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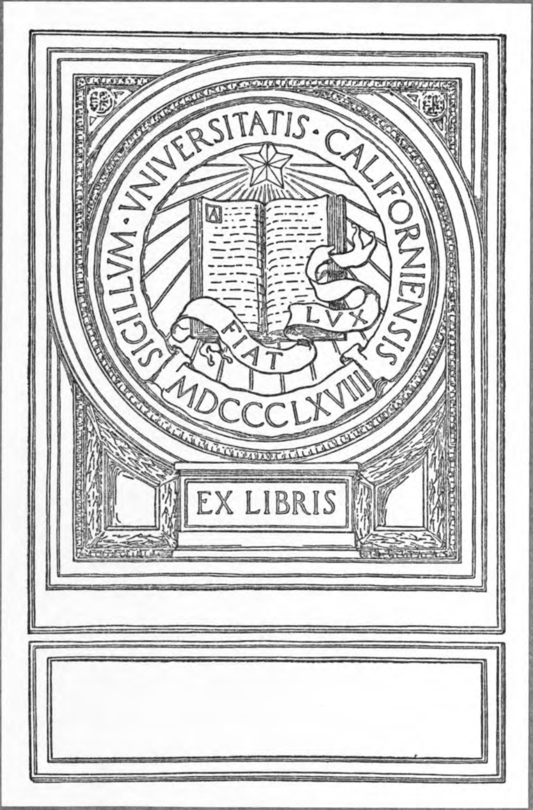
Recent advances in organic chemistry

Alfred Walter Stewart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BY
A. W. STEWART, D.Sc.
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WITH AN INTRODUCTION BY
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PROFESSOR OF ORGANIC CHEMISTRY IN UNIVERSITY
COLLEGE, LONDON

SECOND EDITION

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1911

To

MY FATHER AND MOTHER

PREFACE TO THE FIRST EDITION

In the present volume the Author has aimed at giving a general idea of the researches which have been carried out in Organic Chemistry within the last ten years, but there has been no rigid adherence to this period when it appeared desirable to include earlier investigations. A considerable portion of the material has not previously been collected in volume form; and as far as possible the most recent work in each branch of the subject has been described.

Except in the case of the third* chapter, no attempt has been made to enter into stereochemical questions. Readers desiring information on this subject are referred to the Author's book in Sir William Ramsay's series of "Text-Books of Physical Chemistry."

In dealing with Organic Chemistry two courses are open; for we may consider the matter either historically or from the synthetic point of view. In the present volume the second method has been adhered to as far as possible; and when the synthesis of a substance is known, its constitution has been deduced from the method of formation rather than from its decomposition products. The latter, when important, are reserved for consideration after the constitution has been demonstrated. For the sake of clearness, each step in the syntheses has been treated in a separate section, so that at any moment the reader can see exactly how far he has advanced, and can easily refer back to any stage which he may wish to read again.

As no one ever consults a book of this type when they wish to know the boiling-point of a compound, it would have been superfluous in the following pages to give more than the most general account of the physical properties of the substances mentioned. Full details on the subject are to be found in

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* **Chapter XI. in the present Edition.**

Beilstein's "Handbuch der organischen Chemie," to which the reader is referred for information on these points.

A bibliography of the subject has been appended to the book, but it must be understood that it is not intended to be complete; while the same may be said with regard to the references at the foot of the pages. In both cases the aim has been to furnish a guide to readers unacquainted with the literature rather than to give a complete list of publications.

For the convenience of the reader, explanatory footnotes are distinguished by asterisks, while references to the literature are numbered. This, it is hoped, will obviate much unnecessary reference to the foot of the pages.

Some chapters on the relations between chemical constitution and physical properties were originally projected; but in view of the approaching publication of a book on this subject by Assistant-Professor Smiles in Sir William Ramsay's series, it seemed unnecessary to go into the matter in this volume.

In conclusion, the Author desires to thank Professor Collie for many suggestions made during the writing of the book; and especially for the Introduction which he has contributed. He is much indebted also to Professor Inglis for improvements made in the manuscript and for his kindness in reading the proofs of the work.

A. W. S.

University College, London,
September, 1908.

PREFACE TO THE SECOND EDITION

Since 1908, when this book was first published, further researches have been carried out in several of the lines which were then dealt with; and consequently in this new edition considerable modifications have been made in order to bring the volume up to date. The original division of the alkaloids into synthetic and unsynthesized types has ceased to be useful owing to the number of these bodies which have recently been synthetically prepared; and on this account the two chapters of the first edition have been fused into one. The Grignard reaction, though novel in 1908, has now become so hackneyed that there appears to be no advantage in devoting a chapter to it; this subject has therefore been omitted. The same fate has befallen the chapter dealing with the chemical action of light. At the time the last edition was published, this field of research seemed to stand in need of a collected statement of the known facts; but at the present time the ramifications of the subject are increasing to such an extent that it is almost impossible to weave the disconnected data into a homogeneous whole; and as the space which the chapter occupied was required for other questions, it seemed best to omit the subject from this volume. Two new chapters, one on the quinoles, the other on the triphenyl-methyl problem, have been introduced.

In the present volume the arrangement of the material differs somewhat from that adopted in the first edition. Omitting the first and last chapters, the book falls into two main sections. The first of these, Chapters II.–VII., includes the syntheses and constitution determination of important natural bodies and their root-substances; while the latter half of the book is devoted to compounds and problems which have some bearing on our theoretical views.

In the preparation of this edition I have been much indebted to Professor Inglis, Assistant-Professor Smiles, Messrs. Austin, Clarke, Crymble, and Hilditch.

I should also like to tender my thanks to my numerous reviewers both for their criticisms of the previous edition and for their encouragement. When writing the first edition, I tried to bear in mind that science is not a mere collection of data, but is rather a rapidly changing series of hypotheses by means of which we attempt to group the facts with which we are acquainted; and consequently I endeavoured (as one of my reviewers put it, more clearly than I could do) "to illustrate the principles upon which modern chemistry moves — not stands—and to undermine the conservatism which exists in all but strikingly original minds." The reception accorded to the volume showed that this mode of regarding the subject is more general than I had anticipated.

A. W. S.

THE SIR DONALD CURRIE LABORATORIES,
THE QUEEN'S UNIVERSITY OF BELFAST,
October, 1910.

CONTENTS

INTRODUCTION

At the present time it is not altogether easy to say on what lines a text-book of Organic Chemistry should be written. To state in the preface that the Author "hopes it will supply a long-felt want" is not always an injudicious method of announcing the Author's belief in the readers of text-books. For if the "long-felt want" of the public is to have a restatement of all the old facts once more, with nothing new, no critical faculty shown, and an obvious lack of evidence that the book can be used to broaden our outlook on other sciences as well as chemistry, then no doubt the desire of the public for the time being is satisfied.

It certainly is to be regretted, however, that so many books on Organic Chemistry are published regardless of the fact that Organic Chemistry is a growing science. If one wants to know about a new piece of country, to obtain a large number of photographs all taken from the same place is obviously a foolish thing to do. Yet book after book on Organic Chemistry is published, covering the same ground, with a fine disregard of the fact that to the pioneers the outlook is constantly changing. A book that has practically nothing new in it except the description of a few more compounds is unnecessary. Fortunately, however, there are some text-books which are not mere narrations of facts, and which do point out, not only what has been done, but what might be accomplished, and which do make the reader think.

At no time, moreover, is a change wanted in the method of writing text-books more than at present. Deluged as we are with unnumbered facts that have often neither explanation nor obvious connection with one another, Organic Chemistry has become a vast rubbish heap of puzzling and bewildering compounds. The sanguine chemist expresses a hope that some day, perhaps, a few of these may be useful. All knowledge ought to be useful, even that obtained by the manufacture of the thousands of new substances which are annually produced in chemical laboratories. But where is it to stop? When one looks at Beilstein's "Handbook" or Richter's "Lexicon," or takes up a current volume of any chemical journal, how many of the compounds or the papers are of interest even to the most enthusiastic chemist? The game of permutations and combinations goes on, the chief object apparently being merely to supplement the already existing myriads of laboratory-made organic compounds.

How, out of all this undigested mass, is the writer of a text-book to glean what is of interest or tell what ought to be taken and what left? The result is that many text-books are not much more than abridged chemical dictionaries. The only tax on the reader's mind is to remember as many facts as possible. The text-book is rare that stimulates its reader to ask, Why is this so? or, How does this connect with what has been read elsewhere?

Indeed, it is not inconceivable that a useful text-book might be written on the constitutional formula of a single organic compound; for instance, alcohol. Its manufacture and physical properties would have to be considered. This would necessitate a knowledge of many typical organic compounds, and also of many kinds of reactions. The evidence thus obtained could then be summed up for the purpose of expressing all these facts by the chemical formula. Here the theory of the constitution of organic compounds would have to be dealt with, beginning with the ideas in vogue at the beginning of last century: Berzelius' Electro-chemical Hypothesis, of how the nature of the elements present had the chief influence on the properties of the compound; Dumas' Type-theory, and how he was the first (about 1840) definitely to recognize the arrangement of the atoms in the molecule: how this idea took about a quarter of a century to get into the text-books; how Frankland, in 1852, started the idea of valency, from which sprang the modern ideas of chemical structure and linking of atoms; how Kekulé first definitely put forward the idea of the quadrivalence of carbon; how Crum Brown, in 1865, suggested the present form of graphic formulæ and pointed out that they were "not to indicate the physical but merely the chemical position of the atoms." All these ideas have more or less centred round alcohol and its derivatives; and any one who carefully had followed the reasoning that led to these various mechanical methods for representing by a chemical formula the molecular structure of organic compounds would be in a position easily to recognize that our present ideas must in future suffer change just as they have done in the past.

Berzelius' ideas were those of a great mind; but in his day narrower theories were necessary for the more detailed development of chemistry. Dumas' Type-theory, on the other hand, was too narrow; it was a very restricted system of classification, and one that led to many false analogies. Up to the present day, the Frankland-Kekulé conceptions of valency and graphic formulæ have held their own, but there are signs that these, too, will have to be modified; physical as well as chemical properties will have to be accounted for.

The present volume should be of great use to students of organic chemistry. The subject-matter is put in an eminently lucid form that enables the reader easily to follow all the arguments, while at the same time his critical faculty is stimulated. The book, moreover, is unlike so many modern text-books in that it is not a mere compilation of facts; several novel theories on organic chemistry are dealt with, theories that up to the present can hardly be said to have assumed definite shape, but which rather point to the paths along which the pioneers of the science are likely to go in the immediate future.

J. NORMAN COLLIE.

CHAPTER I

MAIN CURRENTS IN ORGANIC CHEMISTRY DURING THE LAST HALF CENTURY

SPEAKING exclusively of observational and experimental sciences, it is obvious that progress can be accomplished only at the cost of destroying or modifying current theories; for if a theory suffices to explain facts discovered after its promulgation, knowledge may be increased; but there is no true progress unless our general outlook is altered. Thus in science we have an alternation of two courses: in the first the aim is the accumulation of facts and yet more facts; while the second is directed towards classifying these facts in the most convenient manner. At irregular intervals some facts are discovered which cannot be fitted into the accepted scheme of arrangement, and in order to make room for them the scheme has to be altered and recast into some new form.

In every science which is at all progressive there must arise from time to time conflicts between the older generation of workers and the leaders of the new; for, to those who have grown up along with it, a theory generally becomes invested with a sort of sanctity which is quite out of keeping with its true make-shift character. The longer a theory stands the harder does it become to shake it, and the greater is the tendency of the science to become stereotyped. There is another side to the question. Without any disrespect, it may be said that the majority of scientific investigators are not possessed of strikingly original minds—we cannot all be Pasteurs—and hence there is a very pronounced tendency to take things as they are and work along the beaten track rather than to push out in the wilderness and risk the chance of losing the road altogether. Thus round every theory there grows up a little band of workers, whose one aim seems to be to accumulate evidence confirming their favourite hypothesis; and in this way the theory gains a considerable weight of supporting data. On the other hand, the solitary worker who happens to differ from the majority of his fellows has to overcome a tremendous weight of unconscious prejudice before he is able to obtain even the semblance of an impartial hearing. In spite of these difficulties, however, progress is made.

Chemistry has proved no exception to the general rule. From the time of the phlogiston theory to the recent work of Ramsay upon radium, the subject has been intermittently developing, older theories have been reluctantly abandoned, and a gradual change of standpoint can be traced, each advance being forced upon the chemist by the impossibility of bringing new facts into line with the older views.

When we examine the history of the origin and growth of scientific theories it is curious to note how certain ideas seem to pervade men's minds at a given period, though they may remain unformulated for some years to come. Again and again it has been found that two investigators have independently pursued the same line of thought, and even accumulated vast stores of facts with regard to the same subject, before any suggestion has been put forward publicly. When we examine these cases more closely we are often able to trace the evolution of the idea far further back than seemed possible at the time; the independent investigators themselves may have been unaware of the existence of previous suggestions which bore upon their views, but one can hardly avoid the view that at given periods certain ideas are "in the air," having been carried so far by previous workers that the new view forces itself upon several minds simultaneously.

Such a crisis occurred in organic chemistry almost half a century ago, when the foundations of our modern structural theory were laid. Up to that time the theory of types had served as a stop-gap, but it was too clumsy and inflexible to respond to the ever-growing needs of a rapidly developing science. Only those who have had occasion to refer frequently to papers written previous to 1860, and who have been forced to transliterate the older formulæ into those employed at the present day, can have any idea of the tremendous change brought about by the work of Frankland,[1] Couper,[2] and Kekulé.[3] It is not necessary to enter into any discussion of the part played by each of these in the growth of the modern structure chemistry; all three contributed an important share to the theory upon which our work for the last fifty years has been based. We may commence our present survey with the period immediately preceding the publication of Kekulé's first paper on benzene.

Though the formulæ of Couper and Kekulé proved most powerful weapons in the hands of those chemists who were engaged in investigations of aliphatic substances, the equally important class of aromatic bodies still remained in a state of confusion equal to that which prevailed under the type theory. It was the farsightedness of Kekulé which brought this to an end within less than a decade by a further advance along structural lines. In 1865 he published a paper on this subject;[4] and a year later the whole problem was thoroughly examined by him in a treatise[5] which is probably as fine a piece of reasoning as has yet been devoted to a chemical question.

Kekulé took as his first premise the fact that every aromatic compound contains at least six carbon atoms; secondly, when a compound contains more than six carbon atoms it is often possible to break it down into one containing six carbon atoms, and further decomposition is resisted at this point, which appears thus sharply to mark a definite stage in the process. From these two points he was led to imagine that there was something in the arrangement of these six carbon atoms which differentiated them from six carbon atoms grouped as in an aliphatic substance. Another step completed the new theory. Having advanced so far, Kekulé had but to ask himself in what way one could arrange six atoms so that they would not form an open chain; and it is now obvious to us that the simplest reply is, in a ring. To us to-day, this seems such a self-evident solution that we are apt to overlook the greatness of the discoverer and to imagine that "any fool could have done it."

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[1] Frankland, *Phil. Trans.*, 1852, **142**, 417.

[2] Couper, *Phil. Mag.*, 1858, IV. **16**, 104.

[3] Kekulé, *Annalen*, 1858, **106**, 129.

[4] Kekulé, *Bull. soc. chim.*, 1868, 1, 98.

[5] Kekulé, *Annalen*, 1866, **137**, 129.

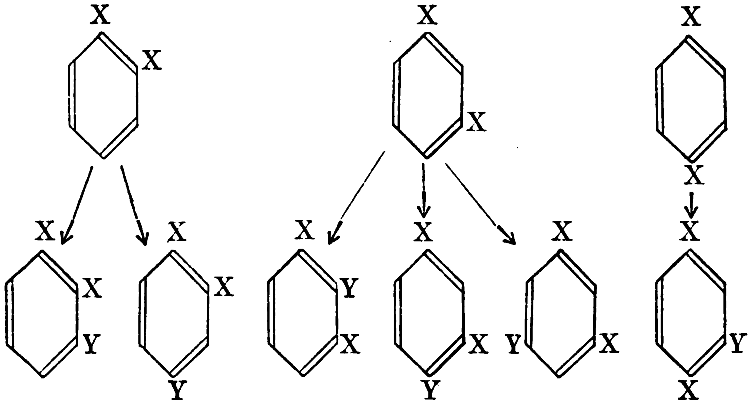
There is a certain element of truth in this, for it is apparent that such a discovery might quite well have been the result of a chance idea; in fact, Kekulé himself uses language which might give colour to this view, though probably he did not intend to convey that impression. But Kekulé was not content with a mere statement of the problem's solution; he was able to forecast at once the line of research which would have to be followed if the theory were to be put to the test of experience.

First, however, Kekulé had to explain how the six carbon atoms in the benzene ring could be linked together and united with the six hydrogen atoms which are needed to make up the complete benzene molecule. One of his early views was speedily found to be untenable, as it presupposed two sets of hydrogen atoms—three and three, so placed that a mono-substituted benzene derivative might occur in two isomeric forms. In its final form, the benzene ring was written practically as we write it now, with a double bond between every alternate pair of carbon atoms and single bonds between the other pairs.

At the time the benzene theory was developed, however, the data which had been accumulated with regard to aromatic compounds were not sufficiently numerous to establish definitely its truth or error. But the new view imparted such a stimulus to the investigators of that period that in a very short time it was shown beyond a doubt that the Kekulé theory was capable of furnishing an interpretation of all the facts which had previously been incapable of any clear arrangement.

No sooner had the benzene formula proved its value in this way than a new problem was mooted. Given the benzene ring, it is obvious, as Kekulé himself pointed out in his paper already referred to, that there must be a certain fixed number of isomers for each substituted benzene derivative. For instance, if the substituent introduced is always the same, there will be one mono-substitution product, three di-substitution products, three tri-substitution products, and so forth. The question then at issue was the possibility of determining the constitution of any given isomer; or, in other words, if a poly-substituted benzene derivative were produced in any reaction, what means must be employed to discover the order in which the hydrogen atoms and substituents lay round the ring?

The investigator who contributed most to the development of this section of the subject was Kekulé's pupil, Körner. If we take a di-derivative of benzene and introduce into the ring one additional substituent (thus forming a tri-derivative) it will be found that the number of possible tri-derivatives depends upon the constitution of the di-derivatives from which the start was made. As can be seen from the figures below, an ortho di-derivative will yield two tri-derivatives, a meta di-derivative gives three tri-derivatives, while from a para-compound only one tri-derivative is formed. The relations of the tri-derivatives among themselves can be established by an analogous method—



Körner, Griess, Ladenburg, Graebe, and Baeyer all aided to establish the relations between the various substitution products of benzene, and in a comparatively short space the filiation between all the various classes of benzene derivatives had been made clear.

It is a curious study to see how far one can trace in the early controversies on the constitution of benzene the germs of other theories which came later to their full development. We may take one instance now. Ladenburg[1] was the first to point out that while ortho-di-substituted benzene derivatives occurred in one form only, the Kekulé hexagonal formula permitted two, which can be expressed by the formulæ below.

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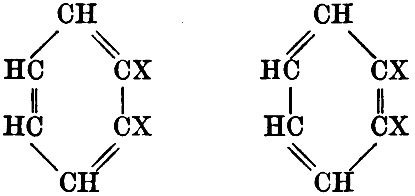
[1] Ladenburg, *Ber.*, 1869, **2**, 140.

In the one case the carbon atoms carrying the substituents are joined by a double, in the other case by a single, bond—



Ladenburg adduced the supposed parallel case of crotonic and vinyl-acetic acids, which differ in the position of the double bond with reference to the carboxyl group—

$CH_3—CH:CH—COOH$ Crotonic acid.
$CH_2:CH—CH_2—COOH$ Vinyl-acetic acid.

He alleged that if the shift of a linkage made no change in benzene, it should be equally without effect in the case of these two substances. But as they actually existed in isomeric forms, the same was to be expected in benzene, if the Kekulé theory were correct.

Ladenburg was responded to by Kekulé,[1] and also by Victor Meyer.[2] The latter pointed out that while in benzene the only difference between the two supposed isomeric forms was produced by a mere change in the grouping of linkages, the case of the two acids shown above was further complicated by the fact that a hydrogen atom has also shifted its position from the end of the chain to the carbon atom next the carboxyl group. Thus the two cases are not really analogous at all.

Kekulé attacked the Ladenburg view from a different standpoint, and we cannot do better than quote his own expression of the case—

> "The atoms in the systems which we call molecules must be considered to be continually in motion. This view has often been expressed by physicists and chemists, and I have already discussed it in my handbook. Hitherto no explanation as to the form of this intramolecular motion has been given, as far as I know. Chemistry must, at all events, bring forward the claim that such a mechanical hypothesis accounts for the law of the linking of atoms. A planetary motion seems, therefore, not inadmissible; the movement must be of such a kind that all the atoms forming the system retain

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[1] Kekulé, *Annalen*, 1872, **162**, 87.

[2] V. Meyer, *Annalen*, 1870, **156**, 265; 1871, **159**, 24.

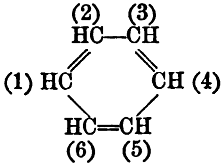
the same relative arrangement—in other words, that they return to a mean position of equilibrium. If we now select from the numerous conceptions which may be formed, that which gives the most complete account of the chemical claims and which coincides most closely with the hypothesis of modern physicists as to the mode of the motion of molecules, the following assumption will appear the most probable.

"The simple atoms of the system approach each other in what may be considered a straight line, and rebound like elastic bodies. What we call valency would then have a mechanical meaning. Valency is the number of contacts experienced by one atom on the part of other atoms in unit time. In the same time that the monad atoms of a diatomic molecule strike each other once, the dyad atoms of a diatomic molecule come twice into contact with each other, the temperature being the same in both cases. In a molecule made up of one dyad and two monads the number of contacts, under the same conditions, in unit time is two for the dyad and one for each monad atom.

"If two atoms of tetrad carbon are linked together by one combining unit of each, they strike together once in unit time, or in the same time that a monad hydrogen atom makes a complete vibration. During this time they encounter three other atoms. Carbon atoms, which we call doubly linked, come in contact twice in unit time, and further in the same period collide twice with other atoms.

"If we now apply these views to benzene, the formula which I have proposed appears as an expression of the following conception. Each carbon atom strikes against two others in unit time, once against one and twice against the other. In the same unit of time it comes once into contact with hydrogen and completes one vibration.

"If we now represent benzene by the hexagon formula and fix our attention on one of the carbon atoms (that marked 1, for instance)—



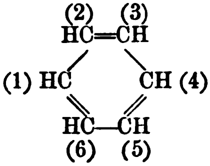
we can express the contacts it experiences during the first unit of time by—

(I.) 2, 6, *h*, 2,

where *h* stands for the hydrogen atom. In the second unit of time that carbon atom which has just encountered No. 2 turns next to No. 6. Its collisions during the second unit of time are—

(II.) 6, 2, *h*, 6.

While the contacts during the first unit of time are represented by the hexagonal arrangement above, those during the second unit of time are represented by—



The same carbon atom, therefore, is during the first unit of time doubly linked to one of the adjoining carbon atoms, while during the second unit of time it is in double linkage with the other carbon atom.

"The most simple mean of all the contacts of one carbon atom is found from the sum of the contacts during the first two units of time, which then repeat themselves periodically—

2, 6, *h*, 2, 6, 2, *h*, 6 . . . .

and we see now that each carbon atom strikes against the two others with which it is directly combined, an equal number of times; in other words, it bears the same relation to each of its neighbours. The ordinary formula for benzene only represents the contacts made during the first unit of time, or only one phase, and thus the view has sprung up that the di-derivatives with the positions 1, 2 and 1, 6 must be different. If the above hypothesis or any similar one be considered to be correct, it follows that this difference is only apparent, not real."

Thus early in the history of modern structural chemistry did the vibrational hypothesis make its appearance, and from that time to the present day the view has slowly grown that the intramolecular arrangement of atoms can best be represented by a series of vibration phases rather than as a rigid assemblage of particles.

The next stage in the evolution of this theory was taken in view of quite different evidence. The Kekulé benzene oscillation had been put forward to explain why two apparently different structures had the same properties; but in the question of the acetoacetic ester constitution, which came to the front soon after this, the crux of the problem lay in the fact that one substance reacted as if it had either one or other of two totally different structures.

In 1876 Butlerow[1] was led to suggest that in the cases of certain bodies a kind of intramolecular vibration was continually taking place, which explained why some substances reacted now in one way and again in another according to the type of reagent with which they were treated. Some years later, Laar[2]

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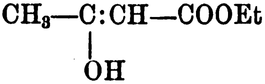
[1] Butlerow, *Annalen*, 1876, **189**, 76.

[2] Laar, *Ber.*, 1885, **18**, 648; 1886, **19**, 730.

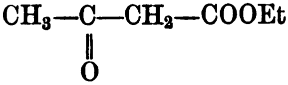
collected a number of cases in which by shifting a hydrogen atom from one atom to another in a chain it was possible to give some idea of how the substances were able to act as if they had two different constitutions. For instance, in the case of acetoacetic ester it is found that with certain reagents it acts as if it contained a hydroxyl group, while with other substances it behaves as if it were a pure ketonic compound. This can be expressed by saying that in the one instance it reacts as if it had formula (I.), while in the other it appears to have the structure (II.)—

(I.)



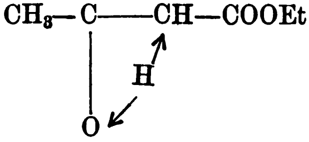
$$CH_3\text{—}\underset{\displaystyle OH}{\overset{}{C}}\text{:}CH\text{—}COOEt$$

(II.)



$$CH_3\text{—}\underset{\displaystyle O}{\overset{}{C}}\text{—}CH_2\text{—}COOEt$$

This might be explained by supposing that what we call acetoacetic ester is really a mixture of the two structure isomers (I.) and (II.). Laar took a different view. According to him, acetoacetic ester was a simple substance, but instead of the hydrogen atom being attached either to the carbon or to the oxygen atom it wandered or vibrated in space between them, and was finally influenced in its choice of position by the action of the reagent applied to the acetoacetic ester. We may represent this by the following picture:—



Substances of this type Laar proposed to call "*tautomeric*" (ταὐτό, the same; μέρος, a part).

This idea of intramolecular vibration, however, soon received an extension by the discovery of some cases in which substances not only reacted as if they had two different structures, but could be actually isolated in the two structurally distinct forms. This showed that in some cases at least the Laar hypothesis was incorrect, or, rather, was too narrow a statement of the case; for, instead of the wandering atom remaining always like Mahomet's coffin midway between two extremes, in these cases it was actually found at both ends of the vibration range. A substitute for the Laar hypothesis was brought forward by Jacobson.[1] On his view, certain substances may occur in either of two structurally different forms, and the change of one form into the other takes place only under the action of some reagent. Since any such change must be produced by a shifting of the bonds within the molecule, Jacobson proposed to describe the phenomenon by the name of "*desmotropy*" (δεσμός, bond; τρόπος, change).

Hantzsch and Herrmann[2] suggested that the whole subject should be treated as one, so that if a substance could be isolated in two stable forms it should be called *desmotropic*, while if it could not be so isolated it should be termed *tautomeric*. We need not go further into the question of desmotropy at present. Enough has been said to show the growth of the idea of a labile grouping of atoms within the molecule, which at the present day has been carried as far as it can serve any purpose.

These views (which we may call "dynamic" in contradistinction to the "static" conception of molecules as fixed groupings of atoms) did not come to a head in time to save Baeyer from one of the greatest pieces of misdirected research which the chemical world has seen in recent years. The work itself is magnificent both from the practical and the theoretical standpoint. But Baeyer carried out the whole of his investigations upon one assumption, viz. that in the structural formula of benzene there was a fixed, unalterable arrangement of valencies which could be deduced from the results of oxidations, reductions, and other reactions. By this time many different modifications of the original benzene hexagon had come into existence, and Baeyer endeavoured to settle, by means of his researches, which one of these actually represented the formula of benzene. We cannot spare space to deal with the details of his work, much of which has been of great service in directions other than those in which it was originally aimed. Finally, Baeyer himself was driven to conclude that there is no one formula which will explain all the reactions of benzene. Collie[3] has shown how all the proposed benzene formulæ may be harmonized and expressed by a simple vibrational system in

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[1] Jacobson, *Ber.*, 1887, **20**, 1732; 1888, **21**, 2628.

[2] Hantzsch and Herrmann, *Ber.*, 1887, **20**, 2803.

[3] Collie, *Trans. Chem. Soc.*, 1897, **71**, 1013.

three dimensions, and it seems unlikely that this will be improved upon to any great extent.[1]

From his examination of the benzene question, Baeyer was led to take up the subject of the terpene constitutions, which at that time was in its infancy. These substances are in most cases derivatives of reduced benzene rings, so that Baeyer passed from the one subject to the other quite naturally. To his work in that line we owe much of our present knowledge of terpene chemistry; but we are even more indebted to Wallach, who began work in this subject about the same time as Baeyer. We cannot give even the briefest summary of Wallach's work in the space at our disposal here, but must content ourselves with referring the reader to special treatises on the terpenes and ethereal oils.

This brings us to the camphor controversy, which for a decade raged through a corner of the chemical world. Every organic chemist of note seems to have considered himself in duty bound to propose some formula for camphor or a camphor derivative, and the confusion resulting from this prodigality was only banished by the synthesis of camphoric acid and camphor, which we shall describe in the chapter upon the dicyclic terpenes.

The reader will now have some idea of the extraordinary fertility of the theory of aromatic compounds put forward by Kekulé. We must next turn to another question in which Kekulé, if not the actual originator, was at least one of a long chain of investigators whose work has had a tremendous influence upon our ideas of intramolecular arrangement.

When one looks back upon the work of scientific discovery, one is struck most, not by the fact that certain things have been discovered, but by the very slightness of the barrier which so often stood between the success and failure of a certain line of research at a given period. Again and again subjects have been approached and their problems virtually solved, yet for want of just one connecting link, or even the addition of a few words to a statement which in itself contains the key to the problem, the question may go unanswered for years. No better example of this is to be found than that furnished by the evolution of stereochemical theory.

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[1] A discussion of the various space formulæ for benzene will be found in the author's "Stereochemistry."

In 1860 Pasteur[1] carried out an investigation of the tartaric acids, in which he was able to show that crystals of dextro- and lævo-tartaric acid are related to one another as an object is related to its image in a mirror. At this time the structure theory was in its very infancy, and Pasteur does not seem to have thought of applying it to the case with which he was dealing. He contented himself with putting forward as a possible explanation the view that the atoms in the tartaric acid molecule were arranged in right- or left-handed spirals, or were grouped at the corners of a tetrahedron. This was the germ of the whole of modern stereochemistry, but, for want of a slight addition to these expressions, it remained for later investigators to reap the credit of establishing the correctness of this view. In 1869 Paternó[2] proposed to explain certain cases of isomerism by means of tetrahedral models. Kekulé,[3] two years previously, had described a tetrahedral model, but it seems doubtful whether he really intended it to convey an idea of the distribution of valencies in four directions in space. No notice was taken of either of these suggestions by the chemical world in general, and it appears to have been Wislicenus[4] to whom we owe the next definite pronouncement on the subject. After proving that the structures of the isomeric lactic acids were identical, he added, "The facts force us to explain the difference between isomeric molecules of the same structure by a different arrangement of atoms in space."

The ultimate solution was published simultaneously by Le Bel[5] and van't Hoff,[6] who pointed out that all organic substances showing optical activity contained at least one *asymmetric carbon atom, i.e.* an atom whose four valencies are attached to four dissimilar groups. A slight extension of the theory sufficed to explain the occurrence of isomeric substances containing a double bond; and Baeyer[7] applied it also to the

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[1] Pasteur, "Récherches sur la dissymmetrie moléculaire des produits organiques naturels."

[2] Paternó, "*Giorn. di Scienze Naturali ed Econ.*" V. Palermo, 1869.

[3] Kekulé, *Zeitsch. f. Chem.*, 1867, N.F., **3**, 217.

[4] Wislicenus, *Annalen*, 1873, **167**, 343.

[5] Le Bel, *Bull. soc. chim.*, 1874, II, **22**, 377.

[6] Van't Hoff, "Voorstell tot uitbreiding der structuur formules in de ruimte." Utrecht, 1874.

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

case of cyclic substances. But the theory has been by no means limited to carbon compounds alone. In 1890 Hantzsch and Werner[1] had recourse to stereochemical ideas to explain cases of isomerism among the oximes; in 1893 Werner was able to bring some semblance of order into the class of metal-ammonia derivatives; while in 1894 Hantzsch[2] put forward a theory of the diazo-group. On the side of the question dealing with optical rotatory power, the work of Le Bel[3] on nitrogen, Smiles[4] on sulphur, Pope and his students[5] on selenium and tin, and Kipping[6] on silicon, have shown that asymmetric atoms of these elements may also give rise to activity.

So much for the statical side; but there is another point of view from which we may regard the relations between the positions of atoms in space. In this new field Victor Meyer and Bischoff have contributed by far the greatest additions to our knowledge. They have shown that reactions may be hindered, or even completely impeded, by certain groupings of atoms in given positions. For example, if in benzoic acid we substitute methyl groups for the two hydrogen atoms in the ortho-positions to the carboxyl group, the acid becomes at once much more difficult to esterify. This phenomenon is termed "*steric hindrance.*"

We have not space to enter into any question of stereochemistry in detail at present; but in this connection we must mention one of the greatest pieces of research which have been carried out in the past twenty years. When Emil Fischer and his students first began methodically to examine the sugars, the investigation of that class of bodies was regarded as one of the most hopeless problems which an organic chemist could set himself. The substances were often uncrystallizable, and differed so little among themselves that it seemed hopeless to try to separate one isomer from a mixture. Further, the enormous complication of their isomerism, due to the numerous asymmetric carbon atoms they contain, seemed to make the attack upon this branch of stereochemistry one of the least

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[1] Hantzsch and Werner, *Ber.*, 1890, **23**, 11.

[2] Hantzsch, *Ber.*, 1894, **27**, 1702.

[3] Le Bel, *C. R.*, 1891, **112**, 724; 1904, **129**, 548.

[4] Smiles, *Trans. Chem. Soc.*, 1900, **77**, 1174.

[5] Pope and Peachey, *Proc. Chem. Soc.*, 1900, **16**, 42, 116; Pope and Neville, *Trans. Chem. Soc.*, 1902, **81**, 1552.

[6] Kipping, *Trans. Chem. Soc.*, 1907, **91**, 209, 717; 1908, **93**, 457; 1909, **95**, 69.

promising. There seems no doubt that with ordinary means at his disposal Fischer could never have accomplished the work; but his genius had stood him in good stead in one of his earlier researches. In 1877 he discovered the compound phenylhydrazine,[1] and by means of this substance he was able to convert the imperfectly crystallizable sugars into crystalline hydrazones, from which he was able to regain the sugar after he had thus separated it from its isomers. In a few years Fischer[2] completed this vast research, in the course of which he established the configurations of all the pentoses and hexoses by experimental means and by reasoning which is unlikely to be surpassed for simplicity and directness.

After leaving the sugars, Fischer devoted his attention to the purine group, in which he carried out a series of brilliant syntheses; and when this subject in its turn was exhausted he attacked the problem of the decomposition products of the peptones, with results which are described in a later chapter of the present volume.

There are one or two other problems which have been dealt with in the last thirty years, but they are somewhat disconnected with each other and with the parts of organic chemistry which have just been described.

In the first place, there is the pyridine question. After the constitution of benzene had been established, it was inevitable that the same view would sooner or later be applied to pyridine, and in 1869 Körner[3] proposed to represent that substance by a benzene ring in which one of the —CH= groups was replaced by a nitrogen atom. This theory was supported by some researches of Kekulé,[4] and is to-day accepted as correct. Now, the importance of pyridine and its simple derivatives does not lie in themselves, but rather in the fact that the pyridine ring appears to form the basis of all the natural alkaloids, just as the benzene ring is the foundation of the aromatic series. We need not enter into the alkaloid question here, as a chapter in this volume is devoted to it.

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[1] Fischer, *Annalen*, 1877, **190**, 81.

[2] Fischer, *Ber.*, 1894, **27**, 3189.

[3] The first publication of this idea seems to be due to Dewar, *Zeit. f. Chem.*, 1871, 117.

[4] Kekulé, *Ber.*, 1890, **23**, 564; see also Richter-Anschütz, *Lehrbuch d. Organ. Chemie*, 1905, II. 711, 712.

Since the time of Kekulé, organic chemistry has been for the most part a synthetic science. At the present day considerably over a hundred thousand organic compounds are known, and one need not have the least hesitation in saying that if seventy per cent. of them had never been synthesized we should not feel the lack of them to any appreciable extent. The reason for this enormous flood of synthetic material is to be found in the German University system; for since, under the German regulations, the degree in chemistry is granted only on the results of original research, it follows that every Ph.D. represents so many new compounds—at least, as a general rule. But these do not include all the forces leading to the steady pursuit of the synthetic branch. The great German dye industry employs in itself hundreds of chemists, and from them also flows a steady stream of new compounds. The same may be said of the explosive manufacturers and the firms which produce synthetic drugs.

Before closing this chapter we may cast a glance at the physical methods which have sprung up in organic chemistry during the last half-century. The relation between chemical constitution and optical rotatory power dates, of course, from the time of van't Hoff and Le Bel's papers on the asymmetric carbon atom; and Guye[1] has propounded a theory which, though failing in detail, seems not inapplicable to the general connection between rotation and constitution. Refractive index appears to be a property which is closely connected with the mode of linkage of the atoms in organic compounds, and much work has been done in this line by Brühl and others. The electrical conductivities of acids depend very greatly upon the constitution of the radical to which the carboxyl group is attached. Magnetic rotation, *i.e.* the optical rotatory power which nearly all substances acquire when placed in strong magnetic fields, has been studied in great detail by the late Sir W. H. Perkin, who showed that by its aid the constitution of many substances, especially desmotropic bodies, could be determined. Absorption spectra, both optical and electric, have been used in the determination of doubtful structures; the first have been employed by Hartley, the second by Drude.

We have now completed our survey of modern organic

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[1] Guye, *C. R.*, 1890, **110**, 714.

chemistry. It has, of course, been impossible to deal with many pieces of work which are quite as important as some of those we have actually mentioned, but, on the whole, it is believed that a more or less accurate picture has been given of the evolution of the subject along various lines. If we look only to the principles which lie at the back of the science and which, though they may remain unformulated, still sway our views by some sub-conscious action, we shall find that the history of the last five and twenty years has been one of a gradual passing from a static to a dynamic view of the molecule. In the early days, the ideas of chemists centred round more or less rigid structures which they regarded as approximately "set." The tetrahedron of van't Hoff had the effect of strengthening rather than weakening this tendency; and it is much to be regretted that the van't Hoff view, rather than that of Le Bel, found favour in the chemical world at large. At this period the state of mind[1] of the average organic chemist seems to have been somewhat similar to that of the student who, when asked to explain the atomic theory, said, "Atoms are square blocks of wood invented by Dr. Dalton."

This view of the subject was shaken by the publication of Werner's views on affinity and valency,[2] in which the idea of directed valencies was shown conclusively to be a quite unnecessary assumption; and at the present day the idea of a certain amount of intramolecular "play" is not regarded as absolute anathema by the more advanced school.

The last twenty years of organic chemistry, however, have been rather barren in many directions. The only really outstanding conception which has been evolved and developed into several branches has been the idea of the arrangement of atoms in space. Apart from this, the theoretical side of the subject has not given rise to anything more than a series of very minor theories, none of which (with the exception of Thiele's partial valency hypothesis) seems likely to develop in any wide manner. The reason for this is most probably to be sought in the recent and sudden rise of physical chemistry, which has drawn away from the organic field many

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[1] If this statement appears exaggerated, the reader is recommended to consult the *Annalen*, 1901, **316**, 71, where he will find ample evidence of the persistence of these views even quite recently in certain circles.

[2] Werner, "Beiträge zur Theorie der Affinität und Valenz." 1891.

chemists who would doubtless have carried the older branch much further forward than has been possible without their assistance.

The progress of human thought has been likened by some author to the journey of a passenger on a funicular railway. We leave the starting-point in the valley and pass upward through tunnels and cuttings for a time, until at last we emerge again into daylight to find that though we are still within a stone's throw of our point of departure we have moved in a spiral, and now look down from a new point of view at the station which we have left. In the same way, science appears to progress in cycles; and, after a more or less prolonged period, we find the old views reappearing and the old conflicts beginning once more, though at each new encounter the point of view is slightly shifted as new or more refined experimental methods replace or supplement the older ones.

This periodicity in theory has seldom been displayed more clearly than in the matter of structural formulæ and their meaning. If we examine the views of the two pioneers Couper and Kekulé, we find that, though agreed as to the method of writing down formulæ, they were by no means at one as regards what the formulæ expressed when once put upon paper. Kekulé's view[1] was based upon quite incontrovertible reasoning:—

> "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 these 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 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

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[1] Kekulé, *Annalen*, 1858, **106**, 149.

[2] Couper, *Phil. Mag.*, 1858, IV. **16**, 107.

graphic formulæ are simply shorthand symbols by means of which we can easily and compactly express the results of our chemical experiments; while, 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.

These two theories still persist side by side in the present-day chemical world, and a considerable waste of energy occurs when two upholders of different views try to interpret the same set of results. The conflict between the two schools has become especially acute within recent years owing to the strides which have been made in the correlation of chemical constitution and physical properties of compounds; for a substance may react as though it possessed a given constitution, whereas physical measurements would lead us to quite different conclusions with regard to the atomic linkages of the molecule in question. In the case of a chemical problem, it seems evident that chemical evidence should carry most weight, and the confusion of ideas has been chiefly due to workers on the physical side employing chemical formulæ to denote something which is not chemical. It seems a peculiar process of reasoning which allows a person to base his hypotheses upon the reaction formulæ of chemists, and then, after taking into account some physical property of a substance, to return to chemistry with a proof of the incorrectness of the original reaction formulæ upon which his argumentation is based.

When we look at the present condition of organic chemistry it is rather discouraging. Everything seems to be cut and dried as far as the theory of the subject is concerned, and on the practical side the main tendency seems to be merely to confirm current theories. It is self-evident that we can make no progress by confining ourselves to the confirmation of the views which pass muster at present. If any advance is to be made, it must be begun by investigating those phenomena which do not agree with the standard theory; and, as an instance, we might point to the case of the ionic hypothesis and the ordinary organic reaction. There is, however, another direction in which we may look for a line of research. It is customary in text-books to assume that "water adds on in such and such a way," or, "the bromine atom attaches itself in the usual way to the tertiary carbon atom"; many such expressions can be found, but it never seems to occur to the ordinary person that to state a fact is not to offer an explanation, and while we are all sufficiently glib in describing *how* a reaction takes place, very few of us seem to give a thought to the problem of *why* the reaction takes that particular course rather than another. We have thus accumulated an immense mass of data concerning the results of reactions, but very little indeed with regard to their causes. It seems obvious that if organic chemistry is to get a new lease of life, some attention must be paid to such questions as these. Of course the investigator who takes up such problems will have to invent a new set of methods; but the aim in view would be worth a little trouble.

At the present day it appears to be the fashion to suppose that certain views are so firmly established that no research into their foundations is worth the labour expended on it, and consequently investigators devote much time and energy to the examination of highly complex substances while simpler compounds are supposed to be "worked out." In the same way it was supposed for many years that the composition of the atmosphere was well known, until the work of Ramsay and Rayleigh showed how little we knew of even this common mixture. With this object lesson before them, it is to be hoped that more organic chemists will find time to investigate some of the problems which are passed over by the mass of workers who seem to place a label in the same category as an explanation.

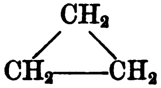
CHAPTER II

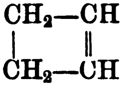
THE POLYMETHYLENES

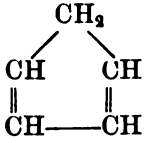
In the succeeding chapters we shall deal with the mono- and di-cyclic systems which are found among the terpenes and camphors; but before entering upon a discussion of these it appears desirable to give some account of the root-substances from which all of them are derived. The present chapter, therefore, will be devoted to the polymethylenes.

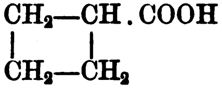
Compounds of this class have the general formula $(CH_2)_n$, where "*n*" is any integer from three to nine; and they are therefore isomeric with the open-chain olefinic compounds of the general formula C_nH_{2n}. The two classes differ widely from each other, both in chemical and in physical properties; this point will be discussed in detail later in the chapter.

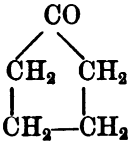
Two nomenclatures are at present in vogue for derivatives of this class of compounds. In the first, the given substance is distinguished as a tri-, tetra-, penta- hexa-, hepta-, octo-, or nono-methylene according as its ring is made up of three, four, five, six, seven, eight, or nine methylene groups. If a carbonyl group occurs in the ring, its presence is indicated by the prefix "keto-," while for a carboxyl group the suffix "-carboxylic acid" is added to the name of the polymethylene. The second system of nomenclature is a more general one. The designation of any polymethylene is found on this second system by taking the name of the corresponding paraffin and prefixing "cyclo-" to it. When a double bond occurs in the compound the termination "ane" is changed to "ene"; and for two double bonds to "di-ene." If a ketonic group occurs in the molecule it is distinguished by changing the termination "ane" to "anone." As can be seen, both systems are somewhat clumsy, and hence it is desirable at times for the sake of clearness to use the one which most simply expresses the compound in question. The following examples will help to make the matter clearer:—


Trimethylene
Cyclopropane.


Cyclobutene.

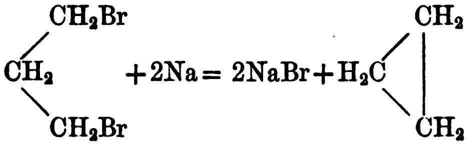

Cyclopentadiene.


Tetramethylene-carboxylic acid.
Cyclobutane-carboxylic acid.


Ketopentamethylene
Cyclopentanone.

There are at present ten principal methods by which we can obtain saturated cyclic carbon compounds; of these, only four yield simple polymethylenes; two others produce homologues of the parent substances; and the remaining methods lead to the formation of acids with a polymethylene nucleus. We may examine all these reactions, and for the sake of convenience in future reference it may be well to number them consecutively.

(1) The simplest method of obtaining a polymethylene compound is to act upon the corresponding open-chain dihalogen derivative with zinc dust or sodium. This is merely a modification of the ordinary Fittig-Würtz reaction—



(2) When the calcium salt of a mono-basic acid is distilled it yields calcium carbonate and a ketone. The same reaction was employed by Wislicenus and Hentzschel[1] in the case of a dibasic acid; and the resulting compound was found to be a cyclic ketone—

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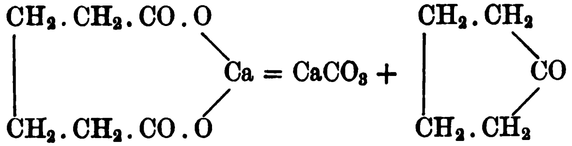
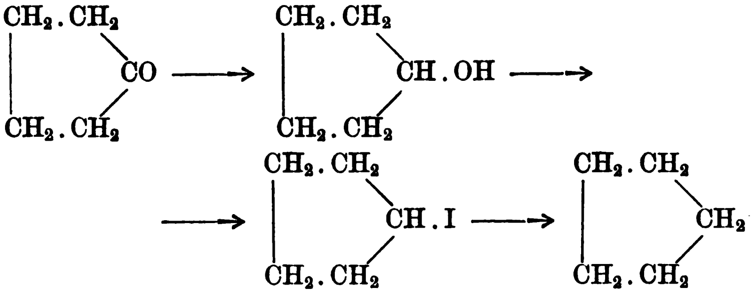
[1] Wislicenus and Hentzschel, *Annalen*, 1893, **275**, 312.



From the ketone the corresponding secondary alcohol was prepared by reduction with sodium in ethereal solution: and from the alcohol, by the action of hydriodic acid at 0° C., the iodide was formed. This, on reduction with zinc and hydrochloric acid, gave the corresponding hydrocarbon—



(3) If the unsaturated cyclic hydrocarbon corresponding to the desired polymethylene is known, the saturated compound may be obtained from it by passing its vapour, mixed with a stream of hydrogen, over finely divided nickel. This method was devised by Sabatier and Senderens.[1] The nickel is heated while the gas is passed over it, the temperature being regulated with care, as the action is apt to be carried too far and to lead to the opening of the ring by further reduction of the polymethylene.

(4) In those cases in which it is possible to obtain the amine derived from the required polymethylene, it can be converted into the parent substance by Kishner's method.[2] In the first place, the amine is converted into the hydrazine by bromination and subsequent treatment with silver oxide; the hydrazine is then oxidized with alkaline potassium ferricyanide. Nitrogen is finally evolved, and the required hydrocarbon remains behind. For the sake of simplifying the formulæ we may take the theoretical case of the production of tetramethylene from amidotetramethylene; the steps in the reaction are indicated below—

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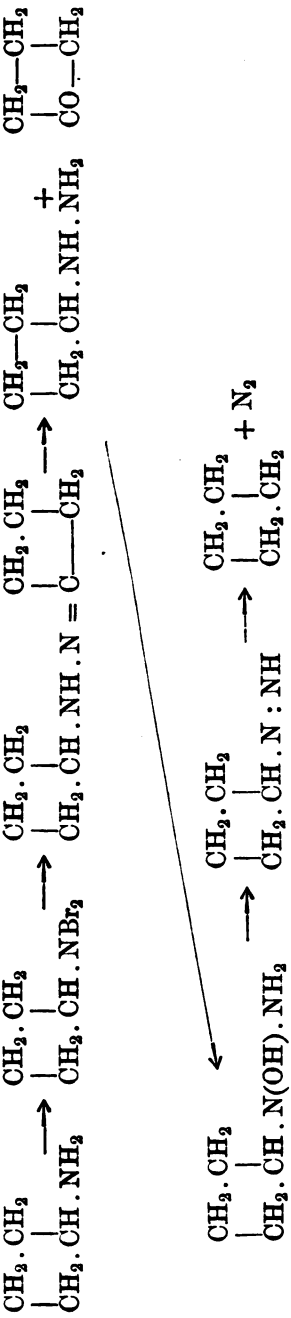
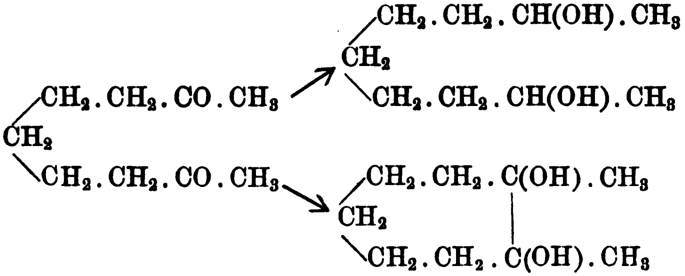
[1] Sabatier and Senderens, *C. R.*, 1901, **132**, 210.

[2] Kishner, *J. pr. Ch.*, 1895, II., **52**, 424.



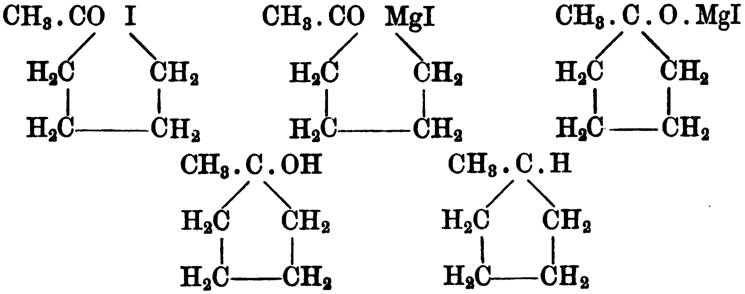
(5) The foregoing methods lead direct to the simple polymethylenes, but homologous compounds may be prepared in other ways. For instance, the reaction of pinacone formation may be modified in such a way as to give us cyclic alcohols. In the case of ordinary pinacone syntheses two molecules of a ketone unite during the reduction process. If for the two ketone molecules we substitute a single molecule of a diketone the reaction-product will in this case also be a pinacone; and in some cases two pinacones are formed, one an open-chain compound, the other a polymethylene derivative. For example, Kipping and Perkin,[1] by the reduction of diacetyl-pentane, obtained a mixture of dihydroxy-nonane (I.) and dimethyl-dihydroxyheptamethylene (II.).


(I.)

(II.)

The hydrocarbon may then be prepared from the pinacone in the usual way.

(6) The Grignard reaction has been applied to the production of polymethylene homologues by Zelinsky and Moser,[2] who prepared methylpentamethylene from ω-aceto-butyl iodide by the action of magnesium. The reaction takes place in the following steps:—



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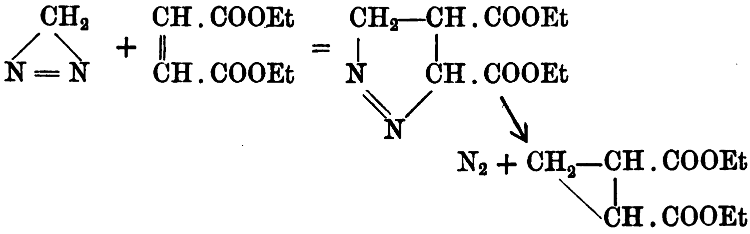
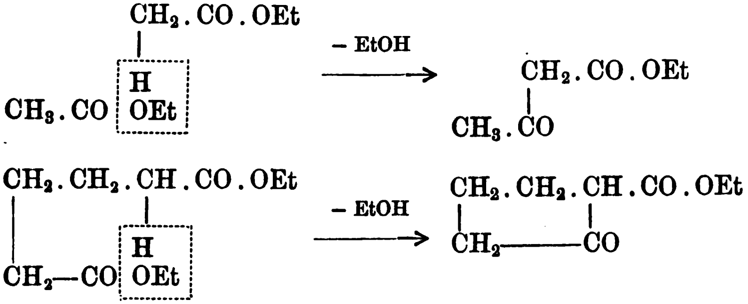
[1] Kipping and Perkin, *Trans. Chem. Soc.*, 1890, **57**, 241.

[2] Zelinsky and Moser, *Ber.*, 1902, **35**, 2684.

(7) Buchner and Curtius[1] were the first to point out that the aliphatic diazo-compounds had the faculty of coupling with unsaturated substances to yield pyrazole or pyrazoline derivatives. These latter bodies, on distillation, break down into nitrogen and trimethylene compounds. For example, in the case of diazomethane and fumaric ester the reaction takes the following course:—



(8) The remaining methods with which we have to deal depend upon such reactions as the acetoacetic or malonic ester condensations. It is obvious that just as we obtained a cyclic ketone by substituting the calcium salt of a dibasic for that of a monobasic acid, we could obtain an intramolecular condensation by substituting for acetic ester the ester of a dibasic acid. For example, if we used adipic ester, and proceeded in the same way as in the ordinary acetoacetic ester synthesis, we should obtain a keto-pentamethylene carboxylic ester—



(9) Again, if we condense oxalic ester with a dicarboxylic ester by means of sodium ethylate we can obtain a diketo-polymethylene dicarboxylic ester—

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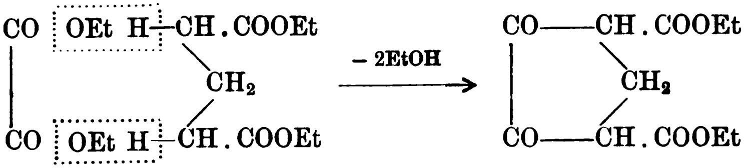
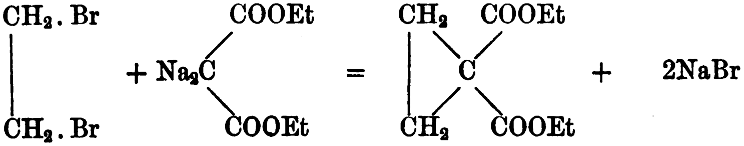
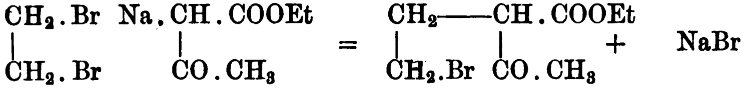
[1] Buchner and Curtius, *Ber.*, 1885, 18, 237.



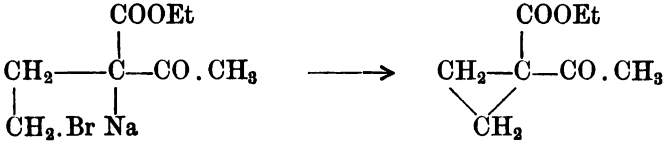
(10) The last series of methods[1] which we need describe depends upon the interaction of alkyl halogen compounds with the sodium derivatives of malonic, acetoacetic, or ethylene tetracarboxylic ester. Some examples will serve to make the matter clear—



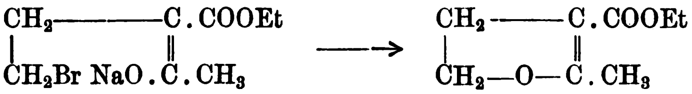


$$\begin{array}{l} CH_2.Br \\ | \\ CH_2.Br \end{array} \begin{array}{l} Na.CH.COOEt \\ \quad\ | \\ \quad\ CO.CH_3 \end{array} = \begin{array}{l} CH_2\text{——}CH.COOEt \\ |\qquad\quad | \\ CH_2.Br\ CO.CH_3 \end{array} + NaBr$$

This bromine compound may now react with more sodium ethylate in either of two ways, yielding in the one case a trimethylene derivative, and in the other an internal ether—

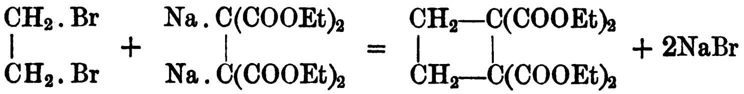


Ketonic form.



Enolic form.

The reaction between an alkylene dibromide and the disodium derivative of ethane tetracarboxylic ester takes place as follows:—



$$\begin{array}{l} CH_2.Br \\ | \\ CH_2.Br \end{array} + \begin{array}{l} Na.C(COOEt)_2 \\ \qquad | \\ Na.C(COOEt)_2 \end{array} = \begin{array}{l} CH_2\text{—}C(COOEt)_2 \\ |\qquad | \\ CH_2\text{—}C(COOEt)_2 \end{array} + 2NaBr$$

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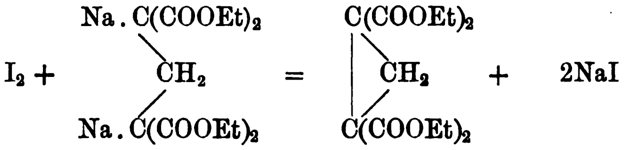
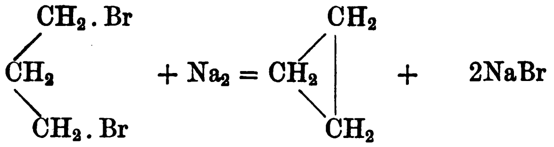
[1] Perkin, *Ber.*, 1884, **17**, 54; Perkin and Freer, *Trans. Chem. Soc.*, 1887, **51**, 833; Baeyer and Perkin, *Ber.*, 1884, **17**, 448; Perkin, *Trans. Chem. Soc.*, 1888, **53**, 1.

This method may be modified by substituting for the ethane tetracarboxylic ester an alkylene dimalonic ester and using iodine instead of the alkyl halide—

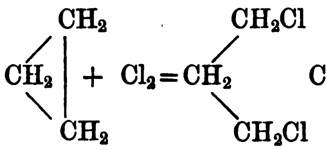


We must now deal with the individual members of the polymethylene series.

The simplest member of the group, trimethylene, was discovered by Freund,[1] who prepared it by the action of sodium upon trimethylene bromide—



It is a gas at ordinary temperatures, melts at −126° and boils at −35° approximately under a pressure of 749 mm.[2] Trimethylene is isomeric with propylene, from which it can be distinguished by means of halogens or halogen acids. In the case of the polymethylene, chlorine breaks the ring and produces trimethylene chloride; while propylene takes up chlorine to form propylene dichloride—



$CH_3.CH:CH_2+Cl_2=CH_3.CHCl.CH_2Cl$

The next member of the series, tetramethylene, has been known only within recent years, though for twenty years attempts to prepare it had been made by various workers, but without success. It was at last produced by Willstätter and Bruce[3] in the following way. Tetramethylene carboxylic acid (I.) was first prepared, for it should be noted that though

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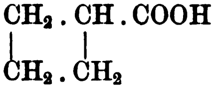
[1] Freund, *Monatsh.*, 1882, **3**, 625; *J. pr. Ch.*, 1885, II. **26**, 367.

