 1916 that a model atom was suggested which fitted our chemical requirements. G. N. Lewis[1] proposed to regard the atomic electronic system as a cubical arrangement of which the corner-points could be occupied by electrons. Since organic chemistry is mainly concerned with atoms belonging to the first two series in the Periodic Table, this cubical model is sufficient for our present purpose, and it is unnecessary to discuss the further extension of the theory which was made by Langmuir.

According to G. N. Lewis, hydrogen is representable by a nucleus carrying one positive charge, attached to which there is a single electron, making the system electrically neutral. The electron is detachable, and when it is removed, the " proton "

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[1] G. N. Lewis, *J. Amer. Chem. Soc.*, **1916, 38, 762.**

of the nucleus becomes what is generally known as a hydrogen ion.

The helium system of Lewis consists of a nucleus carrying two positive charges and neutralized by two electrons. As helium is an inert gas, this model system must be assumed to be extremely stable and the electrons in it are not detachable.

The lithium atom of Lewis is composed of a triply-charged nucleus surrounded by a neutralizing system of three electrons. In practice, lithium salts yield only monovalent lithium ions, so that evidently one of the three electrons differs from the other two. This Lewis expressed by the following model. At the centre is the nucleus carrying three positive charges. Associated with this is a group of two electrons—the helium complex. Outside this lies the detachable electron of the lithium system. At this point the cubical system comes into force, and the detachable electron of lithium is supposed to rest at the corner of a cube which contains the lithium complex of two electrons and which has at its centre the triply-charged positive nucleus.

As we proceed from element to element through the first series of the Periodic Table, electron after electron is fitted into the vacant corners of the cube, and in each case a corresponding positive charge is added to the nucleus. Thus the outer shells of the atoms can be represented by the following diagram (Fig. 1):

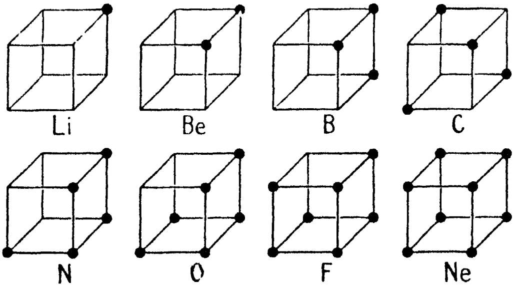

Fig. 1.

With the neon atom, all the corners of the cube are occupied by electrons; and since neon is an inert gas, this octet is assumed to form a stable system which will neither take up nor part with electrons. In order to form the sodium atom, a fresh cube, external to the neon cube, must be commenced; and a single electron must be placed at one of its corners. Thereafter, the model atoms of remaining elements, sodium, magnesium, aluminium, etc., are formed by adding more and more electrons to the cube until with argon the whole second octet is completed and a stable system produced.

The picture of the model atom is completed by adopting Aston's view that the atomic nucleus contains protons equal in number to the figure representing the true atomic weight and intimately united with electrons sufficient to leave a surplus positive charge equivalent to the atomic number.

Since the carbon atom is of special interest in organic chemistry, it will be sufficient to choose it as an example. The atomic weight of carbon is 12, therefore we assume twelve protons in the nucleus. The atomic number of carbon is 6, so six electrons are inserted into the nucleus, leaving the nuclear system with a surplus charge of 6 (the atomic number). Now for electrical neutrality, we need six extra electrons. These are grouped around the nucleus as follows. In an internal region lie the two electrons of the helium complex. Outside these lies the cubical grouping and at four corners of the cube lie the remaining four electrons. This leaves four unoccupied corners; and these are ready to receive electrons by chemical combination of the carbon atom with other atoms, thus completing the octet which is the stable, inert grouping in the cubic atom. For example, methane is represented by the introduction into the carbon system of four electrons derived from four hydrogen systems, and the residual protons of the four hydrogen atoms are retained by electronic forces.

Since this cubical grouping fails to represent the normal tetrahedral arrangement postulated in organic chemistry to account for the asymmetric carbon atom, G. N. Lewis assumes that the electrons can shift from the corners along the edges of the cube so that in methane, for example, they would move from the points marked with faint circles to the positions indicated by the black circles * in the following diagram and thus fall into tetrahedral grouping (Fig. 2):

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* The reason for eight electrons being shown here will be apparent when the formula of methane is discussed. See p. 380.

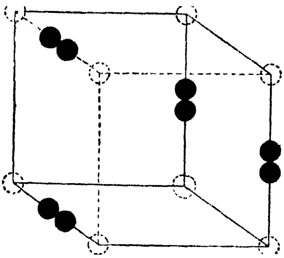


FIG. 2.

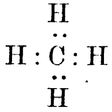
It is now necessary to examine the interpretation which G. N. Lewis's theory places upon valency and to show how by his model atom the apparently antagonistic ideas of polar and non-polar bonds can be harmonized.

From the point of view of organic chemistry, the main basis of the Lewis theory can be stated thus. (1) Electrons may be " shared " between two atoms, thus belonging jointly to both the atomic systems involved. Such " shared electrons " are found in pairs in carbon compounds. (2) Electrons may be wholly transferred from one system to another. (3) When electrons are introduced into the systems of atoms belonging to the first series of the Periodic Table, the tendency is to produce an octet of electrons (a " pseudo-neon " system) in the outer sphere of the atom; and the combination of atoms tends always to produce, if possible, a series of octet groups of electrons.

Representing electrons by dots and assuming the existence of the appropriate positive charges in the nuclei, it is possible to express the various systems quite simply and indicate the various results which follow from Lewis's postulates.

Take the molecule of hydrogen as a first example. The atom of hydrogen can be written as $H^{\cdot}$, the H representing the nuclear proton and the dot the electron. Now when two atoms of hydrogen combine to form molecular hydrogen, they can do so by simply sharing the two electrons and $H : H$ would be the symbol for H_2. Here either proton may be regarded as having attached to it two electrons, so that by the sharing of the pair of electrons two " pseudo-helium " inert groupings are obtained. This gives an example of electron-sharing in its simplest form; and it will be seen that the " shared " electrons occur in pairs. Also, since molecular hydrogen does not dissociate electrolytically, it is clear that "shared electrons" do not constitute a polar bond.

Turn next to the molecule of methane. The carbon atom has four electrons in its cubic system; and there are four electrons in the four hydrogen atoms. This makes a total of eight—the inert octet. Each of the hydrogen atoms inserts its electron into one of the vacant corners of the carbon cube, thus completing the octet round the carbon nucleus; but by this means each of the four carbon electrons becomes part of a hydrogen system, bringing it up to the "pseudo-helium" duplet. Thus the electronic system of methane can be represented by the symbol:

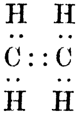


$$\begin{array}{ccccc} & & H & & \\ & & \cdot\cdot & & \\ H & : & C & : & H \\ & & \cdot\cdot & & \\ & & H & & \end{array}$$

wherein the carbon nucleus is surrounded by eight electrons, which simultaneously serve to complete the four duplets of the hydrogen "pseudo-helium" systems.

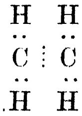
Inspection of this symbol reveals at once that it can be derived from the ordinary graphic formula of methane by writing a duplet of electrons for each Kekulé bond; and from this it follows that the non-polar bonds of the carbon compounds are represented on the Lewis theory by *two electrons jointly shared* between two electronic systems.

By analogy, an ethylenic linking should be represented on Lewis's system by *two* pairs of electrons shared between the two carbon systems which are united by the ethylenic bond:



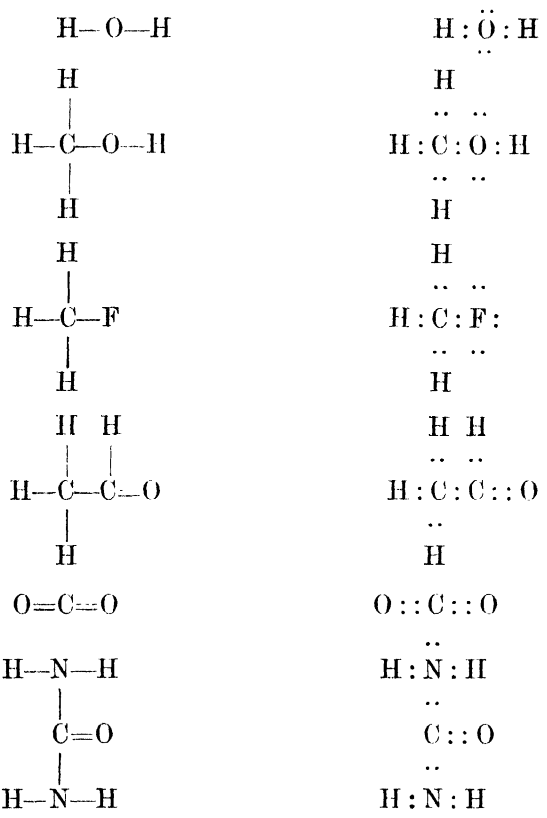
$$\begin{array}{ccc} H & & H \\ \cdot\cdot & & \cdot\cdot \\ C & :: & C \\ \cdot\cdot & & \cdot\cdot \\ H & & H \end{array}$$

or



$$\begin{array}{ccc} H & & H \\ \cdot\cdot & & \cdot\cdot \\ C & \vdots & C \\ \cdot\cdot & & \cdot\cdot \\ H & & H \end{array}$$

One or two other examples of these formulæ will familiarize the reader with the electron-pairs and the octet groups. It must be borne in mind that the numbers of electrons in the cube are respectively, 4 for carbon, 5 for nitrogen, 6 for oxygen, and 7 for fluorine.