[2] Ladenburg and Krügel, *Ber.*, 1899, **32**, 1821.

[3] Willstätter and Bruce, *Ber.*, 1907, **40**, 3979.

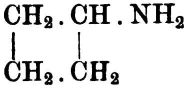
the parent substance was unknown, many tetramethylene derivatives had been prepared by the general methods given above. This acid was converted into the amide (II.), and this, by the usual reaction with bromine and soda, gave the amine (III.). From this, by methylation, tetramethylene-trimethyl-ammonium hydroxide (IV.) was obtained, which, on distillation, broke down into various compounds, the only one which concerns us being the cyclobutene (V.). When this body is reduced by the Sabatier and Senderens method, passing it with a stream of hydrogen over nickel powder at a temperature not exceeding 100°, it is converted into tetramethylene (VI.).


$$\begin{array}{l} CH_2 . CH . COOH \\ | \quad\;\; | \\ CH_2 . CH_2 \end{array}$$

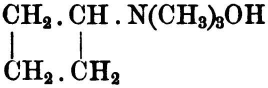
(I.)


$$\begin{array}{l} CH_2 . CH . CO . NH_2 \\ | \quad\;\; | \\ CH_2 . CH_2 \end{array}$$

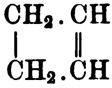
(II.)


$$\begin{array}{l} CH_2 . CH . NH_2 \\ | \quad\;\; | \\ CH_2 . CH_2 \end{array}$$

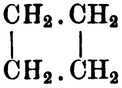
(III.)


$$\begin{array}{l} CH_2 . CH . N(CH_3)_3OH \\ | \quad\;\; | \\ CH_2 . CH_2 \end{array}$$

(IV.)


$$\begin{array}{l} CH_2 . CH \\ | \quad\;\; \| \\ CH_2 . CH \end{array}$$

(V.)


$$\begin{array}{l} CH_2 . CH_2 \\ | \quad\;\; | \\ CH_2 . CH_2 \end{array}$$

(VI.)

Tetramethylene is a gas at ordinary temperatures, but condenses to a liquid with a boiling-point of 11°–12° C. It does not solidify even at −80° C.

Pentamethylene was first produced by Wislicenus and Hentzschel by the second general method given above. It is a light liquid, boiling at 50° C., and remaining unsolidified at −80° C. It is found to occur naturally in Caucasian[1] and also in American[2] petroleum.

Hexamethylene was first synthesized by Baeyer[3] by the reduction of 1, 4-diketo-hexamethylene. Perkin and Haworth[4] produced it by the action of sodium upon a boiling alcoholic solution of di-bromo-hexamethylene, and it is also formed by the reduction of benzene. It is a pleasant-smelling liquid, boiling at 81° C., and solidifying to a solid of melting-point 6° C.

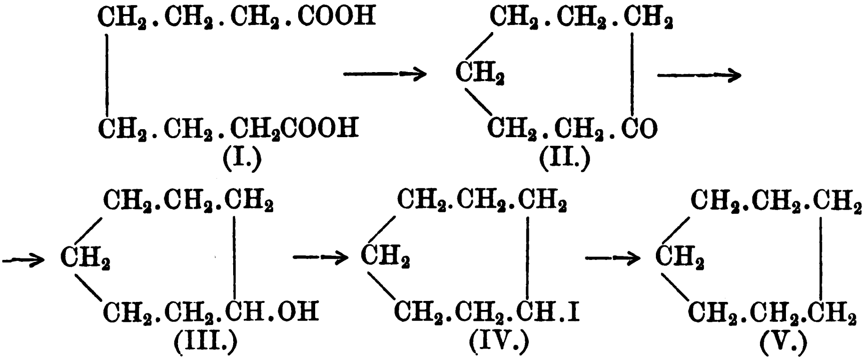
[1] Markownikoff, *Ber.*, 1897, **30**, 974.

[2] Young, *Trans. Chem. Soc.*, 1898, **73**, 906.

[3] Baeyer, *Annalen*, 1894, **278**, 111.

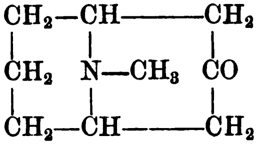
[4] Perkin and Haworth, *Ber.*, 1894, **27**, 216.

Heptamethylene, or suberane, was obtained by Markownikoff[1] from suberic acid (I.) by means of the second general method. The distillation of calcium suberate gave suberone (II.), which was reduced to suberyl alcohol (III.), from which suberyl iodide (IV.) was formed, which on reduction with zinc and hydrochloric acid gave suberane (V.).

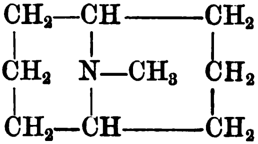


It is a liquid, boiling at 118° C. under a pressure of 726 mm. and having a peculiar odour like naphtha.

The preparation of octomethylene is much more difficult. It has been carried out by Willstätter and Veraguth[2] in the following steps. The bark of the pomegranate tree contains an alkaloid pseudo-pelletierine which is a ring-homologue of tropinone, and has the constitution expressed by (I.). This was converted into the N-methyl-granatanine (II.) in which two hydrogen atoms replace the oxygen of the ketonic compound.



(I.)



(II.)

By exhaustive methylation, this compound is converted into *des*-dimethyl-granatanine (III.), the nitrogen bridge being broken in the process.

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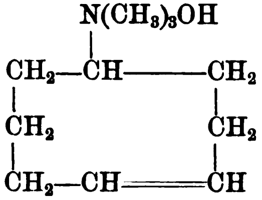
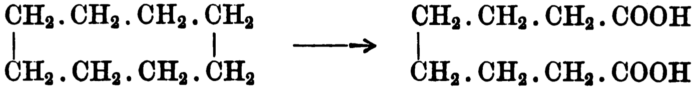
[1] Markownikoff, *J. Russ. Phys. Chem. Soc.*, 1893, **25**, 364, 547; Willstätter and Kametaka, *Ber.*, 1908, **41**, 1480.

[2] Willstätter and Veraguth, *Ber.*, 1905, **38**, 1975; 1907, **40**, 957.



(III.)

This substance, on distillation, breaks down into water, trimethylamine, and a cyclo-octadiene, C_8H_{12}. This last substance is unstable, and polymerizes with almost explosive violence. When hydrobromic acid is allowed to react with it, it forms a dihydrobromide, $C_8H_{14}Br_2$, from which hydrobromic acid can be removed by means of quinoline. The compound thus produced, however, is not the original cyclo-octadiene, but an isomeric and much more stable body, The constitution of neither compound has been established with certainty, but, as will be seen immediately, this does not affect the present question. When the stable cyclo-octadiene is reduced by the Sabatier and Senderens method it produces a hydrocarbon, C_8H_{16}, boiling between 147° and 149°. This substance is not an olefine, as it is unattacked by permanganate of potash; so that it must be a polymethylene of some sort. On oxidation with nitric acid it produces suberic acid, which proves that all the carbon atoms lie in a single straight chain—



The only possible conclusion is that the hydrocarbon is octomethylene. It is a solid, melting at 14·2° C. and boiling at 150° C. under 709 mm. pressure.

The last compound with which we have to deal is nonomethylene, which was recently discovered by Zelinsky.[1] He obtained it by the second general method, starting from sebacic acid (I.), which, by distillation of the calcium salt, he converted into the corresponding ketone (II.), and thence, by reduction, to the alcohol (III.), which, by conversion into the iodide and further reduction, gave nonomethylene (IV.).

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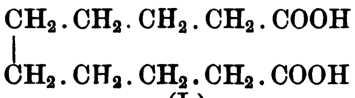
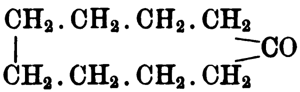
[1] Zelinsky, *Ber.*, 1907, **40**, 3277.

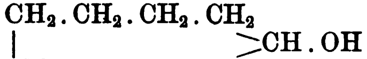


$$\begin{array}{l} CH_2.CH_2.CH_2.CH_2.COOH \\ | \\ CH_2.CH_2.CH_2.CH_2.COOH \end{array}$$

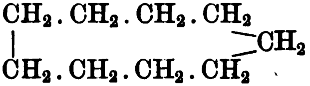
(I.)



(II.)



(III.)



(IV.)

It is a liquid of boiling-point 170°–172° C.

We have now given a sufficient account of the methods by which these substances can be formed, and must next take up the question of the effects which the ring-formation produces upon the general type of polymethylenes. These saturated cyclic compounds occupy a peculiar position in the field of organic chemistry. Related on the one hand to the aromatic series, from which some of them can be derived, they resemble aromatic bodies to some extent in their stability; while on the other hand their actions with certain reagents bring them more into line with the olefines, whose isomers they are. In stability they seem to mark a transition stage between the ordinary olefine and the analogous saturated paraffin. In physical properties also the polymethylenes lie apart from both olefine and paraffin series; and it may be well to examine this part of the subject before dealing with the chemical behaviour of the cyclic group.

From the point of view of chemistry the boiling and melting points of a substance are two of its most important physical properties, as by their aid we can separate or identify isomeric compounds. We may, therefore, begin by considering the boiling-points of the olefinic, polymethylene, and paraffin derivatives, comparing in each case the three compounds which have the same number of carbon atoms in the chain—

No. of carbon atoms.	Boiling-point of		
	Olefine.	Polymethylene.	Paraffin.
3	− 48°	circa − 35°	− 45°
4	− 5°	+ 12°	+ 1°
5	+ 40°	49°	36°
6	69°	81°	69°
7	95°	117°	98°
8	122°	146°	126°
9	—	171°	150°

Thus in every case the boiling-point of the polymethylene is the highest of the three. This emphasizes the peculiar character which the ring-formation confers upon substances, for in most cases the saturated (paraffin) compound has almost the same boiling-point as the corresponding olefinic derivative.

In molecular volumes also[1] the polymethylenes lie quite apart from the olefines and paraffins, as the following table shows:—

No of carbon atoms in chain.	Molecular volumes of		
	Olefine.	Polymethylene.	Paraffin.
4	89·8	79·06	96·5
5	104·3	91·09	112·4
6	119·1	105·19	127·2
7	136·3	118·00	142·5
8	151·5	130·92	158·6
9	—	159·46	174·3

From this it appears that the molecular structure of the polymethylenes is much more compact than that of the corresponding olefines; and, further, the higher polymethylenes are relatively less voluminous than the lower members. For example, the difference in volume between the two isomeric compounds with four carbon atoms is ten units, while that between the volumes of isomeric compounds of eight carbon atoms is twenty units; over the same interval the difference between the olefine and corresponding paraffin remains almost unaltered—seven units.

Brühl[2] has shown that ring-formation has no noticeable effect upon the molecular refraction of compounds; thus the difference between the refractive power of a saturated paraffin and that of the corresponding ring is to be found merely by subtracting the value of two hydrogen atoms from the larger figure, taking no account of the change in constitution.

Stohmann and Kleber[3] have examined the question of the relation between ring-formation and thermo-chemical behaviour in an exhaustive manner. In the following table column I.

[1] Willstätter and Bruce, *Ber.*, 1907, **40**, 3979, and Smiles, *Relation between Chemical Constitution and Physical Properties*, Chapter IV.

[2] Brühl, *Ber.*, 1892, **25**, 1954; Willstätter and Bruce, *Ber.*, 1907, **40**, 3979.

[3] Stohmann and Kleber, *J. pr. Ch.*, 1892, II. **45**, 489.

shows the increase in the heat of combustion when a polymethylene ring is broken and two hydrogen atoms are added on; column II. shows the average loss of energy in calories which the polymethylene system suffers by the addition of two hydrogen atoms:—

	I.	II.
Trimethylene ring . . .	31·9	33·1
Tetramethylene ring . . .	29·1	39·9
Pentamethylene ring . .	52·9	16·1
Hexamethylene ring . . .	54·7	14·3

The only point of importance which can be deduced from these figures is the fact that the penta- and hexa-methylene rings lose much less energy in opening up than the tri- and tetra-methylene ones do. We shall have occasion to refer to this point later in the chapter.

When we come to the chemical side of the question, the evidence is not nearly so complete as is desirable. A good deal of research has been carried out on the problem of the stability of polymethylenes in presence of such agents as halogen acids, permanganate, nitric, and sulphuric acid; but up to the present no one appears to have done any exact comparative experiments which would enable us to consider numerical relations between the different cases. We must, therefore, content ourselves for the present with noting the main features of the matter.

Trimethylene is comparatively unstable. It is attacked by the halogen acids and by sulphuric acid, the ring being opened in each case. Potassium permanganate acts on it slowly, which distinguishes it from propylene, the latter being instantly oxidized. Berthelot[1] gives the following data of comparison between the olefine and polymethylene:—

	Heat in calories of		
	Formation.	Bromine addition.	Sulphuric acid addition.
Trimethylene . .	− 17·1	+ 38·5	+ 25·5
Propylene . . .	− 9·4	+ 29·1	+ 16·7

From this it appears that trimethylene has an energy-content eight calories greater than that of propylene.

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[1] Berthelot, *C. R.*, 1899, **129**, 483.

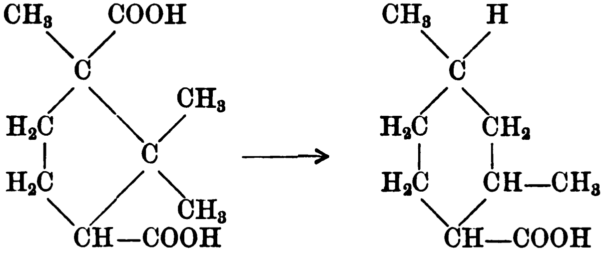
When we turn to the next higher member of the series, tetramethylene, we find that it is more stable. It is not attacked by cold concentrated hydriodic acid or by bromine in chloroform solution. When passed through a heated tube in the Sabatier and Senderens method it requires a temperature of about 200° to reduce it to butane,[1] whereas trimethylene is changed to propylene at 100°[2] by passing it over heated iron. These last two data are not quite comparable, but certainly point to trimethylene being less stable than tetramethylene.

Pentamethylene is a stable substance, being unattacked by hydriodic acid even when boiling.

Hexamethylene appears to be as stable as pentamethylene. It is attacked by chlorine, but instead of the ring being opened, substitution takes place.

The almost equal stability of the penta- and hexa-methylene systems is well shown by a peculiar series of changes by which hexamethylene derivatives can be isomerized into pentamethylene compounds, and *vice versâ*. Many such changes are known, and for the sake of illustration we may quote one or two here.

Aschan[3] has shown that when hexamethylene is treated with anhydrous aluminium chloride it is converted below 100° into methyl-pentamethylene. The change appears to be a purely desmotropic one, for no discoloration of the liquid was observed, nor were any bye-products of condensation found, such as were to be expected if the hexamethylene ring had been broken. Perkin and Yates[4] found that when camphoric anhydride was treated with aluminium chloride, hexahydro-xylylic acid was formed—



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[1] Willstätter and Bruce, *Ber.*, 1907, **40**, 3979.

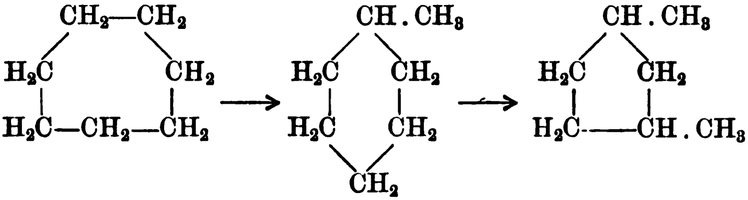
[2] Ipatjeff, *Ber.*, 1902, **35**, 1063.

[3] Aschan, *Annalen*, 1902, **324**, 11.

[4] Perkin and Yates, *Trans. Chem. Soc.*, 1900, **79**, 1373; Lees and Perkin, *ibid.*, 1901, **79**, 332.

This tends to show that the five- and six-membered rings are of almost equal stability.

The ring in the next homologue of the series, heptamethylene, is less stable than either the five- or six-membered substances. Markownikoff[1] has observed that when iodo-heptamethylene is heated with hydriodic acid to 250° it is converted into methyl-hexamethylene and dimethyl-pentamethylene—



With regard to the behaviour of octomethylene and nonomethylene, the experimental data at our disposal are too scanty to allow of any but very general conclusions being drawn with regard to their stability. It appears that they are less stable than the five- and six-membered rings, but no exact measurements have been made.

Enough has now been said to prove that the polymethylenes show somewhat peculiar relations between their stabilities and the number of carbon atoms in the ring. The five- and six-membered rings are the most stable, and the stability decreases from this maximum, whether the number of carbon atoms in the ring be increased or diminished. Thus, if we take trimethylene and increase the size of the ring by a methylene group, we obtain the more stable tetramethylene; a further introduction of a methylene group yields a further increase in stability, pentamethylene being formed. The next methylene group, leading to hexamethylene, hardly affects the stability; but any further inclusion of methylene radicals, instead of increasing the stability as before, tends now in the opposite direction, hepta-, octo-, and nonomethylene being each in turn less stable than its lower homologue.

Taking this into account, Baeyer[2] put forward what is

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[1] **Markownikoff,** *Ber.*, 1897, **30**, 1214.

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

generally known as his "Strain Theory," which may be formulated as follows:—

> "The four valencies of a carbon atom act parallel to the lines joining the corners of a regular tetrahedron to its centre, making an angle of 109° 28′ with each other. The direction of the valencies can be altered, but any such alteration produces a strain whose amount is proportional to the angle through which the valencies are diverted."

On Baeyer's view, the state of strain in the ring is a measure of the ring's stability; the greater the strain the less stable the ring is likely to be. We must now apply this theory to the seven polymethylenes, and see how far it agrees with experimental results.

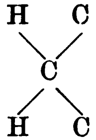
In trimethylene the centres of three carbon atoms will lie at the corners of an equilateral triangle, so that the valencies joining these carbon atoms to each other will make an angle of 60° with each other. But in the original state of things these valencies were supposed by Baeyer to be inclined to each other at an angle of 109° 28′; so that two of the valencies of any carbon atom have been diverted through an angle of (109° 28′ – 60°), and each valency has been diverted through half this angle, viz. 24° 44′. Similarly, in the case of a tetramethylene ring, the four carbon atoms lie at the corners of a square, and the valencies will make an angle of 90° with each other. Thus, each pair of valencies has been diverted through an angle of (109° 28′ – 90°), and each single valency has been turned through half this angle, viz. 9° 44′. The general formula giving the deviation for a ring-compound containing *n* carbon atoms is—

$$\frac{1}{2}\left[109^\circ 28' - \frac{2(n-2)}{n} . 90^\circ\right]$$

Applying this to the seven polymethylenes, we obtain the following values for the deviation in each case:—

	Angle of deviation.
(Ethylene)	**54° 44′**
Trimethylene	**24° 44′**
Tetramethylene	**9° 44′**
Pentamethylene	**0° 44′**
Hexamethylene	**– 5° 16′**
Heptamethylene	**– 9° 33′**
Octomethylene	**– 12° 46′**
Nonomethylene	**– 15° 16′**

These results are in moderate agreement with the actual relations between the stabilities of the polymethylenes. The positive deviations are more in accordance with experimental results than the negative ones. Of course it must be understood that in no case could the Strain Theory pretend to exactitude, since it assumes that the four valencies in the grouping—



are evenly distributed in space, which is most unlikely. Apart from this, however, the agreement between the theory and the facts is noteworthy; and it is very desirable that we should have more exact data at our disposal with regard to the stability relations of these compounds, in order to discover, if possible, what the Strain Theory actually corresponds to in physico-chemical relations.[1]

We have now completed our survey of the polymethylenes, and in the next chapter we shall examine the derivatives of the simple ring compounds which occur among the terpenes.

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[1] Compare Smiles, *Relations between Chemical Constitution and Physical Properties*, 1910, pp. 268 *et seq.*

CHAPTER III

THE MONO-CYCLIC TERPENES

1. *Introductory*

When the saps and tissues of certain plants (such as pines, camphor, lemons, and thyme) are distilled, the distillates are found to contain among other things a mixture of substances which are classed under the general head of ethereal oils. For the most part these ethereal oils contain unsaturated hydrocarbons of the general formula $(C_5H_8)_n$ (or derivatives of these substances), and these may be divided into three classes—

1. Open-chain olefinic compounds.
2. Mono-cyclic hydrocarbons (reduced benzene derivatives).
3. Cyclic compounds containing more than one ring.

In the following chapters we shall consider the first and third of these classes, while the present chapter will be devoted to the mono-cyclic substances.

In the naturally occurring compounds it is found that by far the greater number of these hydrocarbons have the empirical formula $C_{10}H_{16}$; and it is not without interest that Collie,[1] in polymerizing ethylene by means of the silent electric discharge, found that the major part of the substance used was converted into compounds containing either ten or fifteen carbon atoms.

The nomenclature of these substances is at present somewhat in confusion. It has been customary to apply the name terpene to any compound having the composition C_5H_8, or any polymeric variety of this type. This general type was then divided into two others: the "true terpenes," cyclic substances of the formula $C_{10}H_{16}$; and the "olefinic terpenes," which are open-chain bodies having the formulæ C_5H_8 and $C_{10}H_{16}$. Another system of nomenclature classes the whole group under

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[1] Collie, *Trans. Chem. Soc.*, 1905, **87**, 1540.

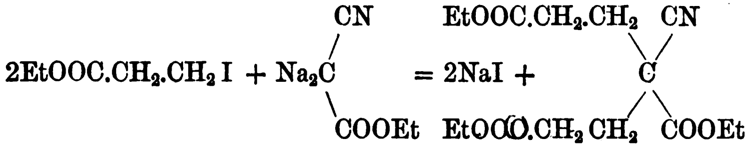
three heads: hemi-terpenes, C_5H_8; terpenes, $C_{10}H_{16}$; and sesquiterpenes, $C_{15}H_{24}$. It will best serve our purpose to divide the terpenes into the three classes which we mentioned first, viz. olefinic terpenes, mono-cyclic terpenes, and dicyclic terpenes. The naturally occurring mono-cyclic terpenes are for the most part derived from either *m*- or *p*-hexahydrocymene.

Most of the terpenes are colourless, pleasant-smelling liquids of high refractive power. They boil without decomposition, and are volatile in steam. Some are optically active, some inactive by racemization, while others, containing no asymmetric carbon atom, cannot show activity at all. It is not necessary to deal with their chemical properties at present, as these will be brought out in the following pages when the constitutions of the compounds are described.

2. *The Synthesis of Terpineol.*

In the group of the mono-cyclic terpenes, by far the most important compound is terpineol, for from it most of the other members of the group can be prepared, either directly or indirectly. The constitution of terpineol, therefore, is of considerable value to us in determining the constitutions of other substances which we can derive from it. The inactive form of terpineol has been synthesized by Perkin,[1] and as this synthesis determines the constitution of the substance, we may describe it step by step.

When β-iodo-propionic ester was allowed to interact with the disodium derivative of cyan-acetic ester, γ-cyano-pentane-$\alpha\gamma\epsilon$-tricarboxylic ester was produced—



$$2EtOOC.CH_2.CH_2I + Na_2C\begin{array}{l}\diagup CN\\ \diagdown COOEt\end{array} = 2NaI + \begin{array}{ccc}EtOOC.CH_2.CH_2 & & CN\\ & C & \\ EtOOC.CH_2CH_2 & & COOEt\end{array}$$

From this the free acid was obtained by hydrolysis with hydrochloric acid, and when it was boiled with acetic anhydride and then distilled it was transformed by loss of water and carbon dioxide into δ-keto-hexahydrobenzoic acid—

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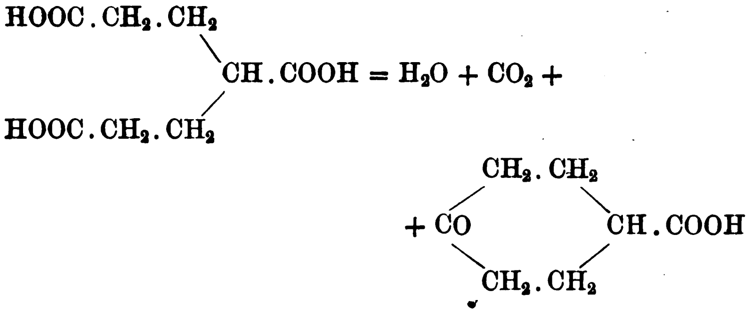
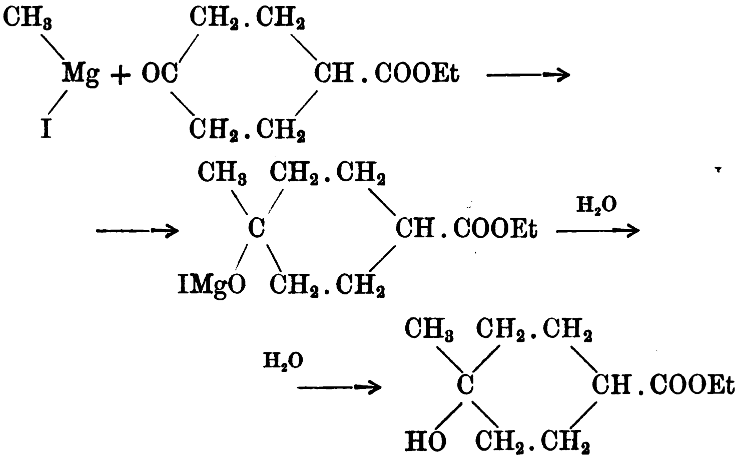
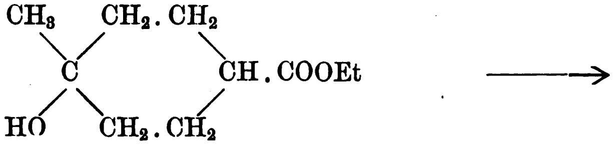
[1] Perkin, *Trans. Chem. Soc.*, 1904, **85**, 654.

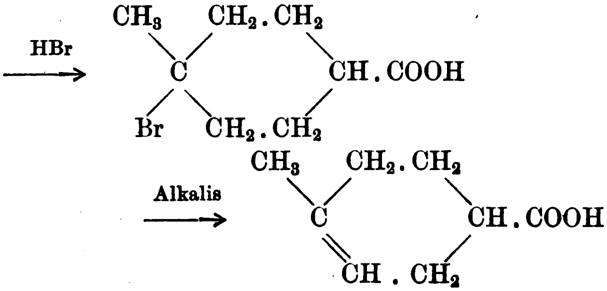


Grignard's reaction was then applied to the ester of this acid, magnesium methyl iodide being allowed to react with the ketonic group, and in this way δ-hydroxy-hexahydrotoluic ester was formed—

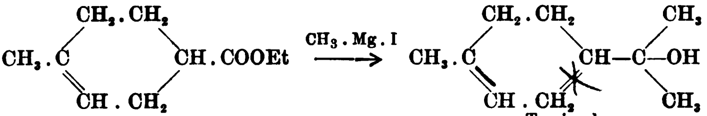


When, by the action of fuming hydrobromic acid, we replace the hydroxyl group in this acid by a bromine atom and then remove hydrobromic acid from the compound by means of weak alkalis or pyridine, we obtain Δ^3-tetrahydro-*p*-toluic acid—





After esterifying the acid, the Grignard reaction can be again employed, with the result that the ester group is attacked, and on treatment with water the intermediate compound breaks down into inactive terpineol.



Terpineol.

If this synthesis be examined step by step it will be seen that there can be no doubt as to the constitution of terpineol, for the reactions can only be supposed to take place in the way shown. Any alternative formulation of any of the reactions would at once lead to contradiction in the later experiments.

An optically active terpineol has been prepared by Fisher and Perkin[1] by resolving the intermediate acid into dextro and lævo forms before continuing the synthesis.

3. *The Decomposition Products of Terpineol.*

The oxidation of terpineol takes place in several steps and produces some compounds of importance in the study of terpene constitutions; we may, therefore, deal with the matter briefly in this place.

It has been shown by Wagner[2] that when a compound containing a double bond is oxidized by means of potassium permanganate, the first step in the process is the breaking of the double bond and the addition of a hydroxyl group to each of the atoms between which the double bond originally lay—

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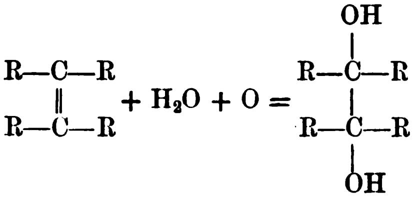
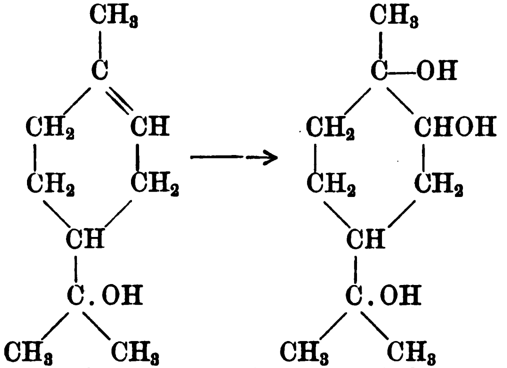
[1] Fisher and Perkin, *Trans. Chem. Soc.*, 1908, **93**, 1871.

[2] Wagner, *Ber.*, 1888, **21**, 1230, 3359; 1891, **24**, 683.

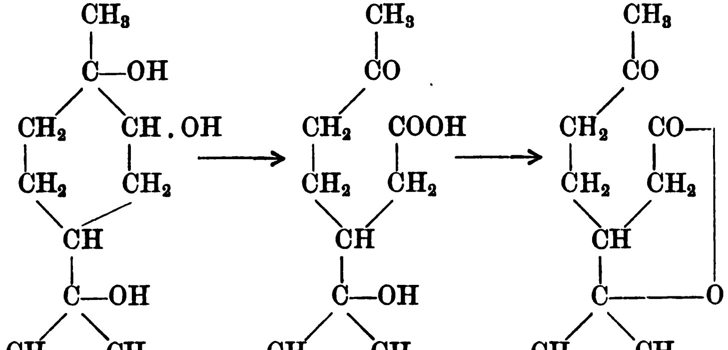


In the case of terpineol this rule holds, and it is found that the first oxidation product[1] obtained by the action of permanganate upon terpineol is trihydroxy-hexahydrocymene—



Terpineol. Trihydroxyhexahydrocymene.

This substance, on further oxidation,[2] is converted into homoterpenylic methyl ketone by the rupture of the single bond between the two hydroxyl-bearing carbon atoms—



Trihydroxyhexahydrocymene. Intermediate acid. Homoterpenylic methyl ketone.

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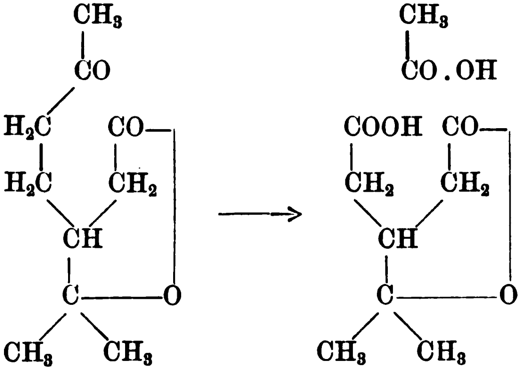
[1] Wallach, *Annalen*, 1893, **275**, 150.

[2] *Ibid.; Ber.*, 1895, **28**, 1773; Tiemann and Schmidt, *ibid.*, 1781.

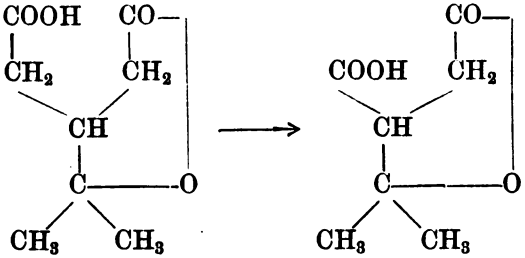
As is shown in the formulæ, the first product of the oxidation is a hydroxy acid which loses water at once between its carboxyl and hydroxyl groups, yielding the keto-lactone. This keto-lactone is the first product which can be isolated when terpineol is oxidized with chromic acid, for the action is so violent that the trihydroxyhexahydrocymene is destroyed as soon as it is formed.

Further oxidation with potassium permanganate[1] converts the keto-lactone into a mixture of acetic and terpenylic acids—



Homoterpenylic methyl ketone. Terpenylic acid.

The latter substance, by the action of a five per cent. solution of permanganate, is still further decomposed into terebic acid—



Terpenylic acid. Terebic acid.

It will be seen that these formulæ for homoterpenylic, terpenylic, and terebic acid illustrate the decomposition of terpineol quite satisfactorily. Any doubt as to their accuracy was removed by the synthesis of the three acids, which was

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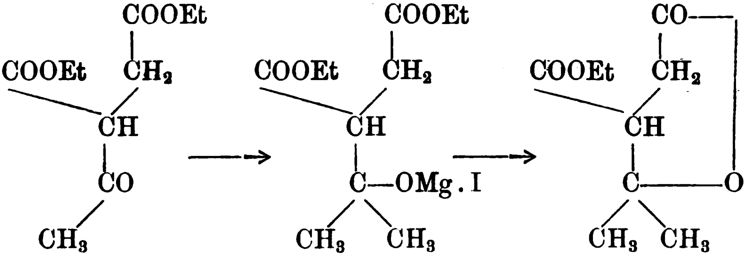
[1] Wallach, *Ber.*, 1895, **28**, 1776.

carried out by Simonsen.[1] Terebic[2] and terpenylic acid[3] had previously been synthesized in different ways. The Simonsen syntheses depend on the application of Grignard's reaction to various ketonic esters. From magnesium methyl iodide and acetyl-succinic ester he obtained terebic ester—



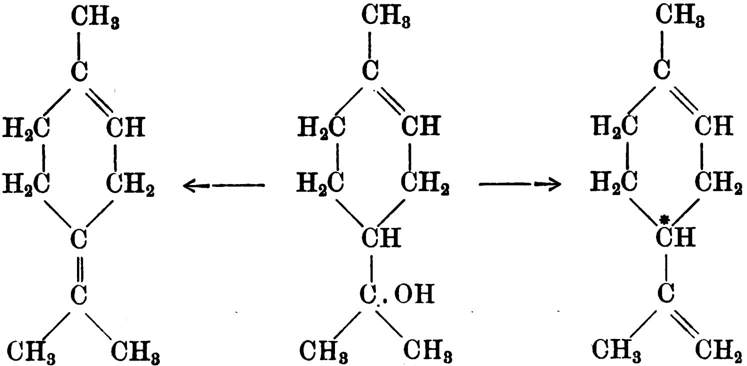
Acetyl-succinic ester. Terebic ester.

In exactly the same way β-acetyl-glutaric ester is converted into terpenylic ester, and β-acetyl-adipic ester into homoterpenylic ester.

The constitution of terpineol, then, may be considered to be completely established, both synthesis and degradation products agreeing with the theory.

4. *The Constitution of Dipentene.*

When terpineol is heated with acid potassium sulphate it loses a molecule of water, and is converted into dipentene. It is evident that we may represent this elimination of water in either of two ways—



(I.) Terpineol. (II.)

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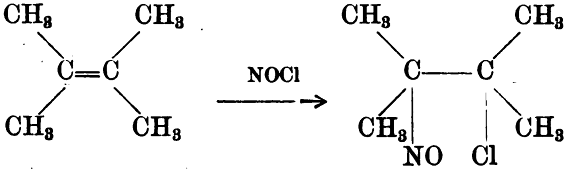
[1] Simonsen, *Trans. Chem. Soc.*, 1907, **91**, 184.
[2] Blaise, *C. R.*, 1898, **126**, 349.
[3] Lawrence, *Trans. Chem. Soc.*, 1899, **75**, 531.

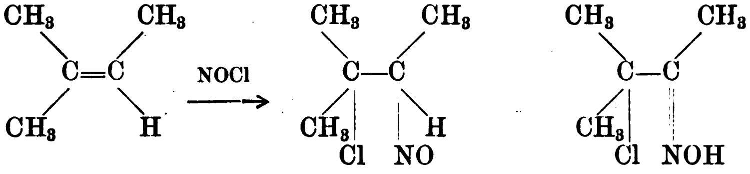
Now, dipentene can be obtained by mixing together equal quantities of dextro- and lævo-limonene. It is, therefore, the racemic form of limonene, and must contain an asymmetric carbon atom. Formula (I.) contains no such carbon atom, but the atom in (II.), which is marked with an asterisk, is asymmetric. Dipentene, then, must have the constitution represented by (II.).

In order to satisfy ourselves that this formula is the correct one, we may test it by seeing how far it agrees with some decompositions which dipentene can be made to undergo.

When nitrosyl chloride is allowed to act upon a compound containing a double bond it may unite with it in either of two ways.[1] If the double bond lies between two tertiary carbon atoms, the chlorine atom attaches itself to the one and the nitroso-group to the other, and the resulting substance is a *blue* nitroso-derivative—



On the other hand, if one of the carbon atoms is a tertiary and the other a secondary one, the chlorine of the nitrosyl chloride attaches itself to the tertiary atom and the nitroso-group to the secondary atom. The hydrogen atom then wanders, as shown in the formulæ below, with the result that a *colourless iso*-nitroso compound is formed—



We must now apply this to the case of dipentene. To make reference easy we shall number each step.

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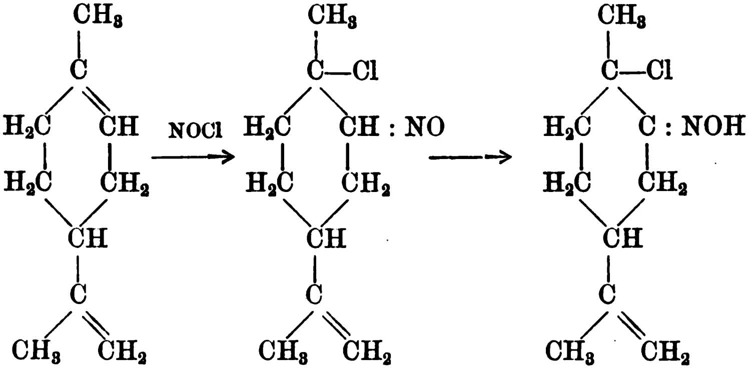
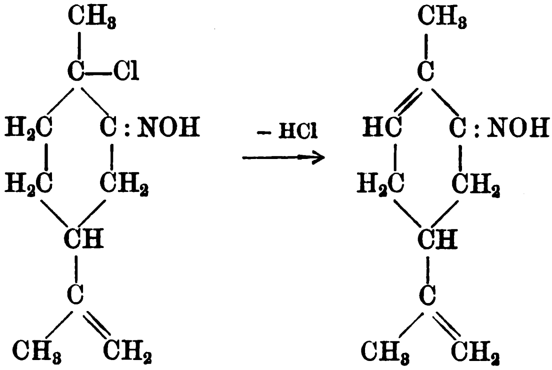
[1] Thiele, *Ber.*, 1894, 27, 455.

I. When nitrosyl chloride acts upon dipentene, it might be supposed that it could react either with the double bond in the nucleus or with that in the side-chain. It actually attacks the nuclear double bond, as we shall show later, and to avoid the complication of two sets of formulæ we may confine ourselves to the case of the addition to the double bond of the nucleus. The reaction, if our formula for dipentene be correct, will take the course shown below—



Dipentene.

II. When the nitrosochloride formed in the last reaction is treated with alcoholic potash it loses one molecule of hydrochloric acid, and is transformed into a compound which proves to be identical with the oxime of the ketone carvone. This can be expressed as follows:—

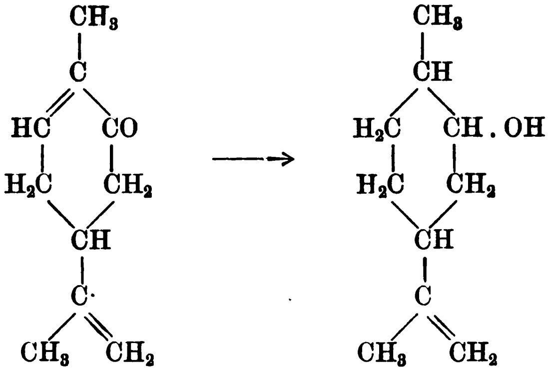


Dipentene nitrosochloride.

Carvoxime.

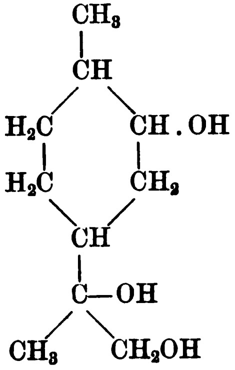
III. By hydrolysis of the oxime, carvone is produced.

IV. Carvone, on reduction, gives dihydro-carveol. This reduction might be supposed to take place either in the nucleus or in the side-chain. As will be shown later (VI.), the nucleus is reduced and the side-chain left untouched. We need not concern ourselves with the alternative set of formulæ, but may again confine ourselves to the one set.

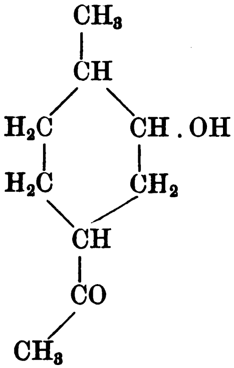


Carvone. Dihydrocarveol.

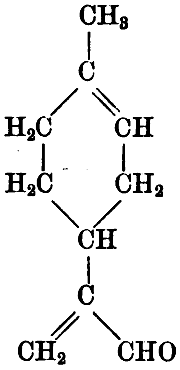
V. On oxidation, dihydrocarveol gives a trihydroxy-hexahydrocymene—



VI. On further oxidation a ketone alcohol is formed—

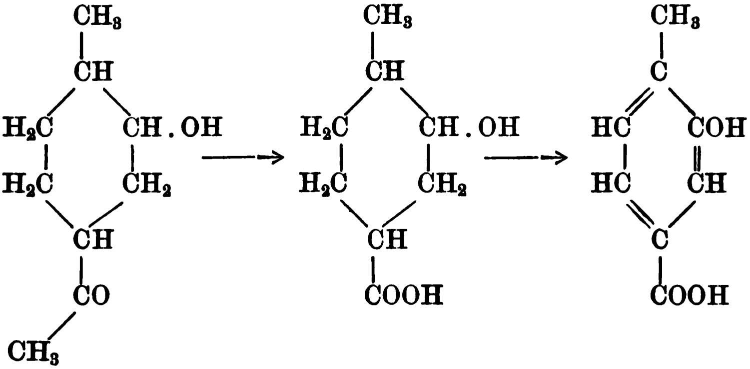


The production of this substance proves what was previously stated in I. and IV., viz. that the nitrosyl chloride attacks the nucleus, and that in the reduction to dihydrocarveol the side-chain double bond is not reduced. If the nitrosyl chloride had attacked the side-chain we should, at Stage III., have produced an aldehyde of the type—



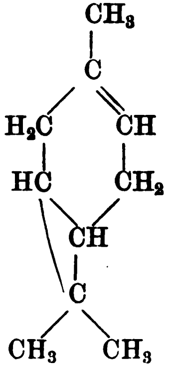
instead of the ketone produced in practice. If the side-chain had been reduced in Stage IV. instead of the nucleus, the nucleus would have been attacked by the oxidizing agent in Stage V., the ring would have been broken, and a ketonic *acid* would have been formed, just as in the case of the oxidation of terpineol.

VII. Further oxidation of the ketonic alcohol produced in Stage VI. yields a hydroxy-acid, which, by the action of bromine at 190° C., loses six hydrogen atoms, and is converted into hydroxy-*p*-toluic acid—

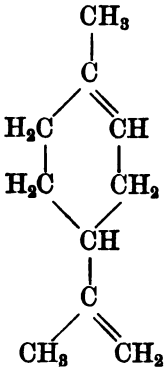


To sum up the matter, we may point out that the series of reactions IV. to VII. prove that the "isopropyl group" contains a double bond, which must also be present in dipentene. Moreover, since this double bond has persisted throughout the whole series of reactions I. to IV., it cannot have been the point at which the nitrosyl chloride attached itself, as this portion of the molecule has given rise to the —CH.OH— group. Further, the nitroso-group must have attached itself to the carbon atom to which the hydroxyl group is attached in the aromatic acid, *i.e.* the one next that which carries the methyl group. These reactions can only be explained by assuming that dipentene has the structure which we attributed to it on account of its synthesis from terpineol.

It might be objected that we have not taken into account the possibility that, in the formation of dipentene, the elimination of water from terpineol may take place between two *non-adjacent* carbon atoms, giving rise to some such compound as—



Any attempt to explain the question on these lines leads, however, to impossible results, and it may be taken as proved beyond doubt by the above experimental data that the formula of dipentene is—

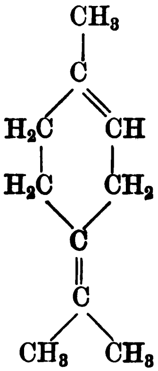


Dipentene.

This, in turn, proves the formulæ of dextro- and lævo-limonene, for as they are the optical antipodes of which dipentene is the racemic variety, they also must possess the same structural formula as dipentene.

5. *The Constitutions of Terpinolene and Terpinene.*

In the last section it was pointed out that the dehydration of terpineol might follow either of two courses: the one leading to a compound containing an asymmetric carbon atom, the other to a symmetrical derivative. The result of dehydration by means of acid potassium sulphate was shown to be dipentene; but when terpineol is dehydrated[1] by means of alcoholic sulphuric acid, an isomeric compound is formed which has the second of the two possible formulæ—



This substance is terpinolene.

Now, according to Thiele,[2] the grouping (I.) is less stable

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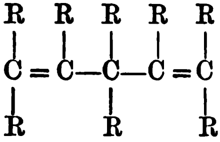
[1] Wallach, *Ber.*, 1879, **12**, 1022.

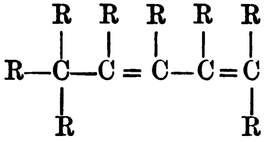
[2] Thiele, *Annalen*, 1899, **306**, 119.

than the grouping (II.) in which the two double bonds are "conjugated"—



$R_2C=CR-CR_2-CR=CR_2$

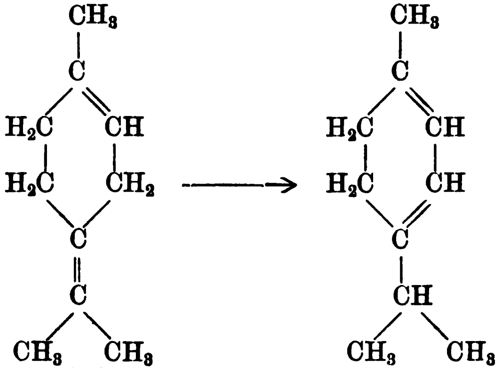
(I.)



$R_3C-CR=CR-CR=CR_2$

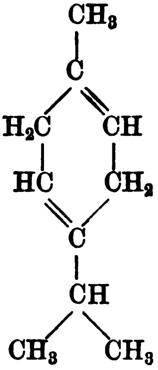
(II.)

We need not enter into the matter in detail here, as it will be dealt with fully in a later chapter. For the present it is sufficient to apply Thiele's view to the behaviour of terpinolene. This substance, on treatment with acids, can be converted into terpinene, while terpinene itself cannot be isomerized at all, and is, in fact, the most stable of all the terpene class. Since the grouping (I.) exists in terpinolene, we may conclude that it is converted by acids into the more stable grouping (II.)—



Terpinolene. Terpinene.

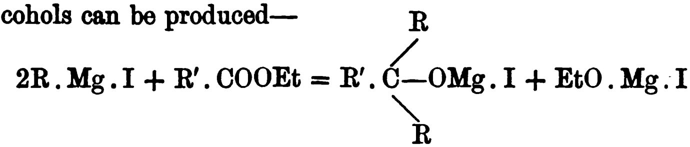
This, however, is only a possibility and not a certainty, for the alternative formula of terpinene—

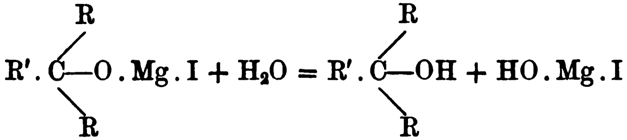


represents some properties of the substance better, though it does not explain its stability so well. The matter is still under discussion, and need not be dealt with further in this place.

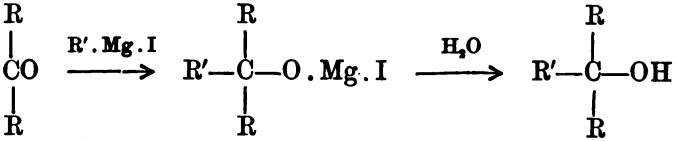
6. *Terpin and Cineol.*

Grignard[1] and others have shown that when the esters of organic acids react with organo-magnesium compounds, tertiary alcohols can be produced—



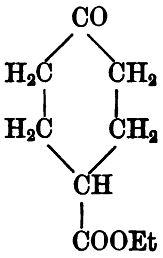


Again, when ketones are treated with Grignard's reagent,[2] tertiary alcohols are formed—

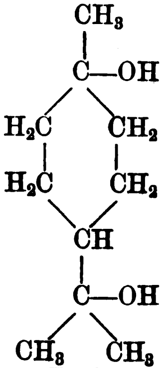


$$\underset{\mathrm{R}}{\overset{\mathrm{R}}{\mathrm{CO}}} \xrightarrow{\mathrm{R'.Mg.I}} \mathrm{R'}-\underset{\mathrm{R}}{\overset{\mathrm{R}}{\mathrm{C}}}-\mathrm{O.Mg.I} \xrightarrow{\mathrm{H_2O}} \mathrm{R'}-\underset{\mathrm{R}}{\overset{\mathrm{R}}{\mathrm{C}}}-\mathrm{OH}$$

Kay and Perkin[3] have combined these two reactions into one, using a ketonic ester, and allowing both vulnerable groups to be attacked simultaneously. By this means, from cyclohexanone-4-carboxylic ester, they obtained the dihydric alcohol terpin.



Cyclohexanone-4-carboxylic ester.



Terpin.

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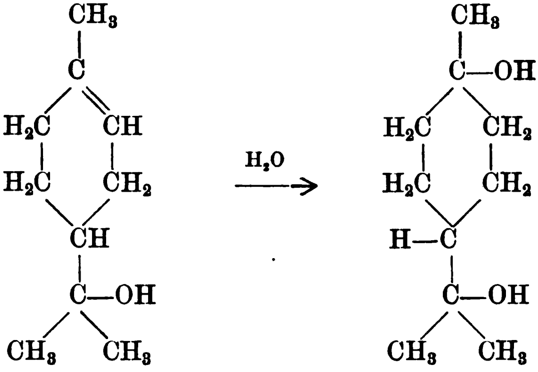
[1] Grignard, *C. R.*, 1901, **132**, 336.

[2] Zelinsky, *Ber.*, 1901, **36**, 3950.

[3] Kay and Perkin, *Trans. Chem. Soc.*, 1907, **91**, 372.

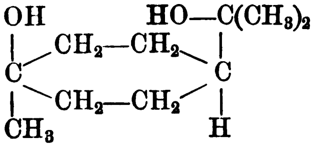
This synthesis proves the formula of terpin beyond any dispute.

Terpin may be also obtained by boiling terpineol with dilute sulphuric acid—

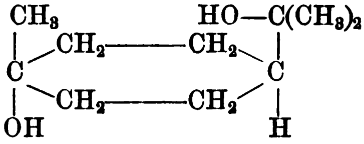


Terpineol. Cis-terpin.

The terpin which is obtained in either of these ways is called *cis*-terpin, from the fact that in its space formula the two hydroxyl groups lie on the same side of the hexamethylene ring, while in the isomeric compound, *trans*-terpin, they lie on opposite sides of the ring—



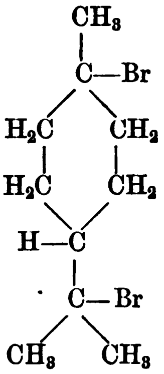
Cis-terpin.



Trans-terpin.

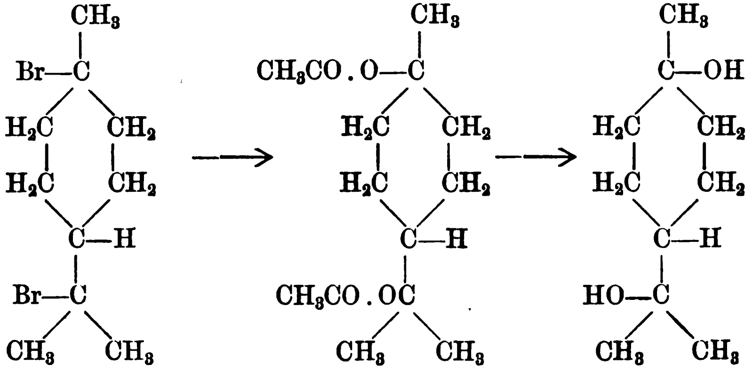
Cis-terpin unites with one molecule of water to form terpin hydrate, a crystalline substance from which it can be regenerated at 100° C. The trans-isomer does not unite with water at all.

Cis-terpin cannot be directly converted into trans-terpin, but the change can be effected by a somewhat roundabout method. In the first place, cis-terpin is subjected to the action of hydrobromic acid, by which means a dibromide is formed. As can be seen from its formula, this substance is identical with the hydrobromide of dipentene—



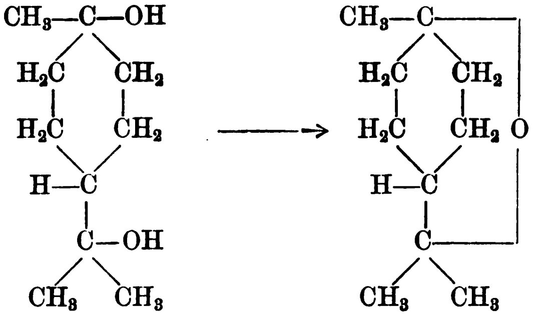
Dipentene dihydrobromide
(Cis-terpin dibromide).

This dibromide is next treated with silver acetate in acetic acid solution, and the diacetate so produced is hydrolyzed with alcoholic potash, yielding *trans*-terpin.

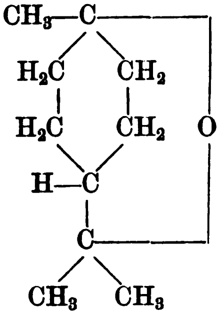


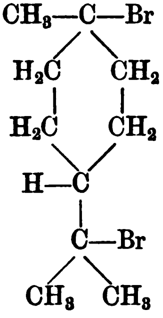
It should be noted that when cis-terpin is converted into its dibromide the product is the *cis*-form of dipentene dihydrobromide; while, on the other hand, the action of hydrobromic acid on trans-terpin produces the *trans*-variety of dipentene dihydrobromide. Thus the change of cis-terpin into trans-terpin cannot be carried out through the bromides alone, as during their formation no change from cis- to trans-form takes place; this only occurs during the hydrolysis of the acetyl derivative.

When cis-terpin is dehydrated, it yields a variety of products (terpineol, dipentene, terpinene, and terpinolene), among which is found the compound cineol, $C_{10}H_{18}O$. This substance contains neither a hydroxyl nor a carbonyl radical, and must therefore be an ether. On this view, its formation from cis-terpin is easily explained—



This formula is supported by the fact that hydrobromic acid in acetic acid solution converts cineol into cis-dipentene dibromide—





The behaviour of cineol on oxidation with potassium permanganate is curious.[1] The first effect is to break the hexamethylene ring, while leaving the ether chain untouched; in this way cineolic acid is produced—

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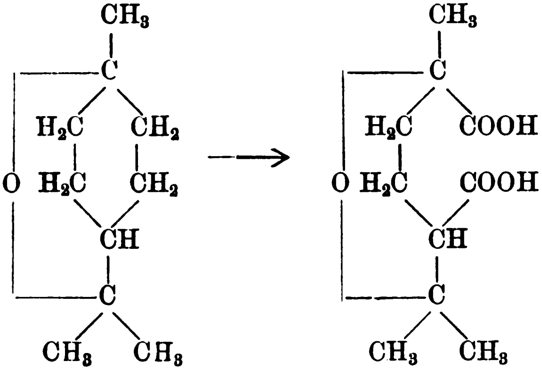
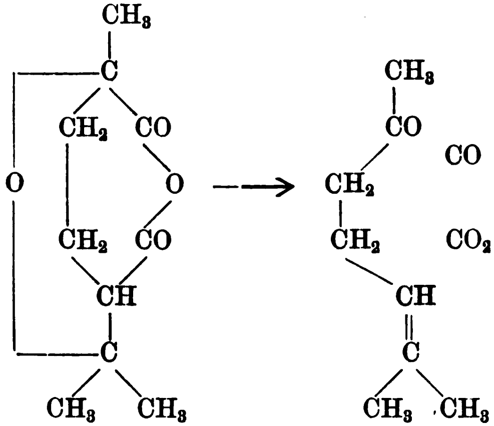
[1] Wallach and Gildemeister, *Annalen*, 1888, **246**, 268; Wallach, *ibid.*, 1890, **258**, 319; Wallach and Elkeles, *ibid.*, 1892, **271**, 21.



Cineol. Cineolic acid.

When cineolic acid is treated with acetic anhydride it yields cineolic anhydride, which, on dry distillation, breaks down quantitatively into carbon monoxide, carbon dioxide, and methyl-heptenone, an aliphatic ketone of considerable interest from its relations to the terpenes—

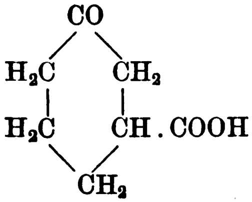


Cineolic anhydride. Methyl heptenone.

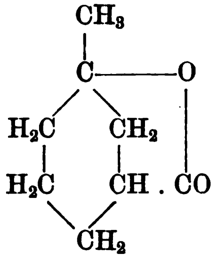
7. *The Synthesis of Carvestrene.*

Until quite recently, carvestrene could be obtained only by a very long and complicated series of reactions; and the constitutions of some of the intermediate compounds produced had not been well established. Perkin and Tattersall[1] have now succeeded in synthesizing it by a series of reactions analogous to those employed by Perkin in his synthesis of terpineol.

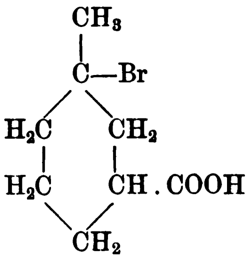
The starting-point of this new synthesis was *m*-hydroxybenzoic acid. This was first reduced with sodium and alcohol, forming hexahydro-*m*-hydroxy-benzoic acid; from which, by oxidation with chromic acid, γ-keto-hexahydrobenzoic acid (I.) was obtained. The ester of this acid reacts with magnesium methyl iodide, giving the lactone of γ-hydroxy-hexahydro-*m*-toluic acid (II.). When this is heated with hydrobromic acid it yields γ-bromohexahydro-*m*-toluic acid (III.), which on treatment with pyridine loses hydrobromic acid, and is changed into tetrahydro-*m*-toluic acid (IV.). After esterification, this is treated with magnesium methyl iodide and water, whereby an alcohol (V.) is produced which differs from terpineol in that the hydroxyl and methyl groups are in the 1, 3 position to each other, while in terpineol they are in the 1, 4 position. Just as terpineol, when treated with acid potassium sulphate, loses water to form dipentene, this new alcohol loses water and forms carvestrene (VI.).



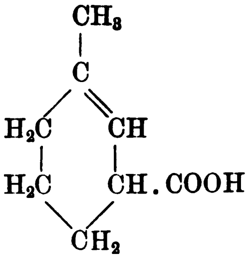
(I.)



(II.)



(III.)



(IV.)

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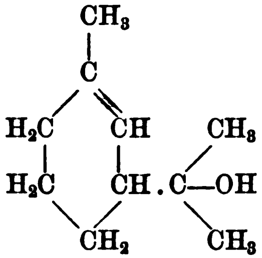
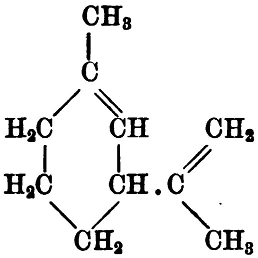
[1] Perkin and Tattersall, *Trans. Chem. Soc.*, 1907, **91**, 480.