Graphic formulæ.	*Lewis formulæ.*
$H-O-H$	$H:\overset{..}{\underset{..}{O}}:H$
$H-\overset{H}{\underset{H}{C}}-O-H$	$H:\overset{H}{\underset{H}{\overset{..}{\underset{..}{C}}}}:\overset{..}{\underset{..}{O}}:H$
$H-\overset{H}{\underset{H}{C}}-F$	$H:\overset{H}{\underset{H}{\overset{..}{\underset{..}{C}}}}:\overset{..}{\underset{..}{F}}:$
$H-\overset{H}{\underset{H}{C}}-\overset{H}{C}=O$	$H:\overset{H}{\underset{H}{\overset{..}{\underset{..}{C}}}}:\overset{H}{\overset{..}{C}}::O$
$O=C=O$	$O::C::O$
$\begin{array}{c}H-N-H\\ \vert\\ C=O\\ \vert\\ H-N-H\end{array}$	$\begin{array}{c}H:\overset{..}{N}:H\\ ..\\ C::O\\ ..\\ H:N:H\end{array}$

Very little consideration is required to reveal the atomic conditions necessitating electron-sharing. If the total number of electrons in the outermost spheres of all the atoms in a molecule is not divisible by eight, then some of the electrons must be shared between the atomic systems in order to complete the stable octets. For example, the cube of the fluorine atom has seven electrons in it; so that the two fluorine cubes of the fluorine molecule have 14 electrons in all. In order to construct two complete octet systems from 14 units, it is obvious that two electrons must be shared between the two systems :—

$:F:F:$ $\qquad$ $:O::O:$

The oxygen molecule must contain a system of four shared electrons (as shown above) if two complete octets are to be constructed from the available twelve electrons.

Hitherto we have been considering Lewis's representation of non-polar bonds; but it is now necessary to turn to the other side of his theory and show how it applies to ionogenic systems. Suppose that the various atoms associated in the molecule contain a total number of electrons which is exactly divisible by 8. Then clearly a system of this kind can arrange itself so as to form a series of complete octets without any electron-sharing. In this case, there are no non-polar bonds present, and the system represents two or more ions held together by purely electrostatic forces.

The simplest case is that of hydrofluoric acid. Since a hydrogen system has one electron and the fluorine system has seven, the two together will suffice to form the complete octet and might be written thus:

$$\mathrm{H}:\overset{..}{\underset{..}{\mathrm{F}}}:$$

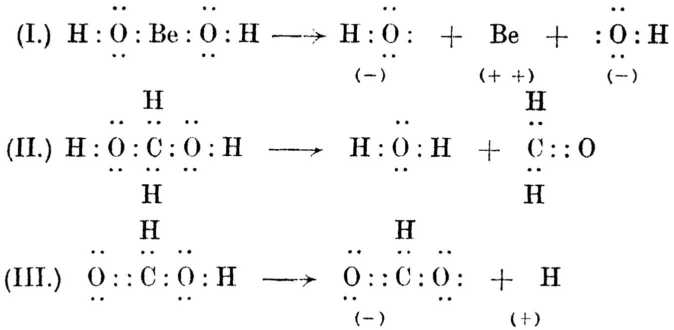
This would represent the sharing of two electrons between the hydrogen and fluorine systems. But if we assume, with Lewis, that the process is not arrested at this stage, but that, instead, the hydrogen electron passes over into the fluorine system in order to make an independent octet of that system, then we have a case of *electron-transference.* The two systems will still remain in contiguity, because the fluorine system now has one excess negative charge (due to the engulfed electron), whilst the hydrogen proton (having lost its companion electron) has a free positive charge. We have, in fact, two ions which will attract each other by simple electrical affinity; and which, in the proper circumstances, may drift apart thus:

$$\left[\mathrm{H}\right]^{+} \qquad\qquad \left[:\overset{..}{\underset{..}{\mathrm{F}}}:\right]^{-}$$

Hydrogen ion. **Fluorine ion.**

It is now clear that Lewis's ideas can be used to symbolize both polar and non-polar types of union; the non-polar type being represented by electron-sharing, the polar type by electron-transference: and, further, that the two types may shade into one another in such a way as to account for the carbonium salts derived from triphenylmethane,[1] wherein ionogenic power is manifested by bonds which normally might be regarded as non-polar in character.

An interesting application of the Lewis theory is to be found in the cases of beryllium hydroxide, dihydroxy-methane, and formic acid. In the first case, the molecule yields basic ions, in the second example the decomposition is spontaneous and produces water and the neutral substance formaldehyde, whilst formic acid yields hydrogen ions. These three processes are represented as follows on the octet symbolism.



$$\text{(I.)}\quad H:\ddot{\underset{\cdot\cdot}{O}}:Be:\ddot{\underset{\cdot\cdot}{O}}:H \longrightarrow \underset{(-)}{H:\ddot{\underset{\cdot\cdot}{O}}:} + \underset{(++)}{Be} + \underset{(-)}{:\ddot{\underset{\cdot\cdot}{O}}:H}$$

$$\text{(II.)}\quad H:\ddot{\underset{\cdot\cdot}{O}}:\overset{H}{\overset{\cdot\cdot}{\underset{\underset{H}{\cdot\cdot}}{C}}}:\ddot{\underset{\cdot\cdot}{O}}:H \longrightarrow H:\ddot{\underset{\cdot\cdot}{O}}:H + \overset{H}{\overset{\cdot\cdot}{\underset{\underset{H}{\cdot\cdot}}{C}}}::O$$

$$\text{(III.)}\quad \ddot{\underset{\cdot\cdot}{O}}::\overset{H}{\overset{\cdot\cdot}{C}}:\ddot{\underset{\cdot\cdot}{O}}:H \longrightarrow \underset{(-)}{\ddot{\underset{\cdot\cdot}{O}}::\overset{H}{\overset{\cdot\cdot}{C}}:\ddot{\underset{\cdot\cdot}{O}}:} + \underset{(+)}{H}$$

In (I.), it is evident that the molecule contains two complete octets centred in the oxygen atoms; and these might separate from the beryllium atom—which is not the nucleus of an octet—and so form two hydroxyl ions. In Case (III.), the carbon octet is present in the centre of the molecule so that a breakdown of type (I.) could occur only by the rupture of this octet. Since the octet is assumed to be a stable grouping, this collapse is not to be expected. Instead, electron-transference occurs in such a way as to maintain the maximum number of octets, and a hydrogen ion is formed. In Case (II.), either of the hydroxylic hydrogens might be expelled as an ion; but here it would find a hydroxyl radicle (not present in formic acid) which it might attack in order to form water; and thus the whole system would suffer decomposition as shown.

3. *Octet Stabilities*

In his initial exposition of his theory, G. N. Lewis pointed out that "great as the difference is between the typical polar

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[1] Walden, *Z. physikal. Chem.*, 1903, 43, 442.

and non-polar substances, we may show how a single molecule may, according to its environment, pass from the extreme polar to the extreme non-polar form, not *per saltum*, but by imperceptible gradations, as soon as we admit that an electron may be the common property of two shells. . . . The pair of electrons which constitutes the bond may lie between the two atomic centres in such a position that there is no electrical polarization, or it may be shifted toward one or the other atom in order to give to that atom a negative, and consequently to the other atom a positive charge."[1]

Lewis illustrated this variation in the situation of the electron-pair by means of the hydrogen molecule, the molecule of sodium hydride, the hydrogen chloride molecule, and the ions of hydrochloric acid :—

$$\mathrm{H:H} \qquad \mathrm{Na:H} \qquad \mathrm{H} \quad :\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}: \qquad \left[\mathrm{H}\right]^{+} + \left[:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{Cl}}}:\right]^{-}$$

In the hydrogen molecule the electron-pair is placed symmetrically between the two atoms. In sodium hydride, the electrons lie nearer to the hydrogen than to the sodium, making the hydrogen negative. In hydrogen chloride the electron-pair is shifted toward the chlorine, endowing the hydrogen with a positive charge ; and in presence of a polar solvent the chlorine assumes full possession of the electrons and complete ionization ensues.

This idea has been utilized by Kermack and Robinson[2] in order to give a physical basis to their views on alternative polarity in carbon chains. According to their hypothesis, if in the system $:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{A}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{B}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{C}}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{\mathrm{D}}}:$ the octet surrounding A becomes unstable from any cause, external or internal, this will automatically involve more or less appropriation of the two electrons shared with B, the octet of which is therefore unstable and tends to disintegrate. The stability of the B octet having thus been shaken, the atom C will be able to appropriate the electron-pair common to B and C and produce around itself a stable octet, in

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[1] See G. N. Lewis, *Valence*, p. 83 (1923), and also his earlier papers, *J. Amer. Chem. Soc.*, 1916, **38**, 762 ; *Proc. Nat. Acad. Sci.*, 1916, **2**, 586.