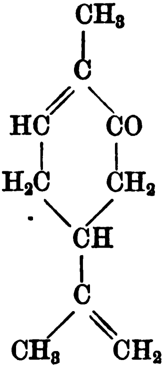


(V.)

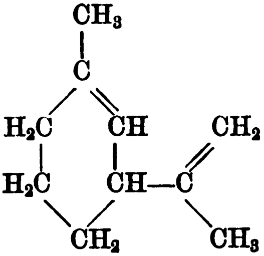


(VI.)

Though since the discovery of this new synthesis the old way of preparing carvestrene has lost its value as a practical method, we may give a very brief description of it here on account of one transition which occurs in the course of the reactions. The starting-point for the old synthesis was the substance carvone, which we have already encountered. Now, as can be seen from the formulæ of the two substances, to convert carvone into carvestrene we must shift the isopropylene group from one carbon atom to the adjacent one. How this is done will be seen in due course.



Carvone.



Carvestrene.

Carvone is first reduced with zinc dust and alcoholic potash to dihydro-carvone; hydrobromic acid is then added on, giving dihydrocarvone hydrobromide *—

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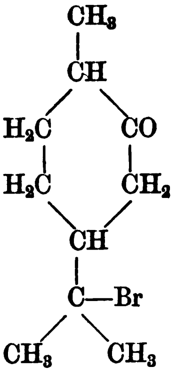
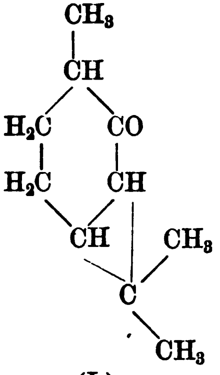
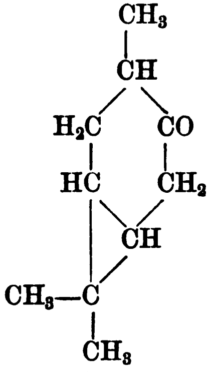
* When a halogen acid is added on to the double bond of an unsaturated substance, the negative part (*i.e.* the halogen atom) always unites with that carbon atom to which the *fewest* hydrogen atoms are attached. For example, in the



Now, when this substance is treated with alcoholic potash it gives up hydrobromic acid, but instead of regenerating a carvone derivative it yields a new ketone, carone. Since on oxidation carone yields 1, 1-dimethyl-2, 3-trimethylene dicarboxylic acid (caronic acid), it must contain a trimethylene ring. The simplest way in which this can be explained is to assume that carone has either of the formulæ (I.) and (II.).



(I.)



(II.)

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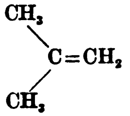
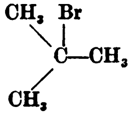
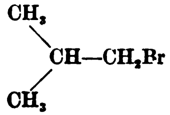
case given below the compound formed by the addition of hydrobromic acid to (I.) is (II.), and not (III.)



(I.)



(II.)

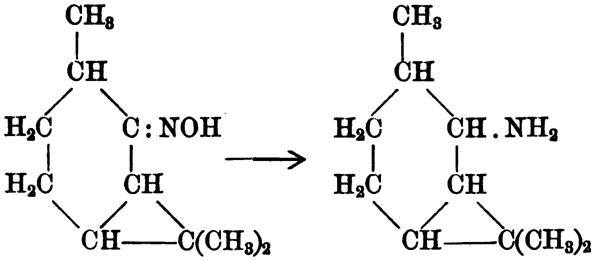


(III.)

This is called the "Markownikoff Rule" (*Ber.*, 1869, **2**, 660; *Annalen*, 1870, **153**, 256).

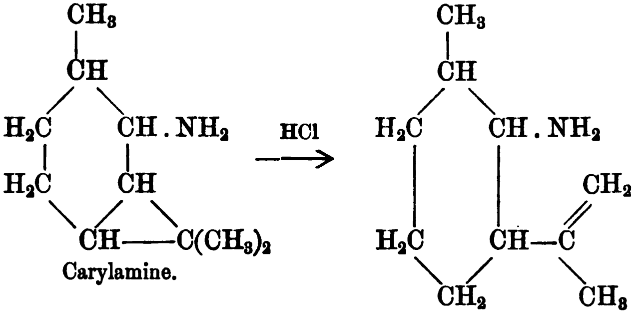
The first of these formulæ is the one usually ascribed to carone. We cannot enter into the details of the evidence here.

When carone is allowed to react with hydroxylamine it forms the substance carone oxime, which, on reduction, produces the amino-compound carylamine—



Carone oxime. Carylamine.

When this body is treated with alcoholic acid it undergoes isomeric change, and is converted into the hydrochloride of vestrylamine, the trimethylene ring being now broken. By this means we have transferred the isopropylene group from one carbon atom to the other—



Carylamine. Vestrylamine.

Vestrylamine hydrochloride, on dry distillation, breaks down into carvestrene by loss of ammonium chloride—

$$C_{10}H_{17} . NH_2 . HCl = C_{10}H_{16} + NH_4Cl$$

Carvestrene is a racemic compound, the dextro-antipode of which is found in nature as sylvestrene.[1] The latter has recently been synthesized by Perkin.[2]

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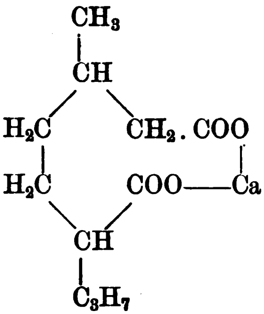
[1] Baeyer, *Ber.*, 1894, **27**, 3485.

[2] Perkin, *Proc.*, 1910, **26**, 97.

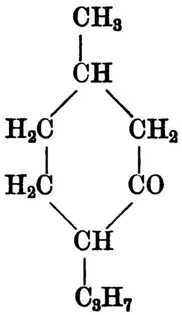
8. *The Synthesis of Menthone.*

Though menthone had been synthesized in different ways by Einhorn and Klages,[1] Kötz and Hesse[2] and Haller and Martine,[3] none of these methods furnished any proof of the constitution of the substance. It was not until 1907 that synthetic evidence was obtained upon this point.

Kötz and Schwarz[4] first synthesized β-methyl-α′-isopropyl-pimelic acid, and by the distillation of its calcium salt they produced menthone—

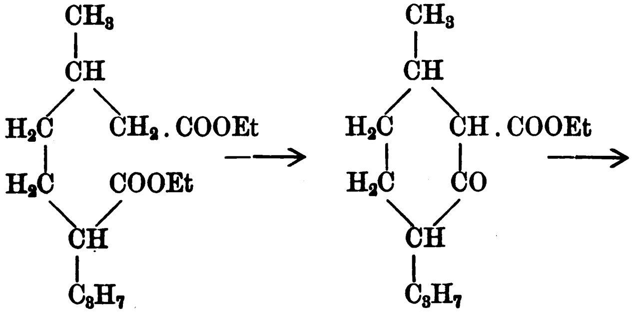


Calcium β-Methyl-α′-isopropyl-pimelate.



Menthone.

A similar result is obtained by making the ester of this acid undergo intramolecular acetoacetic ester condensation by means of sodium, and then hydrolyzing the ester thus obtained and splitting off carbon dioxide in the usual way.



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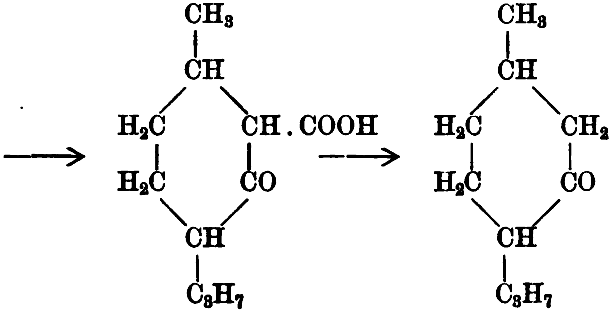
[1] Einhorn and Klages, *Ber.*, 1901, **34**, 3793.
[2] Kötz and Hesse, *Annalen*, 1905, **342**, 306.
[3] Haller and Martine, *C. R.*, 1905, **140**, 130.
[4] Kötz and Schwarz, *Annalen*, 1907, **357**, 206.

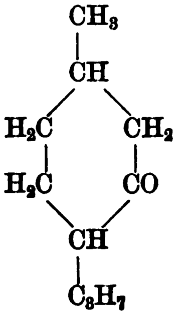


By means of this synthetic method, Kötz and Schwarz have produced an active menthone which is strongly dextro-rotatory.

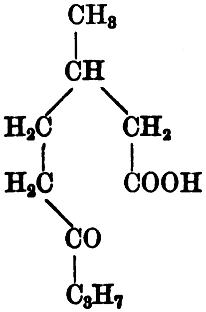
9. *The Decompositions of Menthone.*

Before the discovery of the syntheses which we have just described, it had not been possible to show synthetically that the methyl and iso-propyl radicals in menthone lay in the para-position to each other. The evidence for this had, however, been obtained from the decomposition reactions of menthone.

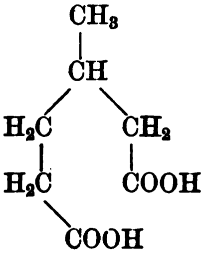
When menthone is oxidized by means of potassium permanganate, the first product is hydroxy-menthylic acid,[1] which, on further oxidation, is converted into β-methyl-adipic acid—



Menthone.



Hydroxymenthylic acid.



β-Methyl-adipic acid.

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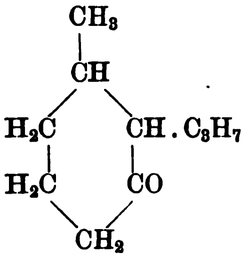
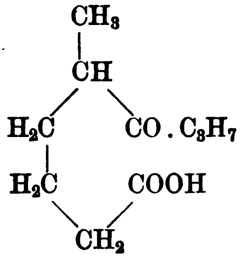
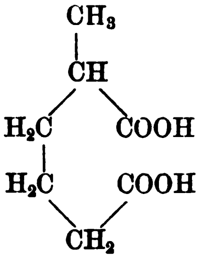
[1] Arth, *Ann. Chim. Phys.*, 1886, VI., 7, 433; Beckmann and Mehrländer, *Annalen*, 1896, **289**, 367.

These substances could be formed only if the isopropyl and methyl radicals were in the para-position to each other; for if we take them in any other position, as shown below, the resulting products are not the same—



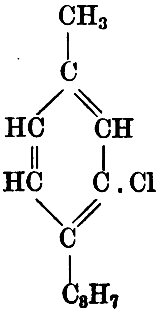


Keto-acid.



α-Methyl-adipic acid.

Again, the action of phosphorus pentachloride on menthone gives a dichloro-tetrahydro-cymene,[1] which, by successive treatment with bromine and quinoline, produces a chlorocymene[2] of the constitution—

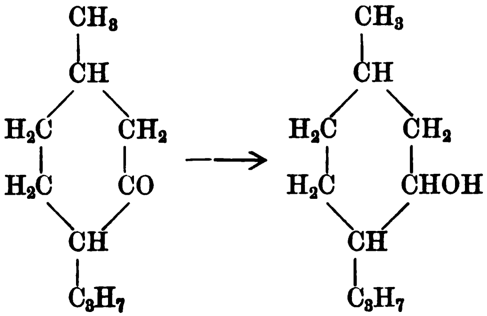


10. *The Syntheses and Constitutions of Menthol and Menthene.*

Menthol is the alcohol corresponding to menthone, from which it can be prepared by reduction. Since we have established that menthone is (I.), it is obvious that menthol must be (II.).

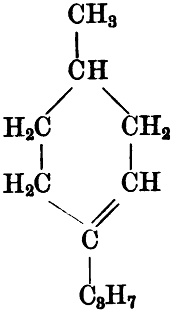
[1] Berkenheim, *Ber.*, 1892, **25**, 694.

[2] Jünger and Klages, *Ber.*, 1896, **29**, 314.

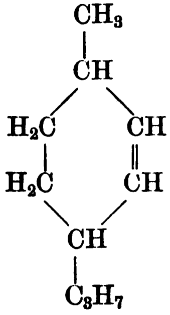


(I.) (II.)

Now, when we dehydrate menthol, a hydrocarbon, *d*-menthene, is formed. This might be either (A.) or (B.), since we can suppose that water is removed in either of two ways—

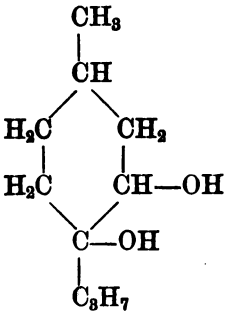


(A.)



(B.)

The decision between the two formulæ can be made by the aid of the evidence of the oxidation products of menthene.[1] When the menthene obtained from menthol is oxidized with potassium permanganate solution, the first product is a glycol, which, according to formula (A.), would have the constitution—



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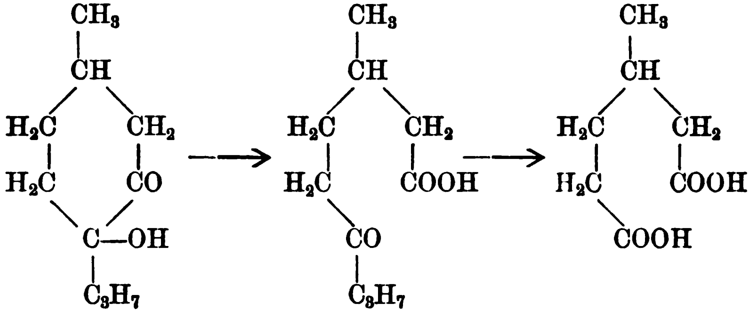
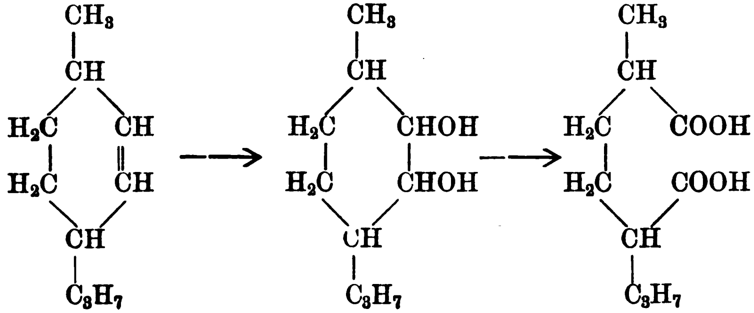
[1] Wagner, *Ber.*, 1894, **27**, 1639.

Further oxidation yields a ketone-alcohol, then hydroxymenthylic acid, and finally β-methyl-adipic acid—

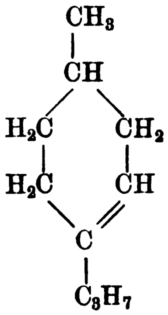


Ketone alcohol. Hydroxymenthylic acid. β-Methyl-adipic acid.

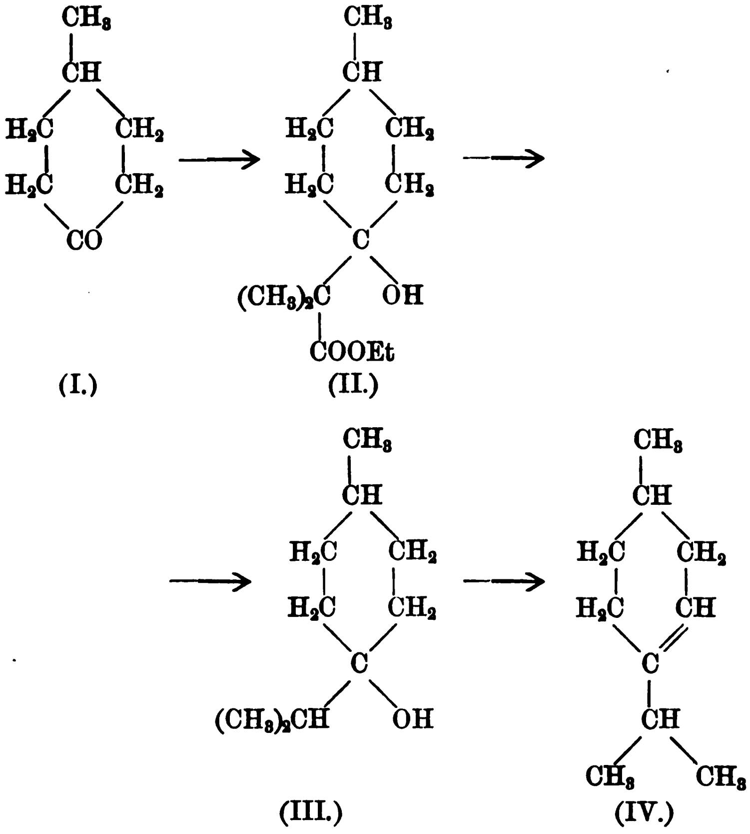
This is in agreement with the experimental results; but if, on the other hand, we start from the second possible formula for menthene, the oxidation products would not be those found in practice, but would be the compounds shown below—



Thus the constitution of menthene must be—



This has been confirmed by Wallach's recent synthesis of menthene,[1] in which he chooses as his starting-point 1, 4-methyl-cyclohexanone (I.). This he condenses with *a*-bromo-isobutyric ester by means of zinc, forming (II.); and then, by hydrolysis and heating, causes the acid to lose carbon dioxide and become converted into an alcohol (III.), which, on boiling with sulphuric acid, loses water and yields menthene.


(I.)

(II.)

(III.)

(IV.)

Menthene.

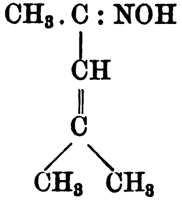
---

[1] Wallach, *Ber.*, 1906, **39**, 2504.

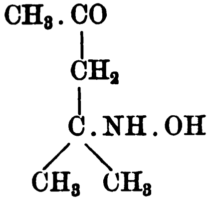
11. *The Constitution of Pulegone.*

The last compound of the menthone group with which we need deal is the unsaturated ketone pulegone.

If a ketone contains a double bond in the *αβ*-position to the carbonyl group, hydroxylamine may react with it in two ways, forming an oxime in the one case, and in the other attaching itself to the double bond to give a hydroxylamine derivative. For instance, in the case of mesityl oxide, we may have either mesityl oxime or diacetone-hydroxylamine produced—



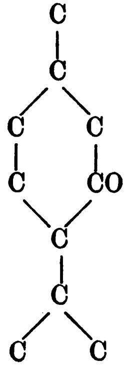
Mesityl oxime.



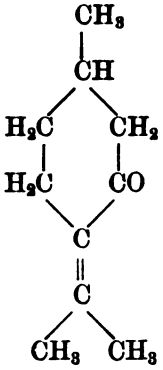
Diacetone-hydroxylamine.

Now, since pulegone shows a similar behaviour, forming either an oxime or a hydroxylamine derivative, the presumption is that it also is a ketone with an unsaturated group in the *αβ*-position to the carbonyl radical.

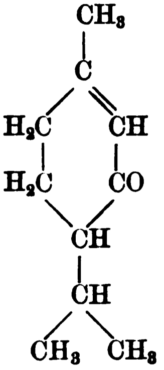
Again, pulegone on reduction is converted into menthone so that it must contain the skeleton—



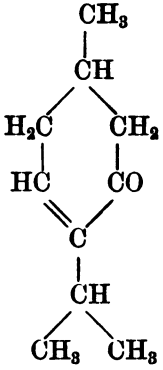
And since we have found that it has the properties of an *αβ* unsaturated ketone it can have only three possible formulæ—



(A.)

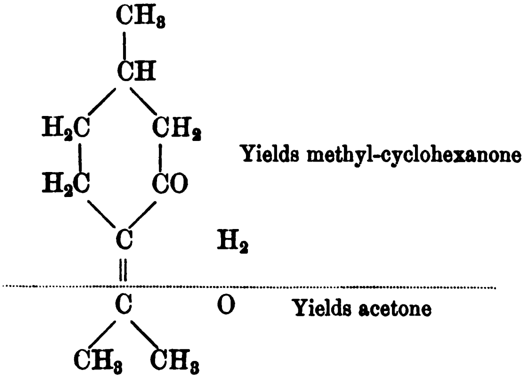


(B.)



(C.)

The evidence which enables us to choose between these three has been supplied by Wallach,[1] who has shown that when pulegone is heated under pressure with water or anhydrous formic acid it undergoes decomposition into acetone and methyl-cyclohexanone. Since this reaction can be explained by Formula A alone, it is obvious that pulegone must have that constitution. The break-down may be formulated in the way indicated below—



12. *The Constitutions of the Phellandrenes.*

The last hydrocarbon of the monocyclic class with which we need deal is phellandrene, and it we must dismiss as briefly as possible.

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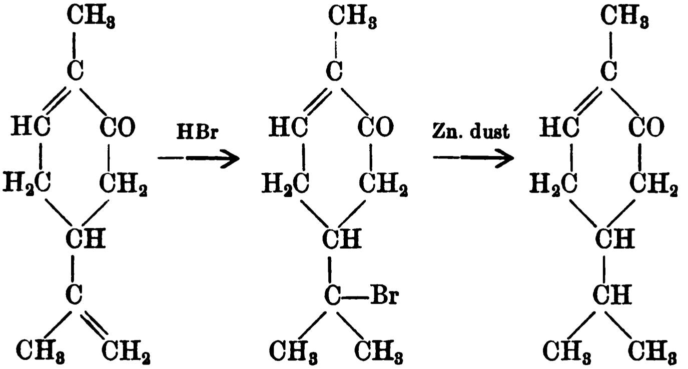
[1] Wallach, *Annalen*, 1896, 289, 337.

Until a very short time ago, phellandrene was supposed to be a simple substance, but in 1903 Semmler,[1] from a study of its oxidation products, was able to show that it must be a mixture of two hydrocarbons, to which he gave the names "*normal phellandrene*" and "*pseudo-phellandrene.*" They are also referred to as the *α*- and *β*-forms of phellandrene in some papers. Both have recently been synthesized, the normal form by Harries and Johnson,[2] and the pseudo-form by Kondakow and Schindelmeister.[3]

The synthesis of the normal form is begun with the substance Δ^6-menthenone-2, but it may be well to show how the constitution of this body is proved before we proceed to the actual steps taken by Harries and Johnson. When carvone is treated with hydrobromic acid it forms a hydrobromide, which, on reduction with zinc dust and methyl alcohol, gives the required menthenone. As can be seen from the formulæ below, no doubt as to the constitution of the compound is possible.



Carvone. Carvone hydrobromide. Δ^6-Menthenone (2).

When this menthenone (I.) is treated with phosphorus pentachloride, its enolic form gives the substance (II.), which, on reduction with zinc dust and methyl alcohol, gives *α*-phellandrene—

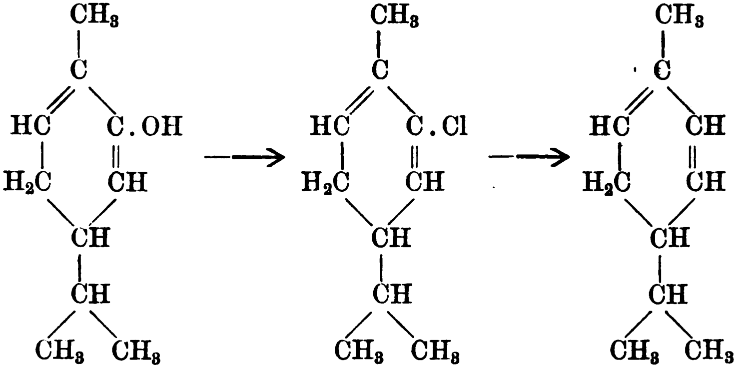
---

[1] Semmler, *Ber.*, 1903, **36**, 1749.

[2] Harries and Johnson, *Ber.*, 1905, **38**, 1832.

[3] Kondakow and Schindelmeister, *J. pr. Ch.*, 1905, II. **72**, 193; 1907, **75**, 141.

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

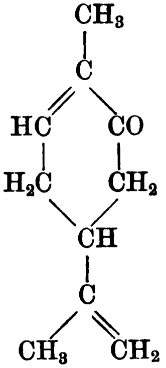


Menthenone.
Enolic form.

α-Phellandrene.

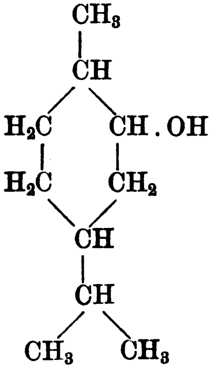
The synthesis of the isomeric β-phellandrene was actually carried out by starting from tertiary menthene, but for the sake of clearness we may go back in this case also to carvone. On reduction, carvone (I.) gives dihydrocarveol and then carvomenthol (II.). This last substance, by loss of water, can be converted into tertiary menthene (III.). By the action of bromine upon this compound a dibromide (IV.) is formed, which, with alcoholic potash, gives a hydrocarbon having all the chemical properties of β-phellandrene.

Carvone.



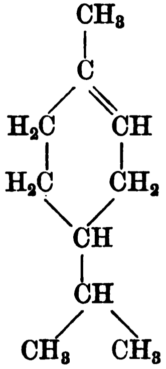
(I.)

Carvomenthol.



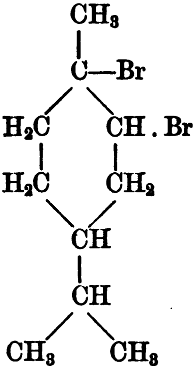
(II.)

Menthene.



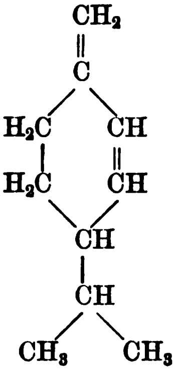
(III.)

Dibromide.



(IV.)

β-Phellandrene.



(V.)

With this substance we may conclude our review of the monocyclic terpenes and turn in the next chapter to those compounds which contain two rings of carbon atoms united together.

CHAPTER IV

THE DICYCLIC TERPENES

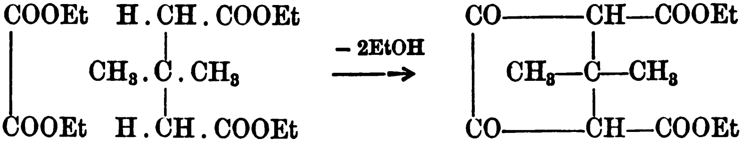
A.—The Camphene Group

1. *Syntheses of Camphoric Acid*

In the series of dicyclic terpenes which we are about to describe there are three important classes of substances. One group is derived from the hydrocarbon camphene, another from pinene, and a third from fenchene. Of these by far the most important is the camphene group, with which we shall deal first. The central substance of this group is the compound camphor $C_{10}H_{16}O$; but in order to prove the constitution of this body it will be necessary to proceed step by step, and in the first place to prove the constitution of camphoric acid, which is obtained from camphor by oxidation.

Komppa[1] and, later, Perkin and Thorpe[2] have synthesized camphoric acid. We may deal with both of these syntheses, beginning with the method employed by Komppa.

In this synthesis, the starting materials are oxalic ester and ββ-dimethyl-glutaric ester. These are condensed together with sodium ethylate in the usual way, producing diketoapocamphoric ester—



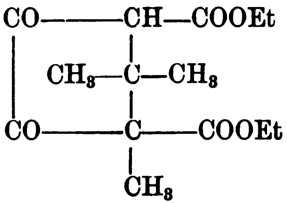
Diketoapocamphoric ester.

This was then methylated by means of sodium and methyl iodide, giving diketocamphoric ester—

---

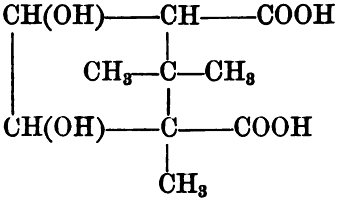
[1] Komppa, *Ber.*, 1903, **36**, 4332; *Annalen*, 1909, **368**, 126; **370**, 209; compare Blanc and Thorpe, *Trans. Chem. Soc.*, 1910, **97**, 836.

[2] Perkin and Thorpe, *Trans. Chem. Soc.*, 1906, **89**, 795.



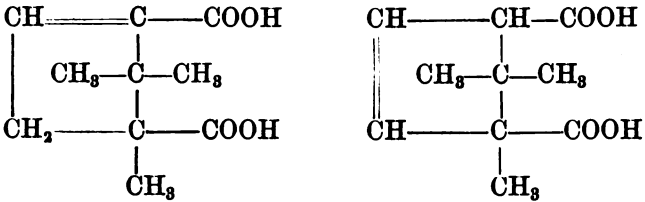
It is obvious that, since the formula is symmetrical, it makes no difference which hydrogen atom is replaced by the methyl group; the end-product in each case is the same.

This diketo-ester was dissolved in sodium carbonate solution and then treated with sodium amalgam in a stream of carbon dioxide; by this means the two carbonyl groups were reduced, and dihydroxycamphoric acid was formed, the ester being hydrolyzed by the alkaline solution.



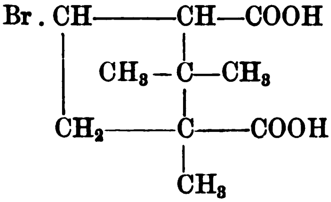
Dihydroxycamphoric acid.

On boiling this substance with hydriodic acid in presence of red phosphorus, it is converted into dehydrocamphoric acid, which may have either of the constitutions shown below—

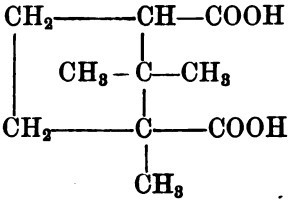


Dehydrocamphoric acid.

The constitution of this acid is of no importance, however, as the next two steps in the synthesis will yield the same final product from either of the two acids formulated above. The dehydrocamphoric acid is heated with hydrobromic acid in acetic acid solution to 125° C., whereby it is converted into a bromo-acid, which is then reduced with zinc dust and acetic acid to a substance which is identical with ordinary racemic camphoric acid—



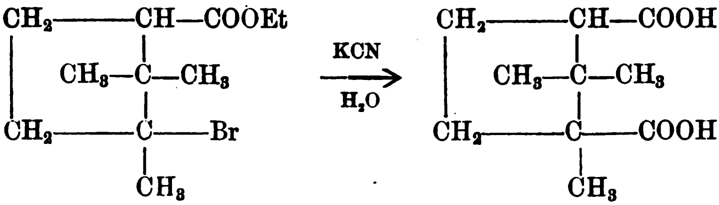
Bromo-acid.



Racemic camphoric acid.

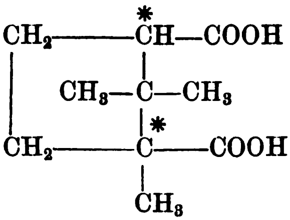
It will be seen at once that the exact constitution of the dehydrocamphoric acid is of no great importance, as the position of the bromine atom in the bromo-acid does not affect the constitution of the final camphoric acid.

The synthesis of Perkin and Thorpe starts from trimethyl-1, 2, 2-bromo-1-cyclopentane carboxylic ester, which is shaken with a mixture of potassium cyanide and hydrocyanic acid solutions. The resulting substance is heated and then boiled with acetic anhydride, whereby racemic camphoric anhydride is formed.

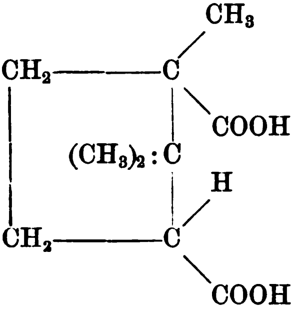


Trimethyl-bromo-cyclopentane carboxylic ester. Camphoric acid.

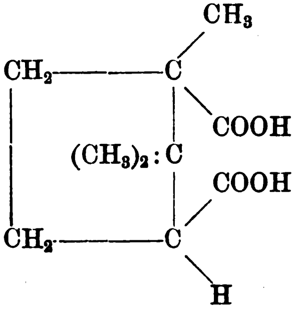
One peculiarity of camphoric acid may be pointed out here. An examination of the formula shows that camphoric acid has two asymmetric carbon atoms in its ring—these are distinguished by asterisks in the following formula :—



Now, when we attempt to racemize dextro-camphoric acid by any of the usual methods, it is found that instead of producing an equimolecular mixture of dextro- and lævo-camphoric acids, we obtain merely a mixture of dextro-camphoric acid with a new substance, lævo-*iso*-camphoric acid. From this behaviour of camphoric acid it is deduced that instead of both asymmetric carbon atoms in the dextro-acid being inverted (which would give us the mirror-image lævo-camphoric) only one is altered; so that half the molecule remains as it was. The change from *d*-camphoric to *l*-isocamphoric would be represented thus—



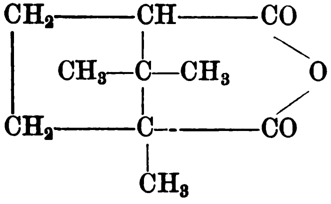
d-Camphoric acid.



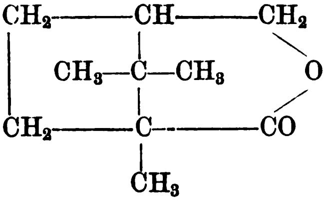
l-Isocamphoric acid.

2. *The Synthesis of Camphor.*

From synthetic camphoric acid we can obtain camphor itself by the following method. When camphoric anhydride is treated with sodium amalgam it is reduced to campholide,[1] the reaction being analogous to the production of phthalide from phthalic acid.



Camphoric anhydride.



Campholide.

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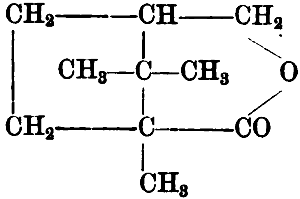
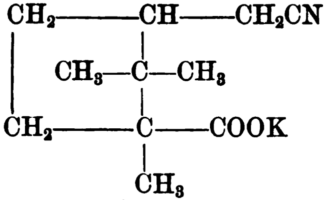
[1] Haller, *Bull. soc. chim.*, 1896, [iii.] **15**, 7, 984; Forster, *Trans. Chem. Soc.*, 1896, **69**, 36.

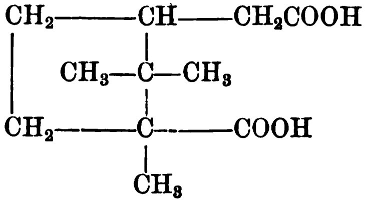
Campholide, on treatment with potassium cyanide, produces a nitrile-salt, which, on hydrolysis, gives homocamphoric acid[1]; this action is exactly like that which produces homophthalic acid from phthalide—



Campholide.

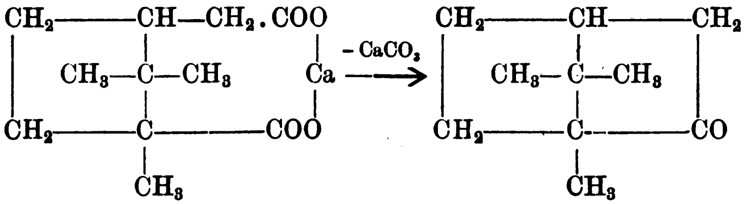


Nitrile-salt.



Homocamphoric acid.

From this homocamphoric acid it is easy to produce camphor itself by distilling the lead or calcium salt of the acid.[2]



This synthesis confirms the camphor formula which was put forward in 1893 by Bredt.[3]

3. *Borneol, Camphene, and Camphane.*

When camphor is reduced by means of sodium and alcohol[4] it yields a secondary alcohol, borneol, which has the formula—

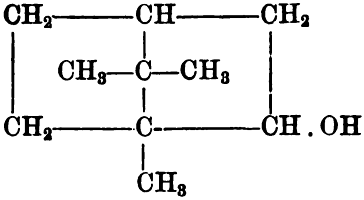
---

[1] Haller and Blanc, *C. R.*, 1900, **130**, 376.

[2] Haller, *C. R.*, 1896, **122**, 446; Bredt and Rosenberg, *Annalen*, 1896, **289**, 5.

[3] Bredt, *Ber.*, 1893, **26**, 3047.

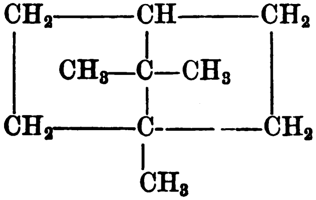
[4] Jackson and Mencke, *Am. Chem. J.*, 1883, **5**, 270; Wallach, *Annalen*, 1885, **230**, 225.



Borneol.

This alcohol occurs in dextro- and lævo-forms, either of which may be obtained at will by reducing the corresponding dextro- or lævo-camphor. Borneol is not the only product of this reaction, however, as at the same time a small quantity of an isomeric isoborneol[1] is produced, whose constitution is not yet definitely proved.

The hydroxyl radical in borneol can be replaced by a halogen atom in the usual way,* and if the bornyl iodide thus formed be reduced by means of zinc dust, acetic and hydriodic acids,[2] a hydrocarbon camphane, is produced, which is the root-substance of the camphor series. It has the formula—



Camphane.

On the other hand, when bornyl chloride or bromide is heated with alcoholic potash it is converted into an unsaturated substance by the loss of a molecule of a halogen acid.[3] The constitution of this new hydrocarbon, camphene, $C_{10}H_{16}$, is as yet undetermined. The simplest possible constitution would be the one shown below; but this has been proved to belong to bornylene,[4] which is produced by the long-continued action of

---

[1] Montgolfier, *C. R.*, 1879, **89**, 101; Haller, *C. R.*, 1887, **105**, **227**.

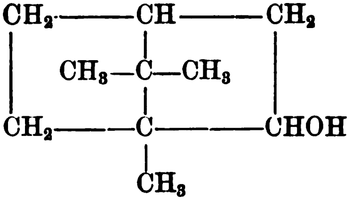
* In practice, however, bornyl iodide is usually prepared by the action of hydriodic acid on pinene, as the yields from borneol are very poor.

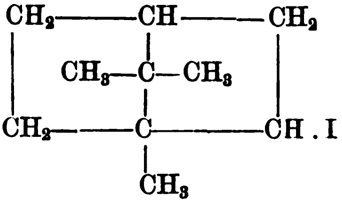
[2] Aschan, *Ber.*, 1900, **33**, 1006.

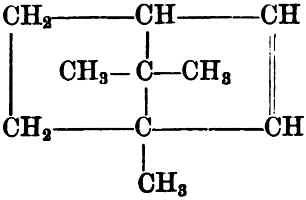
[3] Riban, *Ann. Chim. Phys.*, 1875, V. **6**, 353.

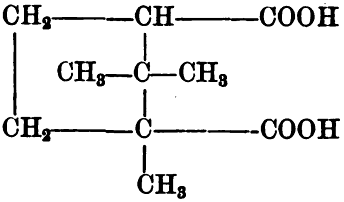
[4] Wagner and Brickner, *Ber.*, 1900, **33**, 2, 21.

alcoholic potash upon bornyl iodide. This substance, bornylene, on oxidation yields camphoric acid, which camphene does not do.


Borneol.


Bornyl iodide.

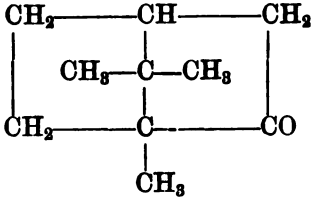

Bornylene.

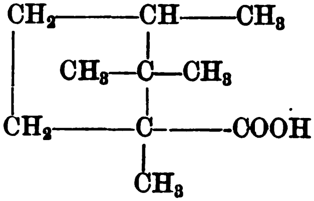

Camphoric acid.

The oxidation products of camphene are much more complicated, and will require a section to themselves. Before dealing with them, however, we must take up the question of the oxidation of camphor itself.

4. *The Decomposition Products of Camphor.*

The most vulnerable point in the camphor molecule is the carbonyl group and the adjacent methylene radical. The ring at this point is so easily attacked that it may be broken by a simple hydrolytic reaction. When camphor is heated with sodium and xylene to a temperature of 280° C., the ring opens; and when the reaction mixture is poured into water, the sodium salt of campholic acid[1] is formed.


Camphor.


Campholic acid.

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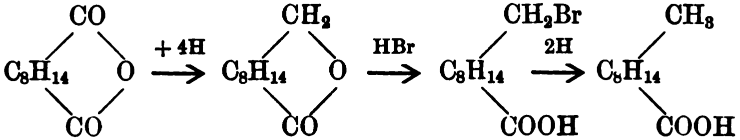
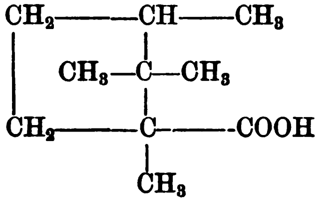
[1] Malin, *Annalen*, 1868, **145**, 201; Kachler, *ibid.*, 1872, **162**, 259.

The same acid has been obtained by Haller and Blanc[1] from campholide, a method of synthesis which establishes the constitution of the substance beyond doubt.

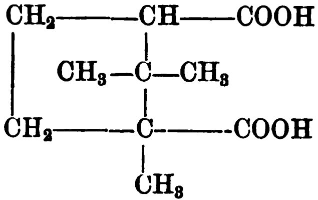


Camphoric anhydride. Campholide. Bromocampholic acid. Campholic acid.

Now, when campholic acid is oxidized with nitric acid, the newly formed methyl group is oxidized to carboxyl, and camphoric acid is formed.

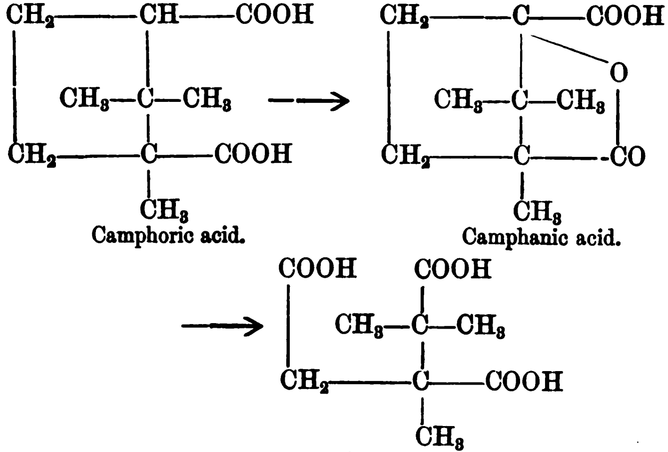


Campholic acid.



Camphoric acid.

Further action of nitric acid upon the latter substance gives rise to camphanic acid, which is oxidized in its turn to camphoronic acid—



Camphoric acid. Camphanic acid. Camphoronic acid.

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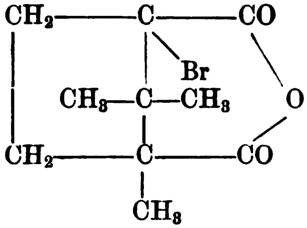
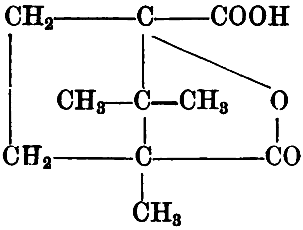
[1] Haller and Blanc, *C. R.*, 1900, **130**, 376.

The constitution of camphanic acid[1] is proved by the fact that it can be obtained from bromocamphoric anhydride by boiling with water—

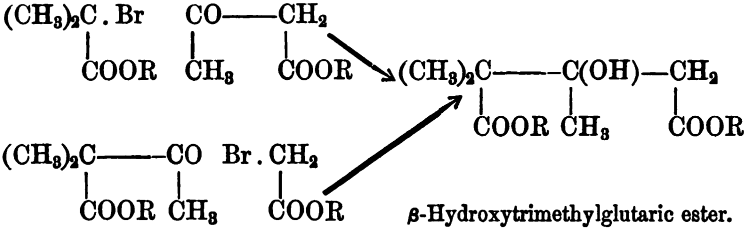


Bromocamphoric anhydride.



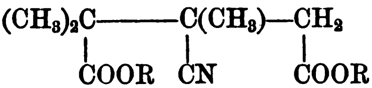
Camphanic acid.

The constitution of camphoronic acid was established by the synthesis of Perkin and Thorpe.[2] These authors first prepared β-hydroxy-trimethyl-glutaric ester by the action of zinc upon a mixture of acetoacetic ester and α-bromo-isobutyric ester, or upon a mixture of dimethyl-acetoacetic ester and monobromacetic ester—



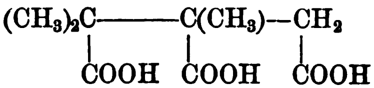
β-Hydroxytrimethylglutaric ester.

By replacing the hydroxyl group first with chlorine and then by cyanogen they obtained the nitrile-ester of camphoronic acid, from which the acid itself was produced by hydrolysis—



$$\underset{\substack{|\\ COOR}}{(CH_3)_2C}-\!\!-\!\!-\underset{\substack{|\\ CN}}{C(CH_3)}-\underset{\substack{|\\ COOR}}{CH_2}$$

Camphoronic nitrile.



$$\underset{\substack{|\\ COOH}}{(CH_3)_2C}-\!\!-\!\!-\underset{\substack{|\\ COOH}}{C(CH_3)}-\underset{\substack{|\\ COOH}}{CH_2}$$

Camphoronic acid.

When camphoronic acid is heated to above 135° C., it loses water and is converted into anhydrocamphoronic acid, $C_9H_{12}O_5$.

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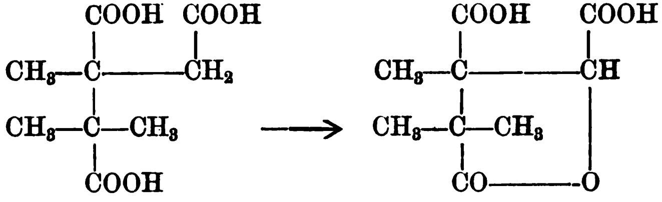
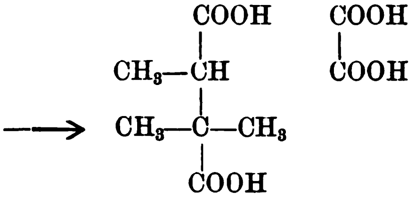
[1] Reyher, "Dissertation," Leipzig, 1891; Bredt, *Ber.*, 1894, **21**, 2097; Lapworth and Lenton, *Trans. Chem. Soc.*, 1902, **81**, 17.

[2] Perkin and Thorpe, *Trans. Chem. Soc.*, 1897, **71**, 1169.

By brominating the chloride of this acid, two isomeric bromoanhydrocamphoronic chlorides are produced, one of which, when boiled with water, gives the lactone of an unstable hydroxycamphoronic acid (camphoranic acid), while the other yields stable hydroxycamphoronic acid. Camphoranic acid, when fused with potash, breaks down into oxalic and trimethylsuccinic acids.[1] These changes may be expressed thus—



Camphoronic acid. Camphoranic acid.



Trimethylsuccinic and oxalic acids.

5. *Camphoic and Apocamphoric Acids.*

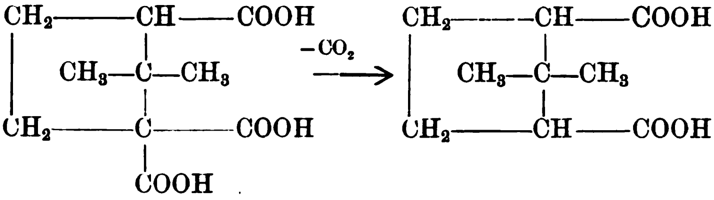
Camphene contains a double bond, by means of which it unites with halogen acids. When it is oxidized by means of dilute potassium permanganate, the usual addition of hydroxyl groups at each end of the double bond occurs, with the formation of camphene glycol,[2] $C_{10}H_{16}(OH)_2$; but if for the permanganate we substitute nitric acid, the first product isolated is camphoic acid.[3] Just as malonic acid on dry distillation loses carbon dioxide and is converted into acetic acid, so camphoic acid loses carbon dioxide and yields apocamphoric acid. From this we may deduce that camphoic acid is a tribasic acid of the constitution shown below—

---

[1] Bredt, *Annalen*, 1898, **299**, 150.

[2] Wagner, *Ber.*, 1890, **23**, 2311.

[3] Marsh and Gardner, *Trans., Chem. Soc.*, 1891, **59**, 64; 1896, **69**, 74.



Camphoic acid. Apocamphoric acid.

The constitution of apocamphoric acid is established by the fact that it can be prepared by the reduction, under suitable conditions, of diketoapocamphoric acid with which we have already dealt.

We must now leave the camphor group and turn to the isomeric substances in the fenchene and pinene series.

B.—Fenchone and its Derivatives.

1. *The Constitution of Fenchene.*

Fenchone is a ketonic compound, isomeric with camphor, and resembling it in many respects. When dextro-fenchone is reduced it yields D-*l*-fenchyl alcohol[1]; the name indicates that though derived from a dextro-ketone the substance is actually lævo-rotatory. When this is treated at a low temperature with phosphorus pentachloride it gives lævo-rotatory D-*l*-fenchyl chloride; which, by the action of aniline, loses hydrochloric acid and is converted into D-*l*-fenchene, just as bornyl chloride is changed into camphene. If the reaction mixture during the formation of fenchyl chloride be allowed to grow warm, the resulting substances are not D-*l*-fenchyl chloride and D-*l*-fenchene, but D-*d*-fenchyl chloride and D-*d*-fenchene.

The constitution of D-*l*-fenchene has been dealt with in the following way.[2] When it is oxidized with potassium permanganate it is converted into a hydroxy-acid, D-*l*-hydroxy-fenchenic acid, which has the composition $C_{10}H_{16}O_3$. This body, when treated with lead peroxide and sulphuric acid, loses carbon dioxide and two atoms of hydrogen, being converted into D-*d*-fenchocamphorone, $C_9H_{14}O$. By nitric acid this last compound is broken down to apocamphoric acid. This production

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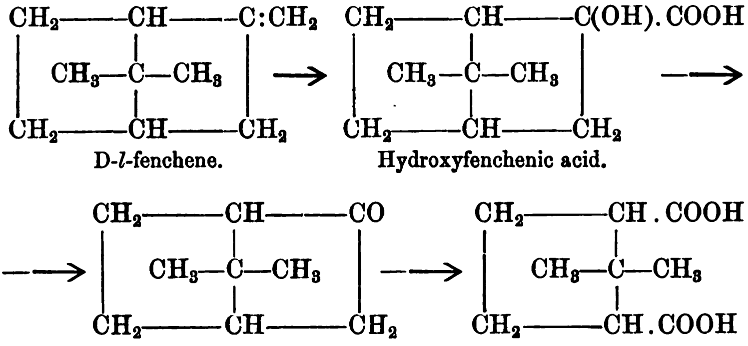
[1] Wallach, *Annalen*, 1891, **263**, 143.

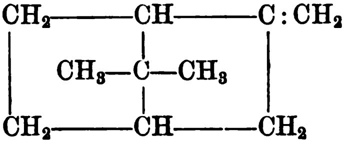
[2] Wallach, *Annalen*, 1898, **300**, 294; 1901, **315**, 283.

of apocamphoric acid from fenchene shows that in fenchene itself one of the carbon atoms must be attached to the nucleus at a point different from that at which the methyl group in camphor is placed as otherwise we should find camphoric acid produced in the end instead of its next lower homologue, apocamphoric acid. The only way in which we can satisfy this requirement is shown in the formulæ below—


D-*l*-fenchene. Hydroxyfenchenic acid.

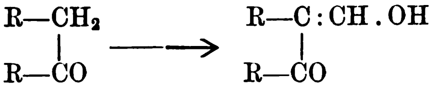
Fenchocamphorone. Apocamphoric acid.

D-*l*-fenchene, therefore, has the constitution expressed by—



2. *The Constitution of Fenchone and Fenchyl Alcohol.*

Claisen[1] has shown that when ketones containing a methylene group next the carbonyl radical are treated with sodium and amyl formate they are converted into oxymethylene derivatives—



$$\begin{array}{l} \mathrm{R—CH_2} \\ \quad\;| \\ \mathrm{R—CO} \end{array} \longrightarrow \begin{array}{l} \mathrm{R—C:CH.OH} \\ \quad\;| \\ \mathrm{R—CO} \end{array}$$

Camphor when dealt with in this manner forms oxymethylene

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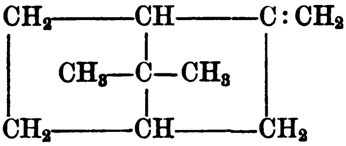
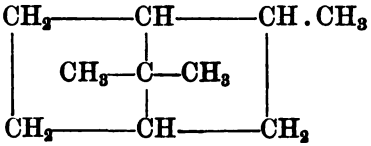
[1] Claisen, *Annalen*, 1894, **281**, 394.

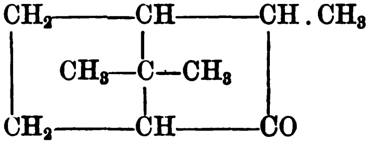
camphor; but when we apply the same reaction to fenchone no such result is obtained. From this we conclude that fenchone contains no methylene group next the carbonyl radical.

We have just proved the formula of D-*l*-fenchene, and from it we can deduce that of the corresponding saturated compound, fenchane—

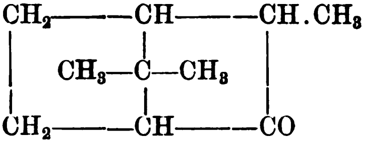

D-*l*-fenchene.

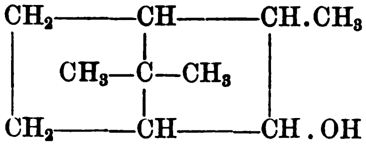

Fenchane.

Now, fenchone is derived from fenchane by replacing a methylene group by a carbonyl radical, and, in accordance with what we have just shown, the carbonyl group so produced must have no methylene group adjacent to it. There is only one formula which fulfils these conditions, so that the constitution of fenchone must be expressed by—


Fenchone.

Since fenchyl alcohol is obtained by the reduction of fenchone, its constitution must be that which is shown below—

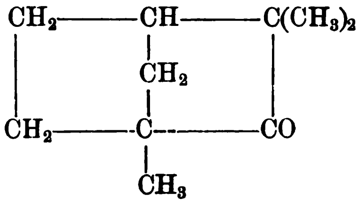

Fenchone.


Fenchyl alcohol.

Another formula for fenchone has been suggested by Semmler[1] and supported by Bouveault and Levallois[2]—

[1] Semmler, *Ch. Ztg.*, 1905, **29**, 1313.

[2] Bouveault and Levallois, *C. r.*, 1908, **146**, 180.



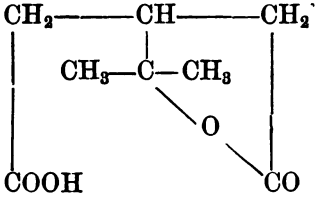
This formula explains certain reactions which Wallach's does not make clear. The matter is still under discussion.

C.—Pinene.

1. *The Constitution of Pinene.*

Pinene is a hydrocarbon isomeric with camphene and fenchene. It was found by Sobrero[1] that when this substance was allowed to stand in sunlight in contact with water and air it was, after several months, converted into a compound sobrerol, $C_{10}H_{16}(OH)_2$, which, on boiling with dilute acids, was changed, by the loss of one molecule of water, into pinol, $C_{10}H_{16}O$. Pinol was found, on further investigation, to be an internal ether of the same type as cineol. Wallach[2] has shown that pinol may also be obtained by the action of sodium ethylate on terpineol dibromide.

When pinol or sobrerol is treated with a one per cent. solution of potassium permanganate the product is a dihydric alcohol,[3] pinol-glycol, $C_{10}H_{16}O(OH)_2$. On further oxidation, a tetrahydric alcohol,[4] sobrerythrite, $C_{10}H_{16}(OH)_4$, is formed, which in turn is oxidized to terpenylic acid. Therefore we should find in pinene, pinol, and pinol-glycol, the same chain of carbon atoms which we know exists in terpenylic acid—



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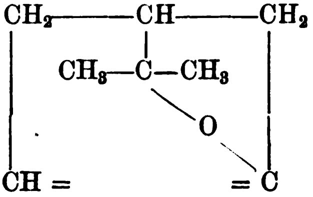
[1] Sobrero, *Annalen*, 1851, **80**, 106.

[2] Wallach, *Annalen*, 1890, **259**, 309.

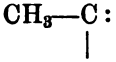
[3] Wagner and Slawinski, *Ber*, 1894, **27**, 1644.

[4] Wagner and Ginsberg, *Ber.*, 1894, **27**, 1648; 1896, **29**, 1195.

In other words, the pinol skeleton must contain the grouping—

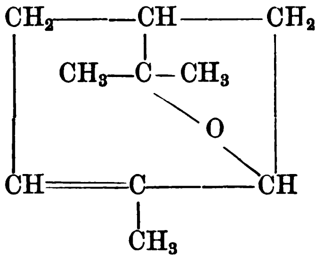


Into this scheme we have now to fit a hydrogen atom and the group—

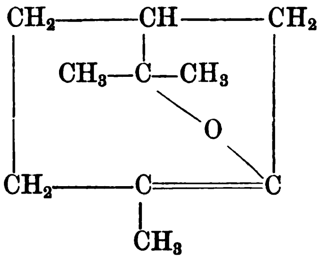


$CH_3{-}\underset{|}{C}:$

and, as can at once be seen, there are two possible ways of doing this—

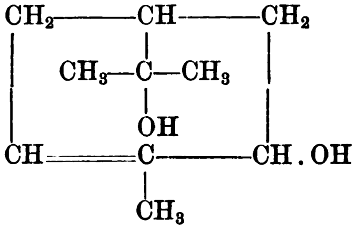


Pinol I.

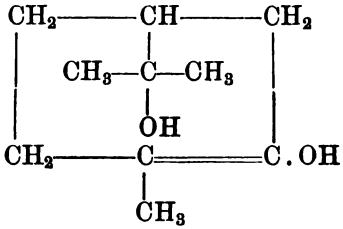


Pinol II.

On these two assumptions sobrerol, which is obtained from pinol by the addition of water, would have either of the formulæ—

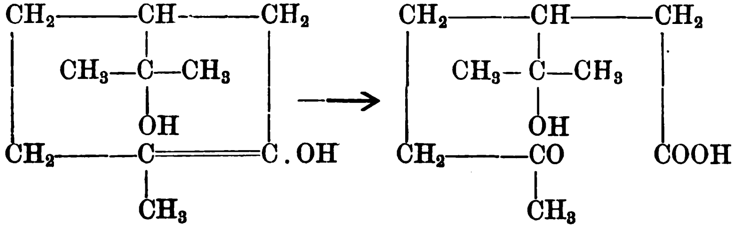


Sobrerol I.*a*.



Sobrerol II.*a*.

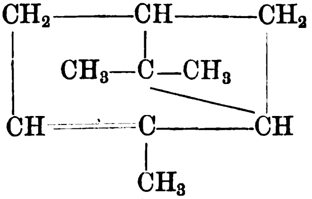
Now, sobrerol, on oxidation with a one per cent. solution of potassium permanganate, gives a tetrahydric alcohol, sobrerythrite. This can only be explained by using the formula (I.*a*), for (II.*a*) would produce a hydroxy-ketone—



Sobrerol II.*a*. Hydroxyketone.

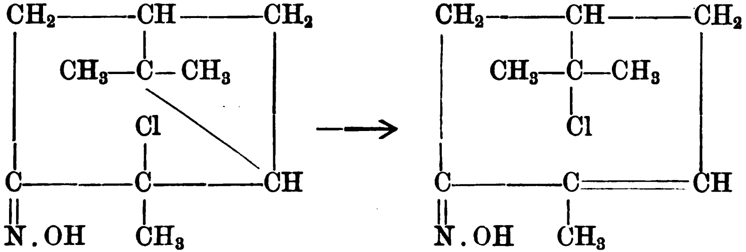
Sobrerol, therefore, has the formula (I.*a*) and pinol the formula (I.).

From this we may conclude that the formula of pinene itself is—



Pinene.

In virtue of the double bond in its molecule, pinene is capable of uniting with hydrochloric acid or nitrosyl chloride. Pinene hydrochloride resembles camphor in appearance and smell, and is used commercially under the name of "artificial camphor." Pinene nitroso-chloride,[1] on standing in presence of hydrochloric acid, is converted into hydrochlorocarvoxime by the wandering of a chlorine atom and the rupture of the pinene tetramethylene ring.



Pinene nitrosochloride. Hydrochlorocarvoxime.

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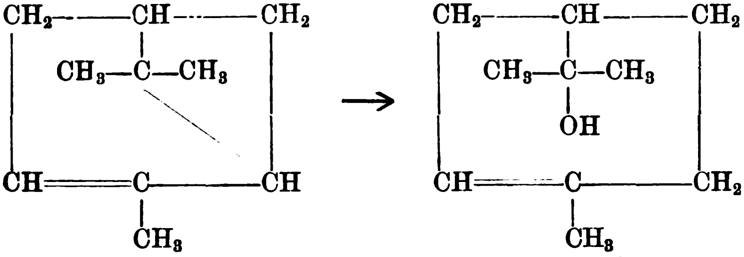
[1] Baeyer, *Ber.*, 1896, 29; 20.

Pinene itself is converted into terpineol by hydration with dilute acids—



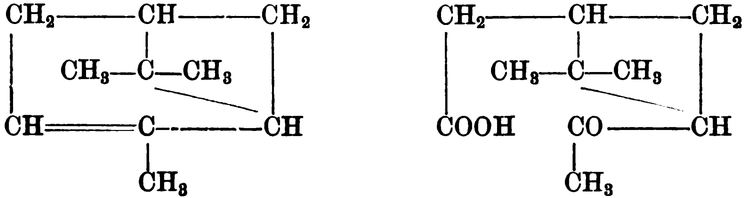
Pinene. Terpineol.

2. *Pinonic and Pinic Acids*

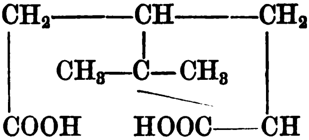
When pinene is oxidized with potassium permanganate, the first product is a ketonic acid[1] which, according to the conditions of the experiment, can be obtained either as a single substance or as a mixture of two isomers. When the single substance is produced it is found to have the composition $C_{10}H_{16}O_3$, and has been named α-pinonic acid. It contains the group $CH_3—CO—$, for, on treatment with bromine and potash, it loses a methyl group, takes up hydroxyl, and is converted into pinic acid, $C_9H_{14}O_4$—

$$\underset{\text{Pinonic acid.}}{C_8H_{13}O_2—CO—CH_3} \xrightarrow{\text{KOH and Br}} \underset{\text{Pinic acid.}}{C_8H_{13}O_2—COOH} + CHBr_3$$

These changes are expressed in the following formulæ:—



Pinene. Pinonic acid.



Pinic acid.

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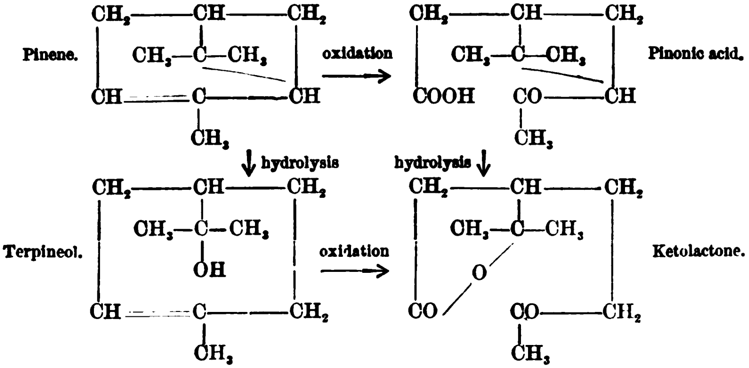
[1] Baeyer, *Ber.*, 1896, **29**, 3.

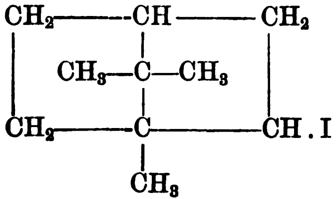
Now, on hydrolysis with fifty per cent. sulphuric acid, pinonic acid gives a keto-lactone,[1] $C_{10}H_{16}O_2$, which proves to be identical with that obtained in the oxidation of terpineol. A similar hydrolysis converts pinene into terpineol, so that we may draw up the following scheme to show the relations between the four substances:—



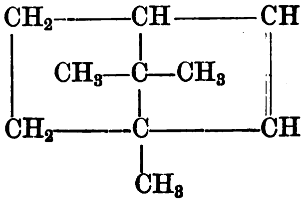
D.—Bornylene and the Thujenes

In this section we may deal very briefly with the two substances, bornylene and thujene.

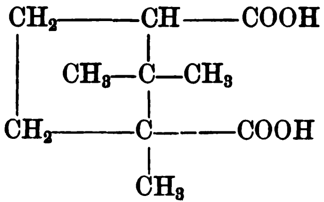
Bornylene is obtained from bornyl iodide by the action of alcoholic potash. On oxidation it gives camphoric acid. From this we can deduce that its formula must be that which is shown below—



Bornyl iodide.



Bornylene.



Camphoric acid.

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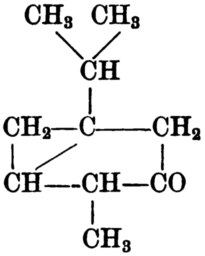
[1] Baeyer, *Ber.*, 1896, **29**, 3.

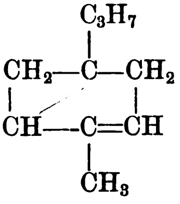
Thujone is a ketone isomeric with camphor. Its constitution has not yet been established by a synthesis, but at the present time it appears almost certain that it has the formula ascribed to it by Semmler,[1] in which it is represented as a combination of a six-membered with a three-membered ring—



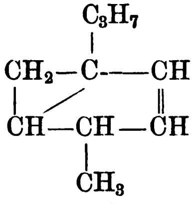
When thujone is reduced it yields thujyl alcohol; and from this we can produce the thujyl derivative of xanthogenic acid (sulphothio-carbonic acid). When this substance is distilled it breaks down into carbon oxysulphide, methyl mercaptan, and a hydrocarbon, thujene—

$$C_{10}H_{17}O\,.\,CS\,.\,SCH_3 = COS + CH_3SH + C_{10}H_{16}$$

Tschugaeff[2] has shown that thujene thus obtained is a mixture of two hydrocarbons, to which he attributes the formulæ—



α-Thujene.



β-Thujene.

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[1] Semmler, *Ber.*, 1900, **33**, 275, 2459.

[2] Tschugaeff, *Ber.*, 1901, **34**, 2279; 1904, **37**, 1481.

CHAPTER V

THE OLEFINIC TERPENES

A.—INTRODUCTION

WE have now described all the important cyclic terpenes, and in pursuance of the plan laid down in the first section dealing with these bodies, we must next examine the olefinic substances which are often included in the terpene group. It might have been more logical to have dealt with the open-chain compounds first, and the cyclic ones later, but as we should in that case have had to assume the constitution of certain cyclic terpenes which are closely connected with the olefinic ones, the present method of arrangement is more convenient.

Those unsaturated open-chain substances which are found in ethereal oils, and which, in many cases, can be transformed into cyclic terpenes, are termed olefinic terpenes, or terpenogens. They occur as hydrocarbons, aldehydes, or alcohols, and are derived from hydrocarbons of the formula C_5H_8. In many cases the odour of ethereal oils is very largely due to the olefinic terpenes contained in them.

The chemical importance of the olefinic terpenes lies in the fact that from them we can build up some of the more complicated terpene derivatives by means of very simple reactions; but they are of interest also from the commercial point of view as forming the basis of many natural and artificial perfumes.

B.—ISOPRENE.

Isoprene is the simplest of all the olefinic terpenes; it contains two double bonds, and has the composition C_5H_8. Its synthesis has been carried out by Euler,[1] and also by Ipatjew,[2]

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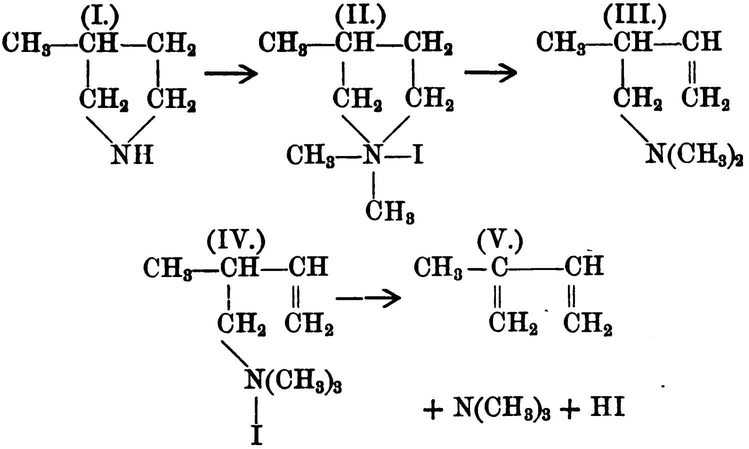
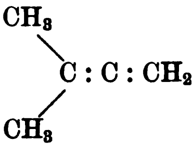
[1] Euler, *J. pr. Ch.*, II. **57**, 132.

[2] Ipatjew, *ibid.*, **55**, 4.

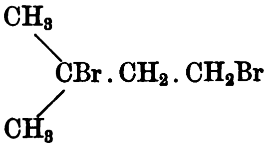
in the one case starting from methyl-pyrrolidine, and in the other from dimethyl-allene. In the first case, the methyl-pyrrolidine (I.) is allowed to interact with methyl iodide with the formation of dimethyl-methylpyrrolidinium iodide (II.). This substance is then decomposed with potash, whereby the ring is broken and *des*-dimethyl-methylpyrrolidine (III.) is produced. The addition of methyl iodide and decomposition of the product (IV.) with potash gives trimethylamine and the required isoprene (V.).



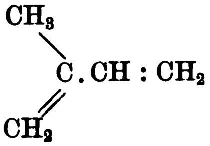
The synthesis from dimethyl-allene is much simpler. Two molecules of hydrobromic acid are added on, forming 2-methyl-2, 4-dibromobutane, from which hydrobromic acid is again split off by means of alcoholic potash—



Dimethyl-allene.

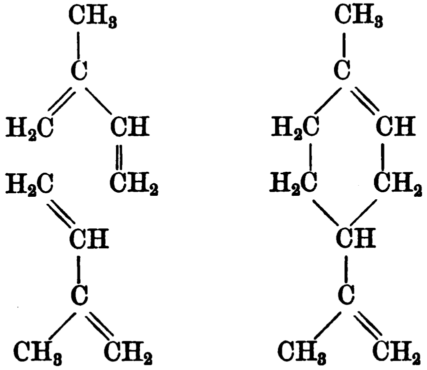


Methyl-dibromobutane.



Isoprene.

Isoprene is produced by the dry distillation of indiarubber and by the decomposition of turpentine oil at a dull red heat. Concentrated hydrochloric acid converts it into a polymer which has all the physical properties of indiarubber, and the same change takes place on long standing or with traces of acids in sunlight. When heated to 300° C., isoprene is polymerized to a di-isoprene, which seems to be identical with dipentene.[1]



In a somewhat similar manner isoprene might be supposed to give a sesquiterpene in which three isoprene molecules would coalesce to form a compound of the composition $C_{15}H_{24}$. In any probable reaction of this type, it is worth noting, at least one unsaturated chain will be left untouched and ready to react with further molecules if the proper conditions are obtained; and it is doubtless to this side chain that we owe the more complex polymer which resembles indiarubber.

C.—CITRONELLAL.

We must now pass to the consideration of a substance rather more complicated than isoprene—the compound citronellal, which was discovered by Dodge[2] in citronella oil. Citronellal is an aldehyde, for on reduction it gives the alcohol citronellol, and on oxidation it forms citronellic acid. Since it is optically active it must contain an asymmetric carbon atom.

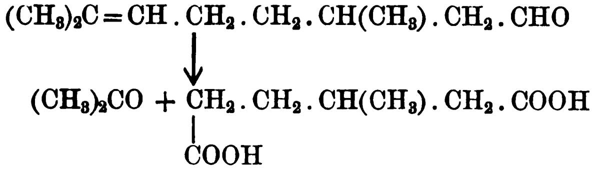
Tiemann and Schmidt,[3] oxidizing it in *aqueous* solution, obtained as products acetone and β-methyl-adipic acid, from which they concluded very naturally that citronellal had the constitution—

---

[1] Tilden, *Trans. Chem. Soc.*, 1884, **45**, 410; Bouchardat, *C. R.*, 1875, **80**, 1446; 1878, **87**, 654; 1879, **89**, 361, 1117.

[2] Dodge, *Am. Chem. J.*, 1889, **11**, 456.

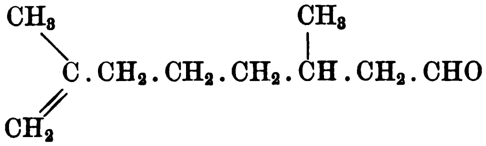
[3] Tiemann and Schmidt, *Ber.*, 1896, **29**, 903; 1897, **30**, 22, 33.



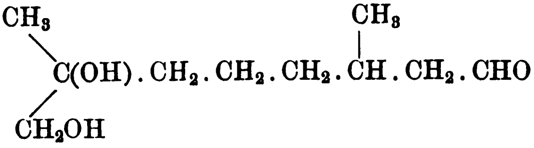
$$\begin{array}{l}(CH_3)_2C{=}CH\,.\,CH_2\,.\,CH_2\,.\,CH(CH_3)\,.\,CH_2\,.\,CHO\\ \qquad\qquad\quad\downarrow\\ (CH_3)_2CO + \underset{\displaystyle COOH}{\underset{|}{CH_2}}\,.\,CH_2\,.\,CH(CH_3)\,.\,CH_2\,.\,COOH\end{array}$$

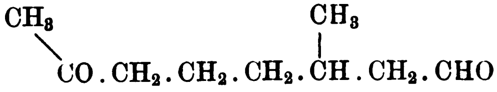
The reason for placing the methyl group in this position will be seen later when we deal with the production of pulegone from this body.

This constitution, however, is not in agreement with the work of Harries and Schauwecker,[1] who approached the matter from a slightly different standpoint. Instead of oxidizing citronellal itself, they prepared its dimethyl-acetal and replaced the aqueous solution of Schmidt and Tiemann by an acetone one. Under these circumstances they found that the oxidation product with potassium permanganate was the acetal of a dihydroxy-dihydrocitronellal, which, on further oxidation with chromic acid, could be converted into a keto-aldehyde. This shows that the double bond must lie at the extreme end of the chain, so that citronellal would have the constitution—



On this view the dihydroxy-compound and the keto-aldehyde would be—





The results obtained by Tiemann and Schmidt would be explained by supposing that under the influence of the aqueous oxidizing agent the position of the double bond was changed

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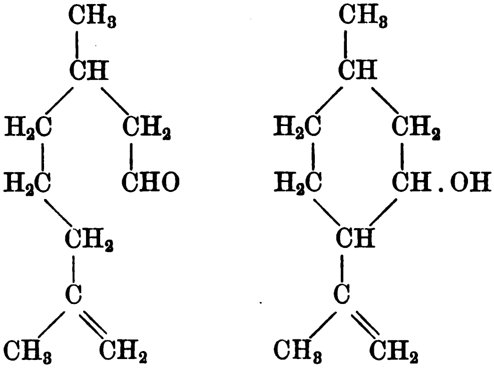
[1] Harries and Schauwecker, *Ber.*, 1901, **34**, 1498, 2981.

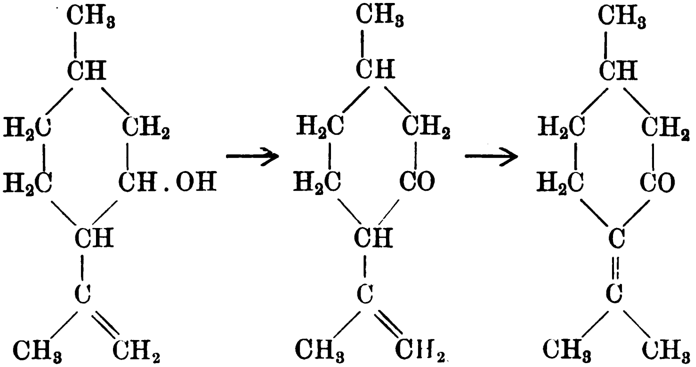
from the ultimate to the penultimate pair of carbon atoms in the chain.

So far we have not proved the position of the methyl group, but we shall now give some evidence bearing upon the point. When citronellal is allowed to stand by itself for a considerable time it is converted into the isomeric substance isopulegol.[1] The same change is brought about more rapidly by heating citronellal with acetic anhydride [2] to 180° C. The change may be represented in the following manner:—



Citronellal. Isopulegol.

The proof of the constitution of isopulegol depends upon its conversion into pulegone. When it is oxidized it yields the ketone isopulegone, which is converted into pulegone by the wandering of a double bond.



Isopulegol. Isopulegone. Pulegone.

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[1] Labbe, *Bull. soc. chim.*, 1899, [iii.] **21**, 1023.

[2] Tiemann and Schmidt, *Ber.*, 1896, **29**, 913; **30**, 27

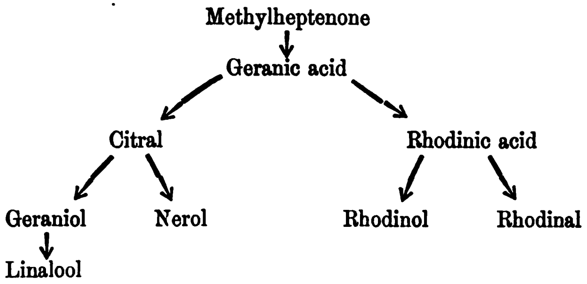
From this it is evident that the methyl group in citronellal must be in the position which we attributed to it as otherwise the isopropylene group would not come into the 1, 4-position with it in the pulegone formed from citronellal.

We may postpone the consideration of the alcohol citronellol and of citronellic acid until later, as they are closely connected with some members of the class of compounds with which we are about to deal in the next section.

D.—The Citral Group.

1. *General.*

The group of olefinic terpenes, of which citral is the most important member, can all be derived from the unsaturated ketone methyl-heptenone. It will perhaps be best, before entering upon a detailed consideration of the group to give a small table showing the relations between the different members.

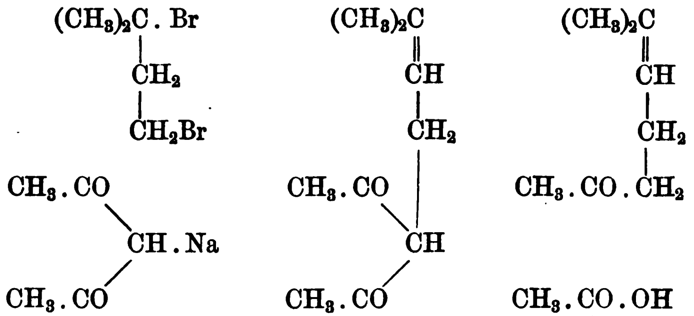


We must now proceed to trace out the various changes by which the several substances are obtained.

2. *Methyl-heptenone.*

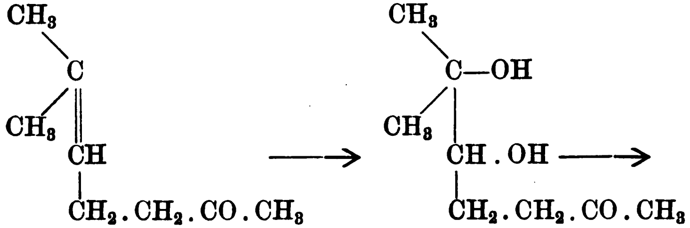
As can be seen from the foregoing table, the substance from which all the other members of the citral group are built up is the ketone methyl-heptenone. We have already encountered this compound among the decomposition products of cineolic acid, but in that place we did not deal with its constitution.

Methyl-heptenone has been synthesized in different ways by Barbier and Bouveault,[1] Verley,[2] Tiemann,[3] Leser,[4] and Ipatjew.[5] We need only give one synthesis here, and may choose that of Barbier and Bouveault. In the first place, 2-methyl-2, 4-dibromobutane is condensed with the sodium derivative of acetylacetone. This gives the unsaturated diketone (II.), which can be broken down by strong alkali into acetic acid and methyl-heptenone (III.).



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

This establishes the constitution of the substance, but if further proof were required it is to be found in the behaviour of methyl-heptenone (A) on oxidation. The first product (B) is a dihydroxy-ketone, which, on further oxidation, breaks down into acetone and lævulinic acid (C).



(A.) (B.)

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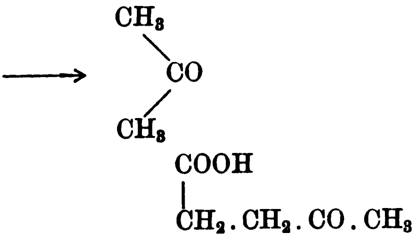
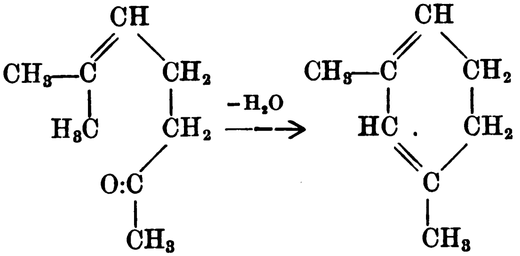
[1] Barbier and Bouveault, *C. R.*, 1896, **122**, 393.
[2] Verley, *Bull. soc. chim.*, 1897, [iii.] **17**, 180.
[3] Tiemann, *Ber.*, 1898, **31**, 824.
[4] Leser, *Bull. soc. chim.*, 1897, [iii.] **17**, 180.
[5] Ipatjew, *Ber.*, 1901, **34**, 594.



(C.)

In itself, methyl-heptenone is of no great importance, and we may confine ourselves to one of the reactions which it undergoes. When shaken with seventy-five per cent. sulphuric acid it loses a molecule of water and is converted into dihydro-*m*-xylene—



Methylheptenone. Dihydro-*m*-xylene.

3. *Geranic Acid.*

Following upon their synthesis of methyl-heptenone, Barbier and Bouveault[1] were enabled to synthesize geranic acid by means of a simple series of reactions with which we must now deal. By the action of zinc and iodo-acetic ester upon methyl-heptenone they prepared a hydroxy-acid, which, on boiling with acetic anhydride, broke down into geranic acid.

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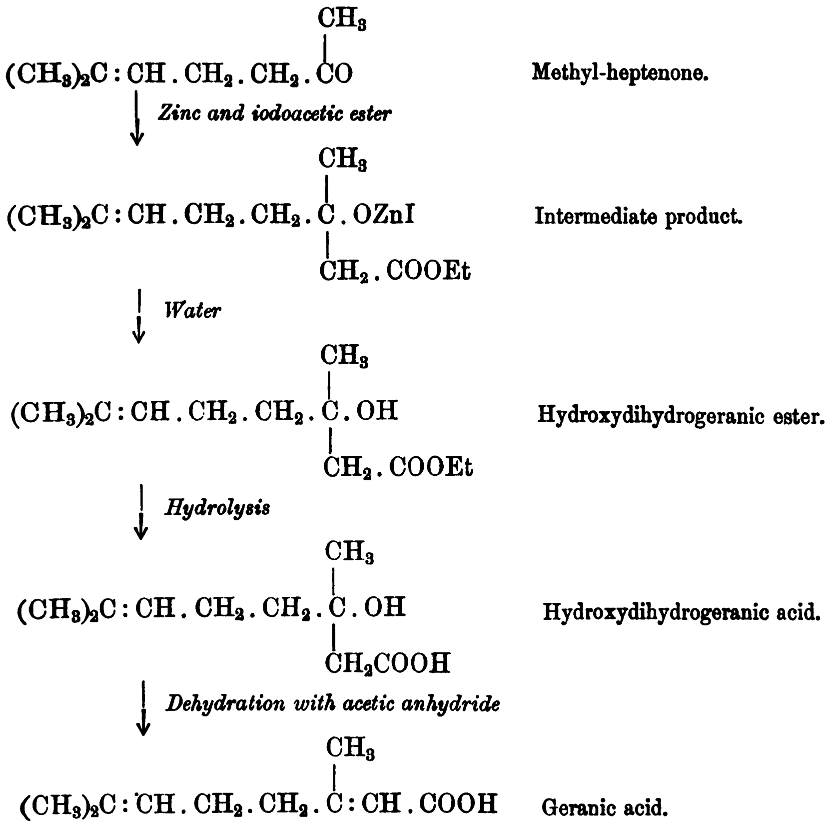
[1] Barbier and Bouveault, *C. R.*, 1896, **122**, 393; see also Tiemann, *Ber.*, 1898, **31**, 825.

The formulæ below indicate the course of the synthesis—



$$(\mathrm{CH_3})_2\mathrm{C:CH.CH_2.CH_2.}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{O}$$

Methyl-heptenone.

$$\Big\downarrow\ \textit{Zinc and iodoacetic ester}$$

$$(\mathrm{CH_3})_2\mathrm{C:CH.CH_2.CH_2.}\underset{\mathrm{CH_2.COOEt}}{\underset{|}{\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}}}\mathrm{.OZnI}$$

Intermediate product.

$$\Big\downarrow\ \textit{Water}$$

$$(\mathrm{CH_3})_2\mathrm{C:CH.CH_2.CH_2.}\underset{\mathrm{CH_2.COOEt}}{\underset{|}{\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}}}\mathrm{.OH}$$

Hydroxydihydrogeranic ester.

$$\Big\downarrow\ \textit{Hydrolysis}$$

$$(\mathrm{CH_3})_2\mathrm{C:CH.CH_2.CH_2.}\underset{\mathrm{CH_2COOH}}{\underset{|}{\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}}}\mathrm{.OH}$$

Hydroxydihydrogeranic acid.

$$\Big\downarrow\ \textit{Dehydration with acetic anhydride}$$

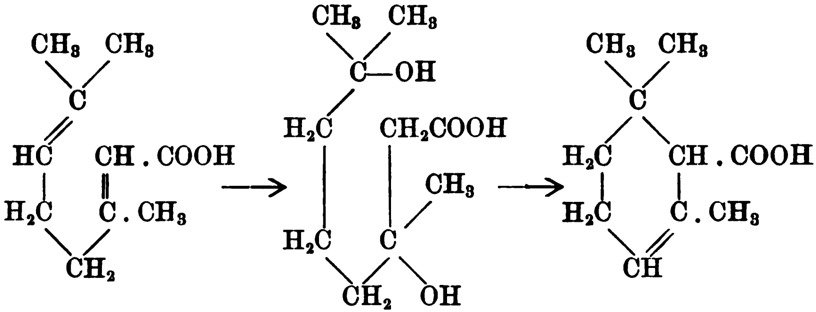
$$(\mathrm{CH_3})_2\mathrm{C:CH.CH_2.CH_2.}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{:CH.COOH}$$

Geranic acid.

Like methyl-heptenone, geranic acid is of very little importance in itself. The only reaction which specially concerns us is its condensation to α-cyclogeranic acid,[1] which, like the corresponding condensation of methyl-heptenone, takes place under the influence of seventy per cent. sulphuric acid. In order to explain the geranic acid change, it is necessary to assume the formation and decomposition of an intermediate product which has not yet been isolated—

---

[1] Tiemann and Semmler, *Ber.*, 1893, **26**, 2726; Tiemann and Schmidt, *ibid.*, 1898, 31, 881; Tiemann and Tigges, *ibid.*, 1900, 33, 3713; Barbier and Bouveault, *Bull. soc. chim.*, 1896, [iii.] 15, 1002.

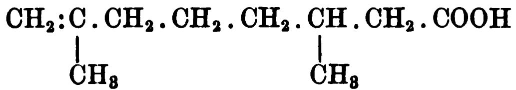


Geranic acid. Hypothetical intermediate product. α-Cyclogeranic acid.

As the table shows, geranic acid gives rise to two series of compounds; on the one hand, by reduction, we may obtain rhodinic acid and its derivatives, while on the other we may produce the aldehyde citral, from which in turn several substances may be formed. In the first place, we may deal with the smaller group, rhodinic acid and its allied compounds.

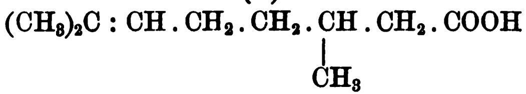
4. *Rhodinic Acid, Rhodinol, and Rhodinal.*

When the ethyl ester of geranic acid is reduced by means of sodium and amyl alcohol it is converted into inactive rhodinic acid.[1] The active, lævo-rotatory form of this acid has been obtained from the active alcohol rhodinol. These two acids are isomeric with citronellic acid, which is obtained by the oxidation of the aldehyde citronellal, and it has been suggested that citronellic acid is the dextro-form of rhodinic acid. On the other hand, from the constitution of citronellal, we should expect that citronellic acid obtained from it by oxidation would have the formula (I.), while rhodinic acid from geranic acid should have the formula (II.).



$$CH_2{:}\underset{\displaystyle CH_3}{C}.CH_2.CH_2.CH_2.\underset{\displaystyle CH_3}{CH}.CH_2.COOH$$

Citronellic acid.
(I.)



$$(CH_3)_2C : CH.CH_2.CH_2.\underset{\displaystyle CH_3}{CH}.CH_2.COOH$$

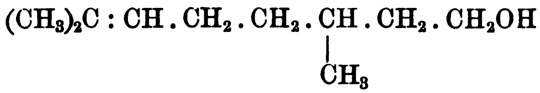
Rhodinic acid.
(II.)

---

[1] Tiemann, *Ber.*, 1898, **31**, 2901.

The literature of the subject is somewhat contradictory, and it does not seem necessary to go into the question in detail here.

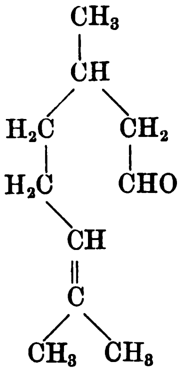
When the ester of rhodinic acid is reduced by means of sodium and absolute alcohol it yields the corresponding alcohol[1] rhodinol—



$$(CH_3)_2C : CH . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CH_2 . CH_2OH$$

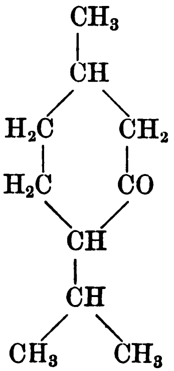
which is isomeric with citronellol. Here, again, the literature is contradictory, and it seems impossible to decide whether the two compounds are stereo-isomers or differ in structure.

Rhodinal,[2] the aldehyde corresponding to the alcohol rhodinol, is obtained by distilling together calcium formate and the calcium salt of rhodinic acid. Barbier and Bouveault regard it as having the structure (I.), because of its conversion into menthone. Citronellal, with which it is isomeric, when submitted to the action of acetic anhydride, is changed into isopulegol, as we have already described. On the other hand, rhodinal when treated in the same way yields menthone—



Rhodinal.

(I.)



Menthone.

(II.)

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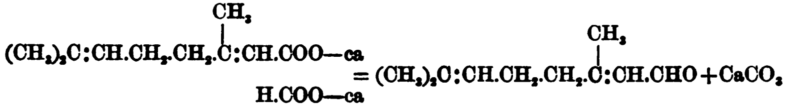
[1] Bouveault and Gourmand, *C. R.*, 1904, **138**, 1699.

[2] Tiemann, *Ber.*, 1898, **31**, 2902.

5. *Citral.*

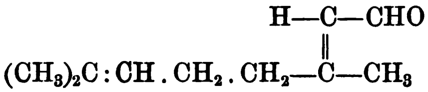
By distilling together the calcium salts of formic and geranic acids we obtain the aldehyde citral.[1] Since this is a general reaction, the constitution of citral would probably be that shown in the equation below—



$$\begin{matrix}(CH_3)_2C{:}CH.CH_2.CH_2.\overset{CH_3}{\overset{|}{C}}{:}CH.COO\text{—}ca \\ H.COO\text{—}ca\end{matrix} = (CH_3)_2C{:}CH.CH_2.CH_2.\overset{CH_3}{\overset{|}{C}}{:}CH.CHO + CaCO_3$$

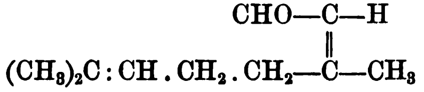
In support of this formula we may quote the decomposition of citral into acetaldehyde and methyl-heptenone, which takes place when the substance is warmed with a solution of sodium carbonate.

Citral, therefore, represents rhodinal or citronellal, from which two hydrogen atoms have been withdrawn; and differs from them further in that it contains no asymmetric carbon atom. But though it loses this possibility of isomerism, it retains another, for it has been found to occur in two geometrically isomeric forms[2]—



$$(CH_3)_2C{:}CH.CH_2.CH_2\text{—}\overset{H\text{—}C\text{—}CHO}{\overset{\Vert}{C}}\text{—}CH_3$$

Citral *a.*



$$(CH_3)_2C{:}CH.CH_2.CH_2\text{—}\overset{CHO\text{—}C\text{—}H}{\overset{\Vert}{C}}\text{—}CH_3$$

Citral *b.*

These have been shown by Harries and Himmelmann to be structurally identical; and the relative configurations have been deduced from the relations of the two compounds to geraniol and nerol, with which we shall deal later.

Like the other olefinic terpenes, citral can be converted into cyclic substances with great ease. When it is boiled for a long time with glacial acetic acid it is changed into cymene[3]—

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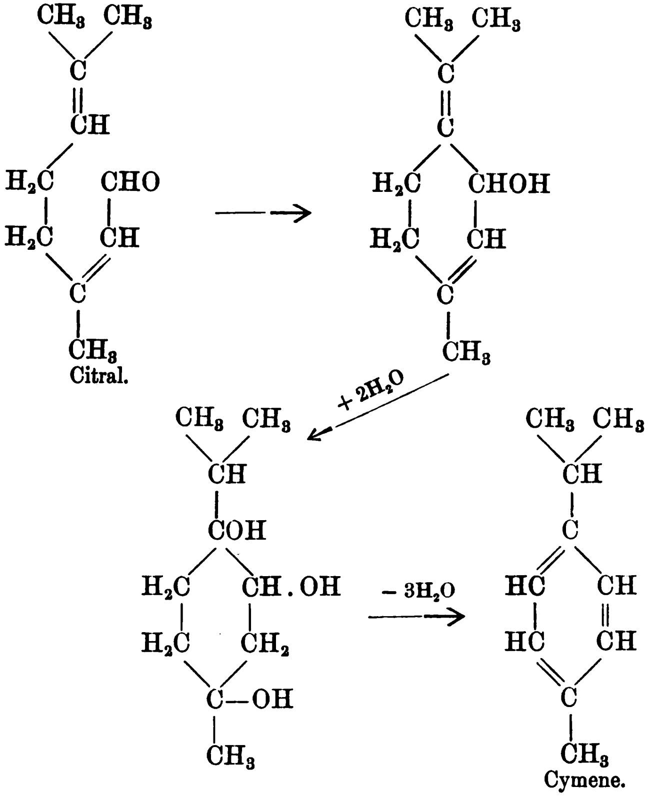
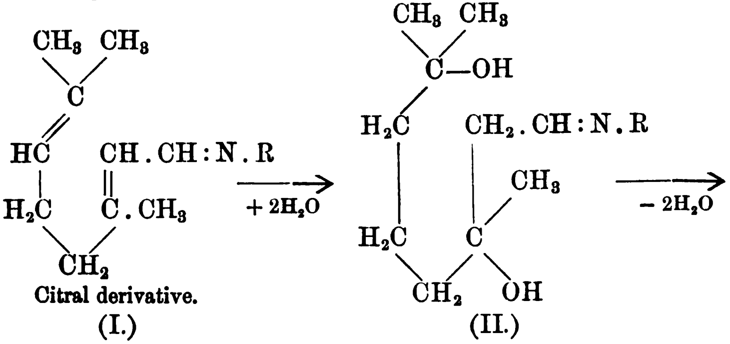
[1] Tiemann, *Ber.*, 1898, **31**, 827, 2899.

[2] Tiemann, *Ber.*, 1899, **32**, 115; 1900, **33**, 877; Bouveault, *Bull. soc. chim.*, 1899, [iii.] **21**, 419, 423; Barbier, *ibid.*, 635; Kerschbaum, *Ber.*, 1900, **33**, 886; Zeitschel, *Ber.*, 1906, **39**, 1783; Harries and Himmelmann, *Ber.*, 1907, **40**, 2823.

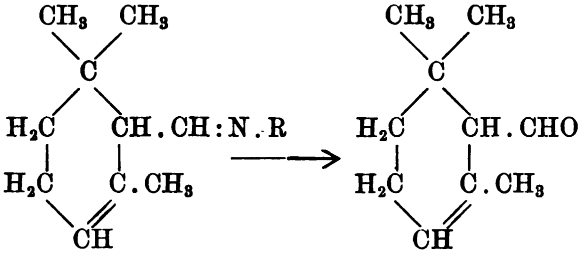
[3] Tiemann and Semmler, *Ber.*, 1895, **28**, 2134.



A second condensation of citral takes place when the aldehyde group is so treated that it takes no part in the action. For instance, if we condense citral with a primary amine, we obtain a cyclo-citral by a simple wandering of bonds and ring-formation—



Citral derivative.
(I.)
(II.)

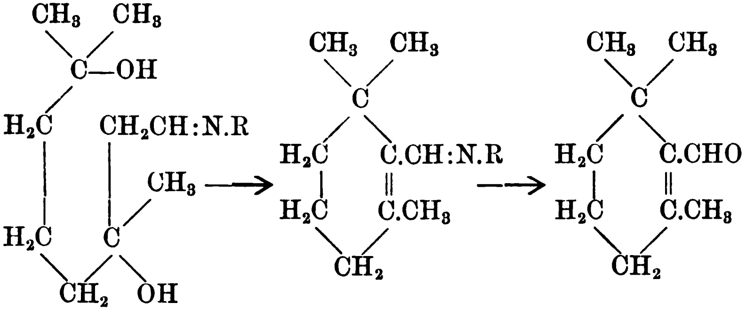


α-Cyclocitral.

(III.) (IV.)

The same result may be obtained by condensing citral with cyan-acetic ester instead of an amine. In each case, the amine or cyan-ester can be split off after the condensation to cyclocitral has taken place.

Cyclo-citral occurs in two isomeric forms,[1] the formation of either being dependent upon the manner in which water is eliminated from the molecule of an intermediate hydration product (II.). The formation of β-cyclocitral takes place as shown below.



β-Cyclocitral.

(II.)

The practical interest of citral lies in the fact that when it is condensed with acetone by means of baryta, it yields a substance, pseudo-ionone, which, by the action of sulphuric acid, is changed into ionone,[2] the basis of artificial violet perfume—

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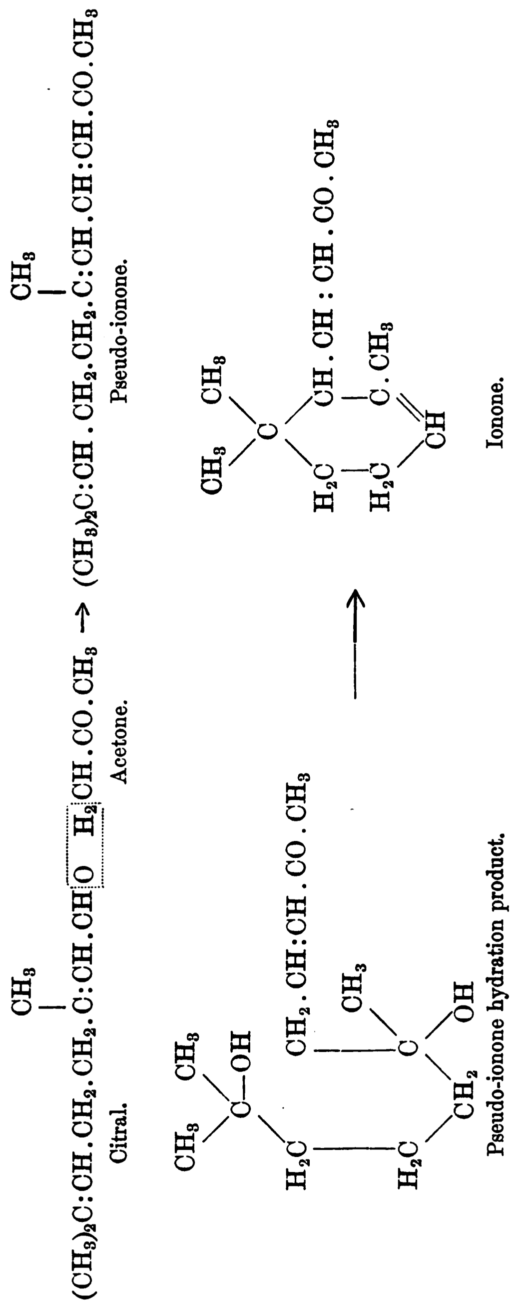
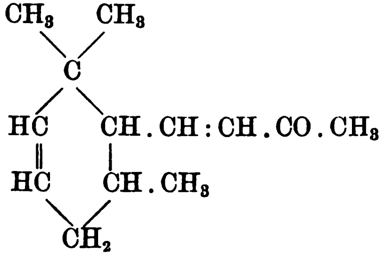
[1] Tiemann, *Ber.*, 1900, **33**, 3719.

[2] Tiemann and Krüger, *Ber.*, 1893, **26**, 2691; Tiemann, *ibid.*, 1898, **31**, 808, 867, 1736, 2313; 1899, **32**, 827; Tiemann and Schmidt, *ibid.*, 1900, **33**, 3703.



$$(CH_3)_2C{:}CH.CH_2.CH_2.\overset{CH_3}{\overset{|}{C}}{:}CH.CH\boxed{O\quad H_2}CH.CO.CH_3 \rightarrow (CH_3)_2C{:}CH.CH_2.CH_2.\overset{CH_3}{\overset{|}{C}}{:}CH.CH{:}CH.CO.CH_3$$

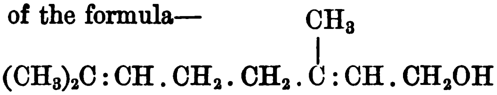
This body differs from the natural substance irone (to which the odour of violets is due) only in the position of a double bond—



Irone.

6. *Geraniol, Nerol, and Linalool.*

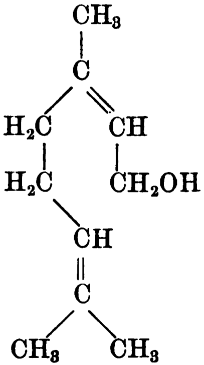
If we reduce citral with sodium amalgam in an alcoholic solution weakly acidified with acetic acid, a mixture of two isomeric alcohols, geraniol and nerol, is obtained. These two bodies, on oxidation, regenerate citral, and on this ground, as well as on account of other reactions common to both, it is assumed that they are structurally identical but stereoisomeric substances of the formula—



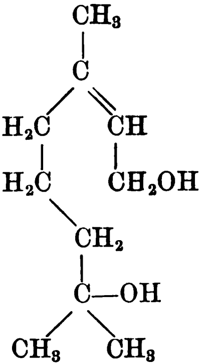
$$(CH_3)_2C:CH.CH_2.CH_2.\overset{\overset{CH_3}{|}}{C}:CH.CH_2OH$$

Proof of the correctness of this formula is afforded by the fact that when geraniol is heated with water to 150° C. it gives ethyl alcohol and methylheptenone; while on oxidation it gives acetone, lævulinic acid, and oxalic acid.

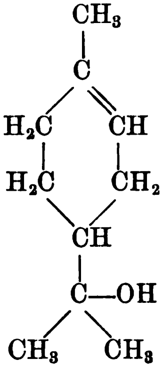
By the action of acetic acid, to which one or two per cent. of sulphuric acid has been added, both nerol and geraniol give terpineol—



Geraniol.

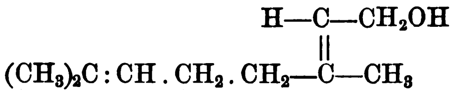


Hypothetical glycol.



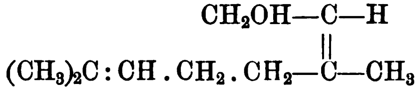
Terpineol.

Now, this reaction takes place nine times faster with nerol than with geraniol; and if the two bodies are geometrical isomers, this difference allows us to draw a conclusion with regard to their configurations.[1] A comparison of the two formulæ below will suffice to show that in (I.) the groups which unite to form the terpineol ring are further apart in space than they are in (II.). The ring-formation will therefore occur more easily in the case of (II.) than in that of (I.). Hence we must ascribe to geraniol the first formula, and to nerol the second—



$$\begin{array}{rcl} \mathrm{H{-}} & \mathrm{C} & \mathrm{{-}CH_2OH} \\ & \| & \\ \mathrm{(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2{-}} & \mathrm{C} & \mathrm{{-}CH_3} \end{array}$$

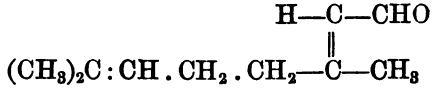
Geraniol.
(I.)



$$\begin{array}{rcl} \mathrm{CH_2OH{-}} & \mathrm{C} & \mathrm{{-}H} \\ & \| & \\ \mathrm{(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2{-}} & \mathrm{C} & \mathrm{{-}CH_3} \end{array}$$

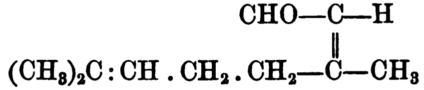
Nerol.
(II.)

We are now able to deal with the space formulæ of the two citrals. The oxidation of geraniol gives a mixture of citral *a* and citral *b*, in which citral *a* predominates; while with nerol the proportions are reversed, more citral *b* being formed. From this we may deduce that citral *a* has the same configuration as geraniol, while citral *b* has its groups arranged as in nerol—



$$\begin{array}{rcl} \mathrm{H{-}} & \mathrm{C} & \mathrm{{-}CHO} \\ & \| & \\ \mathrm{(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2{-}} & \mathrm{C} & \mathrm{{-}CH_3} \end{array}$$

Citral *a* (Geranial).



$$\begin{array}{rcl} \mathrm{CHO{-}} & \mathrm{C} & \mathrm{{-}H} \\ & \| & \\ \mathrm{(CH_3)_2C:CH\,.\,CH_2\,.\,CH_2{-}} & \mathrm{C} & \mathrm{{-}CH_3} \end{array}$$

Citral *b* (Neral).

Both geraniol and nerol are found in nature as inactive substances, which agrees with the formulæ which we have ascribed to them above. The isomeric compound, linalool, however, occurs in both dextro- and lævo-rotatory forms, and must therefore contain an asymmetric carbon atom. The inactive form of linalool is convertible into both geraniol and nerol by the action of acetic anhydride. This reaction can be explained by assuming that linalool has the formula—

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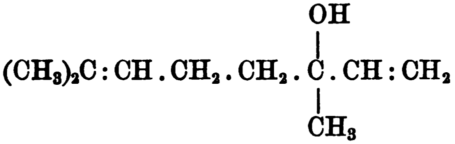
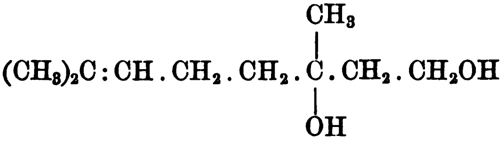
[1] Zeitschel, *Ber.*, 1906, **39**, 1780.



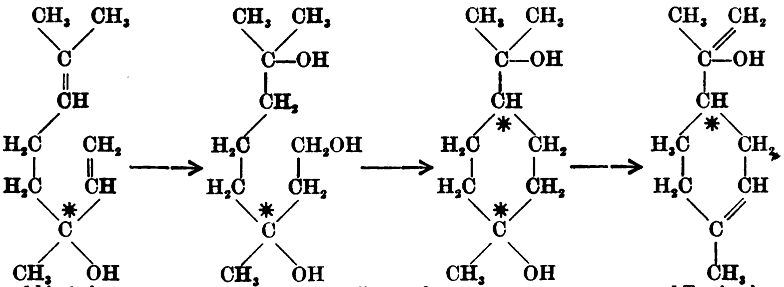
$$(CH_3)_2C:CH.CH_2.CH_2.\overset{OH}{\underset{CH_3}{C}}.CH:CH_2$$

A comparison of the formulæ of geraniol, nerol, and this one proposed for linalool will show that by the addition of water to each of these substances we can produce in all three cases the same glycol of the formula—



$$(CH_3)_2C:CH.CH_2.CH_2.\overset{CH_3}{\underset{OH}{C}}.CH_2.CH_2OH$$

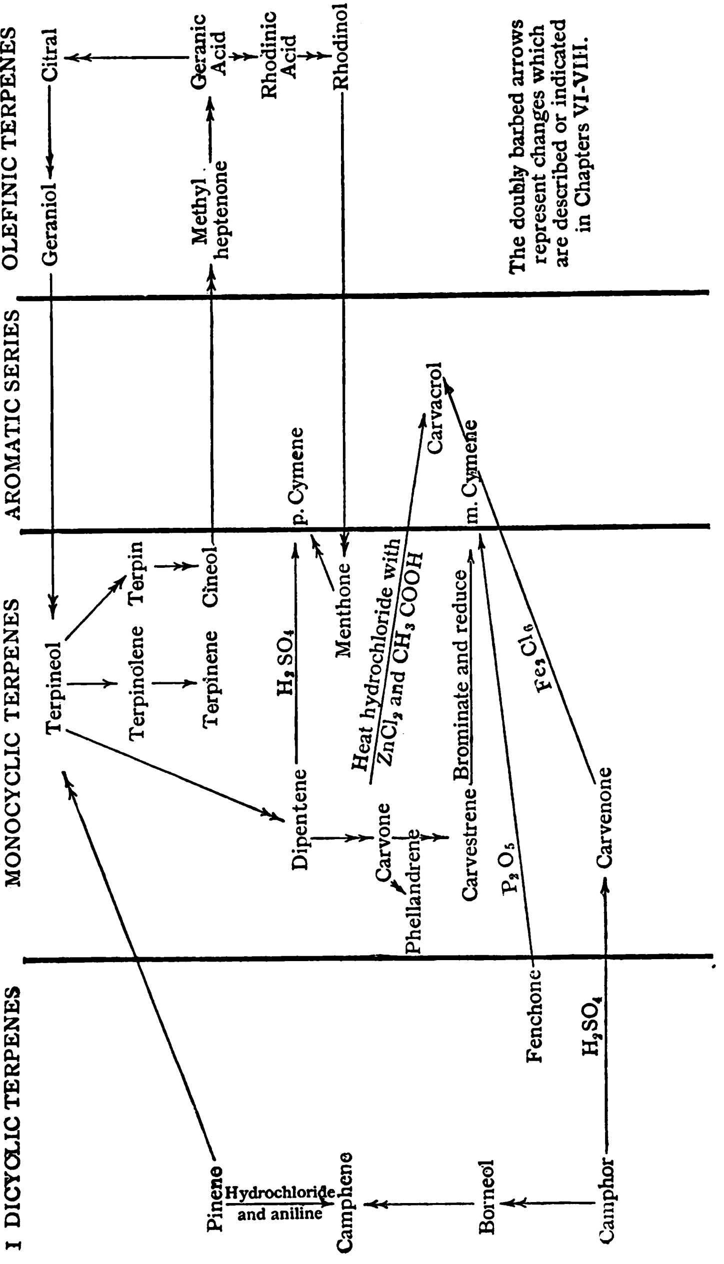
This formation of a common hydration product suffices to explain the interconvertibility of the three isomers; but there is one point which seems to render the linalool formula rather doubtful. When we take lævo-linalool and treat it with acetic anhydride, terpineol is formed along with nerol and geraniol; and this terpineol is found to be dextro-rotatory. But when we compare the formulæ of terpineol and linalool, we find that the asymmetric carbon atom of linalool does not correspond to that in terpineol; in fact, the atom which in linalool was asymmetric is now not asymmetric, while a new asymmetric carbon atom has come into being. How optical activity can persist through such a change as this appears difficult to understand, unless we assume that it is a case of asymmetric synthesis similar to those described later in this volume.



l-Linalool. Intermediate products. *d*-Terpineol.

This terminates our survey of the terpene class. In conclusion, we may append to this chapter a table showing some of the possible conversions of mono-cyclic, di-cyclic, and olefinic terpenes into each other, and also into members of the benzene series.

Table showing some Relations between Terpenes & Benzene Derivatives.



The doubly barbed arrows represent changes which are described or indicated in Chapters VI-VIII.

CHAPTER VI

THE ALKALOIDS

A.—General

When we attempt to define what we mean by the term "alkaloid" our difficulties are not small. On the one hand, our definition may be so drawn as to include almost every naturally occurring nitrogen compound, which is obviously useless as a mode of classification; or it may be so narrow as to exclude some of the most important of the substances which are usually included in the alkaloid group. The most general definition is perhaps the best; and for our present purpose we shall treat as alkaloids those naturally occurring substances which contain cyclic chains, of which at least one member is a nitrogen atom. This definition opens to us a much wider field than we can possibly attempt to cover in the space at our disposal, and in the following pages we shall aim at describing the syntheses and constitutions of a few typical compounds rather than at a survey of the whole subject.

Practically all the important alkaloids are found in the tissues of vegetables; and if we except xanthine derivatives, we might have modified the definition given above by limiting the term "alkaloid" to basic substances found in plants.

The known members of the alkaloid class are very numerous, and the number of workers in the field has been great; this was to be expected from the pharmacological importance of these substances, which renders a knowledge of their structure of the utmost value.

As the following pages will show, the chemistry of the alkaloids resembles that of the aromatic compounds, in that both classes seem to be built up upon the basis of one substance. In the aromatic series benzene lies at the root of all the compounds however complicated they be; while in the alkaloids pyridine appears to be equally essential. And just as among the aromatic types we find a benzene ring condensed with other cyclic chains, so in the alkaloids we may discover compounds in which the pyridine ring is overlaid with others. Even the derivatives of the purine group may be considered to be derived from pyridine by the substitution of a second nitrogen atom in the ring.

According to Guareschi,[1] the alkaloids are the degradation products of protoplasmic action in plants. They do not seem to be again assimilated by the plant once they are formed, but remain in the saps in the same way as uric acid may remain in the human tissues. Pictet[2] has dealt with the subject in some detail, and we may here summarize his views.

In the first place, he believes that alkaloids are not produced in plants by direct syntheses, but are rather to be regarded as the decomposition products of much more complicated substances. But as soon as the alkaloid is formed in the plant, it immediately reacts with some other plant product to form a derivative. For example, some alkaloids, such as soline, are glucosides as well as alkaloids; so that it is probable that in their case the first-formed alkaloid reacts with glucose within the plant-tissues. A more common case, however, is that in which the alkaloid condenses with an organic acid, as in the case of cocaine or atropine. But by far the most common case of all is that in which the alkaloid reacts with an alcoholic radical, usually methyl alcohol, to form an ether. In this class of derivatives the action of formaldehyde apparently lies at the root of the syntheses. Alkaloids which contain a pyrrol ring are probably derived from proteins; and it is noteworthy that while on the one hand Fischer has shown that albumen on hydrolysis gives pyrrol derivatives, it has been proved by Nencki, Köster, Zaleski, and Marchlewski that the same nucleus is to be found in hæmoglobin and chlorophyll.

With regard to the occurrence of the alkaloids in nature, very little generalization is possible. The monocotyledons seem to be the richest in members whose tissues produce these substances; while among the cryptogamia there appears to be

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[1] Guareschi, "Alkaloide," p. 414.

[2] Pictet, *Arch. soc. phys. nat. Genève*, 1905, IV., **19**, 329; *Arch. d. Pharm.*, 1906, **244**, 389.

no alkaloid formation. Just as little regularity is found with regard to the distribution of the alkaloids in the various portions of the plants themselves. Though no general rule can be formulated, it seems probable that alkaloids are most often found in the fruits and sap, or, in trees, in the bark.

Since in most cases alkaloids occur as salts, they are obtained from the actual plant tissues by the action of alkali, which liberates the basic part of the molecule. If this be volatile in steam, the alkaloid is obtained in this way; but if it be not thus volatile it is extracted from the tissues by treating them with acids, which dissolve the alkaloids, forming solutions of their salts, from which the free alkaloid is obtained by the action of alkali. Final purification is carried out by crystallization of the alkaloid or of its salts. When extraction is carried out on a small scale, chloroform is often used to remove alkaloids from the tissues in which they occur.

The majority of alkaloids are solid substances, but one or two are liquids which can be distilled without decomposition. Nearly all of them have powerful actions upon the animal organism; but owing to our ignorance of the relation between chemical constitution and physiological action, not much can be said on the subject. In most cases alkaloids are found to possess lævo-rotation, and it is very seldom that both optically active forms are found in nature.

The alkaloids are usually classed according to the heterocyclic rings from which they are built up. Thus we have the pyridine alkaloids, the quinoline alkaloids, and so forth. For our present purposes this system of classification is very suitable, and we shall therefore deal with the subject under the following heads :—

The Pyridine Group.
The Pyrrolidine Group.
The Quinoline Group.
The Isoquinoline Group.
The Purine Group.

There is another series of substances, the morpholine or phenanthrene group, but the constitutions of its members are at present undetermined, so we shall omit it from our survey.

B.—METHODS EMPLOYED IN THE DETERMINATION OF ALKALOID CONSTITUTIONS

After we have carried out an elementary analysis of an alkaloid we are in a position to state its percentage composition, and by a molecular weight determination we can estimate the number of atoms which its molecule contains. The next step is the determination of the mode in which these atoms are linked together in the alkaloid molecule, and we shall now give a brief account of some common reactions which are employed to solve this problem.

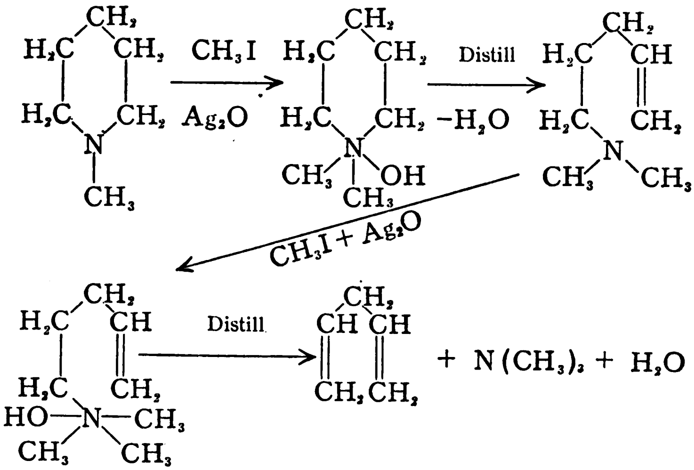
In the first place, since many alkaloids are known to be esters, it is usual to employ some hydrolytic method in order to see whether or not the alkaloid molecule can be decomposed into some simpler grouping. To this end, the alkaloid may be heated with water, acids, or alkalis until it is decomposed into its component acid and base. This method, while breaking up any salt or ester, does not, except in a few cases, result in any further destruction of the structure of the body; so that from the constitutions of the two halves we are able to deduce the constitution of the parent substance.

This method of decomposition, however, may not carry us far enough, and it is usually seconded by a more violent action. For instance, the alkaloid may be fused with alkali, distilled with zinc dust, heated with bromine or phosphoric acid. When reagents such as these are employed, the less durable part of the molecule is usually shattered; and in the reaction-product we find some stable nucleus such as pyridine, quinoline, or isoquinoline, from which the whole alkaloid is derived.

Again, many alkaloids exist in the form of methyl ethers. These can be broken up by boiling with hydriodic acid (Zeisel's method); and by passing the methyl iodide thus formed into silver nitrate solution the number of methyl radicals split off by the hydriodic acid may be estimated, and thus the number of methoxyl groups in the alkaloid can be ascertained.

When the alkaloid contains an oxygen atom, it is of importance to determine whether this occurs in a carbonyl, carboxyl, hydroxyl, or ether group. The first is determined in the usual way by the action of phenylhydrazine or hydroxylamine; the hydroxyl group can usually be detected by acylating it or by the action of dehydrating agents, which split off water and leave an unsaturated substance; while if the alkaloid is an alkyl ether it can often be decomposed by Zeisel's method. If the carboxyl group occurs in the alkaloid under examination, there is not much difficulty in detecting its presence.

All alkaloids contain nitrogen, but it is necessary to discover in what way this nitrogen is linked with the rest of the molecule. Herzig and Meyer have devised a method of determination for methyl-imino groups which is very useful in this branch of research. The hydriodides of bases in which a methyl group is attached to nitrogen, when heated to about 300° C., split off methyl iodide, which can be estimated with silver nitrate just as in the case of the methoxyl group. A somewhat similar decomposition results in the reaction which is usually termed "exhaustive methylation." Here, by the action of methyl iodide and silver oxide, assisted by dry distillation, a cyclic nitrogen compound may be made to lose its nitrogen atom with but little alteration in the rest of the molecule. The formulæ will make the process clear without further explanation.