[2] Kermack and Robinson, *J.*, 1922, **121**, 427 ; compare Lowry, *J.*, 1923, **123**, 822.

the formation of which the octet of D is in turn disintegrated. This can be represented crudely as follows:

$$:\!\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}\!:\ \ \underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}\ \ :\!\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}\!:\ \ \underset{\cdot\cdot}{\overset{\cdot\cdot}{D}}\!:$$

Here, as Lewis points out,[1] the change does not result in any of the atoms having an integral number of units of charge, since this is found only in ions; but nevertheless alternate atoms in the chain have become either more akin to positive ions or to negative ions than they were before the electron-shift occurred.

The most convincing piece of evidence yet brought forward to show the truth of this speculation has been furnished by Macbeth and his collaborators.[2] Since the octet representation would be too intricate for easy reading in this case, it will be better to utilize the symbolism used by Macbeth and mark "pseudo-positivity" by means of a + sign and "pseudo-negativity" by a — sign. The facts of the case are as follows. (1) When tetranitromethane, $(NO_2)_4C$, is acted on by potassium hydroxide, one nitro-group is eliminated and the potassium salt of nitroform is produced. A nitro-group is removed also by the action of titanous chloride, hydrazine, potassium ferrocyanide, and potassium sulphite. (2) The halogen atom of chlorotrinitromethane or bromotrinitromethane is readily removed by potassium hydroxide, yielding the potassium salt of nitroform. The halogen atom is also removed with ease by alkaline reducing agents, potassium ferrocyanide, and titanous chloride. (3) One bromine atom of dibromodinitromethane is removed by potassium hydroxide, potassium ferrocyanide, or hydrazine. Titanous chloride reduces the nitro-groups but leaves the halogen intact. (4) Chloropicrin, when treated with hydrazine, very slowly loses one chlorine atom in the cold. Potassium ferrocyanide is without action. Titanous chloride reduces the nitro-group but leaves the halogens untouched. (5) Monobromonitromethane and dibromonitromethane are unacted on by hydrazine or potassium ferrocyanide. Titanous chloride reduces the nitro-group without removing the halogen.

This series of results obviously displays a regular gradation

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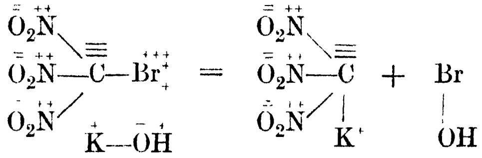
[1] G. N. Lewis, *Valence*, p. 83 (1923).

[2] Henderson and Macbeth, *J.*, 1922, **121**, 892; Hirst and Macbeth, *ibid.*, 904; Macbeth, *ibid.*, 1116.

in the activity of the halogen atoms and also of the nitro-groups. In the cases of tetranitromethane and bromo-trinitromethane

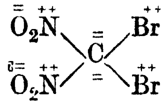
$$(NO_2)_3C—NO_2 \qquad\qquad (NO_2)_3C—Br$$

the nitro-group and the bromine atom are not only removed, but they are replaced by the strongly positive potassium atom. This Macbeth accounts for by assuming that the oxygen atoms of the three nitro-groups exert a polarizing influence on the chain with the result that the nitrogen atoms become positively polarized, the carbon atom is negatively polarized, and the terminal nitro-group or bromine atom becomes positively polarized. Representing the effect of each oxygen atom by a minus sign and indicating its polarizing effect on its neighbouring atom by an equal number of positive signs, the result in bromo-trinitromethane is as shown below; and the reaction with potassium hydroxide finds a simple expression, since the positive potassium is seen to be replacing a bromine atom in which there is a great accumulation of induced positive polarity.

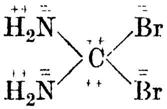


Macbeth regards this induced positivity of the halogen atom as the reason for its ready removal by reducing agents such as potassium ferrocyanide and hydrazine.

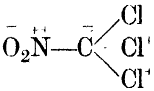
Now, on Macbeth's hypothesis, in dibromodinitromethane and dichlorodinitromethane, the halogen atoms must have much less induced positivity since only two nitro-groups are influencing them here, as against three in bromotrinitromethane. Not only so, but the polarizing influence of the two groups is further diminished since it is distributed over two halogen atoms, as shown in the scheme given by Macbeth:



Here, obviously, each bromine atom has only one-third of the induced positive polarity which it possesses in the formula given above for bromotrinitromethane. Titanous chloride fails to attack the bromine atoms and reduces the nitro-groups instead. Once the nitro-groups are reduced, the whole polarity-chain in the molecule is inverted, and the titanous chloride is unable to remove the halogen atoms :



Finally, the case of chloropicrin is represented by Macbeth in the following scheme :



Here the induced positivity on the halogen atoms is only one-sixth of that allotted in the case of bromotrinitromethane ; and even so, one chlorine atom has no induced positivity at all. In this case potassium ferrocyanide has no action and even hydrazine works very slowly.

It must be admitted that Macbeth's explanation goes hand in hand with the facts ; and this series of reactions furnishes considerable strength to the supporters of the induced polarity idea. Macbeth has extended similar explanations to other classes of compounds ; but for further information the original papers must be consulted.

4. *Ionization and Chemical Action*

In a foregoing section it has been shown that by adopting Lewis's views it is possible to depict the comparatively rigid structures of organic compounds and also the looser complexes formed by the association of ions ; and it may be recalled that the reactions of organic compounds are in general fairly slow, whereas the interactions of ions are instantaneous.

So far back as 1881, Helmholtz[1] voiced the idea that all substances were electrolytes despite the differences among them. In 1885, Armstrong[2] hazarded the conjecture that chemical reaction was " reversed electrolysis " ; and the work of

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[1] Helmholtz, *Vortrage u. Reden*, II., 274 (1896).

[2] Armstrong, *P.*, 1885, **1**, 39.

H. B. Baker[1] has proved that some extremely dry reagents hardly interact at all, though they immediately combine as soon as a trace of water is added to the system. Lapworth[2] suggested in 1901 that reactivity may depend upon the existence of ions or the manufacture of ions by the rupture of non-polar bonds.

With the recent applications of the theory of G. N. Lewis to clarify the representation of molecules and ions, it has been possible to develop these tentative suggestions of Armstrong and Lapworth in a more detailed fashion; and some account will now be given of Lowry's interpretation of the courses of some typical reactions in organic chemistry.[3]

According to Lowry, chemical reaction takes place between ions, free or bound; and the process is the same in both organic and inorganic chemistry. But this implies that the non-polar bonds of the organic compounds must be capable of yielding ions in some manner; and Lowry suggests that a duplet of electrons shared between two atoms may adhere as a whole to one or other of the atomic systems when these are pulled apart.[4] In this way one complete octet and one sextet would be produced:

$$:\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}:\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}: \longrightarrow :\underset{\cdot\cdot}{\overset{\cdot\cdot}{A}}\quad :\underset{\cdot\cdot}{\overset{\cdot\cdot}{B}}:$$

This is in agreement with Lewis's views on the peculiar tendency of electrons to associate in pairs.* Further, it provides a possible explanation of the hitherto incomprehensible phenomena observed by Walden,[5] who found that tin, sulphur, phosphorus, antimony, chlorine, bromine, and iodine when dissolved in liquid sulphur dioxide or arsenic trichloride yielded solutions with marked electrical conductivities. It accounts also for the conducting power shown by solutions of triphenyl-chloromethane.[6] Finally, it furnishes an interpretation of the fact that the union of ethylene with bromine can be markedly

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[1] H. B. Baker, *J.*, 1902, **81**, 400.

[2] Lapworth, *J.*, 1901, **79**, 1266.

[3] Lowry, *Lecture to the Institut international de chimie Solvay*, April, 1925; compare Lowry, *Bull. Soc. chim.*, 1924 (4), **36**, 815, 905; 1926 (4), **39**, 203; *Nature Supplement*, May 29th, 1926, p. 33; *J. Soc. Chem. Ind.*, 1925, **44**, 970.

[4] Compare G. N. Lewis, *Valence*, p. 83 (1923).

* If this pairing were not assumed, then the system shown above might be assumed to break up into two septets of electrons.

[5] Walden, *Z. physikal. Chem.*, 1903, **43**, 385.

[6] *Ibid.*, 1903, **43**, 454.

retarded, if not entirely arrested, by enclosing the reagents in a vessel lined with paraffin wax, although the reaction proceeds rapidly in a vessel having on its walls an adsorbed film of water or a polar compound such as stearic acid.[1]

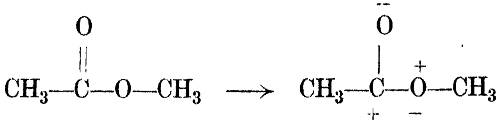
Lowry suggests that organic (non-polar) compounds enter into reaction only by the formation of ions which come into existence by the action of a polar catalyst at the moment when reaction is about to take place. These ions are not supposed to have an independent existence such as the ions have in a salt solution; they are merely in existence for a brief period before being reconverted into neutral molecules.

5. *Hydrolysis and Esterification*

Since the electronic symbols are somewhat confusing in the case of complex structures, it will be convenient to utilize instead the signs + and — attached to the atoms to which polarity is ascribed; but it should be borne in mind that these signs are merely indications of the distributions of the electrons in the systems under review. In this connection it may be well to lay stress once more on the view that when ions adhere to one another there is no real "bond" between them, since they are united by electrostatic attraction and not held together in virtue of a shared duplet of electrons. Thus sodium chloride must be regarded as having the arrangement (I.) and should not be represented by the bonded structure (II.).