The final stages in the constitution determination of any alkaloid are usually those in which the oxidation products of the substance are studied. We need not describe the actions of the various agents employed, as they are all well known. The most useful are potassium permanganate, hydrogen peroxide, dilute nitric acid, and chromic acid.

We must now proceed to the examination of the evidence which has been collected with regard to the syntheses and constitutions of some alkaloids.

C.—THE PYRIDINE GROUP

1. *Coniine.*

The first alkaloid with which we shall deal is the substance coniine, which deserves the foremost place on two grounds: it is the simplest member of the alkaloid class, and it is the first alkaloid which has been completely synthesized from the elements. The complete synthesis will be given in the case of this substance, as it is of historical interest, but in the case of the other synthetic compounds we must confine ourselves to the later steps in the process.

By heating together carbon and sulphur we can produce carbon disulphide, which, by the action of chlorine, is converted into carbon tetrachloride. By heat, this can be changed into perchlorethylene, $Cl_2.C:C.Cl_2$, and when this is acted on by ozonized air it yields trichloracetic acid. Reduction with potassium amalgam in aqueous solution changes trichloracetic acid into acetic acid. From this, acetone is obtained by distillation of calcium acetate, and by reducing the acetone so formed we can produce isopropyl alcohol. The action of zinc chloride upon the alcohol gives propylene by dehydration, and by the addition of chlorine we can then form propylene chloride Propylene chloride and iodine chloride together yield trichlorohydrin, from which glycerine is obtained by heating the trichloride to 160° with a large excess of water. Glycerine, by dehydration, gives allyl alcohol; and this, in turn, allyl bromide; from which, by the addition of hydrobromic acid, we obtain trimethylene bromide. Replacing the bromine atoms by cyanogen groups we produce glutaric nitrile, and this, on reduction, gives us pentamethylene diamine. On dry distillation, the hydrochloride loses ammonium chloride and is converted into piperidine,[1] from which pyridine* can be

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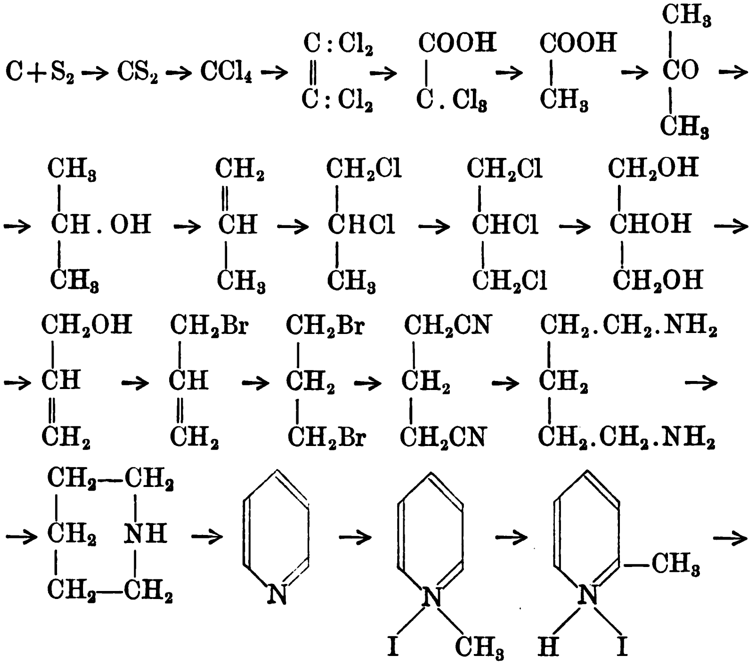
[1] Ladenburg, *Ber.*, 1885, **18**, 3100.

* Pyridine was obtained in a simpler way by Ramsay (*Ber.*, 1877, **10**, 736)

obtained by oxidation. Pyridine combines with methyl iodide, and when the pyridinium methyl iodide thus produced is heated to about 300° C. it suffers intramolecular change and is converted into the hydriodide of α-picoline. Picoline, when heated to a high temperature with paraldehyde, gives α-propenylpyridine, which, on reduction, gives isoconiine.[1] On further heating to 300°, or boiling with solid potash, this is converted into racemic coniine.[2] To separate the right- and left-handed forms, active tartaric acid is used, since this substance can also be obtained synthetically and its two antipodes can be separated from each other by means of the sodium ammonium salt without the interposition of any naturally occurring optically active substance. The formulæ below give the steps which we have mentioned—



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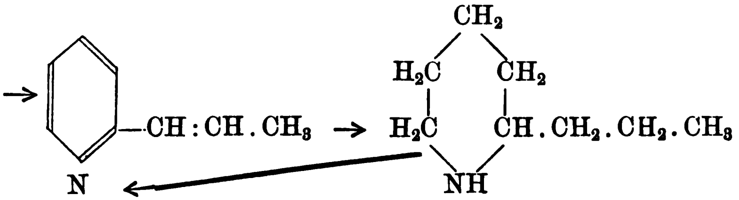
by passing a mixture of acetylene and hydrocyanic acid through a heated tube. Since acetylene is produced by a carbon arc in a hydrogen atmosphere, and hydrocyanic acid is formed by sparking a mixture of acetylene and nitrogen, this forms a simpler synthesis from the elements.

[1] Ladenburg, *Ber.*, 1889, **22**, 1403.

[2] *Ibid.*, 1906, **39**, 2486.



(*d* + *l*)-Coniine → *d*- or *l*-Coniine.

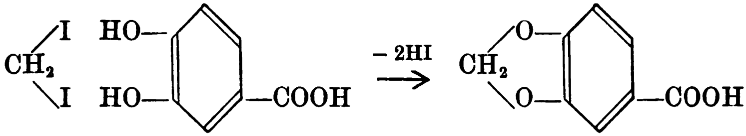
2. *Piperine.*

When the alkaloid piperine is boiled with alcoholic potash it is decomposed into piperidine and piperic acid.[1] The constitution of piperidine is established by the Ladenburg synthesis from pentamethylene diamine, which we mentioned in connection with the synthesis of coniine, as well as by the formation of piperidine from pyridine, by reduction. We have, therefore, only to determine the constitution of piperic acid in order to establish the constitution of piperine.

The decomposition of piperine may be expressed in the following way:—

$$\underset{\text{Piperine.}}{C_{17}H_{19}O_3N} + H_2O = \underset{\text{Piperidine.}}{C_5H_{11}N} + \underset{\text{Piperic acid.}}{C_{12}H_{10}O_4}$$

Fittig, by the action of permanganate, oxidized piperic acid to an aldehyde, piperonal,[2] which has the composition $C_7H_5O_2.CHO$. On further oxidation, piperonal is converted into the corresponding acid, piperonylic acid, $C_7H_5O_2.COOH$. Now, this substance can be synthesized by the action of methylene iodide upon protocatechuic acid in presence of caustic potash, and therefore it must be the methylene ether of that acid.



Protocatechuic acid. Piperonylic acid.

By subtracting the atoms in piperonylic acid from those which make up piperic acid, we find a surplus of four carbon

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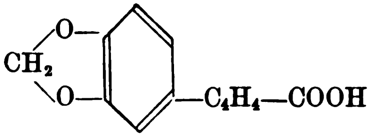
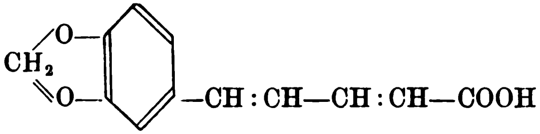
[1] Babo and Keller, *J. pr. Ch.*, 1857, **72**, 53.

[2] Fittig and Remsen, *Annalen*, 1871, **159**, 142.

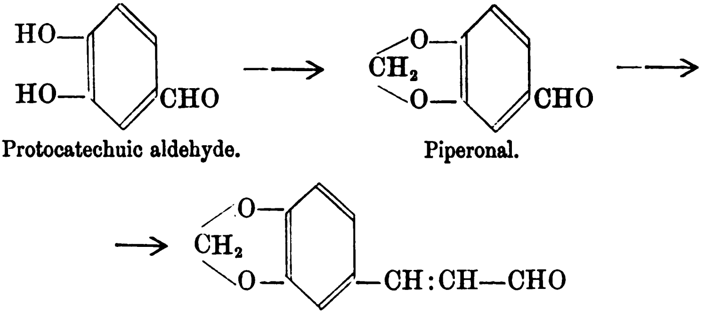
and four hydrogen atoms. This —C_4H_4— must be so attached to the benzene ring of piperonylic acid that on oxidation it disappears entirely and does not give rise to a second carboxyl group in the molecule. The only way in which this condition can be fulfilled is by inserting the group —C_4H_4— between the carboxyl group and the benzene ring of piperonylic acid. Piperic acid would thus be represented by—



When piperic acid is allowed to react with bromine, it takes up four atoms of the halogen, thus showing that it contains two double bonds. These double bonds must be in the side-chain between the nucleus and the carboxyl group, hence we may ascribe the following formula to piperic acid:—



The synthesis of piperic acid may be carried out in the following way. Synthetic protocatechuic aldehyde[1] was converted by methylene iodide and potash into piperonal,[2] which, when warmed with acetaldehyde and very dilute alkali (Claisen's reaction), forms piperonyl-acrolein—



Protocatechuic aldehyde.

Piperonal.

Piperonyl-acrolein.

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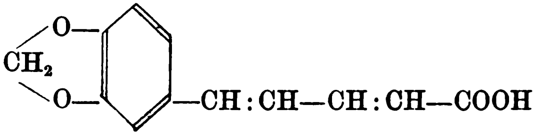
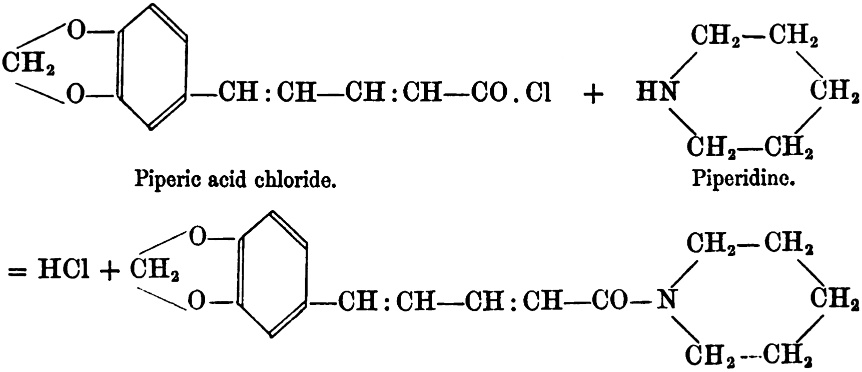
[1] Tiemann and Koppe, *Ber.*, 1881, 14, 2015.

[2] Wegscheider, *Monatsh.*, 1893, 14, 382.

When this acrolein derivative is heated for several hours with sodium acetate and acetic anhydride it condenses with a molecule of acetic acid (Perkin's reaction), and forms piperic acid [1]—



By converting piperic acid into its chloride and heating the latter with piperidine in benzene solution, piperine is formed. [2]



Piperic acid chloride.

Piperidine.

Piperine.

In this way the alkaloid can be synthesized, its constitution being proved by the synthesis and further certified by the decomposition reactions which we have mentioned.

3. *Trigonelline.*

This alkaloid has the composition $C_7H_7NO_2$. It was discovered by Jahns [3] in 1885; and in the following year its constitution was proved by Hantzsch,[4] who obtained it unintentionally in the course of an examination of some derivatives of nicotinic acid.

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[1] Ladenburg and Scholtz, *Ber.*, 1894, 27, 2958.

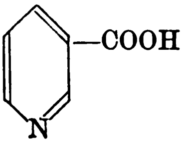
[2] Rügheimer, *Ber.*, 1882, 15, 1390; Fittig and Remsen, *Annalen*, 1871, 159. 142.

[3] Jahns; *Ber.*, 1885, 18, 2518.

[4] Hantzsch, *Ber.*; 1886; 19, 31.

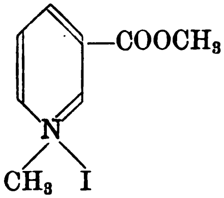
Hantzsch treated nicotinic acid (I.) with caustic potash and methyl iodide, obtaining the methyl ammonium iodide of nicotinic methyl ester (II.). When this is acted on by silver oxide the iodine atom is exchanged for a hydroxyl group, and the compound (III.) is produced, which at once loses water and is converted into a betaine (IV.). This synthetic body was isomeric with trigonelline, and on comparing the two substances Jahns[1] found them to be identical. Trigonelline is therefore the methyl-betaine of nicotinic acid.

(I.)



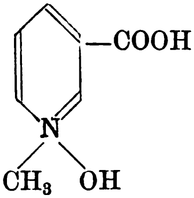
Nicotinic acid.

(II.)



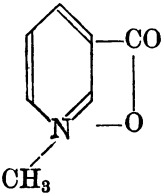
Ester.

(III.)



Hydroxy-acid.

(IV.)



Betaine (Trigonelline).

D.—THE PYRROLIDINE GROUP

1. *Nicotine.*

The alkaloid nicotine stands in a position midway between the pyridine and the pyrrolidine groups; for, as will be shown presently, it contains both a pyridine and a pyrrolidine nucleus. It therefore forms a convenient bridge by which we can pass from the consideration of the one class to the other.

Nicotine is a basic substance having the composition $C_{10}H_{14}N_2$. Its constitution has been established by means of the following reactions:—

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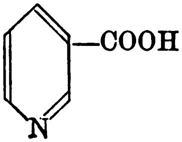
[1] Jahns, *Ber.*, 1887; **20**, 2840.

1. Nitric acid, chromic acid, or potassium permanganate oxidize nicotine[1] to nicotinic acid—

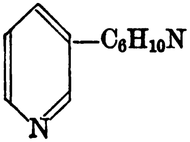


2. By the action of bromine upon nicotine, two derivatives[2] are formed—

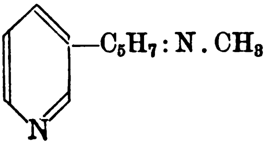
   (*a*) Dibromocotinine, $C_{10}H_{10}Br_2N_2O$.
   (*b*) Dibromoticonine, $C_{10}H_8Br_2N_2O_2$.

3. When dibromocotinine is decomposed by bases it gives methylamine, oxalic acid, and a compound C_7H_7NO. By the same treatment dibromoticonine yields methylamine, malonic and nicotinic acids.
4. Nicotine is a di-tertiary base,[3] giving two isomeric methyl iodide addition products.

From the first reaction, it is obvious that nicotine must be pyridine, with a side-chain in the β-position.



From the third reaction it is clear that of the two nitrogen atoms in nicotine, one carries a methyl group. This one cannot be the pyridine nitrogen. Further, the second nitrogen atom (which *does* carry the methyl radical) cannot belong to a pyridine ring. We may thus go a step further, and represent nicotine by the formula—



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[1] Huber, *Annalen*, 1867, **141**, 271; Weidel, *Annalen*, 1873, **165**, 328; Laiblin, *Ber.*, 1877, **10**, 2136.

[2] Pinner, *Ber.*, 1893, **26**, 292.

[3] Pictet and Genequand, *Ber.*, 1897, **30**, 2117.

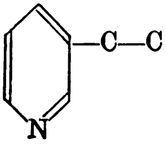
Again, the third reaction shows us that dibromocotinine and dibromoticonine give rise to three carbon chains—

$C—CH_2—C$

Malonic acid chain.

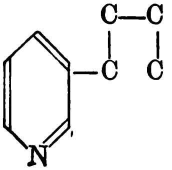
$—C.C—$

Oxalic acid chain.

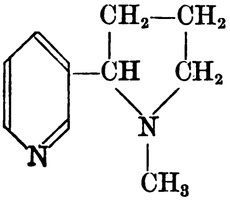


C_7H_7NO chain.

These must be somehow combined in the nicotine molecule, so we may write the nicotine skeleton thus—



To this we must attach the group: $N.CH_3$ in some way. From the fourth reaction we deduce that this nitrogen atom is a tertiary one, so that the two isomeric methyl iodide addition products may be explained by the addition of methyl iodide to a different nitrogen atom in each case. But if the group $:N.CH_3$ is to contain a tertiary nitrogen atom, and also to be attached to the nicotine skeleton given above, the only way is to make the nitrogen atom a member of a ring. The constitution of nicotine would then be—



Nicotine.

The synthetic preparation of nicotine proved to be a much harder task than was anticipated. The first steps were taken by Pictet and Crépieux,[1] who, by heating β-amido-pyridine (I.) with mucic acid, were able to produce (II.) N-β-pyridyl-pyrrol. Like many other N-alkyl derivatives of pyrrol, this substance when passed through a heated tube undergoes a molecular

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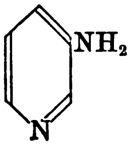
[1] **Pictet and Crépieux, *Ber.*, 1895, 28, 1904.**

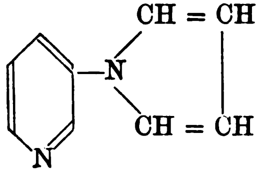
rearrangement, in the course of which the pyridine group is transferred to the carbon atom next the nitrogen in the pyrrol ring. The compound thus formed is αβ-pyridyl-pyrrol (III.).

(I.)



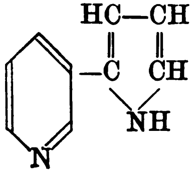
β-amido-pyridine.

(II.)



N-β-pyridyl-pyrrol.

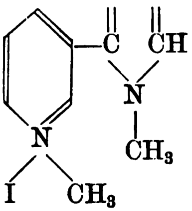
(III.)



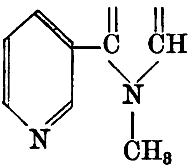
β-pyridyl-α-pyrrol.

From this substance Pictet[1] continued the synthesis in the following way. The αβ-pyridyl-pyrrol forms a potassium salt, the imino-hydrogen of the pyrrol group being replaced in the usual way by the metallic atom; and from this salt, by the action of methyl iodide, we obtain the methyl derivative of the iodomethylate (IV.). On distillation with lime, this forms the base nicotyrine (V.).

(IV.)



(V.)



Nicotyrine.

Now, this body cannot be reduced direct to nicotine, for any agent which attacks the pyrrol nucleus will, at the same time, reduce the pyridine ring. The transformation can be carried out in the following way, however. The nicotyrine (V.) is treated with iodine in alkaline solution, by which means a mono-iodine derivative is produced; it in turn is acted on by tin and hydrochloric acid, whereby it is partially reduced, forming dihydro-nicotyrine (VI.). This substance reacts with bromine to form a perbromide, $C_5H_4N \,.\, C_5H_8N \,.\, Br_4$, which, by reduction with tin and hydrochloric acid, yields inactive nicotine (VII.). This racemic base can, like coniine, be resolved

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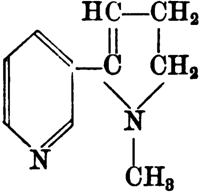
[1] Pictet, *C. R.*, 1903, 137, 860.

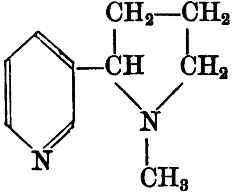
into its antipodes by means of tartaric acid; so that in this way the synthesis of lævo-nicotine, corresponding to the natural alkaloid, can be accomplished.

(VI.)



Dihydronicotyrine.

(VII.)



Nicotine.

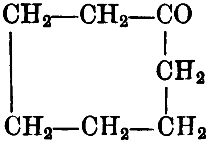
2. *Tropidine.*

Hitherto in this chapter we have confined our attention to substances which contain a single ring of carbon and nitrogen atoms; but with the tropine series we enter a new class in which we shall have to deal with bridged rings analogous to those of the dicyclic terpenes. The first member of the group we are about to examine is tropidine.

Willstätter has succeeded in synthesizing this body in two ways,[1] one of which we may describe. The complete synthesis is made up of two distinct stages, in the first of which cycloheptene is converted into cycloheptatriene; the second stage deals with the formation of the nitrogen bridge across the seven-membered carbon ring.

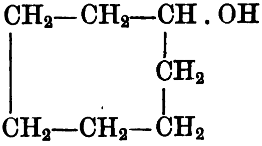
Suberone, the starting material, is obtainable by the distillation of the calcium salt of suberic acid. It can be converted, by reduction, into suberyl alcohol, and hence into suberyl iodide, which, by the action of potash, may be made to lose hydriodic acid and yield cycloheptene.

(I.)



Suberone.

(II.)



Suberyl alcohol.

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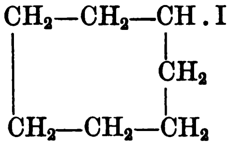
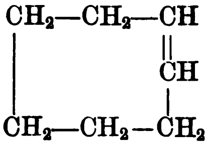
[1] Willstätter, *Annalen*, 1901, **317**, 268; 1903, **326**, 1.

(III.)



Suberyl iodide.

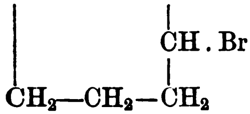
(IV.)



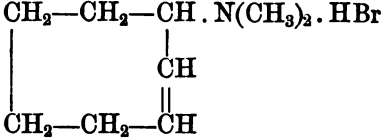
Cycloheptene.

Bromine is now allowed to act upon this, forming the dibromide (V.); from which, by the action of two molecules of dimethylamine, hydrobromic acid is removed, a dimethylamine group being attached to the ring at the same time. The substance (VI.) is thus formed.

(V.)

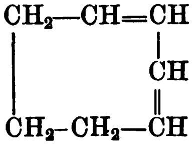


(VI.)



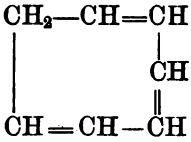
This is subjected to the action of methyl iodide, and the addition compound thus formed is converted into a hydroxide of the ammonium base. On distillation, this body splits off water and trimethylamine, breaking down into cycloheptadiene (VII.). By a repetition of the same process, a third double bond is inserted in the ring; or the same result may be attained by adding two atoms of bromine to (VII.) and splitting off two molecules of hydrobromic acid by means of quinoline. In any case the resulting compound has the constitution of (VIII.).

(VII.)



Cycloheptadiene.

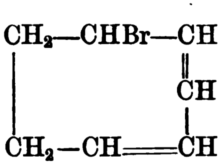
(VIII.)



Cycloheptatriene.

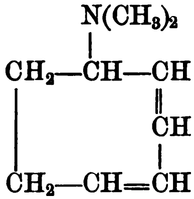
Having thus obtained cycloheptatriene, we must turn to the second stage in the synthesis and examine the means by which the ring is bridged. By the action of one molecule of hydrobromic acid upon the compound (VIII.) we obtain the monohydrobromide (IX.), which reacts with dimethylamine at ordinary temperatures to give dimethylamino-cycloheptadiene, which is identical with α-methyl-tropidine (X.).

(IX.)



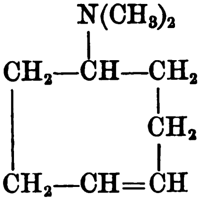
Monohydrobromide of Cycloheptatriene.

(X.)



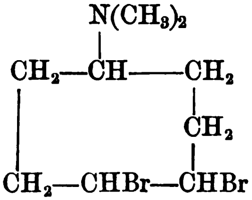
α-Methyl-tropidine.

When acted on by sodium in alcoholic solution, this methyl-tropidine takes up two hydrogen atoms, and is converted into α-methyl-tropane (XI.). The action of bromine in acid solution gives a dibromide (XII.), which, on heating, undergoes intramolecular change into bromotropane-methylammonium bromide (XIII.).



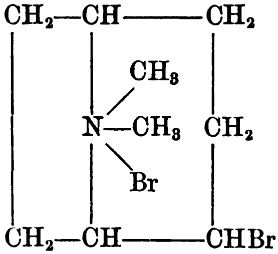
(XI.)

α-Methyl-tropane.



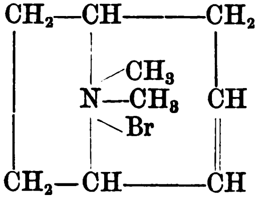
(XII.)

Dibromide.

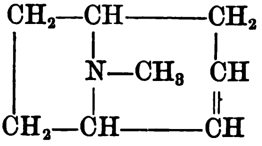


(XIII.)

By the action of caustic potash upon this last substance, hydrobromic acid is split off and the methyl bromide addition product of tropidine (XIV.) remains, which is converted into the chloride and then dry distilled. Tropidine (XV.) is thus produced.

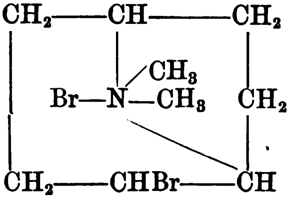


(XIV.)



Tropidine.
(XV.)

This synthesis leaves very little doubt as to the constitution of tropidine. At first sight it might be supposed that if the intramolecular change which converts (XII.) into (XIII.) were to involve the other bromine atom instead of the one chosen above, a different product would be obtained—



Examination will show, however, that this is identical with (XIII.).

3. *Tropine, ψ-Tropine,* and Tropinone.*

We must now consider the question of the synthesis of tropine from tropidine. This cannot be directly accomplished, but is attained through an intermediate product, ψ-tropine, which is stereo-isomeric with tropine. The method is as follows.[1] Tropidine is heated with hydrobromic acid in acetic acid solution, by which means α-bromotropidine hydrobromide (I.) is obtained. When the solution of this substance is treated with ammonia or caustic alkali, bromotropane (II.) is

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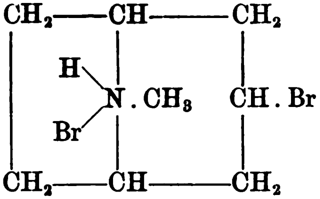
* The Greek ψ is used instead of the word "pseudo." Thus ψ-tropine represents pseudo-tropine.

[1] Willstätter, *Ber.*, 1901, **34**, 3163; *Annalen*, 1903, **326**, 23; cf. Einhorn, *Ber.*, 1891, **23**, 2889.

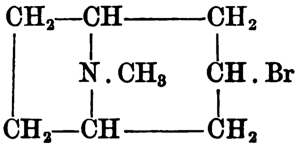
precipitated. On heating this with dilute sulphuric acid above 200° C., the bromine atom is replaced by a hydroxyl group and ψ-tropine (III.) results.

(I.)



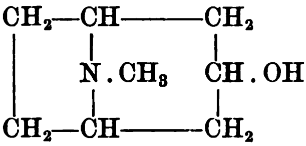
Bromotropidinehydrobromide.

(II.)



Bromotropane.

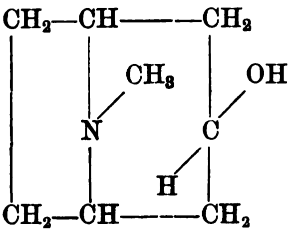
(III.)



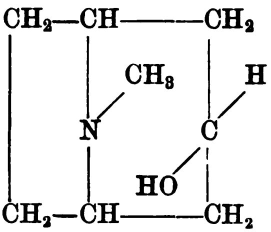
ψ-Tropine.

The isomerism of tropine and ψ-tropine may be explained very simply. If the space formula of a compound having the constitution of tropine be built up, it will be found that there are two possibilities: the hydroxyl and the methyl groups may lie on the same side of the ring as in (A), or on opposite sides as in (B)—

(A)



(B)



Now, of the two, tropine is the labile isomer, so that while we can convert it at will into ψ-tropine, the reverse change is not possible direct. Willstätter and Iglauer,[1] however, have been able to obtain tropine from ψ-tropine by an indirect method. They oxidize ψ-tropine to tropinone—

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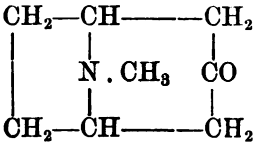
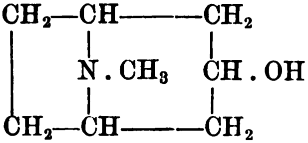
[1] Willstätter and Iglauer, *Ber.*, 1900, 33, 1170.



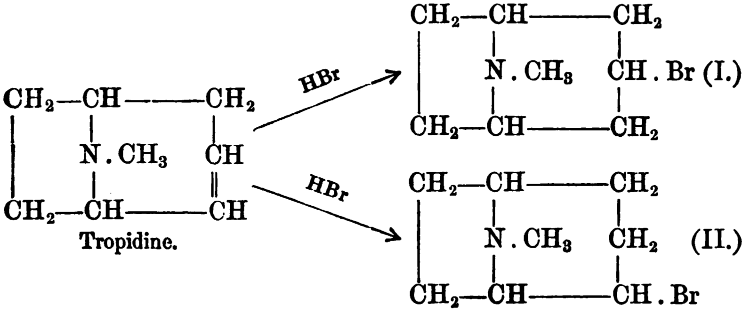
Tropinone.

and from this ketone they obtain tropine itself by the action of zinc dust and concentrated hydriodic acid—



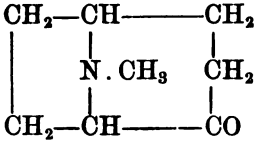
Tropine.

It will be noticed that in the foregoing paragraphs we neglected to take into account a possible alternative formula for bromo-tropane, which, if correct, would invalidate our conclusions with regard to the constitutions of tropine and tropinone. The formula of tropidine is given below, and it will be seen that hydrobromic acid might be added on to it in either of two ways—



Tropidine.

Now, the tropinone derived from formula (II.) would have the following constitution—

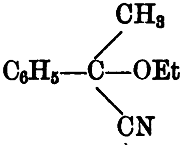


which differs from the tropinone we have already dealt with (derived from (I.)) in having only *one* methylene group next the carbonyl, while the other tropinone has *two* methylene groups, one on each side of its carbonyl radical. But from an examination of the properties[1] of tropinone obtained from bromo-tropane, as already described, it is found that it must have *two* methylene groups adjacent to its carbonyl radical. For example, it forms a *di*-isonitroso-compound with nitrous acid; benzaldehyde condenses with it to form a *di*-benzal compound; while with oxalic ester it gives tropinone-*di*-oxalic ester. The presence of the group $—CH_2—CO—CH_2—$ in tropinone is thus established, which at once disproves the possibility that tropinone is derived from a bromo-tropane of formula (II.).

4. *Tropic Acid.*

By the synthesis of tropine we have approached that of another alkaloid, atropine. This substance, when boiled with baryta water, breaks down into tropine and tropic acid. We have thus established the constitution of half the atropine molecule; and in the present section we shall deal with the constitution of the other half.

Tropic acid has been synthesized by Ladenburg and Rügheimer.[2] Acetophenone is treated with pentachloride of phosphorus, whereby the oxygen atom is replaced by two chlorine ones, and acetophenone chloride is formed. This is allowed to react with potassium cyanide in alcoholic solution to form the nitrile of atrolactinic ethyl ether—



The nitrile is then hydrolyzed, forming the acid. When this body is boiled with concentrated hydrochloric acid it loses alcohol, and is converted into atropic acid—

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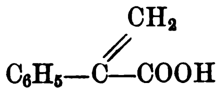
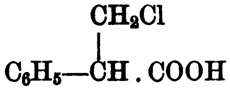
[1] Willstätter, *Ber.*, 1897, **30**, 2679.

[2] Ladenburg and Rügheimer, *Ber.*, 1880, **13**, 376, 2041.



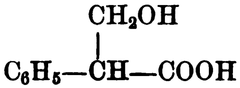
$$\begin{array}{l} \qquad\quad CH_2 \\ \qquad\quad /\!/ \\ C_6H_5\text{—}C\text{—}COOH \end{array}$$

Hydrochloric acid then attaches itself to the double bond, yielding β-hydrochloratropic acid—



$$\begin{array}{l} \qquad\quad CH_2Cl \\ \qquad\quad | \\ C_6H_5\text{—}CH\,.\,COOH \end{array}$$

This substance, when boiled with potassium carbonate, exchanges a chlorine atom for a hydroxyl group, and is converted into tropic acid—

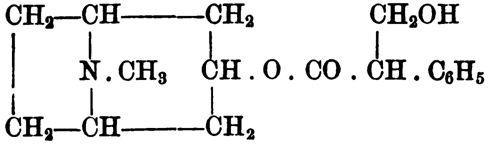


$$\begin{array}{l} \qquad\quad CH_2OH \\ \qquad\quad | \\ C_6H_5\text{—}CH\text{—}COOH \end{array}$$

Tropic acid.

5. *Atropine.*

The constitutions of the two halves of the atropine molecule have now been established, and the atropine synthesis can be carried out by treating a mixture of tropine and tropic acid with hydrochloric acid gas in the usual way.[1] Atropine, therefore, is the tropine ester of tropic acid, and it must have the constitution shown by the following formula:—



$$\begin{array}{lllll} CH_2\text{—} & CH\text{———} & CH_2 & & CH_2OH \\ | & | & | & & | \\ | & N\,.\,CH_3 & CH\,.\,O\,.\,CO\,. & & CH\,.\,C_6H_5 \\ | & | & | & & \\ CH_2\text{—} & CH\text{———} & CH_2 & & \end{array}$$

Atropine.

The synthesis of atropine from the elements may be accomplished in the following steps. Glycerine is obtained by the reactions already described in the section on coniine, and from it glutaric acid is produced. This body, by the electrolysis of the sodium salt of its mono-ester,[2] gives suberic acid, which is then converted into tropine by the method we have described under that head. With regard to tropic acid, we

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[1] Ladenburg, *Ber.*, 1879, **12**, 941; 1880, **13**, 104.

[2] Crum Brown and J. Walker, *Annalen*, 1891, **261**, 119.

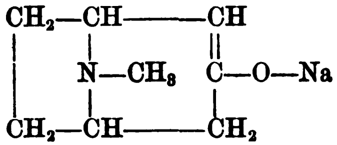
may start from acetylene, which can be produced by a carbon arc in a hydrogen atmosphere. On the one hand, we can convert the acetylene thus obtained into ethylene, ethyl-sulphuric acid, alcohol, acetic acid, and, finally, acetyl chloride; while, on the other hand, we can polymerize it direct to benzene by passing it through a red-hot tube. From the acetyl chloride and benzene we can produce acetophenone by the Friedel-Crafts' reaction, after which we proceed as already described under tropic acid.

6. *Ecgonine.*

Tropinone forms salts with alkalis, and these, by treatment with carbonic acid in the usual way, can be converted into the alkali salts of carboxylic acids.[1] In the case of the sodium salt, it is suspended in ether, and carbon dioxide passed through the liquid at ordinary temperatures; the resulting product is the sodium salt of tropinone carboxylic acid, and when this is reduced with sodium amalgam in a weakly acid solution it yields a mixture of two isomeric bodies having the same composition as ecgonine, $C_8H_{14}NO . COOH$.

The two isomers, however, differ in character. The one has all the properties of ecgonine, except the power of rotating the plane of polarization; it is a true carboxylic acid, forming salts and esters, it also possesses a free hydroxyl group, and can be converted into esters by acids. The second isomer, on the other hand, behaves quite differently. It possesses no free hydroxyl group, nor can it be esterified by the ordinary methods. An explanation of the formation of two such substances is to be found by considering the character of the sodium derivative of tropinone.

It is well known that the sodium salts of ketonic bodies usually exist in the enolic form, so that we should incline to write the formula of the tropinone sodium salt thus—



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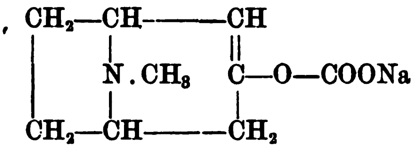
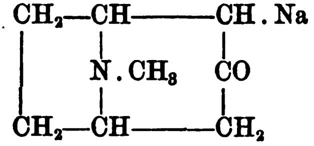
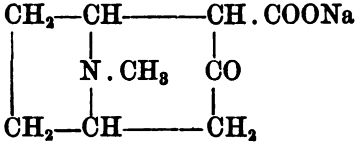
[1] Willstätter and Bode, *Ber.*, 1900, **33**, 411.

The action of carbon dioxide upon this would produce a sodium salt whose constitution could be written—

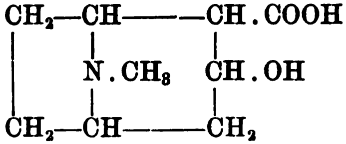


This body forms by far the greater proportion of the reaction mixture, but since the sodium salt of tropinone exists in the keto- as well as in the enol-form, part of the end-product will have the constitution shown below—





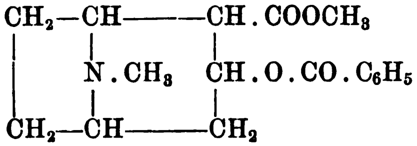
This last substance, on reduction, would give us the alcohol—



which proves to be racemic ecgonine.

7. *Cocaine.*

From ecgonine, cocaine can be prepared by benzoylating the alcohol radical, and then esterifying the carboxyl group with methyl alcohol.



Cocaine.

E.—The Quinoline Group

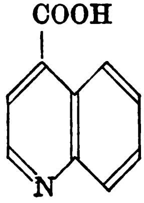
1. *The Constitution of Cinchonine.*

The alkaloid cinchonine has the composition $C_{19}H_{22}ON_2$. The oxygen atom forms part of a hydroxyl group, as is shown by acetylation; and the two nitrogen atoms are tertiary ones.

I. When cinchonine is oxidized by means of chromic acid and sulphuric acid[1] it breaks down into two substances, cinchonic acid and meroquinene, in accordance with the following equation:—

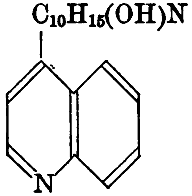
$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} + 3O = \underset{\text{Cinchonic acid.}}{C_{10}H_7O_2N} + \underset{\text{Meroquinene.}}{C_9H_{15}O_2N}$$

Cinchonic acid has been shown to be a quinoline carboxylic acid of the formula—



so that cinchonine itself must be a γ-quinoline derivative.

For the sake of convenience, we will refer to the two halves of the cinchonine molecule as the "quinoline half" and the "second half." It is obvious that the hydroxyl group which is known to exist in the cinchonine molecule must be situated in the "second half"; for if it were in the "quinoline half" it would appear in cinchonic acid. We may therefore formulate cinchonine in the following way:—



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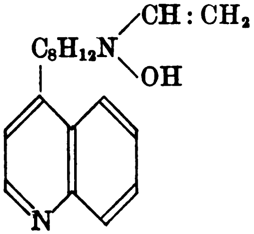
[1] Königs, *Ber.*, 1894, **27**, 1501.

II. Now, when cinchonine is oxidized with potassium permanganate[1] instead of chromic acid, the decomposition products are quite different from those obtained before. The reaction takes the course shown below—

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} + 4O = \underset{\text{Cinchotenine.}}{C_{18}H_{20}O_3N_2} + H.COOH$$

This new oxidation product, cinchotenine, contains the quinoline nucleus (as is shown by its behaviour on further oxidation). It is therefore produced by a decomposition in the "second half" of the molecule. It contains a hydroxyl and a carboxyl group. Cinchonine can take up one molecule of a halogen acid, but cinchotenine has lost this property. Hence the group CH_2 of cinchonine has been split off, leaving the carboxyl group in cinchotenine. We may thus carry our deductions a step further, and write the formula of cinchonine in the following way:—



III. We must now turn to a different reagent. When cinchonine is treated with phosphorus pentachloride and then with alcoholic potash it loses a molecule of water and is converted into cinchene[2]—

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} - H_2O = \underset{\text{Cinchene.}}{C_{19}H_{20}N_2}$$

When heated with twenty-five per cent. phosphoric acid,[3] cinchene takes up two molecules of water and is decomposed into lepidine and meroquinene—

$$\underset{\text{Cinchene.}}{C_{19}H_{20}N_2} + 2H_2O = \underset{\text{Lepidine.}}{C_{10}H_9N} + \underset{\text{Meroquinene.}}{C_9H_{15}O_2N}$$

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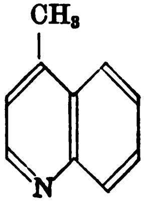
[1] Königs, *Annalen*, 1879, **197**, 374.

[2] Comstock and Königs, *Ber.*, 1884, **17**, 1985.

[3] Königs, *Ber.*, 1890, **23**, 2677; 1894, **27**, 900.

Lepidine is known to have the formula—



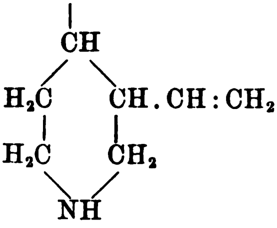
IV. Meroquinene is the next substance whose decompositions must be examined. When it is oxidized with an ice-cold mixture of sulphuric acid and potassium permanganate it gives cincholoiponic acid [1]—

$$\underset{\text{Meroquinene.}}{C_9H_{15}O_2N} + 4O = \underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + H.COOH$$

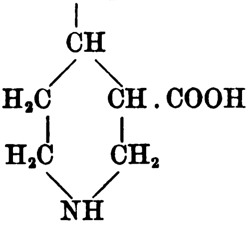
This, by the action of aqueous permanganate, is converted into loiponic acid [2]—

$$\underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + O_2 = \underset{\text{Loiponic acid.}}{C_7H_{11}O_4N} + H.COOH$$

Loiponic acid is an unstable form of hexahydrocinchomeronic acid, for on heating with caustic potash it is converted into that substance by isomeric change. By assuming the *structure* of loiponic acid to be the same as that of hexahydrocinchomeronic acid (the *configurations* of the two being different), we can work back step by step to meroquinene, whose formula must therefore be that shown in the series below—



Meroquinene.



Cincholoiponic acid.

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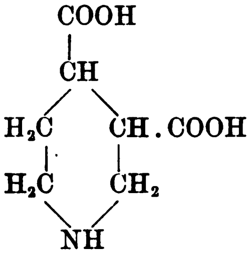
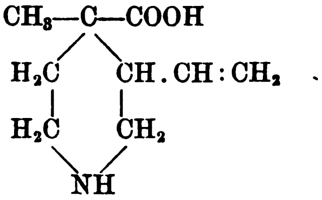
[1] Königs, *Ber.*, 1895, **28**, 1986, 3150.
[2] Skraup, *Monatsh.*, 1896, **17**, 377; Königs, *Ber.*, 1897, **30**, 1329.



Loiponic acid.

The position of the —CH_2.COOH group of meroquinene is uncertain.

The formula above is due to Königs, but the alternative put forward by Miller and Rohde[1]—



has probably as much to recommend it.

Of the ten carbon atoms of the "second half" we have thus established the mode of linkage of eight: five in a piperidine ring, two in a vinyl group, and one in a methyl or methylene group. The ninth carbon atom of the "second half" must be utilized in joining the two halves together. Thus we have only to determine the position of the tenth carbon atom of the "second half."

V. It will be remembered that the two nitrogen atoms of cinchonine are tertiary; but it has been shown that the nitrogen atom of meroquinene is a secondary one. This has been established by the usual reactions of the imido-group, and agrees with the constitution which we have ascribed to meroquinene in the previous paragraph. This peculiar behaviour of the nitrogen atom can best be explained by the assumption that in the "second half" of cinchonine we have a nucleus of either of the types (I.) or (II.)—

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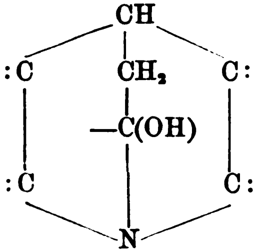
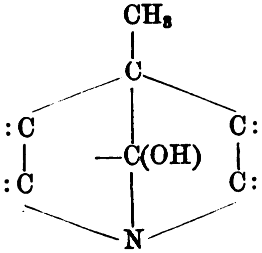
[1] Miller and Rohde, *Ber.*, 1895, **28**, 1060.

Königs' view.



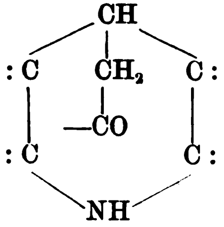
(I.)

v. Miller's view.

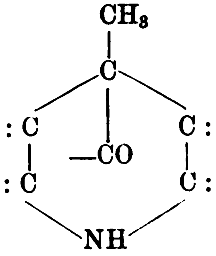


(II.)

When such a nucleus as (I.) is heated with dilute acids it will undergo intramolecular change into an imido-ketone in the way expressed by the formula (I*a*.) below. If the type (II.) be chosen instead of (I.) the analogous substance (II*a*.) would be produced in the same way.



(I*a*.)



(II*a*.)

Such a change actually occurs when cinchonine is heated with dilute acetic acid; an imido-ketone results, which, on account of its poisonous properties, is named "*cinchotoxine*."[1] Thus it is apparent that across the piperidine ring there is a bridge of one carbon atom, and this accounts for the missing tenth carbon atom in the "second half" of cinchonine.

From the foregoing evidence, cinchonine would be represented by either of the two formulæ below—

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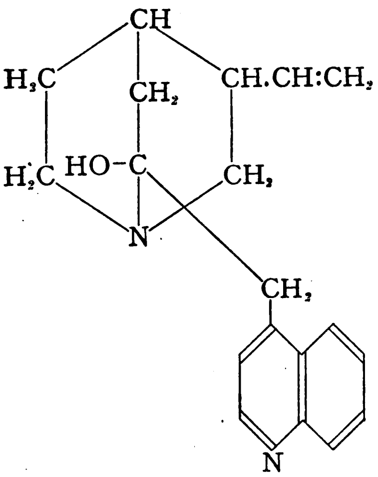
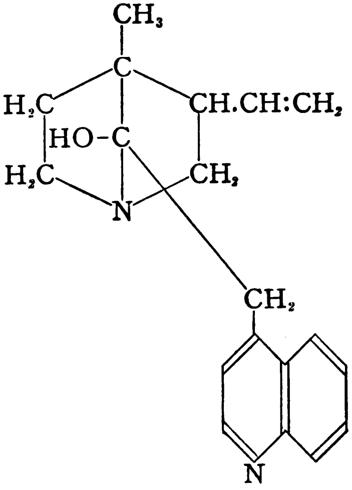
[1] Miller and Rohde, *Ber.*, 1894, **27**, 1187, 1279; 1895, **28**, 1056.





2. *The Constitution of Quinine.*

Knowing the constitution of cinchonine, we can easily prove that of quinine.

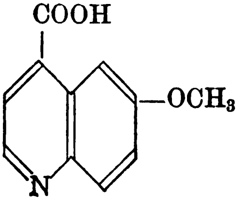
I. Quinine differs from cinchonine by one carbon, one oxygen, and two hydrogen atoms—

$$C_{20}H_{24}O_2N_2 - C_{19}H_{22}ON_2 = CH_2O$$

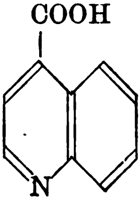
Quinine. Cinchonine.

This points to quinine being a methoxy-derivative of cinchonine, if we bear in mind the similarity in character between the two substances.

II. When oxidized with sulphuric and chromic acids,[1] quinine gives the acid (A); whereas it will be remembered that cinchonine gave cinchonic acid (B). Meroquiuene is one of the oxidation products in both cases.



(A)



(B)

III. This proves the presence and position of the methoxyl

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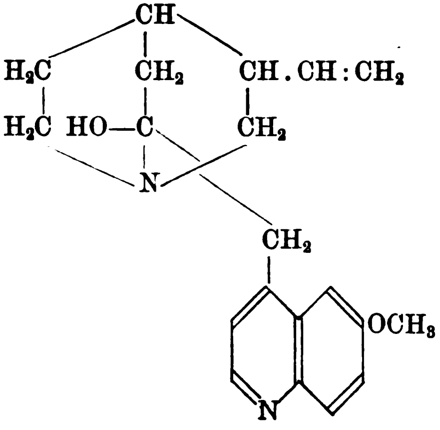
[1] Skraup, *Monatsh.*, 1881, **2**, 591; 1883, **4**, 695; 1891, **12**, 1106; 1895, **16**, 2684.

group in quinine; and since in its reactions quinine forms an exceedingly close analogue to cinchonine, we are justified in concluding that it is a methoxy-cinchonine of the following constitution (accepting Königs' view of the structure of cinchonine):—



Quinine.

3. *Cinchonidine and Conchinine.*

Cinchonine has three asymmetric carbon atoms in its molecule, and therefore it may occur in several stereoisomeric forms. Cinchonidine is supposed to be one of these; while conchinine is a stereoisomer of quinine.

F.—THE ISOQUINOLINE GROUP.

1. *The Constitution of Papaverine.*

The constitution of papaverine is a much simpler question than that with which we have just dealt in the case of cinchonine. There are six steps in the argument.[1]

I. In the first place, the formula of papaverine is $C_{20}H_{21}O_4N$; it contains four methoxyl groups, which can be hydrolyzed, yielding the substance papaveroline, $C_{16}H_9N(OH)_4$. This accounts for all the oxygen atoms.

II. On fusion with alkali, papaverine breaks down into two nuclei, one of which contains nitrogen, while the other nucleus is nitrogen-free. The first was proved to be a dimethoxyquinoline of the constitution—

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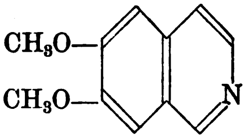
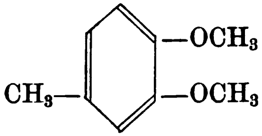
[1] Goldschmiedt, *Monatsh.*, 1883, **4**, 704; 1885, **6**, 372, 667, 954; 1886, **7**, 485; 1667, **8**, 510; 1888, **9**, 42, 327, 349, 679, 762, 778; 1889, **10**, 673, 692.



while the second decomposition product was dimethylhomocatechol—

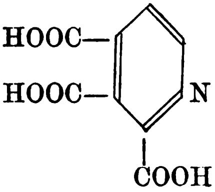


III. The fact that these two groups are *directly* united to one another follows from the composition of the two decomposition products—

$$H_2 + \underset{\text{Papaverine.}}{C_{20}H_{21}O_4N} = \underset{\text{Dimethoxy-quinoline.}}{C_{11}H_{11}O_2N} + \underset{\text{Dimethoxy-homocatechol.}}{C_9H_{12}O_2}$$

IV. We must now examine the question of the manner in which the two nuclei are united. Since papaverine contains four methoxy-groups, and each of the decomposition products contains two, it is obvious that during the decomposition no methoxy-group is destroyed. Now, if the link between the two nuclei had been an oxygen atom, *i.e.* if papaverine had contained the grouping $R—O—CH_2—O—R$, then in the breakdown of the molecule one—$O . CH_2 . O$—group would have been destroyed. We may therefore exclude the idea of joining the two nuclei through an oxygen atom, and must assume that they are directly united, carbon to carbon.

V. Our next problem is to find which carbon atom of the isoquinoline ring is joined to the other nucleus. When we oxidize papaverine with potassium permanganate, we obtain α-carbocinchomeronic acid—



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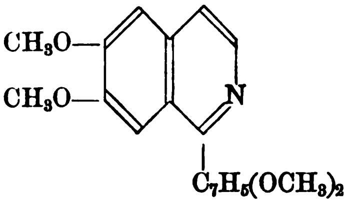
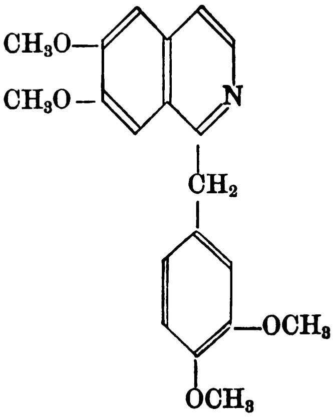
Hence we deduce that the side-chain (second nucleus) was attached at the point now occupied by the carboxyl group, which is marked with an asterisk. Papaverine is therefore—



VI. We have now to settle the constitution of the group —$C_7H_5(OCH_3)_2$. This must be the dimethoxy-homocatechol radical, which has the same composition. We have only to decide whether the two nuclei are joined ring to ring or by the intermediation of the side-chain of the dimethoxy-homocatechol. Without going into details, it may be said that all the evidence points to the union being made through the side-chain. The constitution of papaverine is therefore—



Papaverine.

2. *The Synthesis of Papaverine.*

The synthesis of papaverine has recently been carried out by Pictet and Gams.[1] The reactions may be grouped in five stages.

I. The first step in the process is the synthesis of amino-aceto-veratrone. For this purpose veratrol (I.) is treated with

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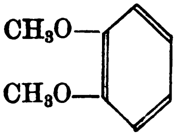
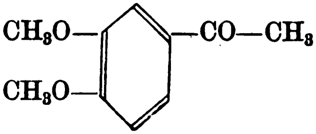
[1] Pictet and Gams, *C.R*, 1909, **149**, 210.

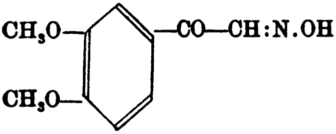
acetyl chloride in presence of aluminium chloride, whereby aceto-veratrone (II.) is formed. When this is treated with sodium ethylate and amyl nitrate, it yields the isonitroso-derivative (III.), which can then be reduced by tin chloride and hydrochloric acid to the hydrochloride of amino-aceto-veratrone (IV.).



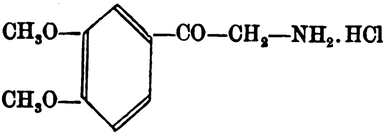
(I.)



(II.)

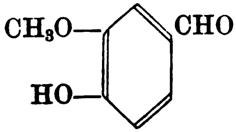


(III.)

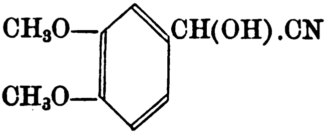


(IV.)

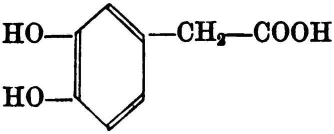
II. We must now turn to the synthesis of homoveratroyl chloride. Vanillin (V.) is methylated and then treated with hydrocyanic acid, giving dimethoxy-mandelic nitrile (VI.). When this is boiled with hydriodic acid three processes take place simultaneously; reduction, hydrolysis and the splitting off of methyl radicals. We thus obtain homoprotocatechuic acid (VII.) and by methylation of the hydroxyl groups followed by the action of phosphorus pentachloride the chloride of homoveratric acid is formed (VIII.).



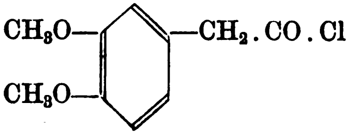
(V.)



(VI.)

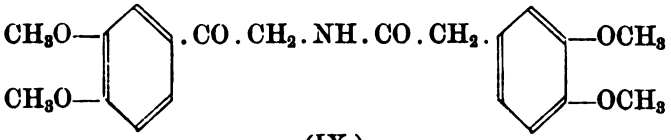


(VII.)



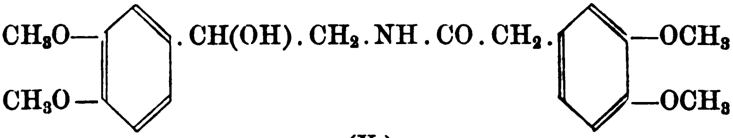
(VIII.)

III. If we now allow the amino-aceto-veratrone hydrochloride obtained in Stage I. to interact with the homoveratric chloride of Stage II. in presence of alkali, we obtain homoveratroyl-amino-aceto-veratrone (IX.).



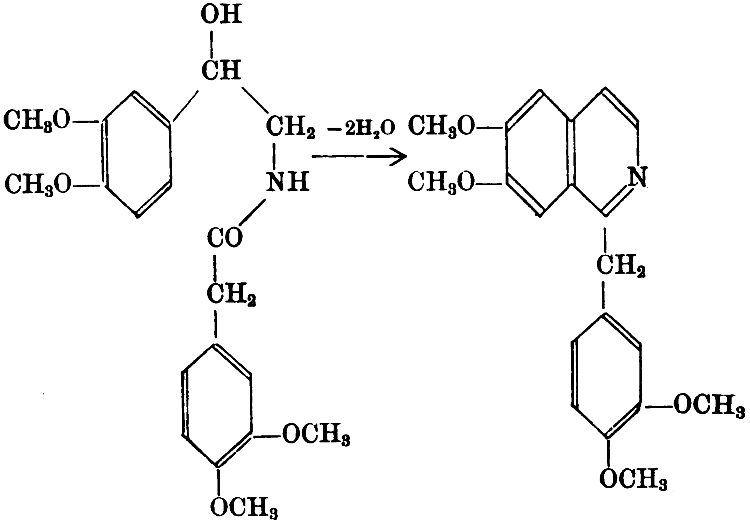
(IX.)

IV. An inspection of the formula (IX.) will show that though the substance contains two carbonyl groups, one of these is a true carbonyl while the other is a radical which originally formed part of a carboxyl group. When the substance is reduced with sodium amalgam in neutral alcoholic solution, the true carbonyl is reduced, while the acidic carbonyl remains unaffected. The product is homoveratroyl-hydroxy-homoveratrylamine (X.).



(X)

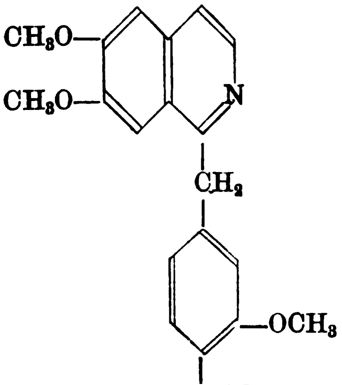
V. When this substance (X.) is treated with phosphorus pentoxide in boiling xylene solution, it loses two molecules of water and is converted into papaverine (XI.).



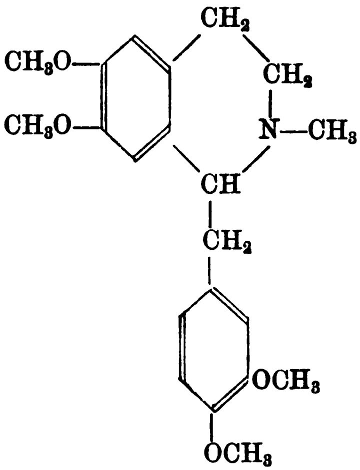
(X.) (XI.)

3. *The Synthesis of Laudanosine.*

In the preceding section we have seen how the synthesis of papaverine may be accomplished, and we are now in a position to consider the question of a closely related alkaloid, laudanosine. This body is very simply produced from papaverine. Pictet and Athanasescu[1] showed that if we form the chloro-methyl derivative of papaverine and then reduce this with tin and hydrochloric acid we obtain methyl-tetrahydro-papaverine. This synthetic substance is of course racemic; and from it the dextro-antipode was obtained in the usual way by making the quinic acid salt of the alkaloid and fractionally crystallizing it. The substance thus obtained was found to be identical with natural laudanosine.



Papaverine.



Laudanosine.

Pictet and Finkelstein[2] have recently carried out the complete synthesis of laudanosine, but as the method is very similar to that which we have already described in the case of papaverine we need not enter into it here.

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[1] Pictet and Athanasescu, *Ber.*, 1900, **33**, 2346.

[2] Pictet and Finkelstein, *Ber.*, 1909, **42**, 1979; *C. R.*, 1909, **148**, 925.

4. *Opianic Acid.*

Though opianic acid itself is not an alkaloid, we must take up its constitution at this point owing to its relation with narcotine, with which we shall deal later.

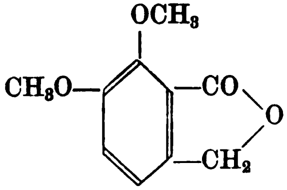
I. When narcotine is hydrolyzed with barium hydrate or sulphuric acid,[1] it decomposes into opianic acid and hydrocotarnine—

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + H_2O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Hydrocotarnine.}}{C_{12}H_{15}O_3N}$$

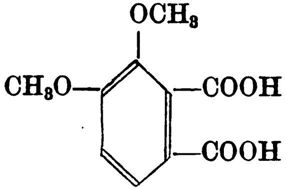
II. Opianic acid is a monobasic acid, and therefore we may write its formula, $C_9H_9O_3 . COOH$.

III. When heated with hydriodic acid, two methyl groups are split off from opianic acid.[2] It therefore contains two methoxy-groups, and may be written thus, $(CH_3O)_2 . C_7H_3O . COOH$.

IV. When heated with potash[3] it gives (by reduction) meconine, and (by oxidation) hemipinic acid—



Meconine.



Hemipinic acid.

This last reaction is parallel to the formation of benzyl alcohol and benzoic acid by the action of potash upon benzaldehyde, so we must conclude that opianic acid contains an aldehydic group; and from the constitution of hemipinic acid it is obvious that this aldehyde radical must be next the carboxyl group of opianic acid.