(I.) $\overset{+}{\mathrm{Na}}\overset{-}{\mathrm{Cl}}$ (II.) $\mathrm{Na—Cl}$

Lowry assumes that under appropriate conditions, the non-polar double bond of the ester radicle may become converted into a polar arrangement, as shown below:



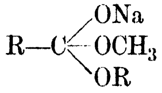
$$\mathrm{CH_3—}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\mathrm{—O—CH_3} \longrightarrow \mathrm{CH_3—}\underset{+}{\overset{\overset{\overset{-}{\displaystyle O}}{|}}{\mathrm{C}}}\mathrm{—}\underset{-}{\overset{+}{\mathrm{O}}}\mathrm{—CH_3}$$

The divalent oxygen atom is well known to have residual polar valencies, as was shown by the discovery of the oxonium salts by Collie and Tickle.[2] The polar character of the "opened-up"

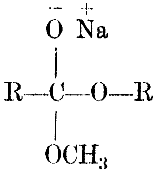
[1] Norrish, *J.*, 1923, **123**, 3006.

[2] Collie and Tickle, *J.*, 1899, **75**, 710.

carbonyl union is suggested by Pechman's observation[1] that sodium methylate forms definite compounds with esters. These compounds are generally given the formula

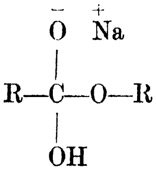


but Lowry prefers to regard them as salts formed by the attraction of ions and not as completely bonded structures :



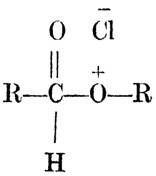
$$R-\underset{\displaystyle OCH_3}{\overset{\overset{-\quad +}{O\ \ Na}}{C}}-O-R$$

Applying these ideas to the case of the hydrolysis of an ester by means of an alkali or an acid, Lowry points out that the initial reaction-product may be regarded as either an oxy-salt or an oxonium salt :



$$R-\underset{\displaystyle OH}{\overset{\overset{-\quad +}{O\ \ Na}}{C}}-O-R$$

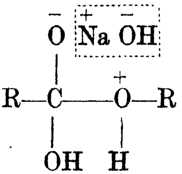
Oxy-salt.



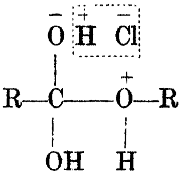
$$R-\underset{\displaystyle H}{\overset{\overset{\quad\ \ -}{O\ \ Cl}}{C}}-\overset{+}{O}-R$$

Oxonium salt.

Since hydrolysis usually takes place in presence of excess of water, Lowry assumes that this water also plays a part in the ionic process, and that whilst a molecule of acid or alkali attacks one new polar grouping in the ester molecule, a water-molecule attaches itself to the other. The resulting structures can be written thus :



$$R-\underset{\displaystyle OH}{\overset{\overset{-}{O}\ \boxed{\overset{+}{Na}\ \overset{-}{OH}}}{C}}-\underset{\displaystyle H}{\overset{+}{O}}-R$$



$$R-\underset{\displaystyle OH}{\overset{\overset{-}{O}\ \boxed{\overset{+}{H}\ \overset{-}{Cl}}}{C}}-\underset{\displaystyle H}{\overset{+}{O}}-R$$

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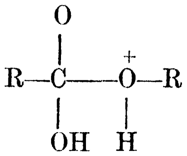
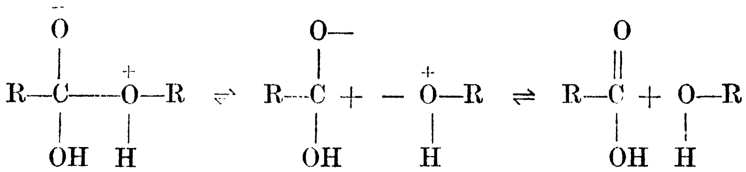
[1] Pechman, *Ber.*, 1898, **31**, 503.

and the skeleton common to both is obviously :



$$\begin{array}{lcccl} & \text{O} & & & \\ & | & & & \\ \text{R—} & \text{C} & \text{——} & \overset{+}{\text{O}} & \text{—R} \\ & | & & | & \\ & \text{OH} & & \text{H} & \end{array}$$

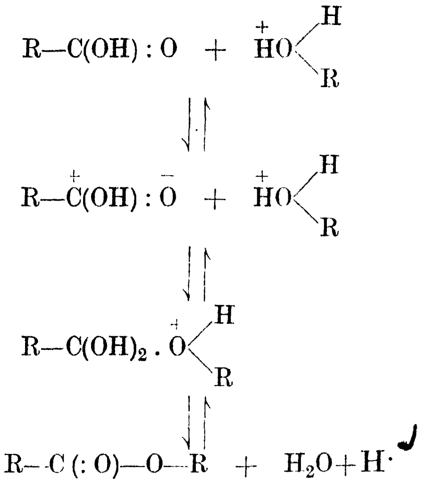
Thus by utilizing the salt-forming properties of a bi-polar molecule, Lowry's hypothesis suggests how three important things can be achieved : (1) the addition of a molecule of water to the ester without immediate disruption ; (2) the production of a molecule of acid and one of the alcohol with all the atoms held together by real bonds and attached to one another only by a superfluous non-polar bond ; (3) the final rupture of this last bond by an ionization which will reconstitute a polar oxygen atom on the one hand and a non-polar double bond on the other, thus



$$\begin{array}{lcccl} & \overset{-}{\text{O}} & & & \\ & | & & & \\ \text{R—} & \text{C} & \text{——} & \overset{+}{\text{O}} & \text{—R} \\ & | & & | & \\ & \text{OH} & & \text{H} & \end{array} \rightleftharpoons \begin{array}{lc} & \text{O—} \\ & | \\ \text{R—} & \text{C} \\ & | \\ & \text{OH} \end{array} + \begin{array}{lcl} & & \\ & & \\ — & \overset{+}{\text{O}} & \text{—R} \\ & | & \\ & \text{H} & \end{array} \rightleftharpoons \begin{array}{lc} & \text{O} \\ & \| \\ \text{R—} & \text{C} \\ & | \\ & \text{OH} \end{array} + \begin{array}{cl} & \\ & \\ \text{O} & \text{—R} \\ | & \\ \text{H} & \end{array}$$

It is usually assumed that esterification and hydrolysis are converse processes; but it must be remembered that this statement is true only with limitations. Acids can act as catalysts in both hydrolysis and esterification ; but bases do not assist esterification though they have a marked effect in hydrolysis reactions.

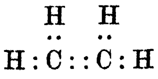
According to Lowry, the following inferences can be drawn with regard to the mechanism of esterification. In the first place, acids act in virtue of their ability to supply protons which are added to the molecules catalysed, thus forming unstable addition-compounds which subsequently yield the final products. These addition-compounds are not derived from the acids undergoing esterification but are oxonium derivatives of the alcohols produced by the addition of a proton to the alcoholic molecule. On the foregoing basis, Lowry represents the esterification process as taking place in the following stages :—



6. *Isomeric Change*

It has been pointed out by Lowry[1] that three distinct types of intramolecular change can be recognized.* In the first type the change consists in a movement of one or more electrons to fresh situations in the molecule. This Lowry indicates by the term *electrotropy*. The second type of intramolecular change is brought about by the wandering of protons and has been named by him *prototropy*. Finally, when complex radicles move from one position to another within the structure, Lowry distinguishes the case as one of *ionotropy*. A brief examination of the various types will bring to light some points of interest.

(*a*) *Electrotropy*.—Lowry regards electrotropy as the principal factor in the activation which he assumes as a frequent prelude to chemical change, especially among the carbon compounds. For example, ethylene can be represented on the Lewis symbolism by



$$\begin{array}{c} \;\;\;\;\mathrm{H}\;\;\;\mathrm{H} \\ \;\;\;\;\ddot{}\;\;\;\;\;\ddot{} \\ \mathrm{H:C::C:H} \end{array}$$

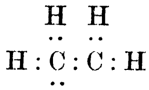
wherein four electrons are shared between the two carbon

---

[1] Lowry, *Lecture to the Institut International Solvay* (1925).

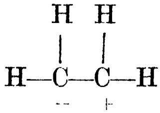
* It should be noted that Lowry expressly refrains from including *all* types of isomeric change in these three categories.

systems. If one duplet now passes completely into the system of one of the carbon systems, the symbol becomes



$$\mathrm{H}:\underset{\cdot\cdot}{\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}}:\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}:\mathrm{H}$$

wherein the left-hand carbon system is now negatively charged whilst the right-hand system has an equal and opposite positive charge :



$$\mathrm{H}—\underset{-}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}—\underset{+}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}—\mathrm{H}$$

Electrotropy, then, may be the means of producing polarity in a molecule, or, conversely, a polar molecule may be reduced to an electrically neutral condition by electrotropic change. Owing to electronic mobility, it seems impossible in practice to isolate two electrotropic isomers from one another ; and Lowry regards it as possible that one electrotrope is a mere phase in the process of reaction.

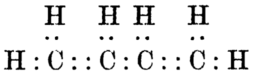
The most interesting case in which the idea of electrotropy can be applied is that presented by Thiele's theory of partial valencies. In the system

$$\overset{1}{\mathrm{CH_2}}:\overset{2}{\mathrm{CH}}—\overset{3}{\mathrm{CH}}:\overset{4}{\mathrm{CH_2}}$$

the points attacked by a bromine molecule are the carbon atoms marked 1 and 4, and a new double bond is formed in the centre of the molecule ; so that the final product is

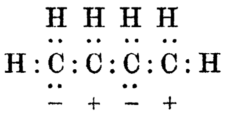
$$\mathrm{CH_2Br—CH:CH—CH_2Br}$$

This can be illustrated by using Lewis's symbolism as follows. In the first place, the electrons are distributed thus :



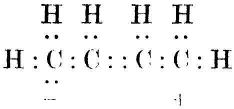
$$\mathrm{H}:\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}::\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}:\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}::\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}:\mathrm{H}$$

Now let an electrotropic change be assumed whereby two duplets of electrons become absorbed into two of the carbon systems, thus producing a phase of ionization :



$$\mathrm{H}:\underset{\underset{-}{\cdot\cdot}}{\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}}:\underset{+}{\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}}:\underset{\underset{-}{\cdot\cdot}}{\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}}:\underset{+}{\overset{\overset{\mathrm{H}}{\cdot\cdot}}{\mathrm{C}}}:\mathrm{H}$$

This arrangement would obviously not concord with the results of experiment, since an ionized bromine molecule would be free to attack any pair of oppositely-charged carbon atoms. It is therefore necessary to postulate a second electrotropic change wherein the duplet of electrons attached to the third carbon atom of the chain becomes shared with the second atom :

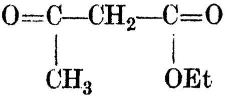


$$H:\underset{\underset{-}{\cdot\cdot}}{\overset{\overset{H}{\cdot\cdot}}{C}}:\overset{\overset{H}{\cdot\cdot}}{C}::\overset{\overset{H}{\cdot\cdot}}{C}:\underset{+}{\overset{\overset{H}{\cdot\cdot}}{C}}:H$$

Inspection of this formula will show that these two movements of the electron duplets have (*a*) produced opposite charges on the terminal carbon atoms, and (*b*) constituted a fresh double bond in the centre of the molecule while leaving this new ethylenic linkage devoid of polarity. In fact, the electrotropic rearrangements have given rise to a structure which would react just as the hydrocarbon does behave in practice.)

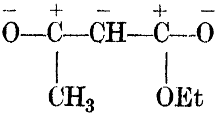
(*b*) *Prototropy.*—This depends on the migration of a proton from one point to another within the molecule, usually with a consequent rearrangement of the bond-forming electrons. Since prototropy entails the shifting of an actual material particle, it is possible in many cases to isolate both isomeric forms of the compound in a pure state. For example, the enolic and ketonic varieties of acetoacetic ester can be separated from each other; and the normal and *aci*-forms of some pseudo-acids have been obtained.

The process of prototropy, when considered from the electronic standpoint, obviously is a somewhat complex one. In the first place, the removal of a proton from the molecule necessarily leaves a negative ion in existence. Further, since the proton re-attaches itself at a fresh point in the molecule, there must be a negative charge at this spot, as well as at the point of detachment. To put the matter in other words, prototropy involves : (*a*) the detachment of the proton ; (*b*) the formation of an ion with a double negative charge ; (*c*) the re-attachment of the proton ; and (*d*) the restoration of non-polarity. In the case of acetoacetic ester, the three structures involved are evidently those shown below :



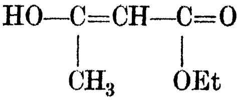
$$O{=}\underset{\underset{CH_3}{|}}{C}—CH_2—\underset{\underset{OEt}{|}}{C}{=}O$$

Ketono.



$$\overset{-}{O}—\underset{\underset{CH_3}{|}}{\overset{+}{C}}—\overset{-}{CH}—\underset{\underset{OEt}{|}}{\overset{+}{C}}—\overset{-}{O}$$

Ion.



$$HO—\underset{\underset{CH_3}{|}}{C}{=}CH—\underset{\underset{OEt}{|}}{C}{=}O$$

Enolic form.

Further light is thrown on the problem when it is recalled that the interconversion of these two prototropic forms can be arrested by working under "acatalytic" conditions.[1] This obviously implies that prototropic change is facilitated (if not actually produced) by some external mechanism; and further support is gained for this view when it is remembered that the mutarotation of nitro-camphor—due to another prototropic change—is arrested by working in inert solvents.[2]

A catalyst may be supposed to influence prototropic change in either of two ways: for it may (1) facilitate the withdrawal of the proton from the parent molecule or (2) promote the addition of the proton to the ion. In the prototropic changes mentioned above. the most efficient catalysts are bases; acids are less effective; and water is still less so. Lowry regards bases as being chiefly effective as proton-removers; whilst acids act as facilitators of the re-insertion of the proton. Water, being amphoteric, can act in both ways; but its low ionization makes it a poor agent in these particular cases. It should be remembered, however, that the efficiency of a base as a proton-remover is also a measure of its activity in preventing the return of the proton to the organic ion. Conversely, though an acid is a good agent for the insertion of protons, it tends to repress the ionization which yields the free proton. The presence of water, owing to its amphoteric character, will facilitate the catalysis of prototropic change by either bases or acids.[3]

Lowry [4] has shown how his electronic views of prototropic change can be applied in order to account for the phenomena of optical inversion, mutarotation, and the Walden Inversion; but space does not permit an examination of these subjects here, and the reader is referred to the original papers for further information.

Ionotropy.—Having now considered the possible results of the shifting of electrons and simple protons within a molecule, it is necessary to turn to a series of phenomena which cannot

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[1] K. Meyer, *Ber.*, 1920, **53**, 1410.

[2] Lowry, *J.*, 1899, **75**, 211; 1908, **93**, 119; 1925, **127**, 1371; compare Purdie and Irvine, *J.*, 1904, **85**, 1049.

[3] Compare O'Sullivan and Thomson, *J.*, 1890, **57**, 869; Lowry, *J.*, 1925, **127**, 1371; Lowry and Richards, *ibid.*, 1385.

[4] Lowry, *Lecture to the Institut international Solvay*, 1925; *J.*, 1925, **127**, 1371; Lowry and Richards, *ibid.*, 1385.

be explained on the basis of either of these changes. At first sight it might seem, as Lowry points out, that isomeric change may be due entirely to an intramolecular turmoil caused by thermal agitation, after which the atoms settle down into a structure different from that existing before heat was applied. There is a limiting factor here which cannot be neglected. In some cases the thermal agitation sufficient to produce isomeric change may be more than sufficient to disrupt the molecular structure completely; and thus any effort to bring about an intramolecular rearrangement by purely thermal means may result in the collapse of the molecular structure into simpler units. For example, if an attempt is made to interchange the hydrogen atom and hydroxyl group in the radicle —CH . OH— in the sugar series, the temperature may be raised to a degree at which the sugar molecule loses water and yet up to that stage no inversion of the secondary alcoholic grouping is observed. It appears, in fact, that in cases such as these the "disruption-temperature" is lower than any possible "rearrangement-temperature."

Thermal agitation alone, then, may prove insufficient to bring about isomeric change; and since many intramolecular rearrangements are facilitated by the presence of catalysts, Lowry prefers the hypothesis of a mechanism akin to that suggested by him in connection with prototropic change. He proposes, in fact, to regard a number of isomeric changes as due to the wandering within the molecule of atomic groups having the character of ions.

Lapworth,[1] as far back as 1901, suggested that "it is to electrolytic dissociation, often doubtless in extremely minute amount, that the majority of changes in organic compounds may be most probably assigned." In the case of isomeric change, this means that an atom, or group of atoms, is detached from the molecule in the form of an ion, and that thereafter it migrates to a fresh point of attachment elsewhere in the structure. Lapworth [2] had previously shown that a large number of these group-migrations were subject to simple rules which may be summarized here. In the first place, Lapworth laid down that in desmotropic compounds the labile group moves from an α-atom to attach itself to the γ-atom, the suitable rearrangement

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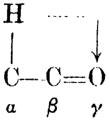
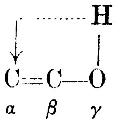
[1] Lapworth, *J.*, 1901, **79**, 1266.

[2] *Ibid.*, 1898, **73**, 445.

of the linking taking place between the three fixed atoms, α, β, and γ.

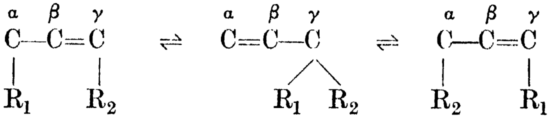


Ketonic form.



Enolic form.

Further, two mobile groups attached to the atoms α and γ may change places without any final alteration of the original disposition of the single and ethylenic linkages; for if a group on the α atom moves to the γ atom and in so doing produces a certain rearrangement of the bonds, this arrangement will be reversed again by the passage of a group on the γ atom to the α atom, and thus the original bond-grouping will be restored as a result of the interchange of the groups.



Finally, a labile group may move along a chain of alternately singly and double bound atoms, the ethylenic and single linkages changing places in the path of the labile group so that this group may travel from the α to the γ and then on to the ε position in the chain.

Now, as Lowry points out, the αγ-rule of Lapworth can be very simply explained by using the conception of polar molecules and multipolar ions which has been discussed in an earlier section of this chapter,[1] since in such rearrangements, positive and negative charges may alternate on the atoms of the chain. In order to cover the whole ground, however, it is necessary to go more closely into the question of the mechanism whereby these ionotropic changes may be brought about.