V. The final proof of the presence of an aldehyde group in opianic acid is furnished by the behaviour of its sodium salt when distilled with soda-lime.[4] Carbon dioxide is split off in the usual way, and the methyl ether of vanillin is left. The formula of opianic acid must therefore be that which is shown below—

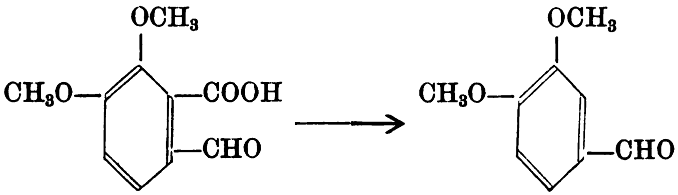
---

[1] Beckett and Wright, *Trans. Chem. Soc.*, 1875, **28**, 583.

[2] Matthiessen and Foster, *Annalen Suppl.*, I. 333; II. 378; V. 333.

[3] *Ibid.*, I. 332; II. 381.

[4] Beckett and Wright, *Trans. Chem. Soc.*, 1875, **28**, 583.



Opianic acid. Methyl ether of vanillin.

5. *The Constitution of Cotarnine.*

The next stage in the proof of the narcotine constitution is reached through the constitution of cotarnine. This substance[1] is obtained along with opianic acid when narcotine is treated with oxidizing agents—

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + O + H_2O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Cotarnine.}}{C_{12}H_{15}O_4N}$$

I. Cotarnine reacts with two molecules of methyl iodide, thus proving that it is a secondary base. The reaction product is called cotarnomethine methyl iodide,[2] and has the composition $C_{11}H_{11}O_4N(CH_3)_3I$.

II. By heating this body with caustic soda, trimethylamine is split off,[3] and cotarnone, $C_{11}H_{10}O_4$, remains. This proves to be an aldehyde, so that its formula can be written $C_{10}H_9O_3 . CHO$.

III. When cotarnone is oxidized with potassium permanganate[4] it gives a lactone, cotarnolactone, $C_{11}H_{10}O_6$, from which, on further oxidation, cotarnic acid, $C_{10}H_8O_7$, is obtained.

IV. By the usual reactions it is found that cotarnic acid[5] is dibasic, contains a methoxyl radical, and has its carboxyl groups in the ortho-position to one another, as is shown by the ease with which it forms an anhydride. When heated with phosphorus and hydriodic acid to about 160° C. it yields gallic acid—

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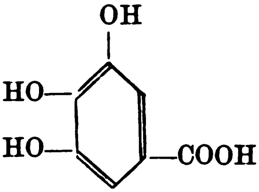
[1] Wöhler, *Annalen*, 1844, **50**, 1.

[2] Roser, *Annalen*, 1888, **249**, 157.

[3] *Ibid.*, 141.

[4] *Ibid.*, 163.

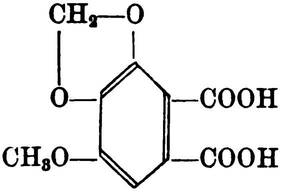
[5] *Ibid.*, 163; 1899, **254**, 341.



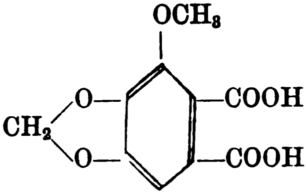
V. Now, gallic acid differs from cotarnic acid by the group $C_3H_2O_2$—

$$\underset{\text{Cotarnic acid.}}{C_{10}H_8O_7} - \underset{\text{Gallic acid.}}{C_7H_6O_5} = \underset{\text{From methoxy group.}}{CH_2} + CO_2 + C$$

Part of this we can account for by the loss of carbon dioxide from a carboxyl group, since cotarnic acid is dibasic, while gallic acid is monobasic. We have thus one carbon atom left unaccounted for. This must be derived from the methylene group of a methylene ether. We are in this way led to formulate cotarnic acid as a methyl-methylene-gallic-carboxylic acid, $C_6H(OCH_3)(CH_2O_2)(COOH)_2$. For such a substance there are only two possible formulæ—

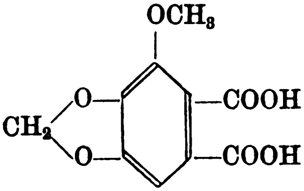


(I.)



(II.)

Without going into details,[1] we may say that the general behaviour of the substance is best represented by (II.). Cotarnic acid therefore has the constitution—



Cotarnic acid.

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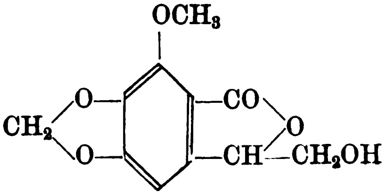
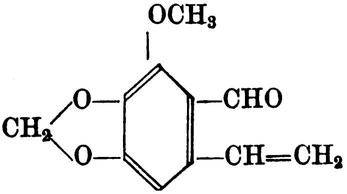
[1] Freund and Becker, *Ber.*, 1903, **36**, 1521.

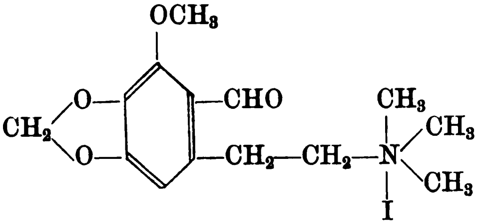
VI. Cotarnolactone must therefore have the formula—



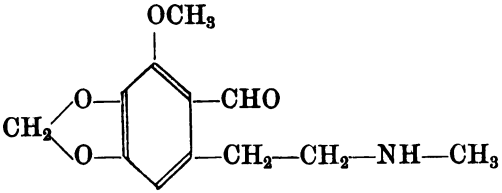
and cotarnone must be—



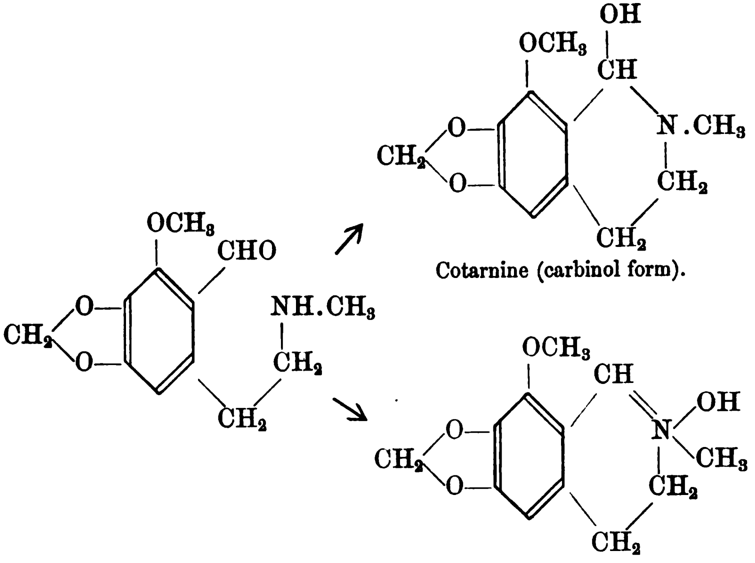
VII. But cotarnone was obtained from cotarnomethine methyl iodide and soda, whence cotarnomethine methyl iodide must have the structure—



VIII. Hence cotarnine should have the following constitution; since cotarnomethine methyl iodide is obtained from it by the action of two molecules of methyl iodide—



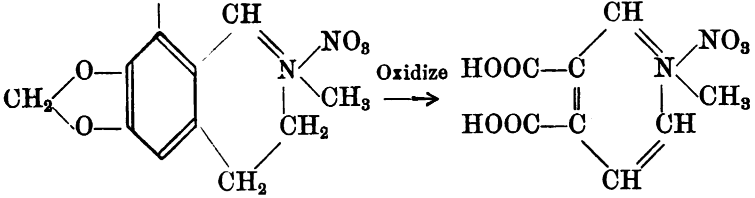
IX. This formula, however, fails to explain the formation of a pyridine derivative, apophyllenic acid, when cotarnine is oxidized with nitric acid;[1] and to account for this we must assume that the free aldehydic group has disappeared in the course of some intramolecular ring-formation, which simultaneously brings into existence a pyridine chain within the molecule of cotarnine. This change we may represent in two ways, as shown in the formulæ below—



Cotarnine (carbinol form).

Cotarnine (ammonium form).

It is generally agreed that the salts of cotarnine are best represented as derivatives of the ammonium form; for instance, the production of apophyllenic acid can be made clear on this assumption—



Cotarnine nitrate.

Apophyllenic acid derivative.

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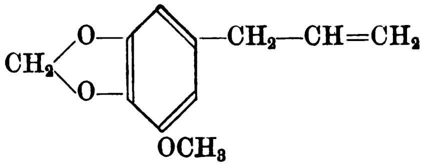
[1] Wöhler, *Annalen*, 1844, **50**, 24.

With regard to the free base, however, the spectroscopic investigations of Dobbie, Lauder and Tinkler[1] have shown that the structure varies with the solvent in which the substance is dissolved. In ether or chloroform the carbinol form is present; but the addition of alcohol to the solution brings into existence the ammonium form; in pure alcoholic solution no less than 25 per cent. of the substance is present as ammonium base.

6. *The Synthesis of Cotarnine.*

In the last section we dealt with the constitution of cotarnine, and we must now take up the synthesis of this substance. Synthetic cotarnine has been prepared by Salway;[2] but as the constitution of one of his intermediate products is left doubtful in the synthesis, it is not possible to establish the cotarnine structure from his work. In the light of the facts given in the last section, however, we can deduce the formulæ of the intermediate compounds.

I. The first stage in the process is the synthesis of β-3-methoxy-4:5-methylenedioxy-phenyl-propionic acid. Salway took as his starting-point the substance myristicin—



which he obtained from oil of nutmeg. This was heated with alcoholic potash to convert it into iso-myristicin; and the latter was then oxidized to myristicin aldehyde by means of potassium permanganate—

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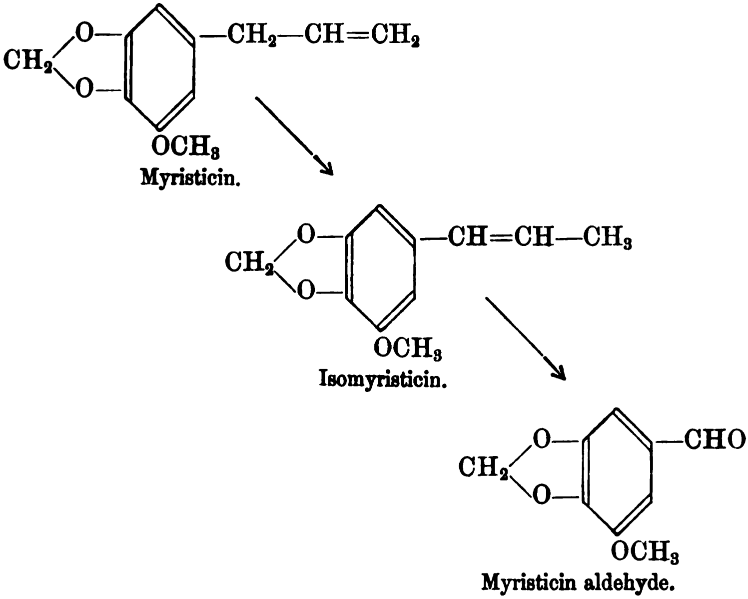
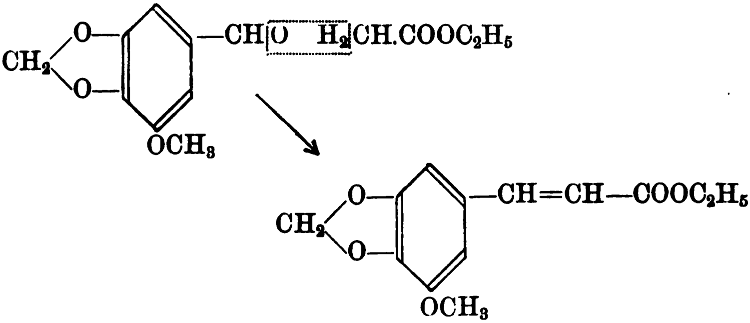
[1] Dobbie, Lauder and Tinkler, *Trans. Chem. Soc.*, 1903, **83**, 598.

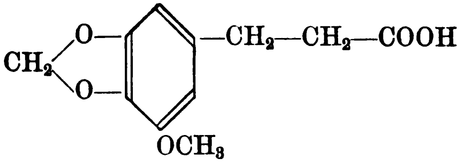
[2] Salway, *Trans. Chem. Soc.*, 1910, **97**, 1208.



The aldehyde was then condensed with ethyl acetate by means of sodium, and the resulting ester was hydrolyzed with alcoholic potash—

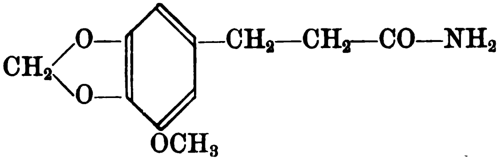


The substituted cinnamic acid thus produced was reduced with sodium amalgam, and in this way the required β-3-methoxy-4 : 5-methylenedioxy-phenyl-propionic acid was obtained.

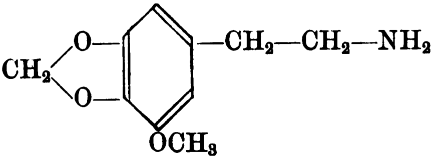


(I.)

II. The second stage ends in the production of phenylacetyl-β-3-methoxy-4 : 5-methylenedioxy-phenylethylamine. The acid (I.) was converted into the amide (II.) in the usual way, and this in turn was changed into the corresponding amine (III.) by Hofmann's reaction—

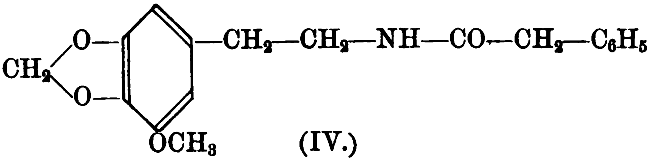


(II.)



(III.)

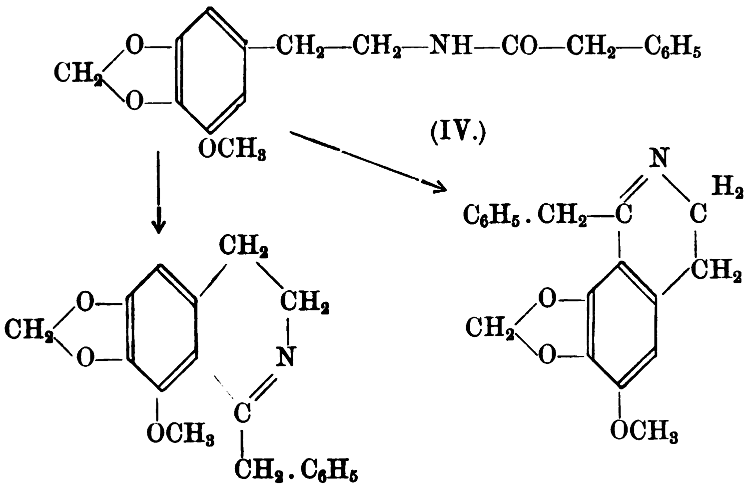
The phenylacetyl derivative (IV.) was then prepared by the ordinary method—



(IV.)

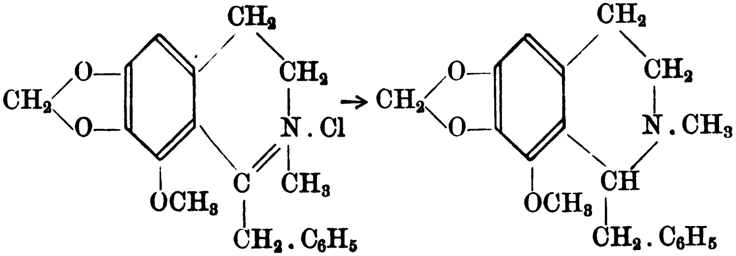
Phenylacetyl-β-3-methoxy-4 : 5-methylenedioxy-phenyl-ethylamine.

III. This phenylacetyl derivative was condensed by heating it with phosphoric oxide in presence of xylene; and in this way a mixture of two isomeric dihydro-isoquinoline derivatives was produced (V. and VI.).

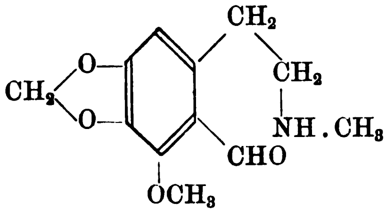

(IV.)

(V.) (VI.)

IV. The substance (V.) is 8-methoxy-6:7-methylenedioxy-1-benzyl-3:4-dihydro-isoquinoline. To convert it into cotarnine, it is necessary in the first instance to form its methochloride (VII.), which is then reduced by means of tin and hydrochloric acid to 1-benzyl-hydrocotarnine (VIII.).


(VII.) (VIII.)

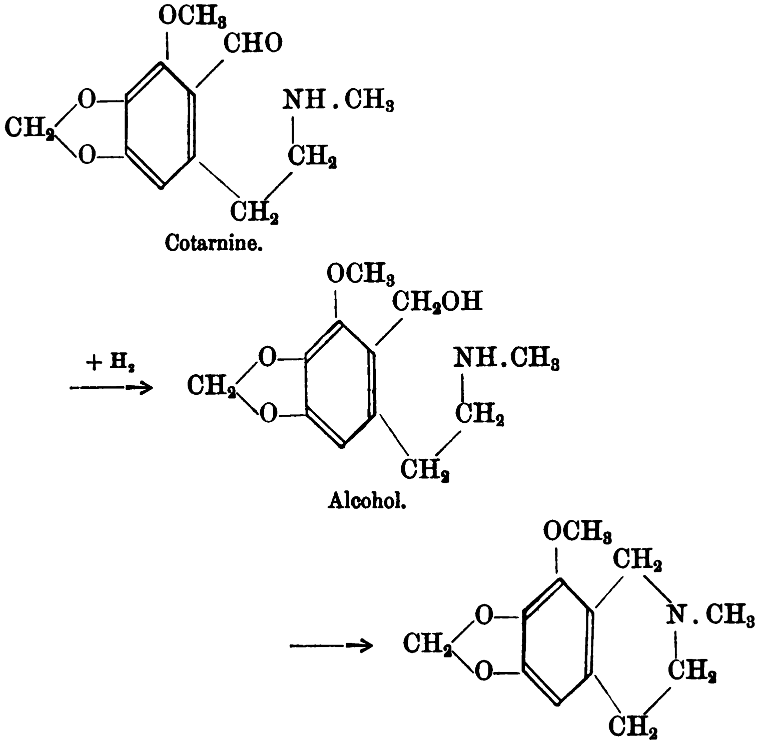
Finally, oxidation with manganese dioxide in presence of sulphuric acid converted the benzyl derivative into cotarnine.



It will be noticed that the substance (VI.), if treated in the same way as (V.), would give rise to an iso-cotarnine; and if the cotarnine constitution were unknown, this synthesis would throw no light upon the relative positions of the methoxy-group and the pyridine ring.

7. *The Synthesis of Hydrocotarnine.*

On reduction, cotarnine is converted into hydrocotarnine,[1] which is formed in the manner indicated by the formulæ below—



Cotarnine.

Alcohol.

Hydrocotarnine.

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[1] Beckett and Wright, *Trans. Chem. Soc.*, 1875, **28**, 577; Bandow and Wolffenstein, *Ber.*, 1898, **31**, 1577.

8. *The Constitution of Narcotine.*

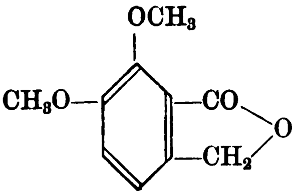
We have now in the course of the previous sections amassed the material which we require in our consideration of the narcotine formula; and we may next proceed to deal with the question.

Narcotine contains no carboxyl or hydroxyl radical. It is made up of one hydrocotarnine nucleus and one opianic acid nucleus, the latter being in the form of the lactone, meconine. This is shown by the action of reducing agents upon narcotine—

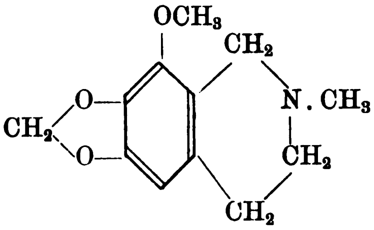
$$C_{22}H_{23}O_7N + H_2 = C_{10}H_{10}O_4 + C_{12}H_{15}O_3N$$

Narcotine. **Meconine.** **Hydrocotarnine.**

We must now consider the mode of linkage of these two nuclei. When we examine the formulæ of meconine and hydrocotarnine—

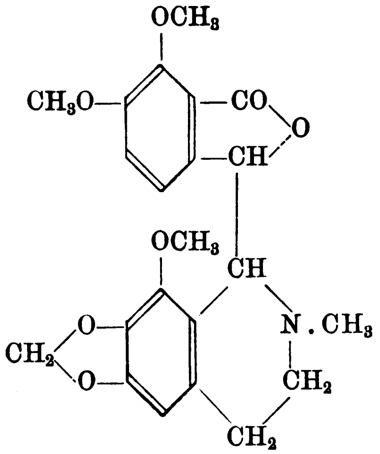


Meconine.



Hydrocotarnine.

it is obvious that the linking does not take place through an oxygen atom, as all of these are fully occupied. It must, therefore, occur by the junction of two carbon atoms, each of which loses a hydrogen atom in the union. The pair of atoms which are most likely to be concerned in the linkage are those which give rise to the aldehyde groups of opianic acid and cotarnine, so that the formula of narcotine would be written—



Narcotine.

9. *The Syntheses of Gnoscopine and Narcotine.*

Perkin and Robinson[1] showed that when cotarnine and meconine are boiled in alcoholic solution in presence of potassium carbonate the substance produced is identical with the alkaloid gnoscopine; and by fractionally crystallizing the *d*-bromocamphorsulphonate of the base[2] they were able to isolate the dextro and lævo forms of narcotine, gnoscopine being the racemic variety. The lævo-narcotine thus obtained was identical with the natural alkaloid.

10. *The Synthesis of Narceïne.*

When the methyl iodide addition product of narcotine is treated with alkalis, it is converted into a substance narceïne, which was first called pseudo-narceïne.[3] The course of the reaction may be formulated in the following way:—

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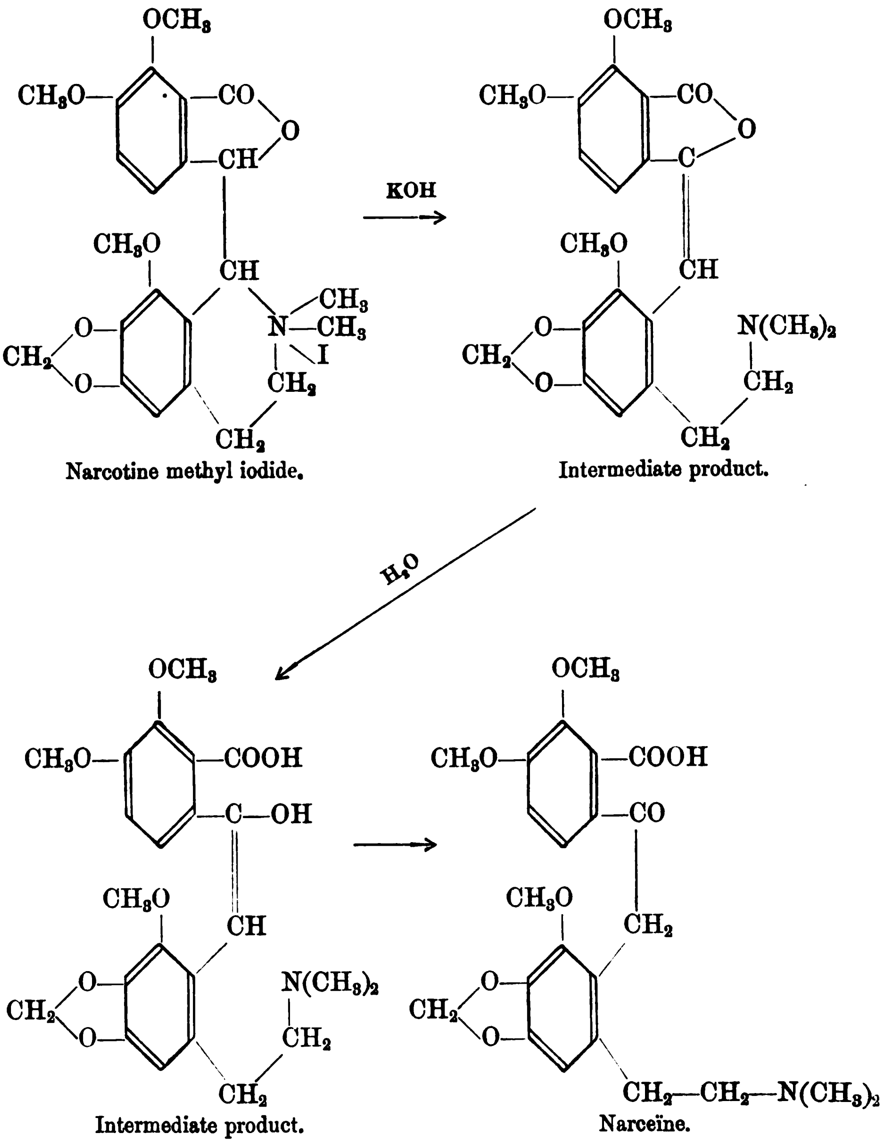
[1] Perkin and Robinson, *Proc. Chem. Soc.*, 1910, **26**, 46.

[2] Perkin and Robinson, *ibid.*, 131.

[3] Roser, *Annalen*, 1888, **247**, 167; 1889, **254**, 357; Freund and Frankforter, *ibid.*, 1893, **277**, 31.



11. *The Synthesis of Hydrastinine.*

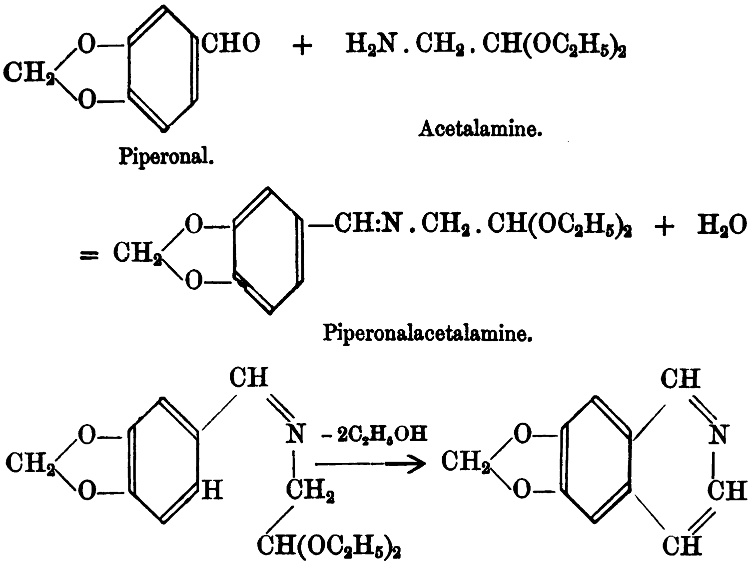
This substance, which occurs among the decomposition products of the alkaloid hydrastine, has been synthesized by

Fritsch[1]; and as a knowledge of its constitution may help us in our consideration of the hydrastine formula, we may give a brief account of Fritsch's work before dealing with the natural alkaloid.

When chloracetal is treated with ammonia, it yields the substance acetalamine, which has the formula—

$$NH_2 . CH_2 . CH(OC_2H_5)_2$$

This substance can be made to condense with aromatic aldehydes; and when the products thus obtained are treated with sulphuric acid, alcohol is split off and isoquinoline derivatives are formed. If we apply this reaction to the case of piperonal, we shall have the following series of reactions:—



Piperonal.

Acetalamine.

Piperonalacetalamine.

Piperonalacetalamine.

Methylenedihydroxyisoquinoline.

When the methyl iodide addition product of this body is reduced by means of tin and hydrochloric acid, it gives the substance hydrohydrastinine—

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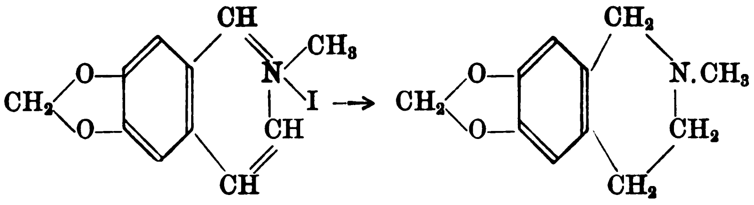
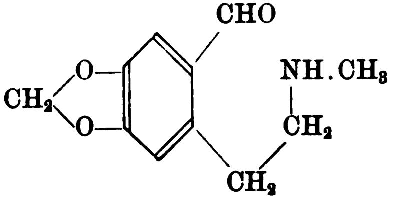
[1] Fritsch, *Annalen*, 1895, **286**, 18.



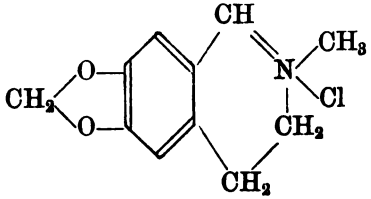
Iodomethylate. Hydrohydrastinine.

This last substance Freund[1] has converted into hydrastinine by oxidizing it with potassium bichromate and sulphuric acid.

Now, from the fact that the behaviour of hydrastinine, on reduction and salt formation, closely resembles that of cotarnine, we are enabled to put forward the following structural formula for it:—



Hydrastinine.



Hydrastinine hydrochloride.

This formula explains why hydrastinine behaves as an aldehyde, why it forms a ring compound in presence of acids, why its salts contain one molecule of water less than the free base, why it yields apophyllenic acid on oxidation, and many other properties which the substance possesses. A comparison of their formulæ will show that cotarnine is a methoxylated hydrastinine.

12. *The Constitution of Hydrastine.*

Hydrastine contains one methoxyl group less than narcotine, but in all other respects it resembles that compound. Now, on oxidation with dilute nitric acid, hydrastine breaks down into hydrastinine and opianic acid just as narcotine breaks down into cotarnine and opianic acid. But, as was shown in the preceding section, cotarnine is methoxy-hydrastinine, so that we may conclude that if we eliminate the

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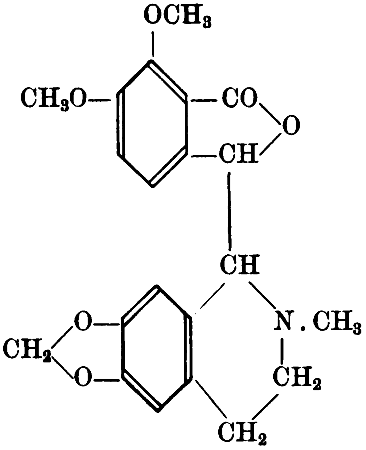
[1] Freund, *Ber.*, 1887, **20**, 2403.

methoxy-group from narcotine we shall have hydrastine. This actually proves to be the case; so that we may write the formula of hydrastine by simply taking that of narcotine and replacing the methoxyl radical of the cotarnine half by a hydrogen atom. Hydrastine would therefore be—



Hydrastine.

G.—The Purine * Group.

1. *The Synthesis of Uric Acid.*

The problem of the constitutions of the purine derivatives has proved one of the most complicated chapters in the recent history of organic chemistry; so complicated is it that we cannot devote sufficient space to allow of any historical treatment of the matter, but must confine ourselves as closely as possible to the actual proofs of the constitutions of some of the purine series.

The most important member of the group is uric acid. This substance[1] has been synthesized in a variety of ways; but for the most part the syntheses throw no very clear light upon the

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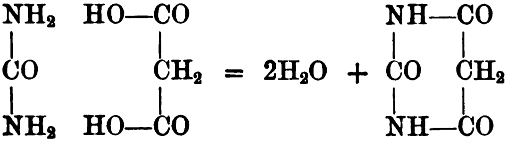
* This, like many other chemical terms, is what Lewis Carroll defined as a portmanteau word; it is derived from the two words *purum uricum*.

[1] Horbaczewski, *Monatsh.*, 1882, **3**, 796; 1885, **6**, 356; 1887, **8**, 201, 584; Behrend and Roosen, *Ber.*, 1888, **21**, 999; *Annalen*, 1889, **251**, 235; Traube, *Ber.*, 1900, **33**, 1371, 3035; Fischer and Ach, *Ber.*, 1895, **28**, 2473; Fischer, *Ber.*, 1897, **30**, 559.

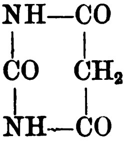
constitution of the body. We may describe very briefly two of these synthetic methods of preparing uric acid, the first being due to Emil Fischer and the second to W. Traube.

When malonic acid is treated with urea, it yields a cyclic ureide, malonyl-urea or barbituric acid—

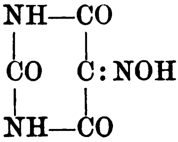


Barbituric acid.

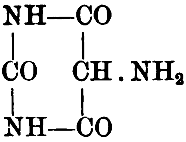
If we treat barbituric acid with nitrous acid, the methylene group is replaced by the isonitroso-radical in the usual way, giving us oximido-malonyl-urea, which is also called violuric acid; and on reduction of this substance the oximido-group is converted into an amido-radical, producing amido-malonyl urea, or uramil—



Barbituric acid.

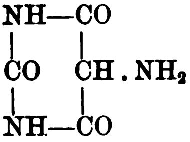


Violuric acid.

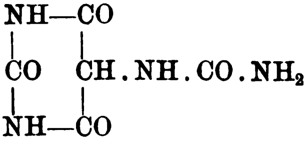


Uramil.

On treatment with potassium cyanate, uramil takes up cyanic acid and is changed into pseudo-uric acid—

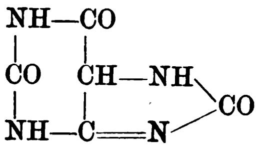


Uramil.

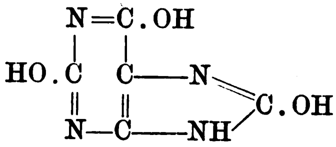


Pseudo-uric acid.

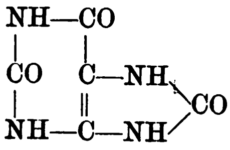
It is very hard to extract water from pseudo-uric acid, but this can be done by heating it with molten oxalic acid or by boiling it with hydrochloric acid. Under these circumstances one molecule of water is lost and uric acid is formed. Uric acid should therefore have the following constitution:—



Its property of forming salts could be ascribed to the existence of an enolic form, such as—

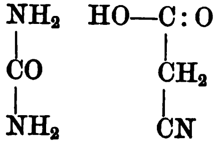


It is more usual, however, to consider uric acid to exist in the isomeric form—

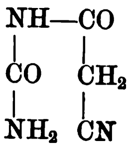


Uric acid.

The second synthesis takes as its starting-point the condensation of urea with cyanacetic acid, which takes place under the influence of phosphorus oxychloride—

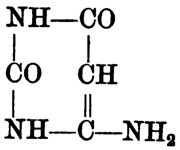


$NH_2-CO-NH_2$ $HO-C:O-CH_2-CN$



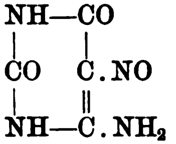
Cyanacetyl-urea.

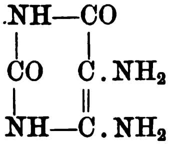
Caustic soda causes cyanacetyl-urea to undergo an intramolecular change by which it is converted into amido-uracil—



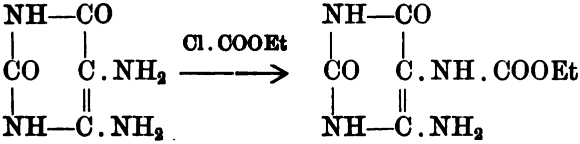
Amido-uracil.

When this is treated with nitrous acid it gives a nitroso-compound which can be reduced with ammonium sulphide to diamido-uracil—


Nitroso-compound.


Diamido-uracil.

The next step is to treat this diamido-derivative with caustic potash and chloroformic ester, by which means a urethane is formed—



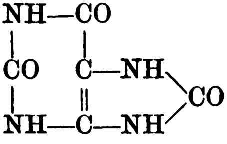
Diamido-uracil. Diamido-uracil urethane.

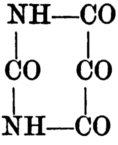
By heating the sodium salt of this substance to 180°–190° C. we obtain the sodium salt of uric acid.

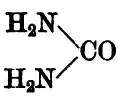
By adapting this last synthesis we can obtain many uric acid derivatives; for we may use substituted ureas instead of the parent substance, or we may replace the urea by guanidine, or, lastly, we may discard the chloroformic ester in favour of formic ester.

Before leaving the question of uric acid we must glance for a moment at the behaviour of that substance when treated with various oxidizing agents.

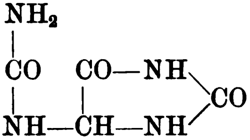
When the oxidation is carried out by means of cold nitric acid, the six-membered ring of uric acid remains intact, while urea is split off. The oxidized ring which remains can be derived from mesoxalic acid and urea; it is termed alloxan, or mesoxalyl-urea—


Uric acid.


Alloxan.

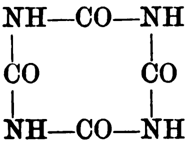

Urea.

If, on the other hand, we use alkaline potassium permanganate solution as our oxidizing agent, the five-membered ring remains unbroken, while the six-membered one is destroyed. The first products in this case are two substances, uroxanic acid, $C_5H_8N_4O_6$, and oxonic acid, $C_4H_5N_3O_4$, which are further oxidized to allantoin—



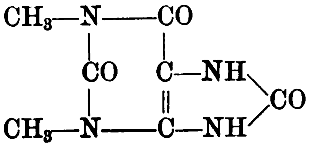
Allantoin.

With hydrogen peroxide the sodium salt of uric acid yields a substance of the formula $C_4H_4N_4O_4$, tetracarbonimide, which acts as a weak tetra-basic acid; on this account the following formula has been tentatively ascribed to it:—

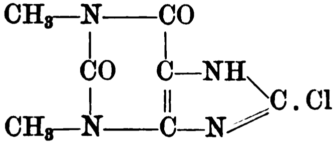


2. *The Synthesis of Theophylline.*

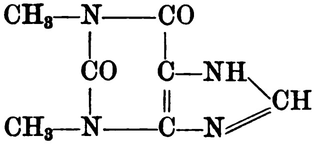
If in the uric acid syntheses we substitute symmetrical dimethyl-urea for the parent substance, we obtain in the end dimethyl uric acid—



When this is treated with trichloride and oxychloride of phosphorus at 150° C. it is converted into a substance chlorotheophyllin, one atom of chlorine replacing a hydroxyl group. Chlorotheophylline must, therefore, have the following constitution:—



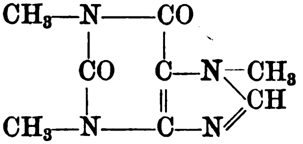
By reducing with hydriodic acid, theophylline[1] is formed—



Theophylline.

3. *The Synthesis of Caffeine.*

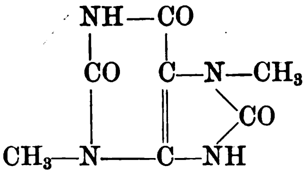
Caffeine[1] is obtained by the action of methyl iodide upon theophylline. Its constitution is therefore expressed by—



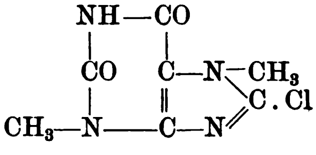
Caffeine.

4. *The Synthesis of Theobromine.*

If we take as a starting-point the dimethyl uric acid which has the constitution (I.) shown below, and treat it with phosphorus oxychloride, we shall find that it gives chlorotheobromine (II.), which, on reduction with hydriodic acid, yields theobromine (III.).[2] The reactions are parallel to those which lead from the isomeric dimethyl uric acid to theophylline.



(I.)



(II.)

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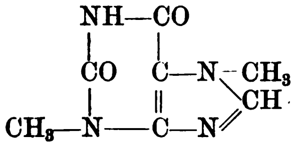
[1] Fischer and Ach, *Ber.*, 1895, **28**, 3135.

[2] Fischer, *Ber.*, 1897, **30**, 1839.

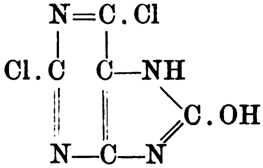


Theobromine.

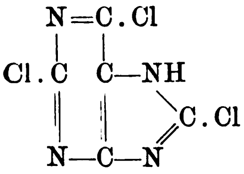
(III.)

5. *The Synthesis of Purine.*

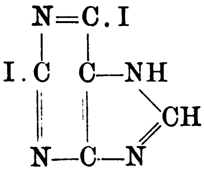
When the sodium salt of uric acid is treated with oxychloride of phosphorus it yields a hydroxy-dichloro-purine of the following formula:—



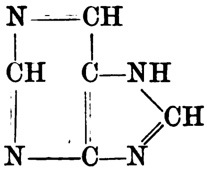
This, by means of trichloride of phosphorus, can be changed into a trichloro-derivative, the third hydroxyl group being replaced by a chlorine atom. The substance thus formed, trichloropurine, is then treated with hydriodic acid at 0° C. whereby di-iodopurine is produced. This, by reduction with water and zinc dust, gives purine itself.



Trichloropurine.

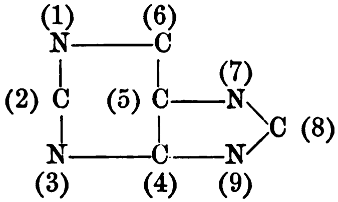


Di-iodopurine.



Purine.

Purine is the substance to which all the substances of the purine group are usually referred; the derivatives being distinguished by means of the system of numbering shown in the following scheme:—



According to this, the substance xanthine is 2, 6-dihydroxypurine; theophylline would be 1, 3-dimethyl-xanthine; caffeine would be 1, 3, 7-trimethyl-xanthine; theobromine would be 3, 7-dimethyl-xanthine; and uric acid 8-hydroxy-xanthine.

CHAPTER VII

THE POLYPEPTIDES[1]

WHEN we examine the contents of the cells from which living tissues are built up, we find that they are for the most part made up of albuminous bodies of extremely complicated chemical character. These albumins are distinguished from all the other naturally occurring substances by the fact that animal life may be supported upon them alone in conjunction with water and salt; whereas fats and carbohydrates do not in themselves furnish nourishment sufficient for the support of animal functions for an indefinite period. The importance of the albumins from the physiological point of view, therefore, can hardly be overestimated; while from the chemical side they furnish one of the most difficult and complicated problems which the organic chemist has yet attacked.

The difficulties of the researches which have been carried out in this branch of organic chemistry can hardly be overestimated. In the first place, many albumins are non-crystalline substances which require special treatment before they can be obtained in crystalline form; this, of course, makes it very difficult to determine the state of purity of any specimen under consideration. Secondly, the extreme sensitiveness of albumins to heat, acids, or alcohol renders them very liable to be altered during the progress of the ordinary chemical reactions. Again, the molecular complication of these substances must be tremendous, if we are to judge from molecular weight determinations: egg albumin has been estimated to have a molecular

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[1] A complete set of references up to 1906 will be found in a lecture by Fischer (*Ber.*, 1906, **39**, 530). See also Fischer, *Ber.*, 1906, **39**, 2893; 1907, **40** 1754, 3704; 1908, **41**, 850, 2860; Fischer and Königs, *Ber.*, 1907, **40**, 2048; Fischer and Schulze, *ibid.*, 943; Fischer and Gerngross, *Ber.*, 1909, **42**, 1485; Fischer and Luniak, *ibid.*, 4752. Fischer's papers have been reprinted in his book "*Die Aminosäuren, Polypeptide und Proteine*" (1906).

weight of at least 15,000, according to the results of the freezing-point method.

In the foregoing chapters we have dealt at some length with the constitutions of various compounds, and it will be remembered that there are two general methods of investigating the constitution of any given substance. We may attack the question from the synthetical side or from the analytical point of view: in the first case we study the general properties of the substance, then ask ourselves in what way we can build up a molecule whose reactions will resemble those of the one we are studying, and having synthesized this body we compare its reactions with those of the original; in the analytical method, we take the molecule to pieces in various ways, and isolate a series of decomposition products, from which we endeavour to guess the manner in which they were arranged in the original molecule. Now, in the case of the albumins, the first line of research turned upon the analytical results. This was to be foreseen, for it seemed almost impossible to build up molecules of such extreme complexity. The analytical method, however, has not carried us very far; and the most important work on the question has been carried out from the synthetical side since Fischer attacked the problem. Before dealing with his work, however, we must cast a glance at the decomposition products which have been obtained from the albumin group.

The oxidation of the albumins cannot be said to have yielded results of any great interest; the greater part of our knowledge of these bodies has been obtained by means of hydrolysis reactions. When ferments are allowed to act upon protein derivatives, the bodies first formed are albumoses and peptones. These intermediate compounds can be further broken down into amido-acids. Hydrolysis by means of alkali takes place more rapidly, while acids decompose the albumins most easily. It is thus made clear that the substances lying at the base of the albumins belong to the class of amido-acids; and, further, that these acid nuclei are linked together in some way which allows them to be separated one from another by means of hydrolysis. It is evident that amide-formation is the most probable method of uniting the nuclei; and from this point of view Fischer took up the work of synthesizing some compounds which, while not themselves of the protein class, would show sufficient resemblance to the naturally occurring substances to allow us to deduce the probable constitution of at least part of the albumin molecule.

To describe these synthetic substances, Fischer proposed the name "*Polypeptides*," by which he intends to denote those compounds which are derived from two amido-acid molecules by the elimination of water. A few polypeptides have been obtained by the hydrolysis of proteins, but by far the greater number are synthetic. We may now give the outlines of the methods employed by Fischer in his researches.

In the first place, it was necessary to obtain mono-amido-acids. This Fischer did by means of the ordinary methods—action of ammonia on the esters of bromo-fatty acids or by Strecker's cyanhydrin method (addition of hydrocyanic acid and ammonia to an aldehyde and hydrolysis of the cyanhydrin thus formed). Now, having obtained these acids, another problem presents itself. If we combine together two racemic acids we shall have not a single reaction product, but a mixture of two new racemic substances. For instance, if we start with racemic alanine and racemic leucine, we should produce a mixture of the four isomers—

d-Alanine-*d*-leucine.	*d*-Alanine-*l*-leucine.
l-Alanine-*l*-leucine.	*l*-Alanine-*d*-leucine.

The two substances in the left-hand column then combine to form a racemic substance, and the two in the right-hand column to form *another* racemic compound, so that we should have two new bodies instead of a pure compound. And, of course, if we coupled together more than two racemic acids we should find the number of stereo-isomers in the product increased in like manner. This evidently threw considerable difficulty in the way, and to avoid it Fischer resolved to use in his condensations optically active acids only. By this means he excluded the possibility of racemic compounds being formed, so that from one pair of amido-acids he obtained only a single reaction product.

This did not clear the experimental difficulties away, however; it only carried them one step further back. For, owing to the very weak acidity of the amido-acids, resolution of these substances into their optically active antipodes by salt-formation with active bases was by no means an easy task. Fischer evaded this difficulty in turn by one of his usual simple artifices. He benzoylated the amido-group of the acid, and thus reduced its basic properties to a minimum; thereafter, resolution into the optical antipodes presented no difficulty, and after this had been accomplished, the benzoyl radical was split off and the optically active amido-acid remained.

I. The first method employed by Fischer in the actual synthesis of polypeptides depends upon the elimination of a molecule of alcohol from two molecules of amido-acid ester—

$$\mathrm{NH_2.CH_2.COOEt + NH_2.CH_2.COOEt = NH_2.CH_2.CO.NH.CH_2.COOEt + EtOH}$$

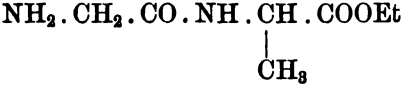
Now, it will be seen at once that if we applied this method as given above to a mixture of two different amido-acids, it would be sheer chance that would govern the production of the end-product. For example, if we were to combine together the two esters (A) and (B) we should get a mixture of (C) and (D) in the reaction product—

(A) $\mathrm{NH_2.CH_2.COOEt}$

(B)

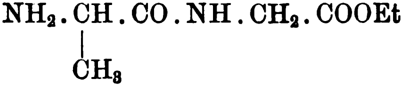
$$\mathrm{NH_2.\underset{\underset{CH_3}{|}}{CH}.COOEt}$$

(C)



$$\mathrm{NH_2.CH_2.CO.NH.\underset{\underset{CH_3}{|}}{CH}.COOEt}$$

(D)



$$\mathrm{NH_2.\underset{\underset{CH_3}{|}}{CH}.CO.NH.CH_2.COOEt}$$

This difficulty in its turn was overcome by Fischer in a very simple manner. Before condensing the two substances together he allowed one of them to react with ethyl chlorocarbonate, which acted upon the amido-group and protected it from further attack—

$$\mathrm{Cl.COOEt + NH_2.CH_2.COOEt = EtOOC.NH.CH_2.COOEt + HCl}$$

When a compound such as this is heated for thirty-six hours with the ester of an amido-acid, alcohol is eliminated between the —NH_2 group of the amido-acid and the —$CH_2.COOEt$ group of the above substance, whose amido-group cannot react in this way. Thus we know at once the constitution of the resulting compound. An example will serve to make the matter clear. If we start with the substance glycyl-glycine,* and treat it with chloro-carbonic ester, we shall obtain the substance shown below, glycyl-glycine carboxylic acid ester—

$$\begin{aligned}&EtOOC.Cl + NH_2.CH_2.CO.NH.CH_2.COOEt\\&\quad = EtOOC.NH.CH_2.CO.NH.CH_2.COOEt + HCl\end{aligned}$$

When this substance is heated for thirty-six hours with leucine ester, ethyl alcohol is eliminated in the following way:—

$$\begin{aligned}&EtOOC.NH.CH_2.CO.NH.CH_2.COOEt + NH_2.CH.(C_4H_9).COOEt\\&\quad = EtOOC.NH.CH_2.CO.NH.CH_2.CO.NH.CH(C_4H_9).COOEt\end{aligned}$$

This substance is the carboxylic ester of glycyl-glycine-leucine; as can be seen from the formulæ, it can have no other constitution than that shown. This carbethoxy-glycylglycyl-leucine ester contains three amido-acid nuclei, and is therefore called a tri-peptide derivative.

II. The yields of end-product from the foregoing method of synthesis were poor, and Fischer therefore turned to another way of attaining his objective. When the ester of the chlorocarbonic derivative of an amido-acid is treated with thionyl chloride, an acid chloride is formed; and this readily condenses with amido-acid esters, forming polypeptide derivatives. For instance, if we start again with the derivative obtained by the action of chloro-carbonic ester upon glycylglycine, and treat it with thionyl chloride, we shall produce the chloride whose constitution is shown below—

$$EtOOC.NH.CH_2.CO.NH.CH_2.CO.Cl$$

When this chloride is condensed with glycylglycine ester—

$$NH_2.CH_2.CO.NH.CH_2.COOEt$$

it yields the tetra-peptide derivative, glycylglycylglycylglycine-carbethoxy-ester—

$$EtOOC.NH.CH_2.CO.NH.CH_2.CO.NH.CH_2.CO.NH.CH_2.COOEt$$

---

* Fischer terms "glycyl" the radical $NH_2.CH_2.CO$— which is derived from glycine (glycocoll) $NH_2.CH_2.COOH$.

III. The drawback of the two foregoing methods lies in the fact that so far no method has been discovered by means of which we can eliminate the group —COOEt, which is attached to one end of the polypeptide chain; so that neither method can be employed to build up a true polypeptide. Fischer therefore devised another method by means of which the polypeptides themselves can be produced. Starting from the ester of a substance like glycine (I.) or glycylglycine, he treated this with chloracetyl chloride (II.) or some similar compound. Hydrochloric acid is eliminated, and the two molecules combine together to form a compound with chlorine at one end of the chain (III.). The ester group at the other end of the chain is then hydrolyzed very carefully, and a chloro-acid produced (IV.), which, on treatment with ammonia, yields a true polypeptide (V.)—

$$
\begin{array}{rl}
\text{(I.)} & NH_2 . CH_2 . COOEt \\
\text{(II.)} & Cl . CH_2 . CO . Cl \\
\text{(III.)} & Cl . CH_2 . CO . NH . CH_2 . COOEt \\
\text{(IV.)} & Cl . CH_2 . CO . NH . CH_2 . COOH \\
\text{(V.)} & NH_2 . CH_2 . CO . NH . CH_2 . COOH
\end{array}
$$

The reason for hydrolyzing the ester (III.) to the acid (IV.) lies in the fact that if this were not done an amide would be formed on treatment with ammonia, and the amido group would be most difficult to get rid of later.

IV. A variation of the previous method may also be used. If we take the substance—

$$Cl . CH_2 . CO . NH . CH_2 . COOH$$

which was formed in the course of the last synthesis we described, and treat it with pentachloride of phosphorus, we convert the acid into the chloride *—

$$Cl . CH_2 . CO . NH . CH_2 . CO . Cl$$

which can then be made to interact with glycine ester, yielding the more complicated substance—

$$Cl . CH_2 . CO . NH . CH_2 . CO . NH . CH_2 . COOEt$$

---

* Thionyl chloride is a better reagent than phosphorus pentachloride for producing acid chlorides. The reaction takes place according to the equation—

$$R . COOH + SOCl_2 = R . CO . Cl + SO_2 + HCl$$

from which it will be clear that the acid chloride can be obtained pure simply by boiling off the sulphur dioxide and hydrochloric acid.

The remaining chlorine atom may then be replaced by the amido-group by means of ammonia; and after hydrolysis of the ester group the tri-peptide glycylglycylglycine is formed—

$$NH_2 . CH_2 . CO . NH . CH_2 . CO . NH . CH_2 . COOH$$

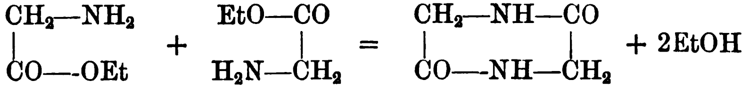
V. This modification has been further extended. When amido-acids are treated with a mixture of acetyl chloride and phosphorus pentachloride, the corresponding acid chlorides are formed. These can be combined with other amido-acids, and in this way we can obtain polypeptides. For instance, if we take glycine and treat it as described we should expect to produce glycyl chloride—

$$NH_2 . CH_2 . COOH \rightarrow NH_2 . CH_2 . CO . Cl$$

This can be condensed with another molecule of glycine, forming glycylglycine—

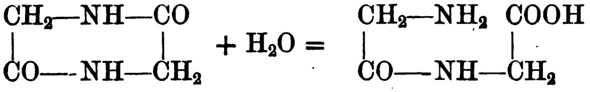
$$NH_2 . CH_2 . CO . Cl + NH_2 . CH_2 . COOH \\ = NH_2 . CH_2 . CO . NH . CH_2 . COOH$$

VI. If we abstract two molecules of alcohol from two molecules of an α-amido-ester, a cyclic substance is produced, which is a derivative of $\alpha\gamma$-diketo-piperazine—



$$\begin{array}{l}CH_2\text{—}NH_2\\ |\\ CO\text{—}OEt\end{array} + \begin{array}{r}EtO\text{—}CO\\ |\\ H_2N\text{—}CH_2\end{array} = \begin{array}{l}CH_2\text{—}NH\text{—}CO\\ |\qquad\qquad\quad |\\ CO\text{—}NH\text{—}CH_2\end{array} + 2EtOH$$

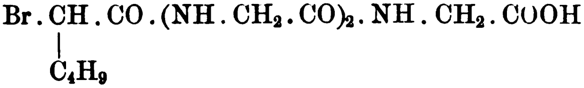
This cyclic compound, when carefully treated with hydrochloric acid, can be opened out into an open-chain body, glycylglycine—



$$\begin{array}{l}CH_2\text{—}NH\text{—}CO\\ |\qquad\qquad\quad |\\ CO\text{—}NH\text{—}CH_2\end{array} + H_2O = \begin{array}{l}CH_2\text{—}NH_2\ \ COOH\\ |\qquad\qquad\quad |\\ CO\text{—}NH\text{—}CH_2\end{array}$$

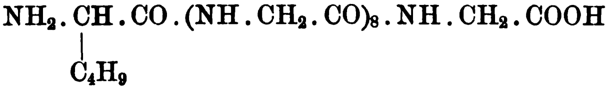
By choosing the appropriate amido-ester from which to start, a given polypeptide may be obtained in this manner.

We cannot go into details with regard to the various substances which have been synthesized by means of the foregoing methods, but there is one substance which is worthy of mention. Fischer has recently synthesized an octadecapeptide in the following manner. Starting from dextro-α-bromo-isocapronyl-diglycylglycine—



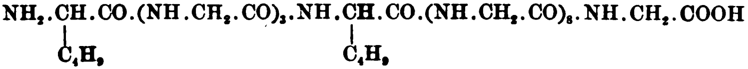
$$\mathrm{Br.\underset{\substack{|\\ C_4H_9}}{CH}.CO.(NH.CH_2.CO)_2.NH.CH_2.COOH}$$

he treated this according to the fourth method, combining it with penta-glycylglycine, and, finally, exchanging the bromine atom for an amido-group, he obtained lævo-leucyl-octaglycyl-glycine—



$$\mathrm{NH_2.\underset{\substack{|\\ C_4H_9}}{CH}.CO.(NH.CH_2.CO)_8.NH.CH_2.COOH}$$

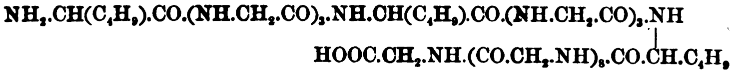
This polypeptide was then coupled with dextro-bromo-iso-caproyl-diglycylglycine, and again treated with ammonia, whereby the tetradecapeptide shown below was formed—



$$\mathrm{NH_2.\underset{\substack{|\\ C_4H_9}}{CH}.CO.(NH.CH_2.CO)_3.NH.\underset{\substack{|\\ C_4H_9}}{CH}.CO.(NH.CH_2.CO)_8.NH.CH_2.COOH}$$

Lævo-leucyl-triglycyl-lævo-lucyl-octaglycyl-glycine.

By a repetition of this series of reactions the octadecapeptide was formed, which has the constitution shown below—



$$\mathrm{NH_2.CH(C_4H_9).CO.(NH.CH_2.CO)_3.NH.CH(C_4H_9).CO.(NH.CH_2.CO)_3.NH} \\ \mathrm{HOOC.CH_2.NH.(CO.CH_2.NH)_8.CO.CH.C_4H_9}$$

l-Leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine.

This extraordinary substance is apparently one of the most complicated systems of known constitution which has hitherto been synthesized. Its molecular weight is twelve hundred and thirteen; while that of the fairly complicated natural body, tri-stearin, is only eight hundred and ninety-one.

We must now briefly summarize the main characteristics of the polypeptide class, and it may be of interest to compare them with those of the naturally occurring proteins. The polypeptides are solids, which usually melt at about 200° C., with some decomposition. They are easily soluble in water, but insoluble in alcohol, like some of the albumins; and instead of having the usual insipid or sweet taste of the ordinary amido-acid, they are bitter, like the protein derivatives. In dilute sulphuric acid solution they are precipitated by phosphotungstic acid, in which behaviour they resemble the albumins. Both the natural and artificial classes give the biuret reaction. The action of ferments, or of acids or alkalis, is the same in both classes; and similar products are obtained when animals are fed with polypeptides and albumins. In the case of ferment action it is found that much depends upon the groups which have been used in building up the polypeptide structure, some polypeptides being much more easily fermented than others.

From these data it will be obvious that the researches of Fischer and Curtius have carried us into a series of substances which, in many respects, resemble the natural bodies of the protein class; how far the parallel holds good, and how high in the scale we can carry our syntheses remains for the future to make clear.

CHAPTER VIII

THE POLYKETIDES AND THEIR DERIVATIVES

BROADLY speaking, plants differ from animals in that they can nourish themselves with water and carbon dioxide alone, while the animal kingdom requires the intermediation of vegetables and other organized matter. The substances which lie at the base of all syntheses of organized tissues must therefore be simple compounds of carbon, hydrogen, and oxygen. Once having synthesized such substances, the plant, as will be shown later in this chapter, could easily build up derivatives of the aliphatic, aromatic, and heterocyclic series.