Though at first sight there appears to be a marked resemblance between prototropic and ionotropic changes, since both types may be regarded as ionic transferences, there is a striking difference between the two sets of phenomena. Speaking generally, prototropic changes are promoted most effectively by basic catalysts and less efficiently by acidic catalysts; whereas in sharp distinction to this it is found that ionotropic changes

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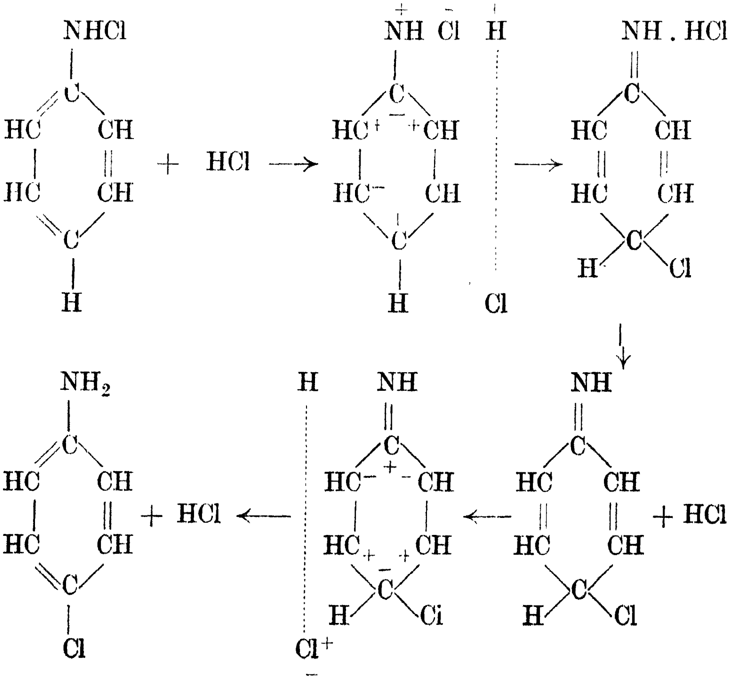
[1] Compare Lowry, *J.*, 1923, **123**, 822; *Bull. Soc. chim.*, 1924, (4), **36**, 815, 905.

are promoted only by acidic catalysts and are actually arrested in neutral or alkaline media. For example, phenyl-chloroamine, $C_6H_5 . NH . Cl$, is stable in presence of alkalis; and whenever the conditions are favourable to its conversion into chloro-aniline, $NH_2 . C_6H_4 . Cl$, hydrochloric acid can be detected in the solution.[1] Similar phenomena were observed in the isomeric change of nitro-amines into nitranilines:

$$C_6H_5 . NH . NO_2 \longrightarrow NH_2 . C_6H_4 . NO_2$$

Lowry infers from these results that the active catalyst for the interchange of the radicles H and X between side-chain and nucleus is generally the acid HX.

As an illustration of Lowry's views on the catalytic mechanism, the conversion of phenyl-chloroamine into *p*-chloraniline by means of hydrochloric acid may be selected. It should be noted that the signs + and − are here used to indicate real electrical charges and do not represent anything in the nature of the vaguer "polarities" which are often symbolized in this way.



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[1] Orton, *Brit. Assoc. Reports*, **1908**, 115; **1909**, 147.

Lowry suggests that the readiness with which chemical changes (especially isomeric changes) involving distant atoms take place in aromatic compounds may be attributed to the manner in which conjugated systems can convey electric charges from one end of the system to the other without any simultaneous migration of the intermediate atoms: a process akin rather to metallic conduction than to ionic conduction.[1]

7. *Conclusion*

In the foregoing pages only a few examples were selected out of the host of interesting results which have flowed from G. N. Lewis's electronic views of chemical affinity; but sufficient has been said to illustrate the simplification which has followed upon the adoption of his ideas of the octet and the electron-pair as the two keys to structural chemistry. Before leaving the subject, it may be well to point out that we are not without experimental evidence tending to show that Lewis's ideas are something more than mere convenient hypotheses.

As has already been indicated, two distinct types of chemical union can be recognized. In the first place, there is the normal non-polar bond which serves us so well in all the non-ionogenic compounds of carbon; and, secondly, we have the polar type of attraction which is found uniting the ions of bases, acids, and salts. It requires little consideration to see how different in quality are these two modes of linkage.

Let us take up first the case of the non-polar bond. Our experience in organic chemistry is sufficient to convince us that this type of union leads to the formation of very stable skeletons. Rigid structures can be built up which resist all but the most intense efforts to disintegrate them. Further, as the phenomena of stereoisomerism show, these non-polar bonds act as struts in the molecular architecture and brace the whole structure so that casual deformation seems of rare occurrence.

In complete contrast with this are the polar bonds which unite the ions. In them, the attractive forces are so weak that often simple fusion of the material is sufficient to rupture the polar bonds and liberate the ions; and dissolution in ionizing solvents is enough to split ion from ion. Again, except in the

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[1] Compare Lowry, *Nature*, 1925, **115**, **376**.

crystalline condition, the ionic bond has no power to form rigid structures. In the liquid state, or in solution, the ions behave simply like charged spheres which are capable of rolling at random and the system is devoid of any specific arrangement.

The new methods of crystal analysis by means of X-rays have thrown a flood of light upon the differences between the two types of chemical affinity. It has been shown that when the non-polar bonds of chemical structure are present, the crystal is built up from atoms; whereas crystals of metallic salts have been proved to be composed of ions as units. Not only so, but the ions are arranged simply as though they were an assemblage of close-packed spheres. For example, Fig. 3 shows the grouping of part of a sodium chloride crystal.

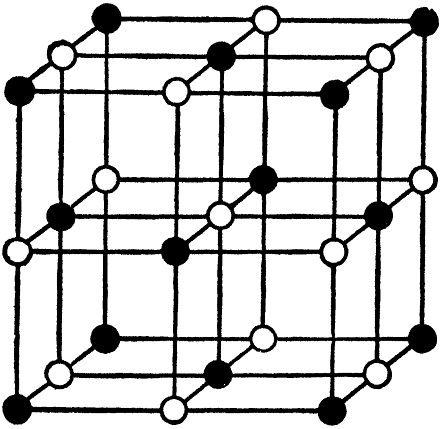


FIG. 3.

Here the white circles represent sodium ions, whilst the dark circles indicate chlorine ions. Obviously each sodium ion is surrounded, in such a crystal, by six chlorine ions which are symmetrically placed about it in space; and similarly each chlorine ion has six sodium ions arranged symmetrically in space around it. This is the grouping which might be expected from a simple close-packing of mutually-attracting spheres. There is no sign of any "directed" bonds such as the van't Hoff-Le Bel theory demands in the case of carbon compounds; and the ions are so placed that the spaces between them are reduced to a minimum.

When we turn to the diamond crystal, wherein the bonds are non-polar in character, a completely different picture is seen. Here the arrangement in space is such that each carbon atom lies at the centre of gravity of a tetrahedron formed by its four nearest neighbours; and the arrangement can also be regarded as being built up from groups of rings with six carbon atoms in each ring. In fact the model can be constructed quite easily from the ordinary models used to illustrate stereochemical questions (see Fig. 4).

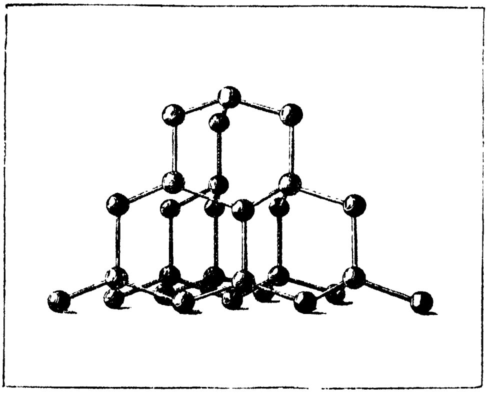


Fig. 4.

Inspection of Fig. 4 will show that instead of the close-packing arrangement of sodium chloride, we have here an open lattice-work in which a great proportion of the total space is necessarily empty. In point of fact, if these open interstices in the crystal did not exist, the diamond would have a density of 8 instead of the actual density of 3·5.

It is thus clear from the evidence of X-ray analysis that the polar and non-polar bonds are different in the groupings which they produce. It may be inferred that polar affinity is evenly distributed over the whole surface of the ion; that it acts uniformly in all directions if necessary; and that it is capable of subdivision even in the case of monovalent ions. The non-polar affinity, on the other hand, acts in specific strength in specific directions.

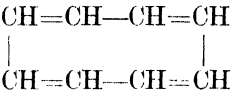
CHAPTER XVII

SOME UNSOLVED PROBLEMS

In the foregoing pages many examples have been given to illustrate the surmounting of difficulties, either practical or in theory, which at first sight appeared insuperable ; and a study of the countless successes which have been achieved by organic chemists in the solution of the problems of chemical constitution cannot fail to raise sanguine hopes that in the future the most complicated structures will be elucidated. Yet it must be freely admitted that even the simplest compounds and reactions remain fruitful fields for further investigation ; for it is precisely in this region that modern organic chemistry is most backward. Whilst the frontier of the subject is being pushed ever onward, the older branches remain very much where the pioneers left them ; and our knowledge of fundamental things has not increased at anything like the same rate as our other acquirements. In the present chapter, an attempt will be made to direct attention to a few of the many points which might repay further thought and experiment.