Given formaldehyde, sugars may be produced by the action of alkalis; and many such examples of the production of complicated natural bodies from very simple substances are known. In the present chapter we shall confine ourselves to derivatives of one class; but as this class is interwoven with all the main groups of organic compounds, it will serve as a skeleton from which the relations between apparently quite dissimilar groups can be deduced. At the same time it must be borne in mind that our laboratory synthetic methods differ in the main from those employed in the living plant. While we, in our syntheses, start from the same elements as the plant does, we usually build up our substances step by step, proceeding from simple to complex. The plant appears to act differently; for it, apparently by condensation, polymerization, or some such process, converts its simple starting substance into an extremely complicated derivative, which then decomposes, yielding those products which have been identified in saps and tissues. Again, while most of our ordinary laboratory reactions can be applied to the production of substances which are found in plants, it is obvious that the plant must obtain the same result in a much simpler manner. For instance, when we wish to attach side-chains to a benzene nucleus, we employ aluminium chloride in the Friedel-Crafts reaction; but such a reagent could not exist in a plant. Further, a great number of our laboratory reactions require the use of high temperatures, which would be fatal to plant-life.

When we examine the compounds known to us in the domain of organic chemistry, it is inconvenient for our present purpose to regard them from the point of view of text-book classification. What is of chief importance to us is the question, Can they be made to react easily? From this point of view we divide compounds at once into two groups, the saturated and the unsaturated, the latter being the reactive ones. This is, of course, speaking in very general terms, for many saturated substances are quite reactive. Now, among unsaturated substances we can again distinguish two classes—the desmotropic and the non-desmotropic. Of these, the desmotropic class is by far the most reactive. The cause of this is obvious, for if a non-desmotropic substance be brought into the presence of a reagent, it has only one way in which it can react, and if combination does not take place the matter ends; with a desmotropic compound, however, if the first form fails to attack the reagent, there is always the possibility that the second form may be more successful.

In nature, we find many desmotropic and tautomeric substances; but the preponderating class is that which contains compounds of the type

$$R—CO—CH_2—R' \rightarrow R—C(OH) : CH—R'$$

This "keto-enol" type is very widely distributed among naturally occurring substances; it is found in nearly every important class of compounds, from the purine group to the terpenes; and, further, its one form is converted into the other isomeride more easily than is the case with practically any other mode of isomeric change.

The simplest member of the class of substances containing this atomic grouping is the compound keten, which has the formula—

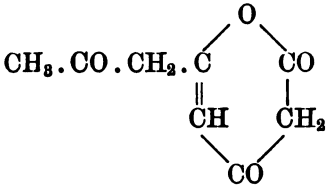
$$CH_2 : CO$$

As will be seen later, this group of five atoms is capable of polymerizing or condensing with other compounds in many ways; and as some general name is required for the whole series, we shall adopt the proposal of Collie,[1] and designate as "*Polyketides*" those substances which are obtained by the polymerization of keten, and subsequent addition of other atoms. For example, acetic acid, $H.CH_2.CO.OH$, which is derived from keten by the addition of water, would be termed a "*monoketide*"; while acetoacetic acid, $H.CH_2.CO.CH_2.CO.OH$, would be a "*di-ketide.*"

The rest of this chapter will be devoted to the discussion of these classes of compounds. In the first place, a rapid survey of the general relations of the group to the rest of organic compounds will be given, after which the reactions and properties of individual polyketide derivatives will be dealt with in so far as they concern the main principles of the subject.

When keten is allowed to stand under pressure at ordinary temperatures, it becomes converted into the dimolecular form, diketen, whose constitution will be discussed later. On treatment with pyridine in benzene solution, this diketen (or keten itself) can be transformed into dehydracetic acid.

There is some dispute as to the actual formula of the last body, but for the present we may adopt one of those proposed, and deal with the whole question later.



Dehydracetic acid.

This substance, dehydracetic acid, is one of the most important of the polyketide derivatives, at least from the synthetic point of view. From it, by three different reactions, we can prepare derivatives of the benzene series, the pyridines and the pyrones. The first of these is obtained by the action of alkalis on dehydracetic acid, and the reaction probably takes the following course:—

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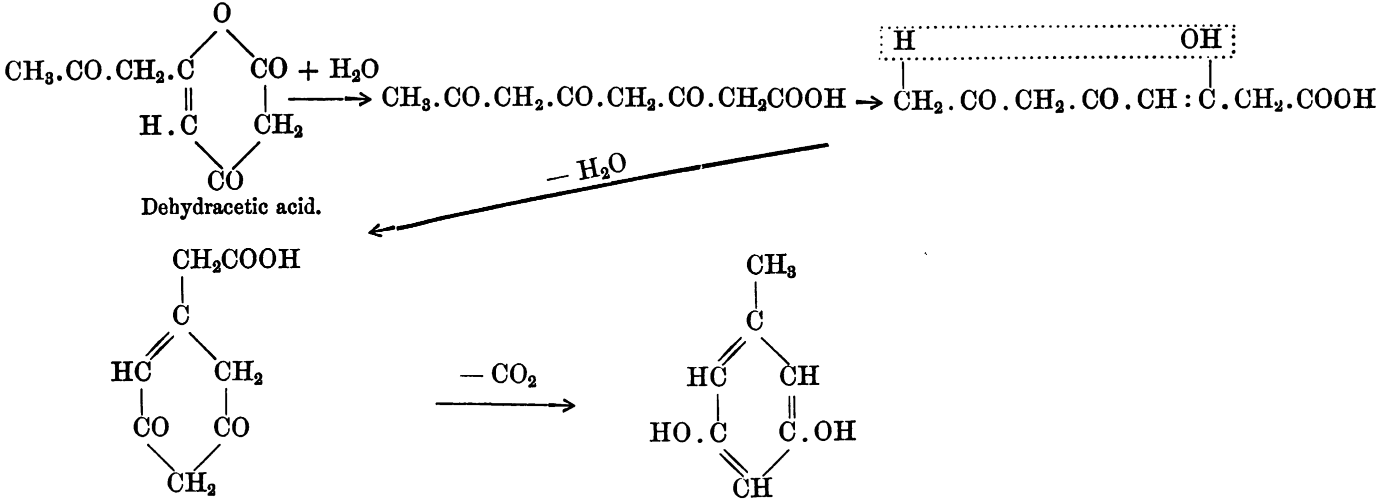
[1] Collie, *Proc. Chem. Soc.*, 1907, **23**, 230.



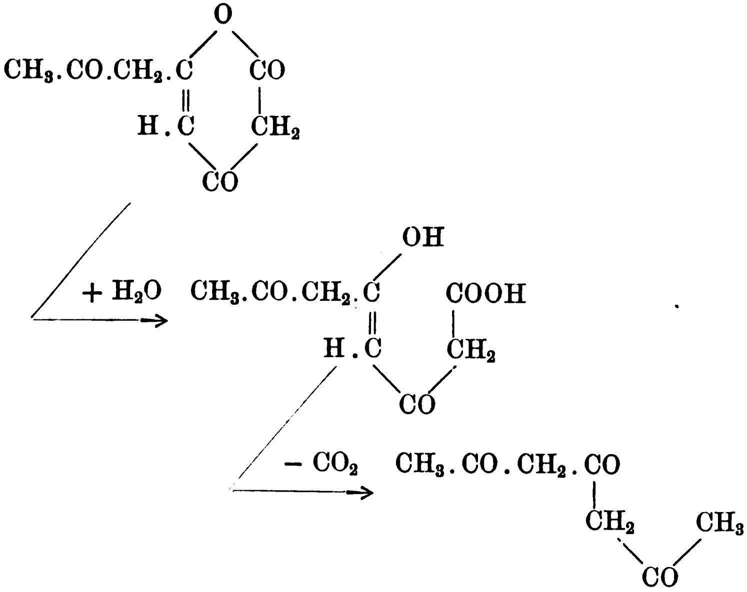
Dehydracetic acid.

Dihydroxyphenyl-acetic acid (ketonic form)

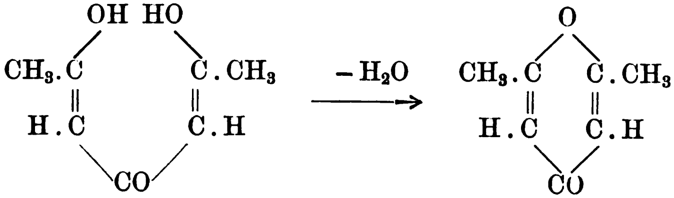
Orcinol.

In this way both dihydroxyphenyl-acetic acid and orcinol are formed.

The two other reactions mentioned, resulting in pyridine and pyrone derivatives, depend upon the intermediate formation of diacetylacetone from dehydracetic acid in the following manner:—

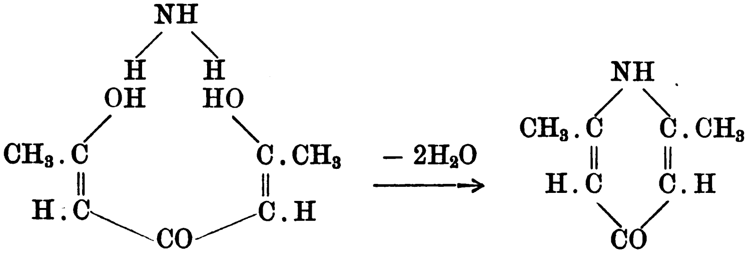


As soon as the diacetylacetone is formed, it may lose water and form dimethyl-pyrone, thus—



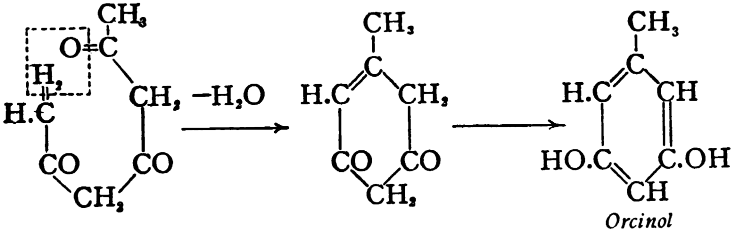
Diacetylacetone. Dimethyl pyrone.

or it may, in presence of ammonia, lose two molecules of water and take up instead the imino-group in the following way:—



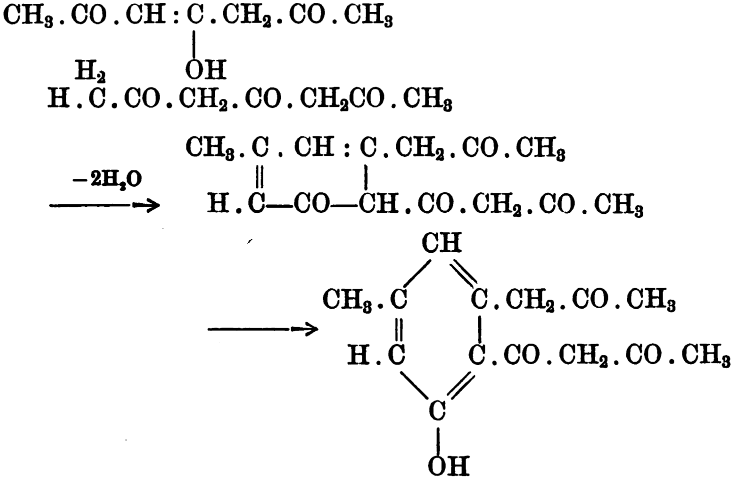
Diacetylacetone. Lutidone.

These reactions by no means exhaust the possibilities of diacetylacetone, however, for from it we may produce benzene, naphthalene, or isoquinoline derivatives by the following steps. In the first place, by loss of one molecule of water, we can produce orcinol—



Orcinol

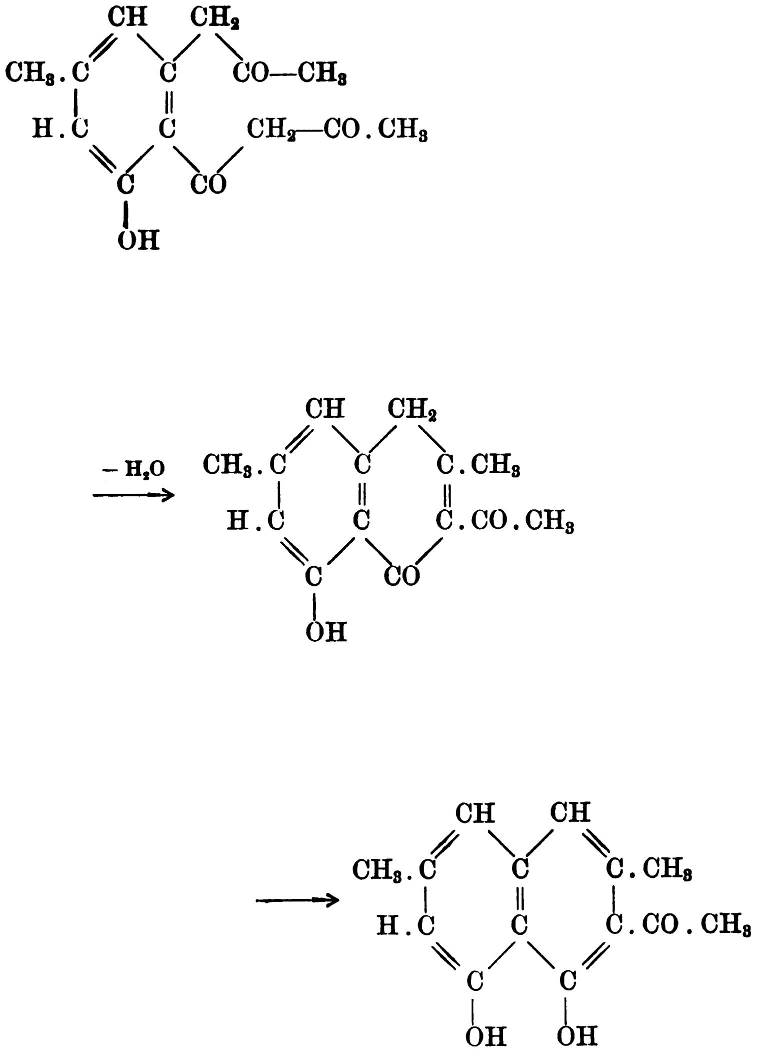
This reaction takes place in strong alkaline solutions, but if we make the alkali very dilute we can extract two water molecules from diacetylacetone in a different way, two diacetylacetone molecules being involved:—



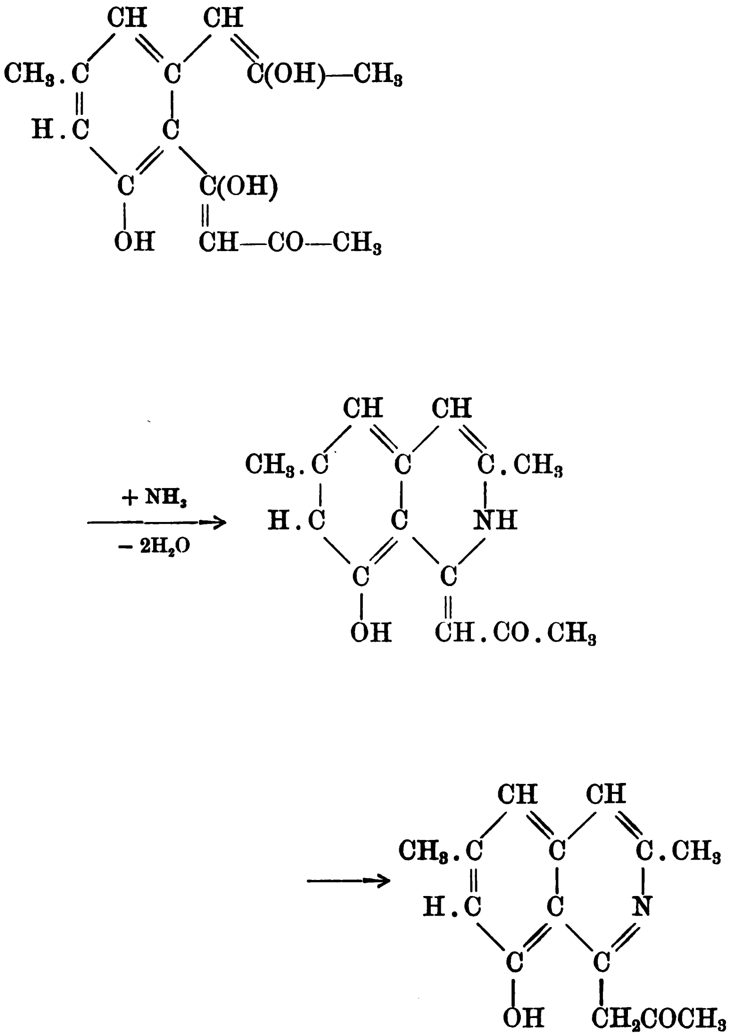
$$\begin{array}{l} CH_3.CO.CH:\underset{\displaystyle \overset{|}{OH}}{C}.CH_2.CO.CH_3 \\ H.\overset{H_2}{C}.CO.CH_2.CO.CH_2CO.CH_3 \end{array}$$

$$\xrightarrow{-2H_2O} \begin{array}{l} CH_3.C\,.\,CH:C.CH_2.CO.CH_3 \\ \quad\;\; \| \qquad\quad\; | \\ H.C—CO—CH.CO.CH_2.CO.CH_3 \end{array}$$

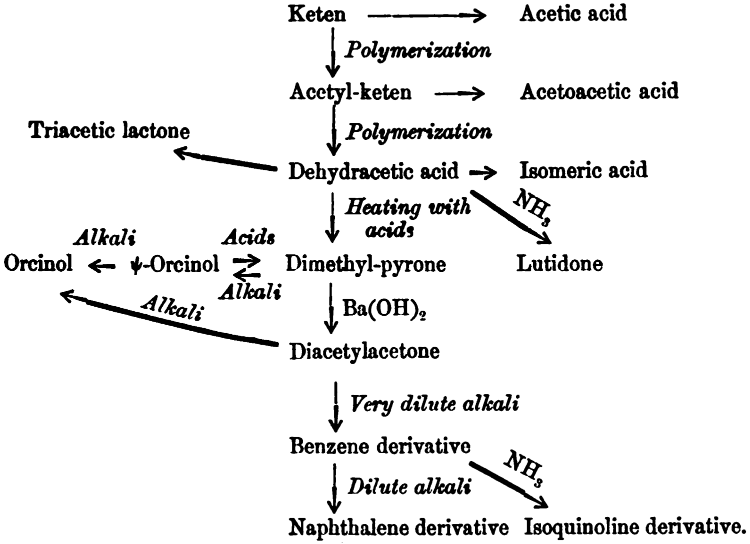
This new benzenoid compound in turn is susceptible to the action of less dilute alkalis, losing another molecule of water and forming the naphthalene derivative shown below—



By allowing the benzene compound to stand at ordinary temperatures in presence of ammonia, an isoquinoline derivative is obtained—

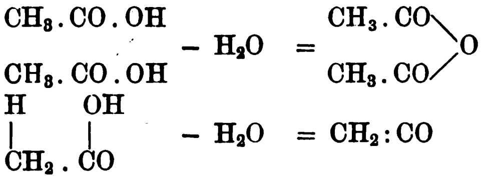


We may summarize these reactions in the following scheme, and then proceed to the examination in detail of the various substances to which we have called attention.



The root-substance of the polyketide class, keten itself, was first prepared[1] by the action of a white-hot platinum wire upon acetic anhydride. About a year later it was shown[2] that it could also be obtained by the removal of the bromine from bromacetyl-bromide, a method which has been applied in the case of ketene homologues also. Keten itself is a colourless gas at ordinary temperatures, condenses in solid carbon dioxide to a colourless liquid, and rapidly polymerizes to a brown oil. Both keten and its polymers have a peculiar penetrating odour.

Keten may be considered to be a second anhydride of acetic acid; for, just as ordinary acetic anhydride is obtained by the removal of a molecule of water from two molecules of acetic acid, keten is obtained by withdrawing a molecule of water from a single molecule of the acid.



$$\begin{array}{l} CH_3.CO.OH \\ CH_3.CO.OH \end{array} - H_2O = \left.\begin{array}{l} CH_3.CO \\ CH_3.CO \end{array}\right\rangle O$$

$$\begin{array}{ll} H & OH \\ | & | \\ CH_2 & .\ CO \end{array} - H_2O = CH_2:CO$$

---

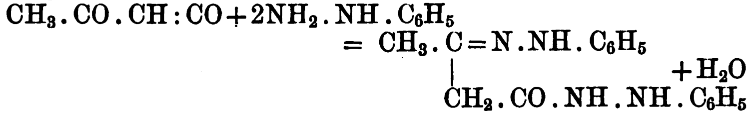
[1] Wilsmore and Stewart, *Nature*, 1907, **75**, 510; Wilsmore, *Trans. Chem. Soc.*, 1907, **91**, 1938.

[2] Staudinger and Klever, *Ber.*, 1908, **41**, 594.

From this it follows that keten should give most of the usual anhydride reactions, and this has been shown to be the case. When passed into water it yields acetic acid; alcohol reacts with it to form ethyl acetate; aniline produces acetanilide; and ammonia forms acetamide. Keten interacts with bromine to form bromacetylbromide, with hydrochloric acid to give acetyl chloride. Thioacetic anhydride is produced by the action of liquid sulphuretted hydrogen upon keten.[1]

We have already mentioned that if keten is allowed to stand at ordinary temperatures it yields a brown condensation product. When this is distilled, the dimolecular polymer of keten passes over as a clear liquid having a very pungent odour.[2] This dimolecular keten, like its parent substance, is a very reactive body. When added to water, it slowly dissolves, yielding a strongly acid solution which, on boiling (especially in presence of hydrochloric acid), gives up acetone and carbon dioxide, losing its acid properties in the process. When it is added to aniline, dimolecular keten forms acetoacetic anilide, while with phenylhydrazine it produces a hydrazone-hydrazide. These reactions are easily explained by assuming that the substance is acetyl-keten, for then the three cases mentioned may be expressed by the following equations:—

$$CH_3.CO.CH{:}CO + H_2O = CH_3.CO.CH_2.COOH$$
$$= CH_3.CO.CH_3 + CO_2$$
$$CH_3.CO.CH{:}CO + NH_2.C_6H_5 = CH_3.CO.CH_2.CO.NH.C_6H_5$$



$$CH_3.CO.CH{:}CO + 2NH_2.NH.C_6H_5 = \begin{array}{l} CH_3.C{=}N.NH.C_6H_5 \\ \quad | \qquad\qquad\qquad\qquad + H_2O \\ CH_2.CO.NH.NH.C_6H_5 \end{array}$$

On the other hand, Staudinger[3] put forward the view that diketen was a tetramethylene derivative, and Wilsmore,[4] after a thorough examination of the compound's properties, inclines to this view. He finds that when diketen, dissolved in carbon disulphide or carbon tetrachloride, is heated first with bromine and then with alcohol, it yields γ-bromo-acetoacetic ester. This tends to prove that diketen has the structure—

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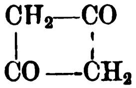
[1] Chick and Wilsmore, *Proc. Chem. Soc.*, 1908, **24**, 78.

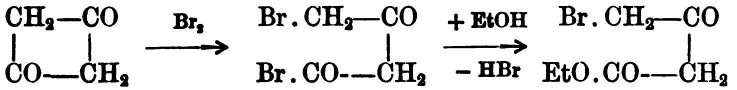
[2] *Ibid.*, *Trans. Chem. Soc.*, 1908, **93**, 946.

[3] Staudinger, *Ber.*, 1909, **42**, 4908.

[4] Wilsmore, private communication to the author.



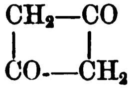
for on this assumption the series of reactions would be expressed simply thus—



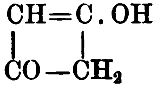
Diketen. γ-Bromo-acetoacetyl bromide. γ-Bromo-acetoacetic ester.

If diketen were acetyl-keten, the product would be the α-bromo-derivative, not the γ-compound. The production of the anilide and hydrazone-hydrazide could also be expressed in accordance with this ring formula for diketen.

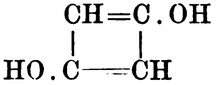
If we assume the cyclic structure for the substance, there are three possible formulæ which must be considered—



(I.)

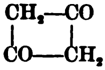
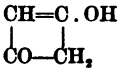
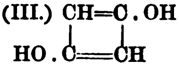


(II.)



(III.)

Against the second and third of these Wilsmore adduces the fact that diketen may be boiled with phenylisocyanate without any interaction taking place between the two compounds. This proves that the presence of hydroxyl groups in diketen is very improbable. The refractivity of the substance does not throw any very definite light upon the constitution. Wilsmore[1] has recently determined the refractive index of the compound, and finds the following:—

	M_α.	M_D.	$M_\gamma - M_\alpha$
Calculated for—			
(I.) 	18·528	18·782	0·472
(II.) 	19·542	19·723	0·635
(III.) 	20·556	20·664	0·798
(IV.) $CH_3.CO.CH{=}CO$	20·364	20·489	0·702
Observed for diketen	20·017	20·144	0·674

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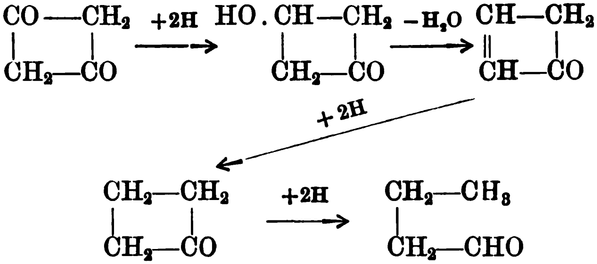
[1] Wilsmore, private communication to the author.

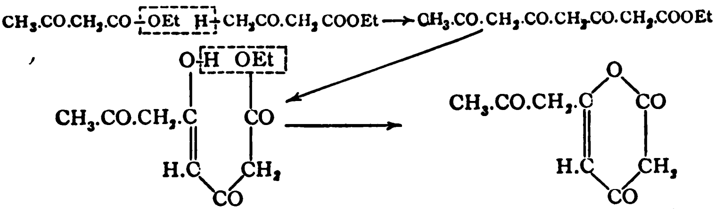
The problem of the constitution of diketen must therefore be regarded as still *sub judice*, but the preponderating evidence from the chemical side points to the compound being 1, 3-diketo-tetramethylene.

When reduced,[1] diketen yields butyraldehyde, the reaction probably taking the course shown below—



From the monoketide ethyl acetate or from diketen we can obtain the diketide acetoacetic ester, whose properties are so well known that it is unnecessary to recapitulate them here; we may therefore pass at once to the consideration of the next polyketide derivative—dehydracetic acid.

This substance can be obtained by polymerizing keten or diketen in benzene solution by means of pyridine or by gentle heating; but it is best prepared by the following method. When acetoacetic ester is heated under a reflux condenser for a time, it loses two molecules of alcohol, and is thus converted into dehydracetic acid, $C_8H_8O_4$. This withdrawal of alcohol may be supposed to take place in either of two ways. In the first case, the two molecules react together to form one long single chain, which then folds back on itself and loses a second alcohol molecule, as shown below—



Collie's Formula.

In the second possible method of formation, one acetoacetic ester molecule reacts in the enolic, the other in the ketonic form—

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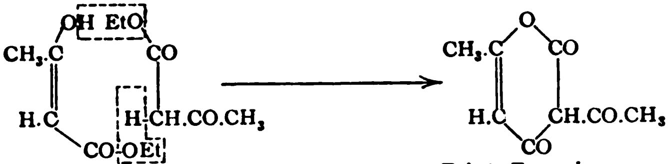
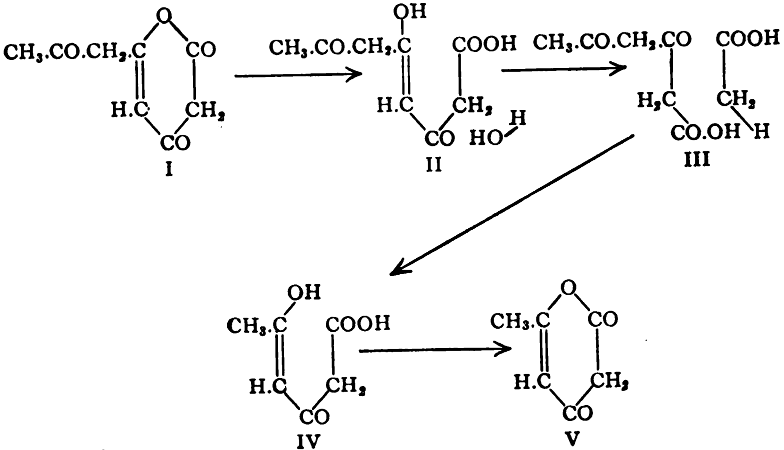
[1] Wilsmore, private communication to the author.



Feist's Formula.

It will be seen at once that the two methods do not lead to identical results; the first, proposed by Collie,[1] yields the lactone of tetracetic acid; while the second, brought forward by Feist,[2] leads to the same nucleus, but produces two side chains instead of one. The Collie formula fails to explain the presence of phenyl-methyl-pyrazyl-phenyl-methyl-pyrazolone as a bye-product in the interaction of phenyl-hydrazine and dehydracetic acid;[3] while the Feist formula cannot be brought into agreement with the fact that with phosphorus pentachloride dehydracetic acid reacts as if it contained two hydroxyl groups.[4] Both formulæ represent the properties of the compound almost equally well, and so far it has been impossible to say which is the correct one. In the following pages the Collie formula will be adopted, as its decompositions are more easily represented than those of the Feist formula.

It will be noticed that the polyketide series which we have described is not quite complete, as we have omitted to deal with triacetic acid. This omission we can now remedy. When dehydracetic acid is heated with ninety per cent. sulphuric acid the ring opens, acetic acid is split off, and the ring closes again, forming triacetic lactone[5]—



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[1] Collie, *Trans. Chem. Soc.*, 1891, **59**, 179.

[2] Feist, *Annalen*, 1890, **257**, 253.

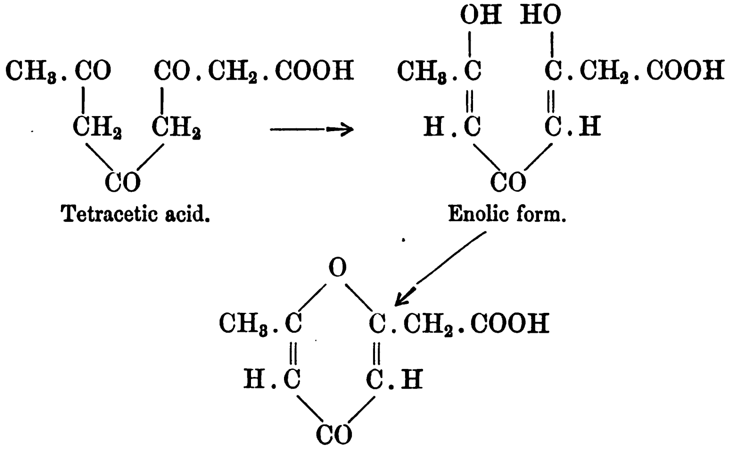
[3] Benary, *Ber.*, 1910, **43**, 1070.

[4] Collie, *Trans. Chem. Soc.*, 1891, **59**, 179.

[5] *Ibid.*, 1891, **59**, 617.

From triacetic lactone we can reproduce dehydracetic acid by the action of acetic anhydride in presence of sulphuric acid.

This production of triacetic lactone, however, is not the only reaction brought about by the action of sulphuric acid. If we dilute the sulphuric acid a little, using eighty-five per cent. instead of ninety per cent. strength, the action takes quite a different form.[1] As in the previous case, water is added on, the ring opens, and tetracetic acid is formed; but instead of breaking down into triacetic and acetic acids, the substance enolizes in a new place and again loses water to form a new acid—



Tetracetic acid.

Enolic form.

Isomer of dehydracetic acid.

This sensitiveness to very slight variations in the reagents used is typical of the polyketide series, as has already been pointed out in the case of the action of weak and stronger alkalis upon diacetylacetone.

The action of concentrated hydrochloric acid, again, differs from those of the two sulphuric acid solutions we have just described. Boiling concentrated hydrochloric acid converts dehydracetic acid into dimethyl-pyrone, the reaction probably taking place in the following way:—

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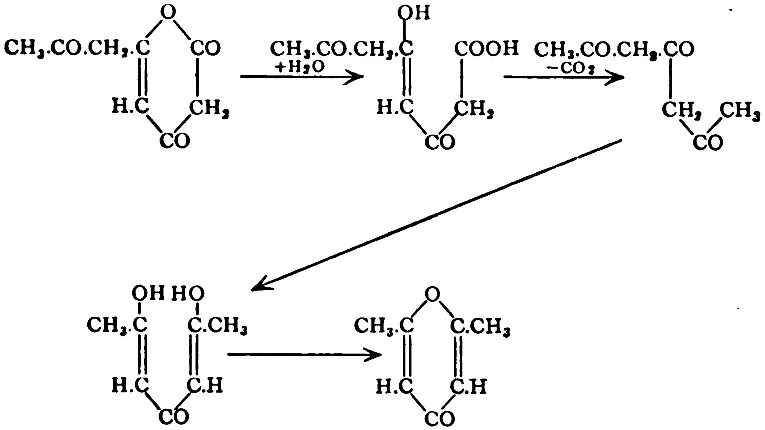
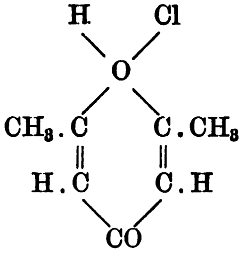
[1] Collie and Hilditch, *Trans. Chem. Soc.*, 1907, 91, 787.



When the dimethyl-pyrone thus obtained is analyzed, however, it is found to have the composition $C_7H_9O_2Cl$, which corresponds to a compound of one molecule of dimethyl-pyrone with one molecule of hydrochloric acid. The substance is not a chlorine substituted pyrone derivative, but behaves exactly like the hydrochloride of an organic base. Collie and Tickle,[1] who were the discoverers of this class of substance, prepared a series of compounds of dimethyl-pyrone with many of the common acids, both organic and inorganic, as well as metallic double salts, and from a study of their properties drew the conclusion that the oxygen atom which forms the bridge in the pyrone nucleus has basic properties akin to those of a tertiary nitrogen atom. Thus, just as tertiary amines form ammonium salts, divalent oxygen compounds may unite with acids to form "*oxonium salts*." The compound of dimethyl-pyrone with hydrochloric acid would on this hypothesis be represented by the formula—



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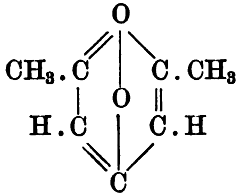
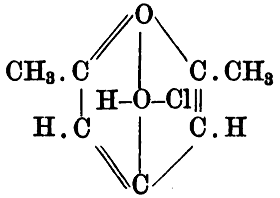
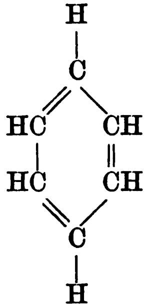
[1] Collie and Tickle, *Trans. Chem. Soc.*, 1899, 75, 710.

Dimethyl-pyrone is a white crystalline solid, subliming at low temperatures and easily soluble in most organic liquids. With acids it forms well-crystallized salts, soluble in, but hydrolyzed by, water. Though it contains a carbonyl group, it does not react with either hydroxylamine or phenylhydrazine. This peculiar behaviour has led Collie[1] to put forward the view that not one but both the oxygen atoms in the pyrone nucleus are quadrivalent in the oxonium salts; while in the base itself one oxygen atom is supposed to be always quadrivalent. On this view the formulæ of dimethyl-pyrone and its hydrochloride would be written thus—

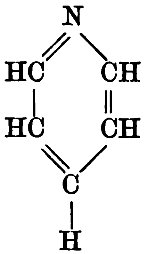




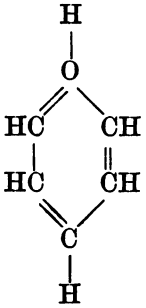
This view of the pyrone structure is supported to a certain extent by an examination of the refractive indices of pyrone derivatives which has been carried out by Miss Homfray.[2] In both of the above formulæ the peculiar resemblance to the benzenoid type is manifest, and Collie has been led to suggest that the root-substance of the pyrone class has a structure which resembles that of pyridine. To this hypothethical compound he has given the name "*oxene,*"[3] as the compound is the oxygen analogue of benzene and pyridine.



Benzene.



Pyridine.



Oxene.

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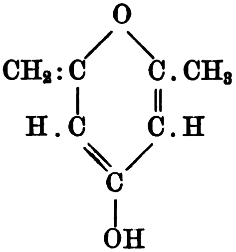
[1] Collie, *Trans. Chem. Soc.*, 1904, **85**, 971; cf. Willstätter and Pummerer, *Ber.*, 1904, 3733; 1905, **38**, 1461.

[2] Homfray, *Trans. Chem. Soc.*, 1905, **87**, 1443.

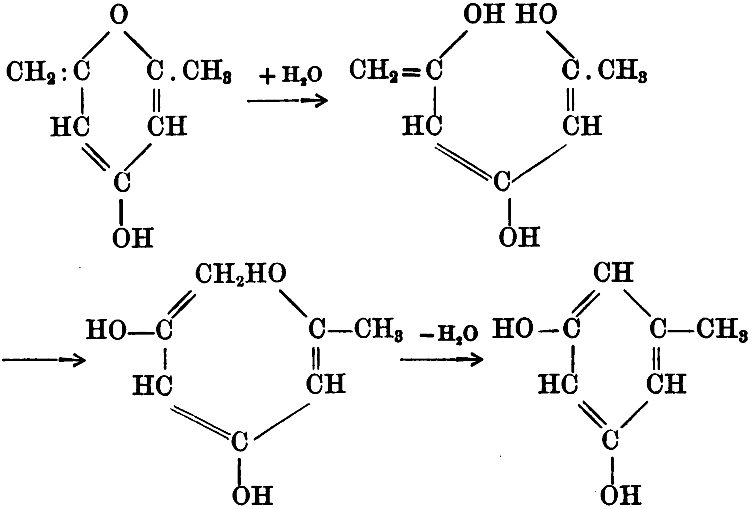
[3] Collie, *Trans. Chem. Soc.*, 1904, **85**, 971.

This view has certain advantages, for upon the ordinary formula it is difficult to explain the comparative stability of the pyrone compounds.

Before dealing with the hydration product of dimethyl-pyrone, mention may be made of a substance[1] which stands midway between the pyrone and benzene series. On treatment with dilute alkalis, dimethyl-pyrone is converted into an isomeric body which appears to have the following constitution:—



When this substance is boiled with acids it is converted into the corresponding salt of dimethyl-pyrone. This change involves only the wandering of a hydrogen atom from the oxygen to the methylene group. On treatment with strong alkali the substance undergoes a more complicated isomeric change and yields orcinol. The steps involved in this reaction are probably the following:—



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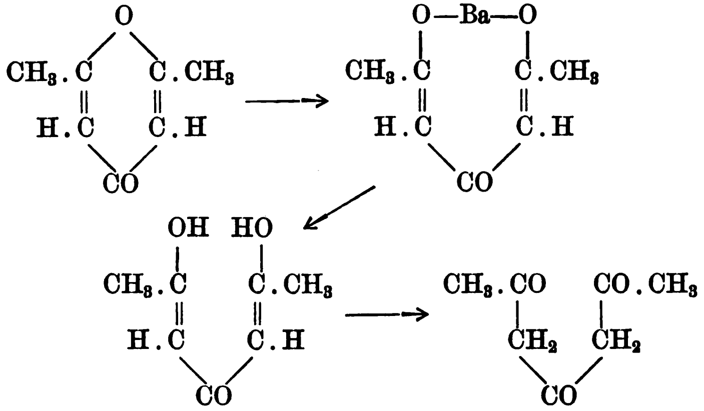
[1] Collie and Stewart, unpublished observation.

Collie[1] has prepared the corresponding diacetyl derivative, which behaves in a similar manner; with acids it is converted into the salt of diacetyl-dimethyl-pyrone, while alkalis change it to diacetyl-orcinol.

We must now turn to the substance which is obtained by the addition of one molecule of water to dimethyl-pyrone. The action requires the presence of alkalis, and is best carried out by boiling dimethyl-pyrone with a strong solution of barium hydrate. After neutralizing the excess of alkali, the solution is shaken out with ether, by which means diacetyl-acetone is extracted. The course of the reaction involves the formation and decomposition of the barium salt of diacetyl-acetone—



Diacetyl-acetone forms colourless mica-like crystals, which volatilize at ordinary temperatures. It is unstable, losing water with great ease, and changing into dimethyl-pyrone; while, under certain conditions, it breaks down into acetone and acetic acid. It forms one of the very small class of triketones, and with it we reach the highest stable member of the polyketide class.

At the beginning of this chapter we called attention to the view that many of the simple substances found in plants were not the results of direct synthesis, but rather of synthesis followed by decomposition, and in diacetylacetone we have a substance which will serve as a typical example of this method. In the first place, by spontaneous dehydration at ordinary

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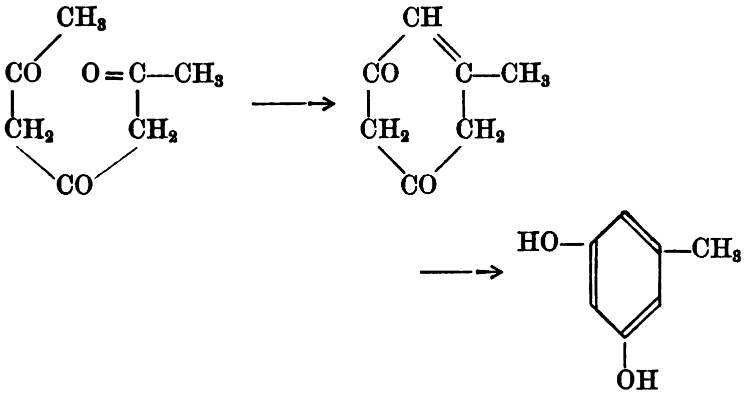
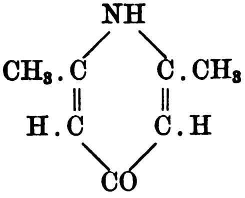
[1] Collie, *Trans. Chem. Soc.*, 1904, **85**, 971.

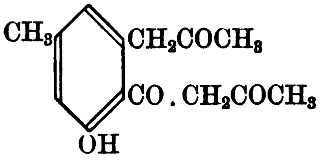
temperatures, we get dimethyl-pyrone. By using acid dehydrating agents we can form orcinol[1]—



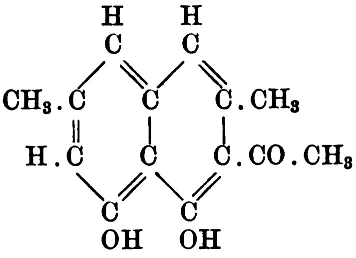
Stronger dehydrating agents produce scarlet dye-stuffs,[2] which are probably similar to those obtained by dehydrating dimethyl-pyrone. We have already described the formation of the pyridine, benzene, naphthalene, and isoquinoline derivatives—



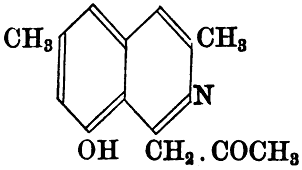
Pyridine compound.



Benzene compound.



Naphthalene compound.



Isoquinoline compound.

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[1] Collie and Myers, *Trans. Chem. Soc.*, 1893, 63, 122.

[2] Collie and Stewart, unpublished observation.

There is one polyketide derivative which we have not yet mentioned. If we treat keten with hydrochloric acid and with ethyl alcohol we get acetyl chloride and ethyl acetate; from the latter we can produce acetoacetic ester, and thence by the aid of the acetyl chloride we can synthesize acetylacetone. This substance completes the series of ketones which we have derived from the simple keten group, and it may be well to give a table showing the relations of each member to the others.

Ketens.	Acids.	Ketones.
Keten $(CH_2 : CO)$	Acetic $H.(CH_2.CO).OH$	Acetone $H.(CH_2.CO).CH_3$
Diketen $(CH_2 : CO)_2$	Acetoacetic $H.(CH_2.CO)_2OH$	Acetylacetone $H.(CH_2.CO)_2.CH_3$
	Triacetic $H.(CH_2.CO)_3OH$	Diacetylacetone $H.(CH_2.CO)_3.CH_3$
	Tetracetic $H.(CH_2.CO)_4OH$	

We may subjoin another tabular statement (see next page), which brings out the relations between dehydracetic acid, the pyrones, and the aromatic series.

So far, we have described only those polyketide derivatives which can be obtained from keten by methods which have actually been worked out experimentally. There is one most important class of substances, however, which do not come within this category, though, theoretically, they belong to the polyketide derivatives. The sugars—though we at present have no means of synthesizing them from keten, or any of its simple derivatives—are very closely related to the keten group. Collie[1] has indicated the lines which should be followed in such syntheses; but at present the proper conditions have not been discovered.

Willstätter and Pummerer[2] have shown that when we act upon pyrone with metallic alcoholates bishydroxymethylene-acetone derivatives are produced. If we consider the effect of opening the pyrone ring with a water-molecule instead of a

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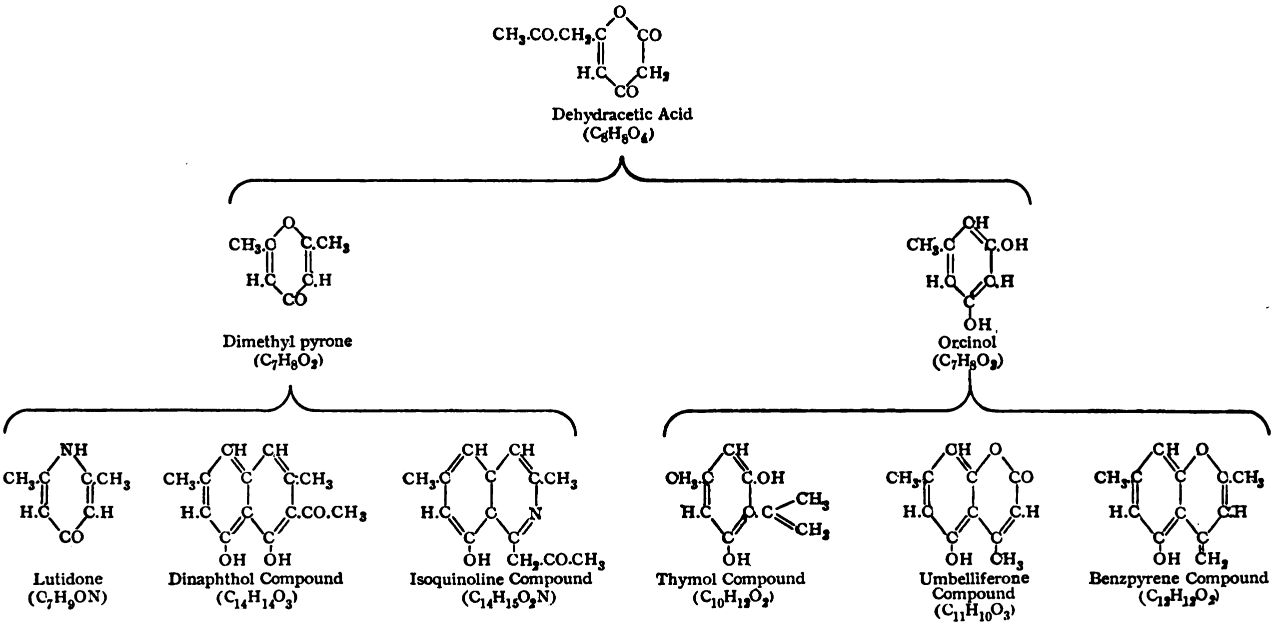
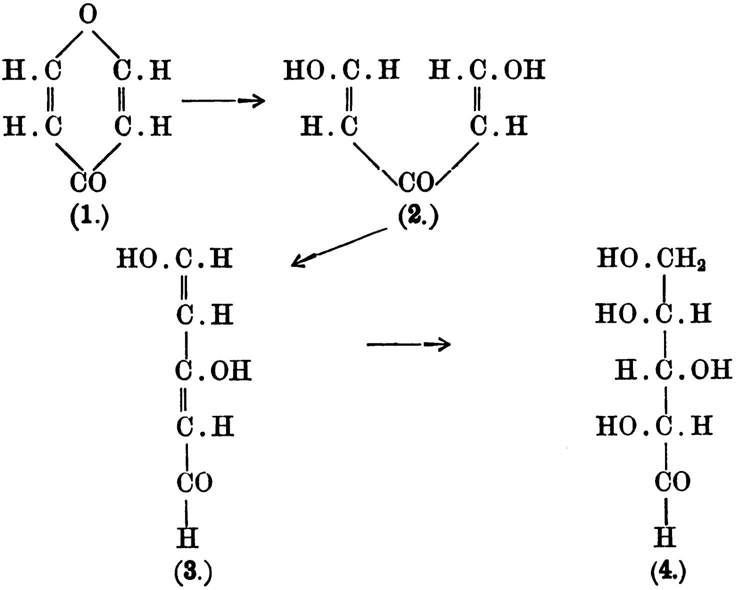
[1] Collie, *Trans. Chem. Soc.*, 1907, **91**, 1806.

[2] Willstätter and Pummerer, *Ber.*, 1905, **38**, 1461.

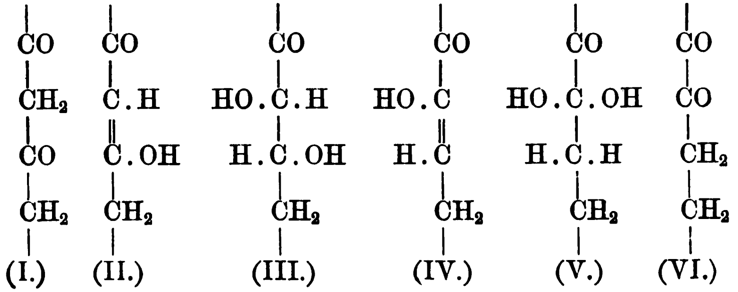


Dehydracetic acid	$C_8H_8O_4 - CO_2 \rightarrow$	$C_7H_8O_2$	Dimethyl pyrone.
	$C_8H_8O_4 - CO_2 \rightarrow$	$C_7H_8O_2$	Orcinol.
Dimethyl pyrone	$C_7H_8O_2$—isomeric change $\rightarrow$	$C_7H_8O_2$	Orcinol.
	$C_7H_8O_2 + NH_3 - H_2O \rightarrow$	C_7H_9ON	Lutidone.
	$2C_7H_8O_2 + 2H_2O - 3H_2O \rightarrow$	$C_{14}H_{14}O_3$	Naphthalene Compound.
	$2C_7H_8O_2 + 2H_2O + NH_3 - 4H_2O \rightarrow$	$C_{14}H_{15}O_2N$ . . .	Isoquinoline Compound.
	$C_7H_8O_2 + H(CH_2CO)_2OH - 2H_2O \rightarrow$	$C_{11}H_{10}O_3$	Umbelliferone Compound.
	$C_{11}H_{10}O_3 + H_2O - CO_2 \rightarrow$	$C_{10}H_{12}O_2$	Thymol Compound.
	$C_7H_8O_2 + C_5H_8O_2 - 2H_2O \rightarrow$ (Acetylacetone)	$C_{12}H_{12}O_2$	Benzpyrene Compound.

molecule of alcoholate, we find that bishydroxymethylene-acetone itself (2) would result. If this could be converted into the isomeric form (3) by the wandering of a hydrogen atom, and the resulting compound could be induced to combine with two molecules of water at the double bonds, the pentose (4) would be produced. So far, no successful attempt has been made to produce this change, but if the proper conditions could be found there seems no reason why it should not be carried out.



By successive hydration and dehydration a different type of product would result—



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 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.

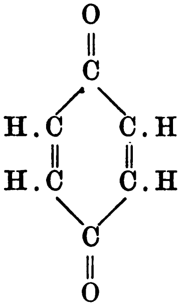
We have now completed our survey of the polyketides and their derivatives, and in conclusion we may point out the salient features of the classes with which we have dealt. The polyketens themselves, $(CH_2 : CO)_n$, are remarkable chiefly for their great reactivity; they are easily attacked by any ordinary reagents, and further possess the power of polymerization to a marked degree. Their union with acid or neutral substances produces compounds which in turn are reactive, though not to the same extent as the parent bodies; but if, on the other hand, the polyketens be combined with basic substances, the products are not at all reactive. The higher members of the polyketide group when combined with water tend spontaneously to lose carbon dioxide, and become converted into ketonic compounds of a lower series, which in turn may be dehydrated to form benzenoid or pyrone derivatives, both of which are comparatively stable. Thus these substances as a class illustrate the dual tendencies at work in the whole field of organic chemistry—the synthetic and the analytic; the simpler, more reactive group tending always to attract other atoms and form more complex derivatives, while these in turn become unstable and break down into new and more stable forms.

CHAPTER IX

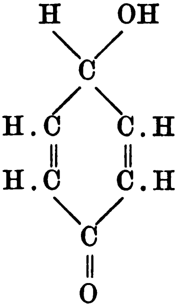
THE QUINOLES

1. *Introductory.*

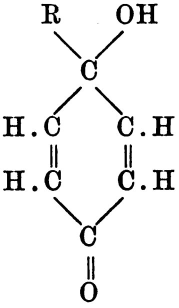
If in the formula of benzoquinone (I.) we replace one of the carbonyl radicles by a secondary (II.) or a tertiary (III.) alcohol radicle, we shall obtain the structural formulæ of two new types of compounds which have been termed quinoles by Bamberger.[1] Compounds of the type (II.) are secondary quinoles; those of the structure (III.) are tertiary compounds.



(I.)



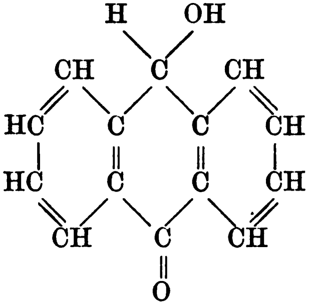
(II.)



(III.)

An examination of the second formula will show that it is the mono-ketonic form of ordinary hydroquinone.

Derivatives of these substances had long been known in the anthracene series, oxanthranol being the simplest of them:



Oxanthranol

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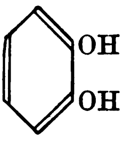
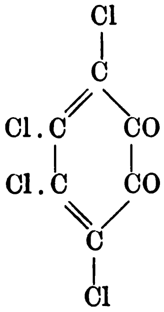
[1] Bamberger, *Ber.*, 1900, **33**, 3607.

but it was not until 1895 that mono-nuclear quinoles were discovered by Zincke,[1] and with this research the history of the quinoles proper begins; for in the anthracene derivatives the specific character of the quinole nucleus is to a great extent concealed owing to the complications introduced into the molecule by the presence of the two benzene nuclei.

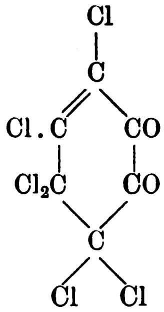
For many years Zincke had been engaged upon the study of the action of chlorine upon various aromatic substances; and his results showed that this reagent was capable of converting the stable and comparatively inert benzenoid nucleus into a most varied and reactive series of products. One example will suffice: the action of chlorine upon catechol.[2] The action takes place in the following stages. The first product is tetrachloro-*o*-quinone (II.), which is then further acted upon by chlorine to give hexachloro-*o*-diketo-R-hexen (III.). When this substance is heated with water, it undergoes intramolecular change, the six-membered ring being converted into a five-membered one, and hexachloro-R-penten-hydroxy-carboxylic acid (IV.) is produced. Oxidation with chromic acid breaks off the side-chains and the ketone hexachloro-R-penten (V.) results, which on treatment with caustic soda opens up, yielding perchloro-vinyl-acrylic acid (VI.), from which ethylidene-propionic acid (VII.) may be obtained by reduction.



(I.)



(II.)



(III.)

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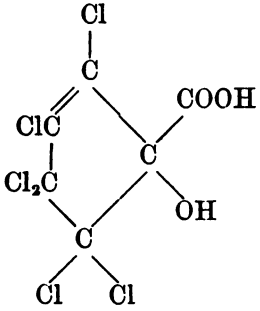
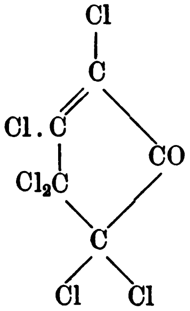
[1] Zincke, *Ber.*, 1895, **28**, 3121.

[2] Zincke, *Ber.*, 1888, **21**, 2719; 1889, **22**, 486; 1891, **24**, 908; 1893, **26**, 2104; 1894, **27**, 3364.


(IV.)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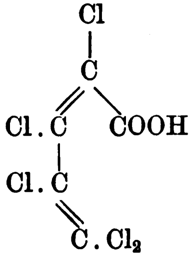
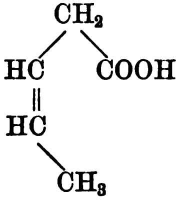
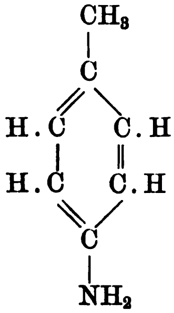
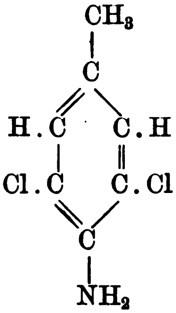
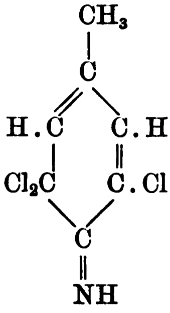

(VI.)


(VII.)

When Zincke applied this reaction to para-cresol[1] he found that the substance was unexpectedly stable, for the end-product of the chlorination process still contained two nuclear hydrogen atoms unreplaced by chlorine, $CH_3 . C_6H_2 . Cl_3O$. Replacing para-cresol by para-toluidine, he obtained as the end-product of the reaction the substance $CH_3 . C_6H_2 . Cl_7O$. Zincke formulates the reaction in the following manner:—


(I.)


(II.)


(III.)

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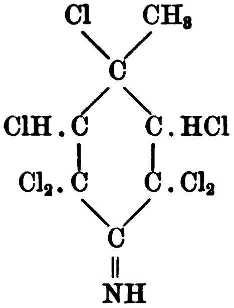
[1] Bamberger, *Ber.*, 1900, **33**, 3607.



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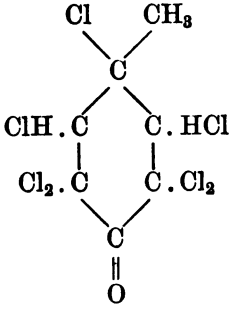
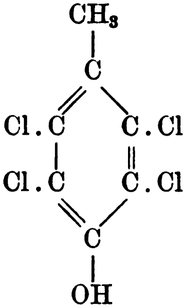


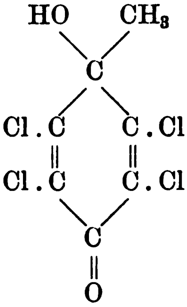
(V.)

The difference between the reactions of the phenol and amido-compound is to be ascribed to the fact that the intermediate imide formed from the toludine is more reactive than the corresponding keto-chloride which is produced from the cresol.

Now if we reduce the keto-chloride (V.) we obtain tetrachloro-para-cresol:



When this was treated with nitric acid, Zincke expected, by analogy with the results obtained by him in other cases, that an ortho-quinone of the formula $CH_3 . C_6Cl_3O_2$ would be produced; but instead of this substance he obtained a compound having the formula $CH_3 . C_6HCl_3O_2$. On reduction, this new substance regenerated tetrachloro-para-cresol, and on the grounds which we shall deal with in a later section, Zincke ascribed to it the formula—



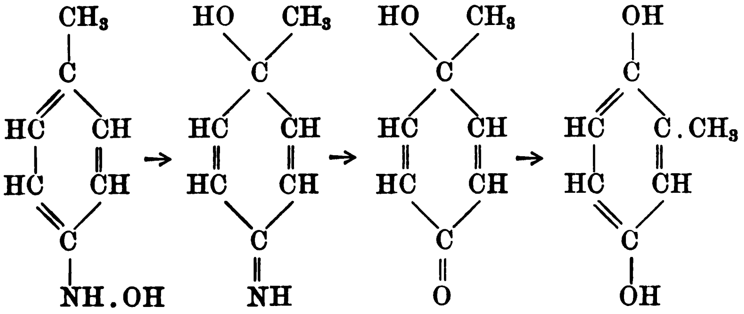
It belongs to the quinole series, and in this way a new line of research was opened up.