The greatest problem before organic chemists at the present day is the application of modern electronic views to the salient phenomena among the reactions of the carbon compounds. The peculiarities of benzene, the extraordinary variety of effects observed in the rupture of double bonds, and especially the influence of conjugation, are examples of fields which seem to offer outlets for a considerable amount of speculation in connection with G. N. Lewis's theory. Since it must be admitted that all octets are not equally stable, a promising line of attack seems likely to be found in correlating the octet theory with the results now included under the head of Michael's Distribution Principle. Not quite so tempting, though yet of considerable interest, is the problem of cyclic groupings and their influence on physical properties such as refractive index. And here, too, the phenomena of spatial conjugation seem to deserve mention.

In the group of cyclic compounds, an unexplained phenomenon meets us at once: the benzenoid character possessed by certain substances. This peculiar series of properties is evidently not produced by one factor alone, but must be the result of at least three coexisting influences. The alternating system of double and single bonds which is characteristic of the benzene system is to be found in other molecules as well. It occurs, for example, in hexatriene: $CH_2 : CH . CH : CH . CH : CH_2$; but no aromatic character is shown by this substance. Again, the mere occurrence of a six-membered ring in a compound confers no benzenoid characteristics on the substance, as is seen in the case of the terpenes or the hexamethylene derivatives. Finally, even the combination of a ring and the alternate grouping of single and double bonds does not suffice to produce aromatic properties, since both such characteristics are present in cyclo-octatetraene:



and yet this substance[1] is not benzenoid in character. It is thus evident that the *number* of the carbon atoms in the ring must have some influence; and that to possess the aromatic characteristics a compound must contain: (1) a cyclic structure; (2) six atoms in the ring; * (3) a symmetrical arrangement of alternate double and single bonds within the ring. Why this particular arrangement should be required and why it and only it can confer aromatic properties upon a hydrocarbon molecule is a point upon which speculation has hitherto failed to throw light. The most plausible solution is to be found in Collie's benzene space-formula;[2] but even it leaves room for further thought on the subject.

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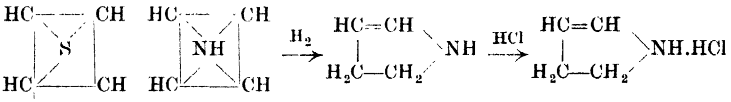
[1] Willstätter and Waser, *Ber.*, 1911, **44**, 3423.

* It should be noted that in such substances as pyridine, atoms other than carbon ones can form part of the ring and still the benzenoid character is maintained to a great extent.

[2] Collie, *J.*, 1897, **71**, 1013.

The resemblance to the benzene characteristics which is exhibited by thiophene is another point upon which no satisfactory views have been expressed. It may be recalled that although the usual formulæ for thiophene and pyrrol contain atoms capable of forming " onium " derivatives by the addition of alkyl iodides, no such addition reaction has been observed in either case. If, however, pyrrol be reduced to dihydro-pyrrol, the nitrogen atom apparently becomes normal in this respect; and ammonium salt formation takes place. This behaviour could be expressed by means of the following formulæ :—



Thiophene. Pyrrol. Pyrroline.

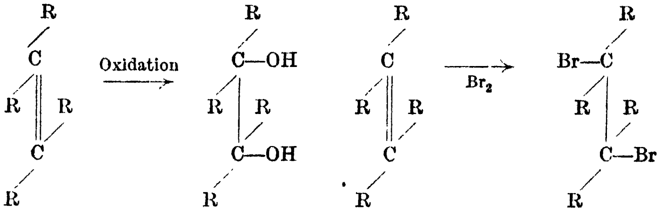
but in view of other reactions it seems doubtful if this view can be maintained.

In the field of optical activity, a most surprising result has been recorded by McKenzie.[1] On crystallizing potassium hydrogen racemate from a solution of *l*-malic acid, he obtained a crop of dextro-rotatory crystals consisting of potassium hydrogen racemate with a small admixture of potassium hydrogen *d*-tartrate. Similar results were observed on adding *l*-malic acid to solutions of potassium or sodium racemate. Fifteen other optically active acids were tried; but none gave the same positive result as malic acid. It may be frankly admitted that these phenomena cannot be explained on the basis of our present ideas about ions and asymmetry; and further investigations in the field must be awaited before the problem can be cleared up.

Another field of inquiry is opened up by the discovery that oxidizing agents and halogen molecules appear to act in entirely different ways upon unsaturated linkages.[2] The oxidizing agent attacks a single " side " of the molecule, whereas the halogen atoms attach themselves in the trans-position as shown below :—

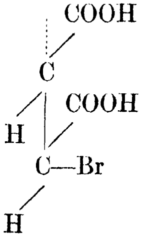
[1] McKenzie, *J.*, 1915, **107**, 440; McKenzie and Walker, *J.*, 1922, **121**, 349; McKenzie, Plenderleith, and Walker, *J.*, 1923, **123**, 2875.

[2] Michael, *J. Amer. Chem. Soc.*, 1918, **40**, 704, 1674.



Cis-addition. Trans-addition

Frankland [1] has suggested that this may be due to the atoms in a halogen molecule being separated by a distance sufficient to bring them on opposite sides of the ethylenic molecule when they react with it. Stewart [2] ascribes the phenomenon to a non-simultaneity in the addition-reaction in the case of the two carbons united by the ethylenic linkage. Thus if one carbon atom is attacked before the other, there will momentarily be formed the grouping:



and the final situation of the second bromine will be determined by the directive forces which this complex exerts upon the entering atom. In Stewart's view, these forces tend to drive the incoming atom into the trans-position. The phenomenon is to some extent akin to that of the Walden Inversion.

Other examples of analogous " directing " agencies are to be found in the phenomena of benzene substitution and in the field of stereochemistry. Thus in the esterification of an active acid with an alcohol it is found that the rate of reaction between the *d*-acid and the *d*-alcohol is different from that of the reaction between the *d*-acid and the *l*-alcohol; similar results are observed in the breakdown of active materials by means of active catalytic agents; and the influence of directive factors in asymmetric syntheses is obvious. Up to the present, there is no " explanation " of these things.

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[1] Frankland, *J.*, 1912, **101**, 673.

[2] Stewart, *Stereochemistry*, 1919, p. 118.

In a similar class we may place those cases wherein the same reagent acts differently upon molecular structures which we symbolize by identical signs. For example, we write the same symbol for a double bond whether it be present in an ethylenic linkage, a carbonyl radicle, or a carbon-nitrogen union; yet these three types differ entirely from each other in their behaviour towards hydrogen and bromine. It may be objected that although the bonds are written in the same way, we mentally interpret them differently according to the atoms which they join; but as we have already seen,* even the ordinary ethylenic bond is used to cover a number of cases wherein the reactions of the compounds are not even remotely alike.

Molecular stability is another problem of which barely the fringe has been surveyed. Why is the compound (I.) extremely stable while (II.) is unstable and (III.) is non-existent under the same experimental conditions?

$C_6H_5—N:N—C_6H_5$ (I.)

$C_6H_5—N:N—OH$ (II.)

$CH_3—N:N—OH$ (III.)

$C_6H_5—P:P—OH$ (IV.)

No satisfactory theory of this apparently simple problem has yet been suggested, nor have we any hypothesis which accounts for the non-isolation of the phosphorus analogue (IV.) of diazobenzene hydrate.

Again, carbonic acid is unstable; but when a sodium atom is substituted for one of the hydrogen atoms, the sodium bicarbonate so formed is fairly stable. The same rule holds good in the cases of sulphurous acid and sodium bisulphite. A plausible explanation may be found in the fact that intramolecular elimination of water is possible in the case of the acids, whereas the removal of water from the salts would demand the co-operation of two molecules. A similar explanation would account for the relative stability of benzene sulphonic acid as compared with sulphurous acid; but here another problem presents itself. Why is potassium bisulphite readily oxidized to potassium hydrogen sulphate, whereas it is impossible to prepare a stable compound of the formula $C_6H_5.SO_4H$ by the oxidation of benzene sulphonic acid?

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* See Vol. I., Chapter XVI.

There appears to be some influence at work which prevents the accumulation of certain atomic groups upon one carbon atom. Thus although tetrachloromethane, CCl_4, and tetranitromethane, $C(NO_2)_4$, are compounds which can be distilled without decomposition at ordinary pressure, the analogous tetra-amino-derivative, $C(NH_2)_4$, is unknown; and reactions leading to its formation[1] produce only guanidine $NH:C(NH_2)_2$. In the case of four hydroxyl radicles attached to one carbon atom the decomposition goes even further; the compound $C(OH)_4$ breaks down instantaneously in order to yield carbon dioxide and water.

In a minor degree this instability can be traced in certain other reactions. Chloroform is unaffected by alkali bisulphites, whereas chloropicrin reacts readily to yield trisulphonates such as $H.C(SO_3K)_3$, so that evidently the introduction of the nitro-group has lowered the stability of the compound.

As an offset to this, the stabilizing action of a chlorine substituent may be noted. At ordinary temperatures acetaldehyde forms no stable addition product with water; whereas the hydrate of chloral is comparatively stable:

$CH_3.CH(OH)_2$	$CCl_3.CH(OH)_2$
Unstable.	Stable.

It appears that an extension of our knowledge of the stabilizing and unstabilizing influences of various substituents in methane might open up a very interesting line of research.

Intramolecular change* furnishes one of the most interesting fields for speculation in organic chemistry. Two problems are evidently involved in the question: for we may inquire, in the first place, why one particular structure is more stable than an isomeric form; or, secondly, we may endeavour to conjecture the mechanism of the process whereby the one isomer is converted into the other. Let us take certain well-known examples of intramolecular changes and see if they can be accounted for by any general principle. It will be sufficient if we examine the pinacone change, the Beckmann rearrangement, the benzilic acid change, and the hydrobenzoin change.

All these four types of rearrangement within the molecule

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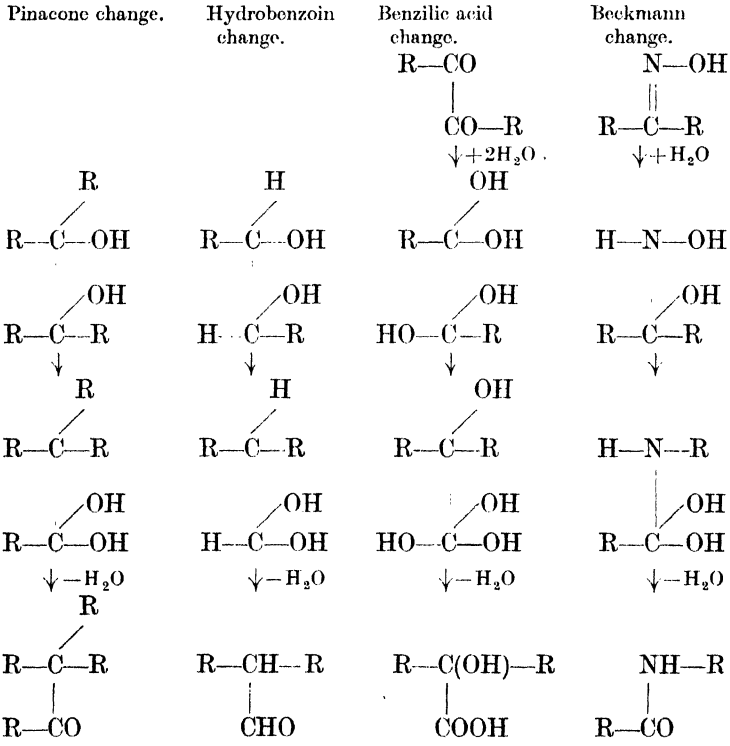
[1] Rakshit, *J. Amer. Chem. Soc.*, 1914, **36**, 1221.

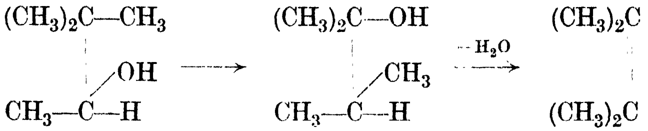
* For some general views on intramolecular change see Lapworth, *J.*, 1898, **73**, 445; Tiffeneau, *Revue gen. d. Sciences*, 1907, 583; and Lowry's lecture to the *Institut international de Chimie Solvay*, April, 1925.

can be brought into line if it be assumed that the first stage in the reaction consists of the addition of an outside reagent, which for the sake of simplicity we may regard as water. The changes would then be expressible as shown below; and the parallelism between them is obvious at a glance:—



The fact that all four reactions can be represented in a common system seems to point to the probability that this view of the mechanism may be near the truth; and it is therefore worth while to examine the matter rather more closely. When we look at the intramolecular rearrangements demanded by this formulation, it is clear that in each case there is a tendency to accumulate hydroxyl radicles upon a single carbon atom instead of allowing them to remain distributed evenly throughout the molecule. Such a grouping is unstable, as is well known; so that once it is formed it would be liable to break up, and would not be reformed to any extent by a back-reaction.

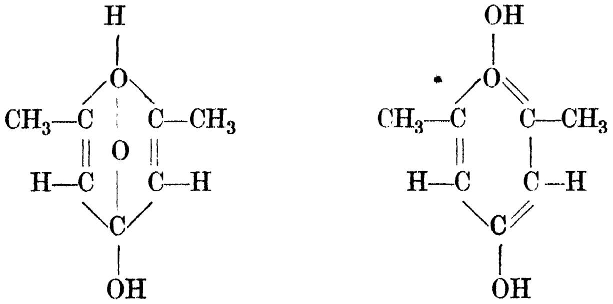
The conversion[1] of pinacoline alcohol, $(CH_3)_3C.CH(OH).CH_3$, into symmetrical tetramethyl-ethylene, $(CH_3)_2C : C(CH_3)_2$, is evidently another process wherein some intermediate stage must occur; since the direct elimination of water would lead by analogy to some such compound as $(CH_3)_3C . CH : CH_2$. Possibly the course of the reaction is as shown below:—



The inertness of the carbonyl radicle in certain compounds is very striking; and the rules governing the phenomenon are still unknown, although many of the facts are familiar to first-year students of organic chemistry. The carbonyl groups of carboxylic acids, esters, amides, and imides, seem completely inert so far as the power of forming oximes or hydrazones is concerned. In addition to these well-known cases there are others just as mysterious. For example, diacetylacetone yields a dihydrazone, but the central carbonyl group refuses to react with phenylhydrazine:

$$CH_3 . CO . CH_2 . \mathbf{CO} . CH_2 . CO . CH_3$$

Since the carbonyl groups in the pyrone series show the same reluctance to form oximes or hydrazones, the soundest interpretation of the results is to assume, with Collie,[2] that no true carbonyl radicle is present in diacetylacetone, but that instead it is representable by one of the following structures:



Collie's Diacetylacetone Formulæ.

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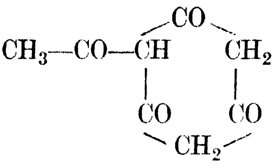
[1] Zelinski and Zelikow, *Ber.*, 1901, **34**, 3250.

[2] Collie, *J.*, 1904, **85**, 971; compare Collie, *J.*, 1921, **119**, 1550; Collie and Reilly, 1922, **121**, 1984.

A more difficult case is furnished by aceto-phloroglucinone [1]



which refuses to react with phenylhydrazine despite its four carbonyl groups and notwithstanding the fact that it contains the structure —CO—CH_2—CO— which is usually very reactive. This compound seems well worthy of further investigation in view of its peculiarities.

The characteristics of the carbonyl groups in ketens have already been discussed.

In concluding this chapter it may be well to draw attention to a number of specific cases * which require further investigation. Some of these may be mere examples of polymorphism, but there are others which cannot be accounted for upon any such hypothesis.

From viscosity measurements,[2] it appears that nitrobenzene exists in two different forms, though the spectra of these appear to be identical.[3] There are two forms of *o*-nitrotoluene, *o*-chlorotoluene, *o*-bromotoluene, *o*-toluidine, *o*-chlorophenol,[4] and *o*-chloroaniline.[5] Two forms of benzophenone exist; and numerous other examples are quoted by Knoevenagel.[6]

Two varieties of 4-quinolinic acid appear to have been isolated which form different salts. Dihydroxy-dinaphthol sulphide exists in two forms which differ from each other in the reactivities of the hydroxyl groups and sulphur atoms.[7] A similar case has been observed in 1-chloro-4-nitronaphthalene, wherein the chlorine atoms have quite different activities in

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[1] Heller, *Ber.*, 1912, **45**, 418.

* I am indebted to Professor Smiles for some of the following examples.

[2] Mühlenbein, *Ueber die innere Reibung von Nichtelektrolyten*, p. 57.

[3] Crymble, Stewart, and Wright, *Ber.*, 1910, **43**, 1183.

[4] Ostromisslensky, *Zeitsch. physikal. Chem.*, 1906, **57**, 341.

[5] Knoevenagel, *Ber.*, 1907, **40**, 508.

[6] Knoevenagel, *Entwicklung d. Stereochemie zu einer Motostereochemie*, 1907, p. 213.

[7] Henriques, *Ber.*, 1894, **27**, 2993; Christopher and Smiles, *J.*, 1912, **101**, 710; Crymble, Ross, and Smiles, *ibid.*, 1146; Nolan and Smiles, *ibid.*, 1420.

the two varieties. The more complex phenanthrene nucleus exhibits analogous phenomena, for 3-phenanthrylamine[1] exists in two forms each of which gives rise to a characteristic series of salts which on decomposition regenerate the isomer from which they were prepared, although both forms of the parent amine give rise to identical acetyl derivatives.

Enough has now been said to show that even among the simplest problems of organic chemistry there remains, despite all the work of the past fifty years, an extremely fascinating field of inquiry. It is one which especially lends itself to the propounding of hypotheses; but it should be remembered that unless a hypothesis suggests lines of further research it is in itself likely to be of little value except as a help to the memory in grouping the known facts in a simpler form.

In the study of phenomena, three questions present themselves in succession. What happens? How does it happen? Why does it happen? In organic chemistry we know the answer to the first question in a vast number of cases; but our replies to the second are by no means so plentiful; and in the majority of cases we have no means of solving the problem which the third question puts before us.

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[1] Werner and Kuntz, *Ber.*, 1901, **34**, 2325.

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THE END

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