2. *Methods of Preparing Quinoles.*

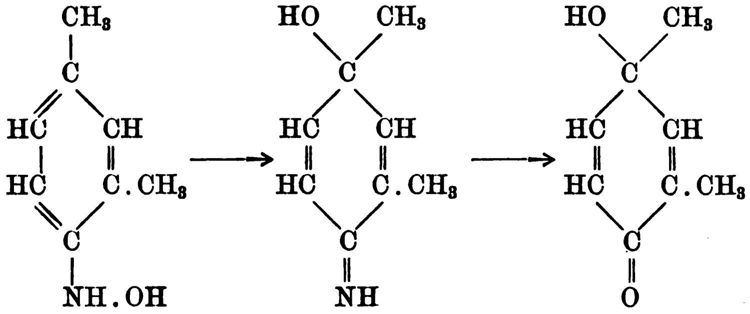
The quinoles which have been prepared up to the present may be divided into three classes: those with no substituents attached to the nucleus; quinoles whose nuclear hydrogen atoms have been replaced by alkyl radicles; and, finally, halogen-substituted quinoles. Since in some instances it is impossible to prepare the parent substances by reactions which answer quite well in the case of derivatives, it will be most convenient to classify the methods of preparation of these substances according to the end-products of the reaction; and we shall therefore take up in turn the three types of quinoles.

I. *Simple Quinoles.*—These were obtained by Bamberger[1] in the following manner. If we subject a para-alkylated aryl-hydroxylamine derivative to the action of dilute sulphuric acid or alum solution, the first product at ordinary temperatures is an imido-quinole; but should the reaction be prolonged, this substance breaks down into ammonia and the corresponding quinole. If the action be not brought to an end at this point, intramolecular change occurs and an alkyl-substituted hydroquinone is formed. For instance, in the case of para-tolyl-hydroxylamine the reaction takes place in the stages illustrated by the formulæ below.

[1] **Bamberger, *Ber.*, 1900, 33, 3615.**



II. *Alkyl-substituted Quinoles.*—There are three methods of preparing this set of derivatives. In the first place, we may apply the aryl-hydroxylamine reaction described above, starting in this case with a di-substituted aryl-hydroxylamine instead of a mono-substituted one. For instance, in the case of 2, 4-dimethyl-phenylhydroxylamine[1] we have the following series of changes, resulting in the production of dimethyl-quinole:—



Caro's reagent applied to di-substituted phenols[2] produces a certain amount of the corresponding quinole; but the yields are small. Of course in both the aryl-hydroxylamine and the phenol which are used as starting-points for the foregoing reactions one of the substituent alkyl radicles must be in the para-position to the hydroxylamine residue or to the hydroxyl group.

A third method[3] of preparing alkyl-substituted quinoles consists in the application of Grignard's reagent to substituted

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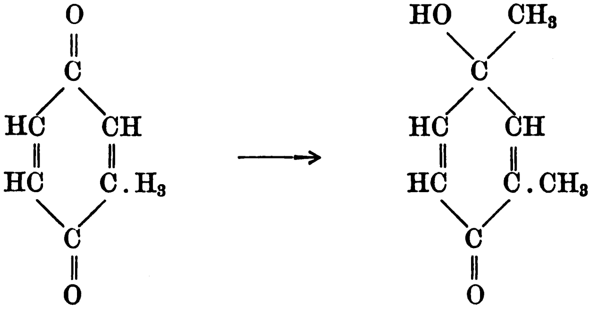
[1] Bamberger, *Ber.*, 1900, **33**, 3647.

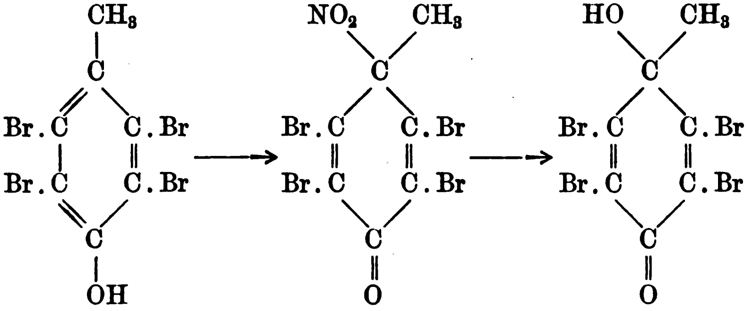
[2] *Ibid.*, 1903, **36**, 2028.

[3] Bamberger and Blangey, *Ber.*, 1903, **36**, 1626.

quinones. Benzoquinone itself does not give a quinole in this way, but when toluquinone is treated with magnesium methyl iodide, a dimethyl-quinole is produced:—



III. *Halogen-substituted Quinoles.*—In the introductory section of this chapter we have seen that these bodies may be prepared by the chlorination of para-substituted aromatic amines. The researches of Zincke[1] and of Auwers[2] have shown that when halogen-substituted phenols are heated with concentrated nitric acid, the corresponding quinoles are produced. In this case the intermediate products are cyclic nitro-ketones, so that the reaction takes the following course:—



Similar results are obtained when halogen-substituted phenols are dissolved in glacial acetic acid and then treated with nitrous fumes.

When bromine is allowed to act upon para-cresol, Zincke and Wiederhold[3] found that there are three possible types of

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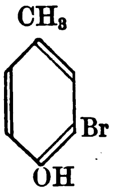
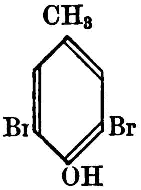
[1] Zincke, *Ber.*, 1895, **28**, 3121; 1901, **34**, 253, *J. pr. Ch.*, [2] 1897, **56**, 157.

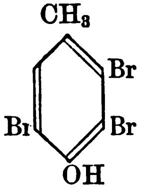
[2] Auwers, *Ber.*, 1897, **30**, 755; *Annalen*, 1898, 302, 153.

[3] Zincke and Wiederhold, *Annalen*, 1901, **320**, 199.

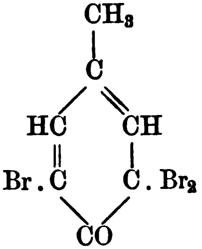
reaction product, one or another preponderating according to the conditions of the experiment. If the bromine acts upon the phenol in chloroform solution at ordinary temperatures, we obtain simply the mono-, di-, and tribromo-derivatives of paracresol:—

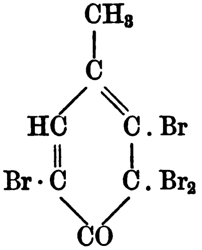


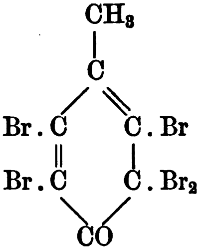




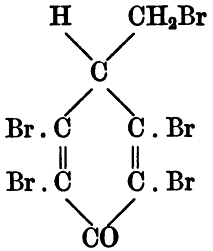
When water is substituted for chloroform, we get normal keto-bromides, such as:—



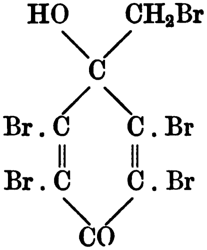




But if we allow bromine in excess to act directly upon the phenol, without any solvent, in a sealed tube at 100° C. for several hours, bromine enters the side-chain, and we get tetrabromo-*p*-cresol-pseudobromide:—



When this substance is boiled with nitric acid (sp. gr. 1·4) it yields pentabromo-toluquinole, which has the following constitution:



3. *The Properties of the Quinoles.*

As a class, the quinoles are distinguished by extreme reactivity and lability of structure. They react with many of the ordinary reagents with great ease; and in addition they are capable of undergoing very far-reaching isomeric changes. With the latter division of their properties we shall deal in a special section; at present we shall confine ourselves to the action of the commoner chemical reagents upon compounds of the quinole type.

In their general chemical character, the quinoles resemble weak acids. They are soluble in caustic alkali, but not to any great extent in sodium carbonate solution. From this behaviour we may deduce the presence of a hydroxyl group in their structure.

When reducing agents such as sulphurous acid, zinc dust and acetic acid, or zinc and aqueous ammonium chloride are employed upon quinoles, reduction takes place with great ease. Bamberger[1] has found that even ferrous sulphate and sodium carbonate solution are sufficient to reduce a dimethyl-quinole to the corresponding phenol. This formation of the benzenoid nucleus in preference to the quinonoid one is, as we shall see later, one of the most characteristic features of the intramolecular changes which have been observed in the quinole group. The tendency is so strong that reduction is brought about by such unlikely substances as hydrobromic acid and phosphorus pentabromide.[2] In all these cases we may formulate the reduction process as a true reduction in one of its stages, the next stage being the loss of water or hydrobromic acid. In the

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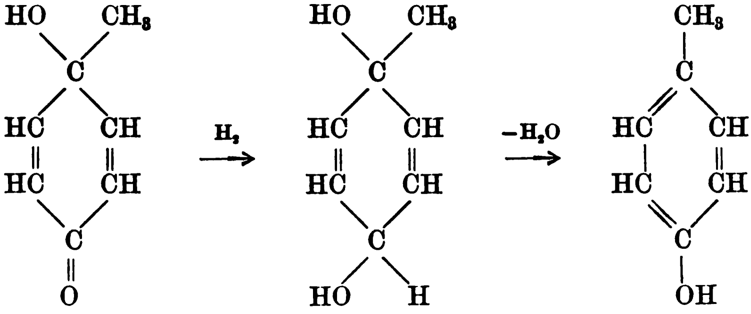
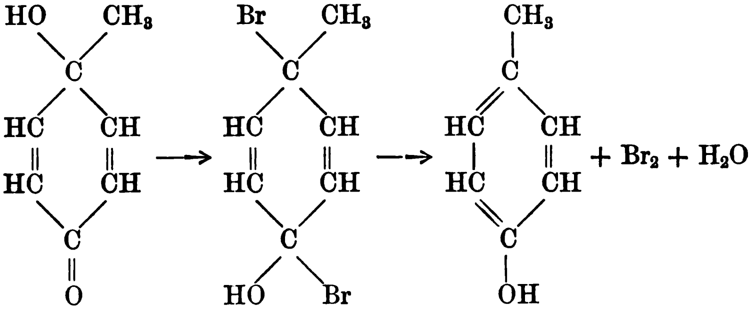
[1] Bamberger, *Ber.*, 1900, **33**, 3616.
[2] Auwers, *Ber.*, 1902, **35**, 445.

reduction by means of pentabromide of phosphorus, the first step appears to be the replacement of the hydroxyl group of the quinole by a bromine atom; the hydrobromic acid thus liberated then reacts as usual with the quinole. The following formulæ give some idea of the reduction of methyl quinole by zinc dust, hydrobromic acid, and phosphorus pentabromide.

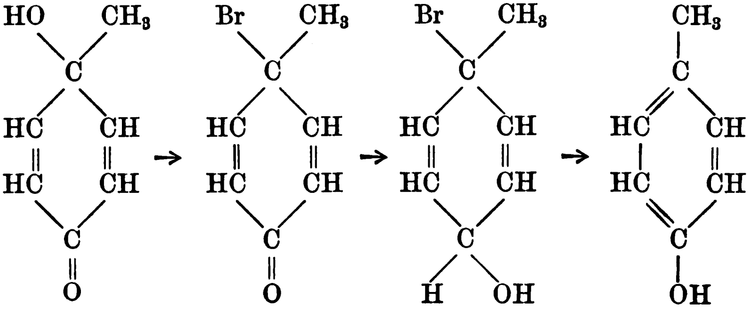
Zinc dust and acetic acid—



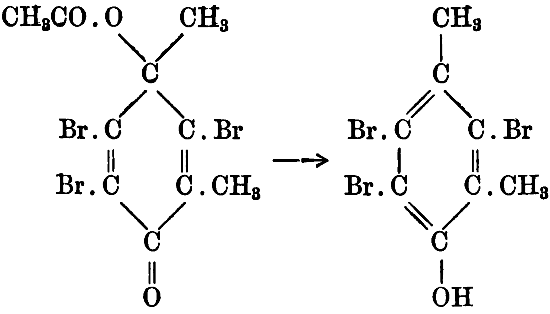
Hydrobromic acid—



Phosphorus pentabromide—



From their behaviour towards alkalis, it was to be expected that the quinoles would yield acyl derivatives; and this has proved to be actually the case. Mono-acetates are produced when quinoles are treated with acetic anhydride or acetyl chloride; and the benzoyl derivatives are formed in the usual way by the Baumann-Schotten reaction. It has been found that in the case of the quinoles derived from brominated phenols, the acyl derivatives are even more easily reduced than the parent quinoles are. Auwers[1] mentions as an example of this the case of tribromo-*m*-xyloquinole. This substance is not attacked at ordinary temperatures by hydrobromic acid in acetic acid solution; reduction begins only at 100° C. But when the acetyl derivative of the quinole is subjected to the same agent, it is reduced even at ordinary temperatures to tribromo-xylenol.



It is easy to see that this power of reduction which hydrobromic acid possesses must exert considerable influence in the case of the action of acetyl bromide upon quinoles. While acetyl chloride yields the ordinary mono-acetate of the quinole employed, it is frequently found that acetyl bromide produces the acetate of the corresponding phenol; so that in the latter case the simple acetylation has been complicated by the reduction of the quinole to the phenol by means of the hydrobromic acid liberated in the course of the reaction. The reducing action of the hydrochloric acid which is liberated when acetyl chloride is used is very much feebler than that of the hydrobromic acid; and consequently the quinole acetate in that case is not transformed into the phenolic derivative.

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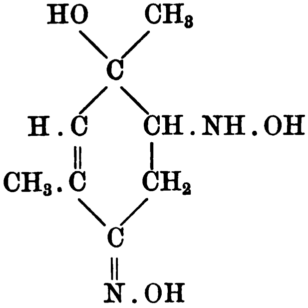
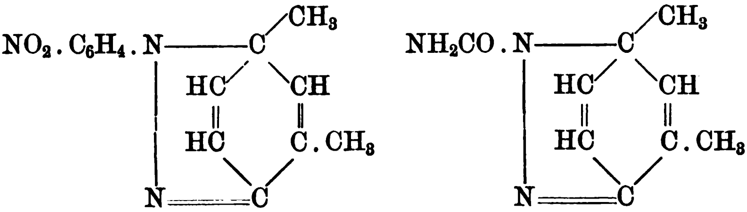
[1] Auwers, *Ber.*, 1902, 35, 446.

Turning now to the reagents which react with carbonyl groups, we find that a difference is to be noted between two classes of the quinoles. Those quinoles which have substituents in the two positions ortho to the carbonyl radicle follow the usual rule in such cases and do not interact with phenylhydrazine, hydroxylamine, or semicarbazide.[1] The case of an unsubstituted quinole differs from this. Bamberger and Rudolf[2] have found that when xyloquinole is treated with hydroxylamine, it reacts with two molecules of the latter, giving a substance which is both an oxime and a substituted hydroxylamine.



With nitro-phenylhydrazine and with semicarbazide, the same quinole gives cyclic substances[3] having the following formulæ :—



From the foregoing, the salient features of the quinoles can be inferred, and in the following section we shall show how the constitution of these substances may be deduced.

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[1] Auwers, *Ber.*, 1902, **35**, 444.

[2] Bamberger and Rudolf, *Ber.*, 1907, **40**, 2236.

[3] Bamberger, *Ber.*, 1900, **33**, 3620.

4. *The Constitution of the Quinoles.*

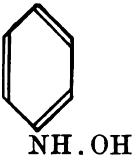
In the previous section we have dealt with most of the material which will be required to establish the structure of the quinoles; and in the present section it will be convenient to deal with the question point by point.

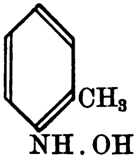
I. *The quinoles contain a ring of six carbon atoms.* This is shown by their conversion into benzene derivatives on reduction.

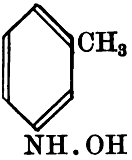
II. *The quinoles contain a hydroxyl group.* This is proved by their yielding acetyl derivatives; and also by the fact that they dissolve in alkalis more readily than in water, and that acids precipitate them from these alkaline solutions.

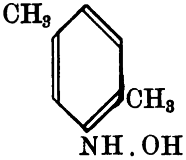
III. *They contain a carbonyl group.* The action of phenylhydrazine, hydroxylamine, and semicarbazide upon quinole derivatives establishes this.

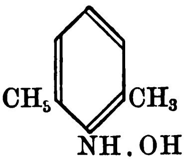
IV. *Quinoles have a methyl radicle in the* 1, 4-*position to the carbonyl group.* The most convincing proof of this is an indirect one. It was found by Brady[1] that quinoles are produced only from phenyl-hydroxylamine derivatives which have an alkyl group in the para-position to the hydroxylamine residue. For example, the five compounds below gave no quinoles when treated in the usual manner with sulphuric acid or alum solution:—











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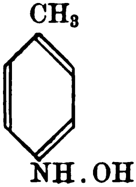
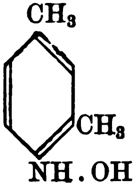
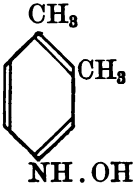
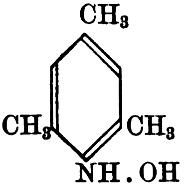
[1] See Bamberger, *Ber.*, 1900, **33**, 3616.

but all the following four compounds yielded quinoles :—



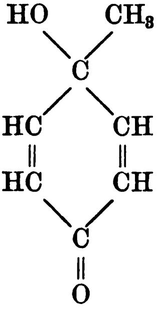




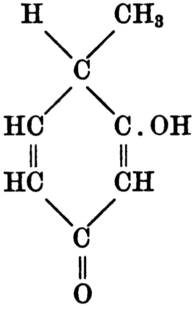


It is clear that quinole formation takes place only when there is a methyl group para to the hydroxylamine residue; and since the group —NH.OH in the aryl-hydroxylamines corresponds to the carbonyl radicle in the quinoles, we may conclude that in the latter compounds the carbonyl and methyl radicles are in the para-position to one another.

Having advanced to this point, it is clear that there are only three possible formulæ for methyl-quinole :—



(I.)



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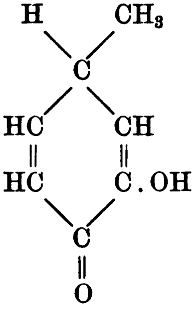
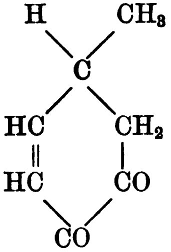


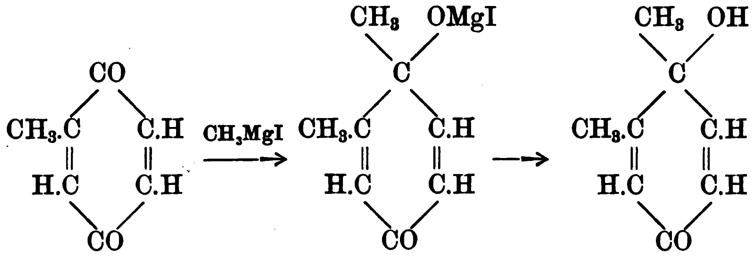
(III.)

The third of these is the enolic form of an ortho-diketone :



and since the properties of methyl-quinole do not correspond to those which we should expect to find in ortho-diketones, we may dismiss this formula. If we examine the second formula, we find that it is a tautomeric form of cresorcinol; so we may reject this formula also. This leaves us with the first formula as the only probable one.

Further evidence in favour of this structure is furnished by the formation of quinoles from quinones by means of the Grignard reaction:—



The yields are so small that this reaction would not in itself furnish a perfectly satisfactory proof of the quinole structure; but it lends additional weight to the other proofs.

5. *Intramolecular Change in the Quinole Series.*

In the foregoing sections we have encountered one or two instances in which the quinole derivatives were converted into benzenoid compounds by the action of suitable reagents; in the present section we shall discuss several other cases of the same type.

It has been shown by Stewart and Baly[1] that the introduction of substituents into the quinone nucleus tends to give the intramolecular vibrations of the system a more and more pronounced benzenoid character; the compounds lose their ketonic properties to a marked extent,[2] and their absorption spectra approximate more and more closely to those of the benzene derivatives. In the case of the quinoles, the replacement of the one carbonyl group of the quinone by a tertiary alcoholic radicle appears to produce an analogous effect; but since in this case there is a possibility of the substances undergoing intramolecular rearrangement, the process is carried a step further than in the simple quinones, and a wandering of radicles ensues which actually produces true benzene derivatives.

In the quinole group, the chief part of the molecule which

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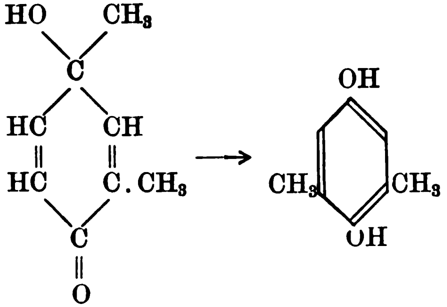
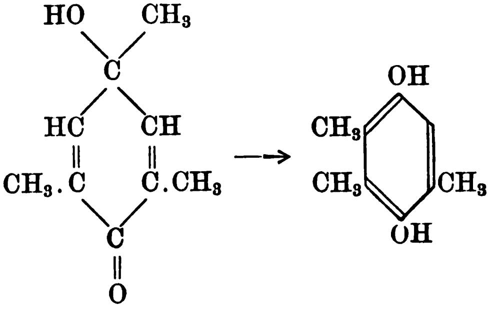
[1] Stewart and Baly, *Trans. Chem. Soc.*, 1906, **89**, 618.

[2] Kehrmann, *Ber.*, 1888, **21**, 3315; *J. pr. Ch.* 1889, **39**, 399; **40**, 257.

is involved in intramolecular change is the tertiary alcoholic radicle, and in most cases the methyl group in this wanders to some other part of the six-member ring. We may now describe several instances in which this methyl radicle is removed from its original position and re-attached to the carbon atom in the ortho-position.

Bamberger[1] has found that when quinoles such as those shown below are subjected to the action of hydrogen, or, better, hydroxyl ions, they are converted into homologues of hydroquinone, as the formulæ indicate:—





In these cases, it is clear that the forces which bring about the intramolecular change are of a strength sufficient to eliminate a hydrogen atom from the nucleus and to replace it by a methyl radicle. A much more powerful action is shown in another case, which was investigated by Zincke.[2] If we treat tetrabromo-ethyl-quinole with concentrated sulphuric acid in the cold, we find that hydrobromic acid is eliminated, and the ethyl radicle replaces the bromine atom which has been driven out of the nucleus:—

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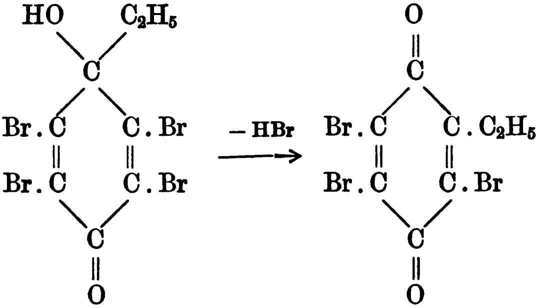
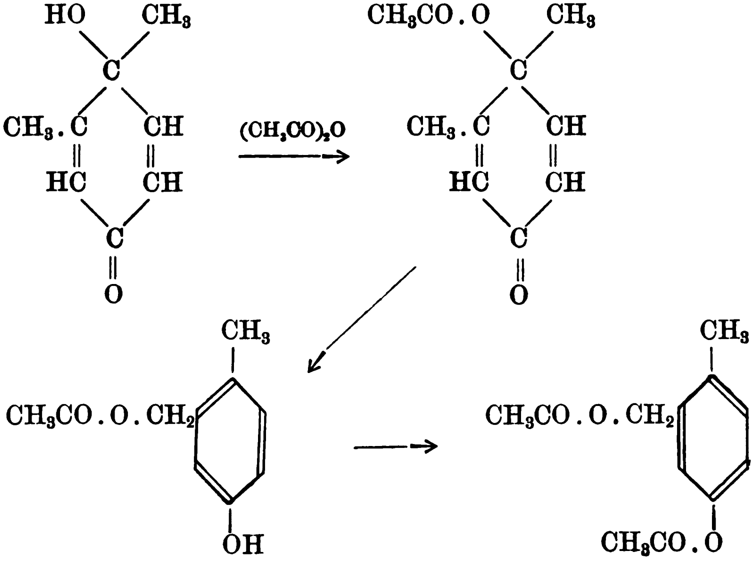
[1] Bamberger, *Ber.*, 1900, 33, 3618.

[2] Zincke, *Ber.*, 1901, 34, 253.



A still more extraordinary wandering is seen in a case mentioned by Auwers.[1] If we heat quinoles with acetic anhydride, they yield monoacetates; but if sodium acetate be present, it is found that a diacetate is formed in the case of those quinoles which have a methyl group in the position ortho to the tertiary alcohol residue. Investigation shows that this second acetyl group has entered the methyl radicle; so that the reaction really takes place in the following stages: (1) acetylation of the hydroxyl group of the quinole; (2) wandering of the acetate group into the methyl radicle in the ortho-position to it; (3) acetylation of the new hydroxyl group formed by the change from the quinolic to the benzenoid structure:—



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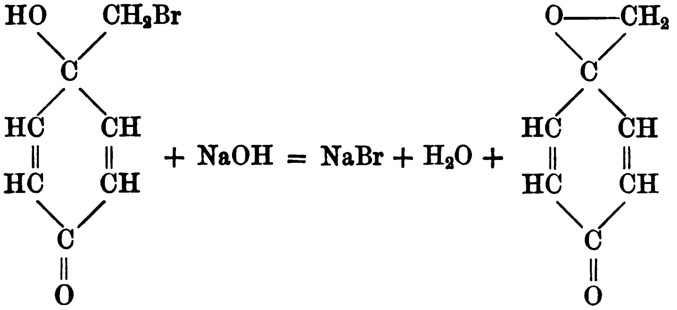
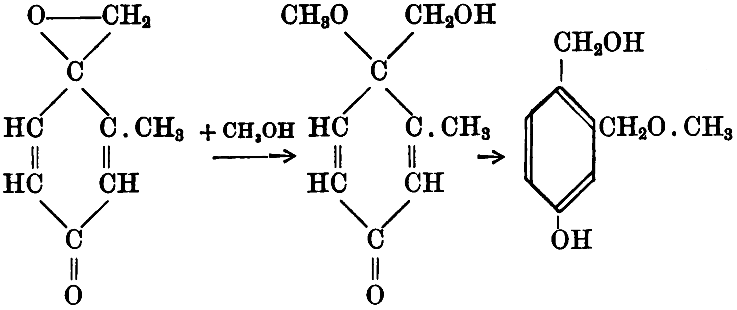
[1] Auwers, *Ber.*, 1902, 35, 449.

If we examine the behaviour of quinoles whose methyl group contains a halogen substituent, a fresh set of changes is presented to us. In the first place, if we allow equimolecular quantities of caustic soda and quinole to interact, we get, as Zincke has shown,[1] an oxide of the following type. formed:—



On the other hand, if excess of alkali be used, and if the quinole contains a methyl radicle in the ortho-position to the hydroxyl, the reaction takes another turn; for the oxide reacts with the solvent (methyl or ethyl alcohol) with the following results:—



In special cases it has been observed that the methyl radicle remains attached to its carbon atom, while another group wanders. For example, Auwers[2] finds that in the

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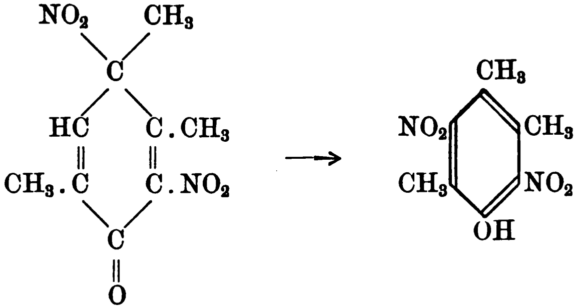
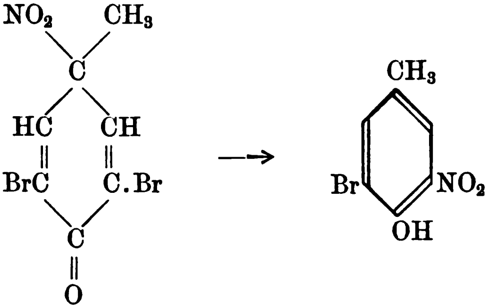
[1] Zincke, *Ber.*, 1895, **28**, 3121; *Annalen*, 1901, **320**, 177; Auwers, *Ber.*, 1902, **35**, 451.

[2] Auwers, *Ber.*, 1902, **35**, 454.

nitro-ketones, the nitro-group wanders sometimes into the ortho- and sometimes into the meta-position, as shown in the following formulæ :—





A similar wandering of the quinole hydroxyl group to the meta-position has been observed in one case.[1] When xyloquinole is treated with alcoholic sulphuric acid, it is converted into a mixture of substances indicated in the formulæ below, from which it will be seen that in the one case the methyl radicle has wandered, while in the second case the hydroxyl group has changed its position in the ring.

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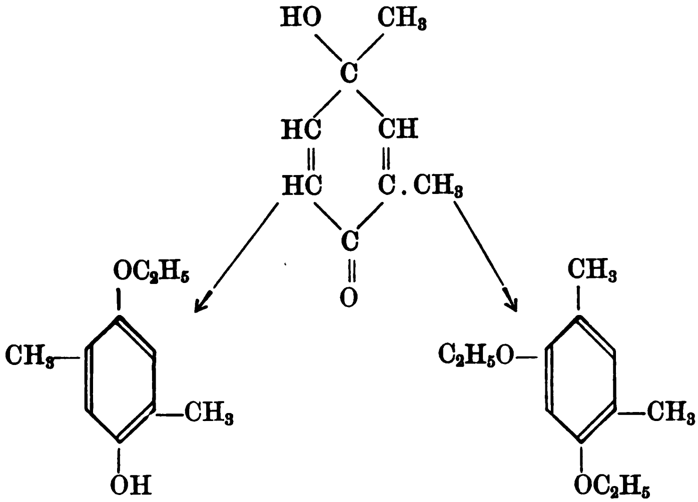
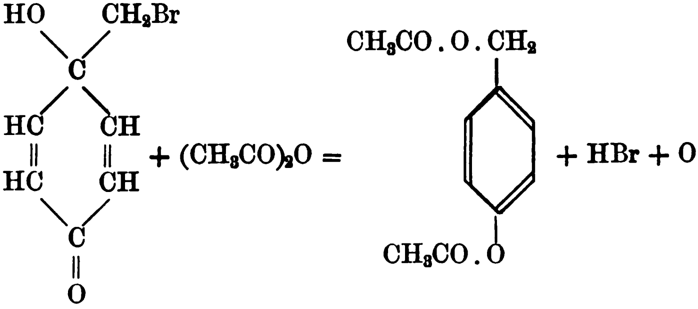
[1] Bamberger, *Ber.*, 1907, **40**, 1895.



In conclusion, we may add two instances in which the groups in the para-position to one another are acted upon simultaneously. In the first place we may take the action of boiling acetic anhydride upon the bromo-substituted quinoles in which the bromine atom is in the side-chain. In this case[1] a loss of hydrobromic acid takes place, but at the same time reduction occurs, and the final product is the diacetyl derivative of para-hydroxy-benzyl alcohol:—

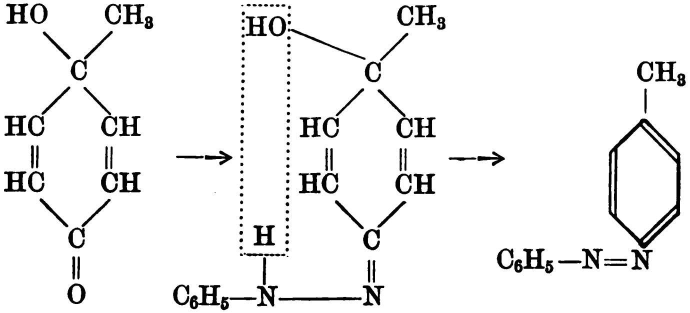


Again, Bamberger[2] has found that in some cases the action of phenylhydrazine ends in the production of azo-compounds, the intermediate step being the elimination of water between the

[1] Auwers, *Ber.*, 1902, **35**, 450.

[2] Bamberger, *Ber.*, 1902, **35**, 1426.

hydroxyl group of the quinole and the hydrogen of the imino-radicle of the hydrazine nucleus :—



6. *Conclusion.*

From the changes dealt with above, the reader will have gathered something of the extraordinary lability of the quinole nucleus. There is hardly another class of compounds which shows such examples of intramolecular interchange of groups; and at present the only determining factor which we can detect underlying the quinole rearrangements appears to be the attempts of the unstable quinoles to revert to the more stable benzenoid type. It seems clear that further investigation of this field might lead us to an understanding of the cause of the stability which the aromatic series in general exhibits towards most reagents. In the quinoles we apparently have a bridge between the alicyclic compounds on the one hand and the aromatic bodies on the other; and as is the case with most intermediate compounds, the quinoles are more reactive than members of either the aliphatic or the aromatic series.

CHAPTER X

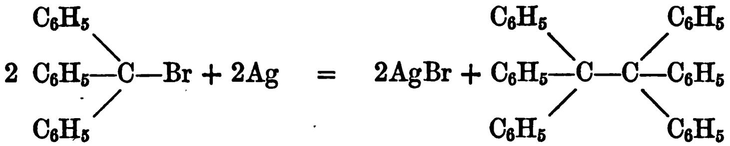
THE TRIPHENYLMETHYL QUESTION

1. *Introductory.*

ANY one who glances through the journals of the chemical world for the last few years must be struck by the enormous production of new compounds which is at present going on; and if he reflects at all, he will be driven to ask himself what criterion should be applied in order to distinguish the really important substances from what we may term the by-products of synthetic chemistry. It is perfectly clear from our experience that the only fate which can overtake the majority of these new compounds is that their dossiers will be "neatly tucked away in Beilstein, the Abstracts published by the various Chemical Societies, or in other equally convenient depositories of information." There they will remain at best in a dormant condition, waiting the time when some *Analogie-arbeit* necessitates a knowledge of their properties. On the other hand, those new bodies which have any interest apart from their melting-points soon become centres of new research; and the more important of them usually lead to investigations extending far beyond the constitution and properties of the original compound. For example, the researches which more than a generation ago took their rise in the constitution of acetoacetic ester have not yet reached their final stages.

This ramification of interest has seldom been so strongly marked within recent years as in the case of the substance termed triphenylmethyl; and it is the rapid extension of the field of research in this division of the subject which makes any treatment of the triphenylmethyl problem difficult. In the present chapter, it will be necessary to confine ourselves as far as possible to the narrow question of the constitution of triphenylmethyl and only to touch lightly upon the wider questions which are closely bound up with it.

The discovery of triphenylmethyl took its rise in an attempt to prepare hexaphenyl-ethane, which was made by Gomberg[1] in 1900. He allowed "molecular" silver to act upon triphenylbromo-methane, and obtained a compound which he naturally supposed to be hexaphenyl-ethane, for the reaction would normally have taken the course expressed in the formulæ below—



On analysis, however, the substance was found to have about six per cent. too little carbon to agree with the hexaphenylethane formula; and further examination showed that it could not be a hydrocarbon at all, but must contain oxygen.

This oxygen might have been introduced in either of two ways: it might have been imported through the silver used in the reaction; or it might have been derived from the air. The experiments were therefore repeated, other metals, such as zinc and mercury, being used instead of silver; and still the resulting substance was found to be oxygenated. From this it was clear that atmospheric oxygen was the origin of the oxygen in the end-product; and further experiments were made in which precautions were taken to exclude air from the apparatus. The end-product in this case differed from that which had previously been obtained; and on analysis it was found to have the composition corresponding to hexaphenyl-ethane.

An examination of its properties, however, brought Gomberg to the conclusion that the substance which he had obtained could not be hexaphenyl-ethane; for he had expected that that body would be an extremely stable compound, whereas his synthetic hydrocarbon was very reactive.

At this point we may give a *résumé* of the chief properties of the hydrocarbon. When first prepared, it is a colourless crystalline solid, which dissolves with great readiness in most

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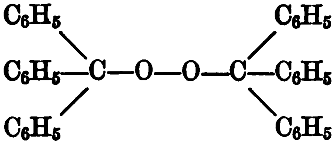
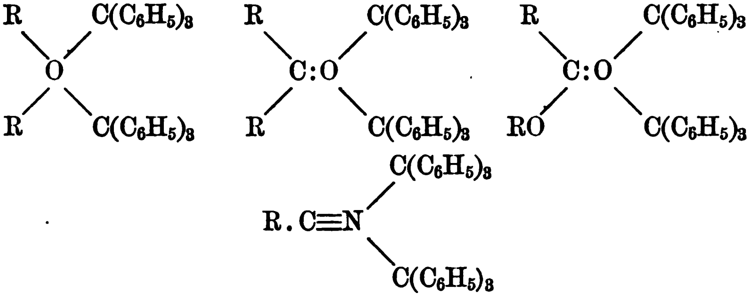
[1] Gomberg, *J. Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.

organic solvents, giving yellow solutions. Even at zero it reacts with iodine to form triphenylmethyl iodide. Exposure to the air even for a short time is sufficient to transform it into a peroxide; and Gomberg[1] has been able to prove that this same peroxide can be produced by the action of sodium peroxide on triphenyl-chloro-methane (but not by the spontaneous oxidation of triphenylmethyl chloride or of triphenyl carbinol under the same conditions). From this we may deduce that the peroxide has the constitution—



The hydrocarbon forms double compounds[2] with ethers, esters, ketones, nitriles, or aromatic hydrocarbons (and amylene), the composition of these substances corresponding to one molecule of ether (or of the other substances) plus one molecule of hexaphenyl-ethane. Gomberg ascribed the formation of the oxygenated derivatives to the change of the oxygen from the divalent to the quadrivalent condition, and formulated the constitution of the substances generally as derivatives of the following types:—



The fact that these substances are actually compounds and not simply mixtures in which the ether or other body is held mechanically is proved by the fact that similar compounds are formed with carbon disulphide and chloroform, and these

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[1] Gomberg, *Ber.*, 1900, **33**, 3150.

[2] *Ibid.*, 1905, **38**, 1333, 2447.

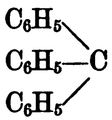
latter bodies can be heated to 110° C. in a stream of carbon dioxide without giving up their full content of chloroform or disulphide.

There is one further point to which we must draw attention, though it does not directly concern the hydrocarbon. It has been shown[1] that the halogen salts, such as triphenylmethyl chloride, $(C_6H_5)_3C.Cl$, and triphenylmethyl bromide, $(C_6H_5)_3C.Br$, when dissolved in solvents such as liquid sulphur dioxide which have strong dissociating power, have conductivities very nearly equal to that of methylamine hydrochloride. This proves that in the yellow solutions obtained in this way, the compounds are split up into two ions, one of which must be $(C_6H_5)_3C$.

From the data which we have given in the preceding paragraphs, it is clear that the problem of the constitution of Gomberg's synthetic hydrocarbon opens up a wide field for speculation; and numerous attempts have been made in recent years to discover the solution. Four views have at one time or another gained a certain amount of support, and we shall deal with these in turn in the succeeding sections of this chapter.

2. *The Trivalent Carbon Hypothesis.*

The reactions of his synthetic hydrocarbon—which we may for the sake of convenience term triphenylmethyl—led Gomberg[2] to put forward the view that the substance contained one carbon atom attached to three phenyl radicles, but having no fourth radicle attached to it:—



The fourth valency of the carbon atom may be supposed to be free, or to be absorbed by the residual valency of the three phenyl groups. This conception of a trivalent carbon atom is really not so extraordinary as it seems; for we might consider that ethylene derivatives contain two adjacent carbon atoms of

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[1] Walden, *Ber.*, 1902, **35**, 2018; Gomberg, *ibid.*, 2045. Compare Gomberg, *Ber.*, 1905, **38**, 1342.

[2] Gomberg, J., *Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.

this type, instead of writing their structural formulæ as we usually do with a double bond between the two unsaturated carbons.

In favour of this constitutional formula for triphenylmethyl we may urge the evidence derived from the reactions of the substance with iodine and with oxygen, both of which can be expressed quite simply:—

$$\begin{array}{ccccc} (C_6H_5)_3C & & I & & (C_6H_5)_3C\,.\,I \\ & + & | & = & \\ (C_6H_5)_3C & & I & & (C_6H_5)_3C\,.\,I \end{array}$$

$$\begin{array}{ccccc} (C_6H_5)_3C & & O & & (C_6H_5)_3C—O \\ & + & \| & = & \quad\;\, | \\ (C_6H_5)_3C & & O & & (C_6H_5)_3C—O \end{array}$$

And we might also adduce the simplicity of the formulæ for the double compounds of triphenylmethyl with ethers, ketones, nitriles, etc.

All that this amounts to, however, is that we can express these reactions in a straightforward manner on the assumption of trivalent carbon. If we can express them equally convincingly by means of a formula containing only quadrivalent atoms, then we should be entitled to reject the trivalent carbon view as adding an unnecessary assumption to our usual ones.

But there are facts which do not agree with the trivalent carbon view. In the first place, Gomberg has shown that in solution triphenyl methyl has a molecular weight corresponding to a formula—

No!

$$2[(C_6H_5)_3C]$$

that is to say, the molecular weight is that of hexaphenylethane or some isomer of that substance. Secondly, Gomberg and Cone[1] have shown that the three phenyl radicles do not possess identical properties, as they should do if the substance actually had the triphenylmethyl structure. We need only outline their proof here, as we shall have to return to it in a later section. By subjecting para-rosaniline to Sandmeyer's reaction they obtained tri-*p*-bromo-triphenyl carbinol, which, by the action of hydrochloric acid, was transformed into tri-*p*-bromo-triphenylmethyl chloride:—

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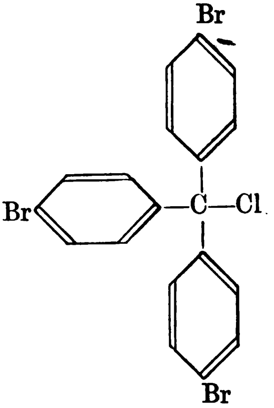
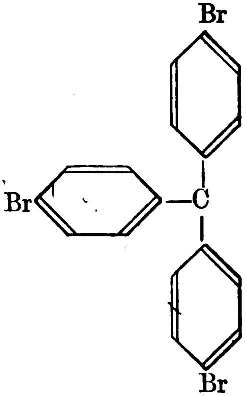
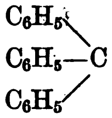
[1] Gomberg and Cone, *Ber.*, 1906, **39**, 3274.



When this substance was treated in the usual way with silver, it gave a substance analogous to triphenylmethyl. This new compound formed a peroxide just as triphenylmethyl does, and therefore (if the trivalent carbon idea be correct) we may safely assume that it is tri-*p*-bromo-triphenyl-methyl :—



Now the tri-*p*-bromo-triphenyl chloride was sealed up in an air-free flask with excess of molecular silver, and the whole was shaken for a considerable time. At the end of this, it was found that the silver had removed all the chlorine (reaction of triphenylmethyl formation), but in addition it had abstracted one atom of bromine from the ring of one of the phenyl groups. Since there was excess of silver present, if all the three phenyl radicles had identical properties we should expect that they would yield up their bromine simultaneously. Further, the new compound produced by the elimination of bromine was not a peroxide similar to that formed by triphenylmethyl, nor did it yield such a peroxide when exposed to air. The experiments were repeated with other halogen derivatives of triphenylmethyl, and led in these cases to similar results. It is thus shown: (1) That the substitution of three bromine atoms in the position para to the "trivalent" carbon of triphenylmethyl in no way interferes with the activity of the substance; (2) further action of silver eliminates only one of the three bromine atoms, so that one nucleus differs from the other two. From (1) the complete analogy between triphenylmethyl and its tribromo-derivative is clear; and hence we are entitled to draw the conclusion that the inference in (2) is valid also for the parent hydrocarbon. But if in triphenylmethyl we have one phenyl nucleus endowed with properties not shared by the other two, it is evident that a symmetrical formula—



cannot give a true representation of the substance's properties. The triphenylmethyl structural formula with trivalent carbon has therefore been abandoned at the present day.

3. *The Hexaphenyl-ethane Hypothesis.*

When Gomberg's hydrocarbon was first prepared, its properties were found to be so different from what had been expected of hexaphenyl-ethane that the latter structure was at once dismissed as incapable of giving a proper representation of the reactions of the new substance; but as time went on, and more information with regard to the properties of the more highly phenylated ethanes was acquired, it seemed as if the earlier view had been rather hasty, and that there was a certain amount of probability in the idea that Gomberg's compound was, after all, merely hexaphenyl-ethane.

For two years, however, this view was kept in abeyance, owing to the fact that Ullmann and Borsum[1] had synthesized

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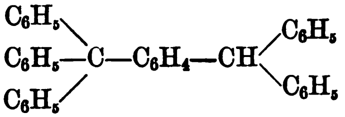
[1] Ullmann and Borsum, *Ber.*, 1902, **35**, 2877; Gomberg, *ibid.*, 3914.

a substance which they regarded as hexaphenyl-ethane. This body was obtained by reducing triphenyl carbinol; and its properties corresponded to some extent with those which had been anticipated for hexaphenyl-ethane. In 1904, however, Tschitschibabin[1] established the constitution of this supposed hexaphenyl-ethane, proving it to be a compound of the following structure:—



This removal of the supposed hexaphenyl-ethane from the literature thus left the possibility open that Gomberg's triphenylmethyl really had the hexaphenyl-ethane structure; and Tschitschibabin[2] put this suggestion forward, basing his views on the following considerations.

In the first place, we have to account for the reactivity of triphenylmethyl, and show why a compound of the hexaphenyl-ethane structure should be reactive. Tschitschibabin pointed out that an accumulation of electro-negative atoms or radicles in a molecule tended to make it much less stable. We have already seen an example of this in connection with Zincke's work on the chlorination of phenols; the accumulation of chlorine atoms in the compound leads to its degradation into simpler substances. Again, spacial factors sometimes come into play and cause a saturated substance like trimethylene to behave as if it were an unsaturated hydrocarbon. These considerations show that we must be prepared for certain anomalies and must beware of judging problems of constitution on too rigid lines. Further, it is not necessary to assume an unsaturated structure for triphenylmethyl merely in order to account for its ready reaction with oxygen to form a peroxide, for Gomberg[3] himself has shown that the fully saturated analogue triphenyl-iodo-methane reacts in a similar manner. A further point in favour of the hexaphenyl-ethane view is Gomberg's proof that in solution his triphenylmethyl had a molecular weight agreeing with the hexaphenyl-ethane formula rather than with that of tri-phenylmethyl. Nor is this all; for

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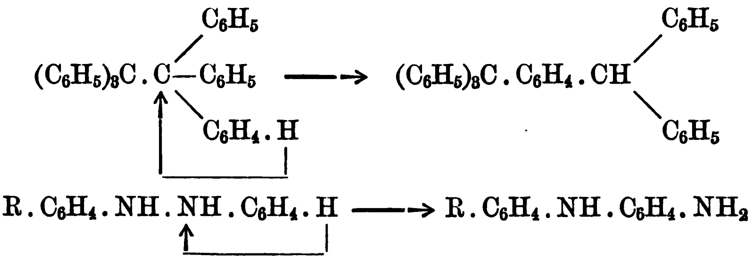
[1] Tschitschibabin, *Ber.*, 1904, 37, 4709.

[2] *Ibid.*

[3] Gomberg, *Ber.*, 1902, 35, 1836.

when we examine more carefully the behaviour of the highly phenylated ethane derivatives we shall find that they are by no means so stable as analogy would lead us to expect. Tschitschibabin[1] has proved that even below its melting-point pentaphenyl-ethane is attacked by air; at a temperature of only 150° C. hydrochloric acid in benzene solution acts on it so powerfully that the bond between the two ethane carbon atoms is broken, and such products as tetraphenyl-ethane, triphenylmethane, and triphenyl-chloro-methane, are formed; while Cone and Robinson[2] found that the action of phosphorus pentachloride in boiling benzene broke down the pentaphenyl derivative into triphenylmethyl chloride.

Against the hexaphenyl-ethane hypothesis we may adduce several arguments. In the first place, triphenylmethyl is a colourless solid, but its solutions are deep yellow in tint: no ordinary benzenoid derivative is known which behaves in this way. Stronger evidence is to be found in the work of Gomberg, which we mentioned in the previous section, by which he showed that one phenyl group had properties different from those of the others. The ordinary hexaphenyl-ethane formula gives no indication of this. Thirdly, Gomberg[3] has proved that his hydrocarbon can easily be converted into that which was obtained by Ullmann and Borsum. On the hexaphenyl-ethane hypothesis, this reaction would take the following course, which is parallel to that which is taken in the semidine change—



$$(C_6H_5)_3C\,.\,C(C_6H_5)_2(C_6H_4\,.\,H) \longrightarrow (C_6H_5)_3C\,.\,C_6H_4\,.\,CH(C_6H_5)_2$$

$$R\,.\,C_6H_4\,.\,NH\,.\,NH\,.\,C_6H_4\,.\,H \longrightarrow R\,.\,C_6H_4\,.\,NH\,.\,C_6H_4\,.\,NH_2$$

But Jacobson,[4] the greatest authority on the benzidine and semidine changes, regards such a change in the triphenylmethyl

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[1] Tschitschibabin, *Ber.*, 1907, **40**, 367.

[2] Cone and Robinson, *Ber.*, 1907, **40**, 2160.

[3] Gomberg, *Ber.*, 1902, **35**, 3918; 1903, **36**, 376.

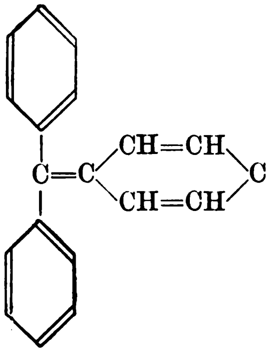
[4] Jacobson, *Ber.*, 1904, **37**, 196.

series as most unlikely. Lastly, we have already seen that one of the most marked characteristics of triphenylmethyl is its capacity for forming double compounds with solvents; but no such property seems to be possessed by compounds analagous to hexaphenyl-ethane.

From the foregoing paragraphs, it is clear that the arguments both in favour of and against the hexaphenyl-ethane view depend to some extent upon analogy; and we must be careful not to lay too much stress upon them unless we are satisfied that the analogies really hold good. If we rule out the arguments based upon what a compound "ought" to do, it will be seen that the evidence remaining—Gomberg's differentiation between the phenyl nuclei—tells against the hexaphenyl-ethane hypothesis.

4. *Quinonoid Hypotheses.*

If we reject the two hypotheses which we have dealt with in the preceding sections, it is clear that we have still a third possibility open to us; for both the triphenylmethyl view and the hexaphenyl-ethane explanation were based on the assumption that the phenyl nuclei in triphenylmethyl were benzenoid in character, so that by assuming a quinonoid structure for the substance we shall arrive at totally different types of formulæ. The quinonoid conception of triphenylmethyl was put forward very early in the compound's history by Kehrmann.[1]



This suggestion, involving as it does the assumption of a

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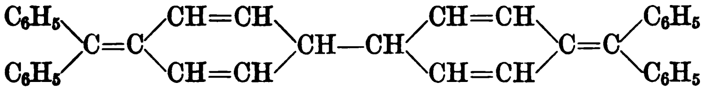
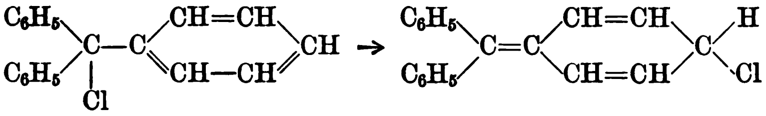
[1] Kehrmann, *Ber.*, 1901, 34, 3818; see also Norris and Sanders, *Am. Chem. J.*, 1901, 25, 117; and Gomberg, *Ber.*, 1902, 35, 1824.

divalent carbon atom, meets with little approval at the present time; and since other formulæ of the quinonoid type have since been suggested which do not necessitate such a postulate, we need not deal further with this one.

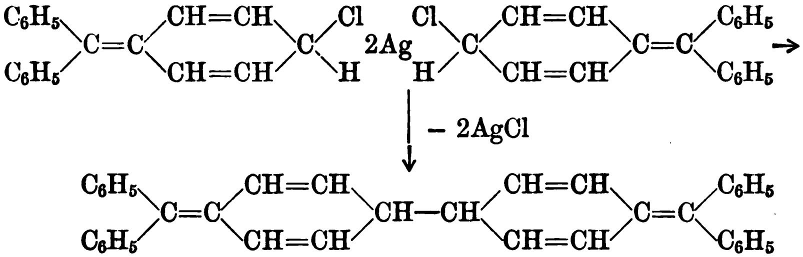
In 1903, Heintschel[1] proposed the formula below—



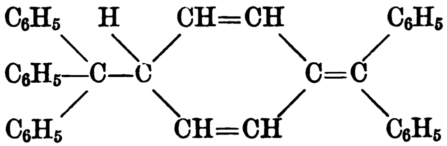
On this hypothesis, the first step in the synthesis of triphenylmethyl is the conversion of triphenyl-chloro-methane into a desmotropic form in which the chlorine atom has been shifted into a position para to the methane carbon atom—



By the action of metals, two chlorine atoms are withdrawn from two molecules of the chloro-compound, and in this way triphenylmethyl is produced—



An examination of Heintschel's formula will show that it contains two quinonoid phenyl nuclei, Jacobson[2] proposed to modify this, making only one phenyl group quinonoid, as shown below—



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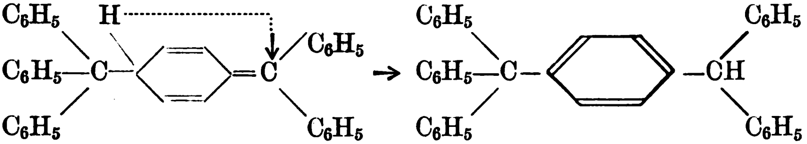
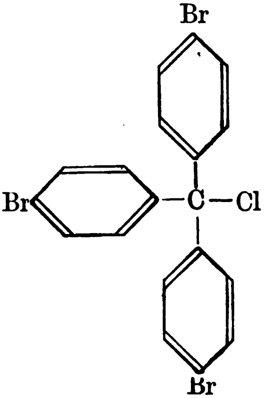
[1] Heintschel, *Ber.*, 1903; **36**, 320, 579.

[2] Jacobson, *Ber.*, 1904, **37**, 196.

This view makes triphenylmethyl a derivative of a substance approaching the quinole type; and as we have already seen that the reactivity of the quinoles is quite abnormal, we might expect considerable reactive power from a body of the structure proposed by Jacobson. The change of the Gomberg hydrocarbon into the substance prepared by Ullmann and Borsum can also be easily explained on this hypothesis, as the wandering of a single hydrogen atom is sufficient to account for the isomerization—



The Jacobson formula helps us to understand the fact that this substance, containing six phenyl radicles, can act as if it had the constitution of triphenylmethyl; for if it be assumed that the molecule is decomposed by halogens in such a way that the single bond between the quinonoid nucleus and the adjacent carbon atom is loosened, then we should have two "triphenyl-methyl" radicles set free which would at once react with halogen atoms giving two molecules of triphenylmethyl halide. The quinonoid formula also makes clear the meaning of the experiments of Gomberg and Cone[1] to which we made reference in a previous section. Let us take for example the case of tri-*p*-bromo-triphenylmethyl chloride—



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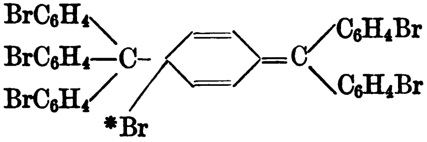
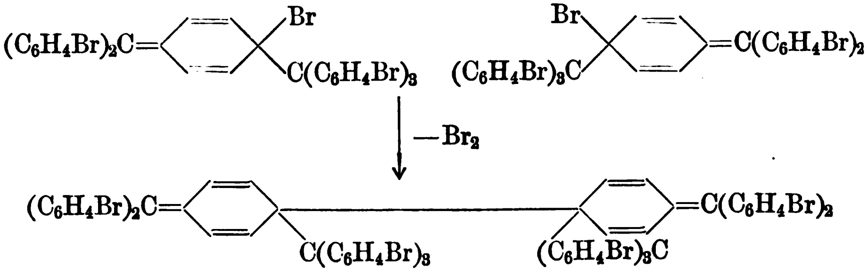
[1] Gomberg and Cone, *Ber.*, 1906, 39, 3274.

it is clear that, when it is converted into triphenylmethyl by the action of metals, one of the phenyl radicles must become quinonoid; and an examination of the formula of the substance which would be formed if the quinonoid view be correct will show that one of the halogen atoms (marked with an asterisk) should possess the properties of a halogen atom attached to an aliphatic chain rather than those which are shown by halogen atoms bound to aromatic nuclei—



Now, such a halogen atom will be more easily attacked by metals than will be the case with the other bromine atoms in the compound in question; so that we should expect that the action of an excess of, say, silver upon the tri-*p*-bromo-triphenylmethane chloride will result in two reactions, the first of which will lead to the elimination of two chlorine atoms, giving rise to the compound whose formula is shown above, while the further action of the silver will remove two bromine atoms from two molecules of this body, the result being the formation of a substance having the constitution shown below—



The results obtained experimentally by Gomberg and Cone proved that one of the phenyl radicles did actually change from the benzenoid to the quinonoid form; but in the view of these experimenters the assumption of this change alone was not sufficient to account fully for the problems which the properties of triphenylmethyl suggest.

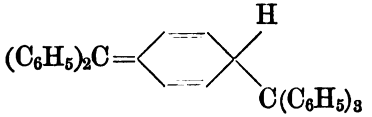
We must now turn to examine the objections which have been brought against the quinonoid view.

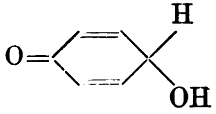
Tschitschibabin[1] points out that one of the most speedy and apparently simple reactions which the triphenylmethyl derivatives undergo is the formation of the peroxide—

$$(C_6H_5)_3C—O—O—C(C_6H_5)_3$$

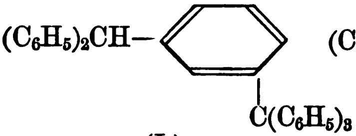
but that if we are to explain this according to the Jacobson formula we should have to assume an extremely complicated isomeric change as the first step in the process.

Gomberg and Cone[2] draw attention to the fact that Jacobson makes triphenylmethyl a derivative of a substance analogous to a secondary quinole—

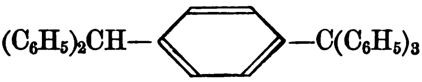




But since secondary quinoles have not yet been proved to be capable of existence, these authors consider doubtful the existence of compounds of the Jacobson type. Furthermore, if we grant the possibility of their existence, it is probable that they will behave like ordinary quinoles, and hence their reactions with acids should resemble to some extent the rearrangements which quinoles undergo under the same conditions. As we have seen in the chapter upon quinoles, the alkyl group in these substances usually wanders to the ortho-position; whence by analogy the substance produced by the action of acids upon triphenylmethyl (Ullmann and Borsum's hydrocarbon) should be represented by the formula (I.) and not by (II.), though Tschitschibabin believed that (II.) was formed. These arguments, as the authors themselves admit, are purely theoretical, and depend largely upon negative evidence.



(I.)



(II.)

From a somewhat similar standpoint Auwers[3] has criticized

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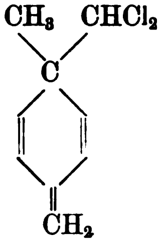
[1] Tschitschibabin, *Ber.*, 1905, **38**, 771.

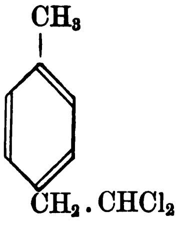
[2] Gomberg and Cone, *Ber.*, 1905, **38**, 2455.

[3] Auwers, *Ber.*, 1907, **40**, 2159.

the Jacobson formula. He points out that the para-methylene quinonoid derivatives show such a tendency to revert to the benzenoid structure that in some cases a profound intramolecular change may take place. For example, in the compound (I.) below, the group $—CHCl_2$ wanders from its original position to the atom next the para-carbon atom in order to facilitate the formation of the benzenoid ring (II.) in preference to the quinonoid one:—

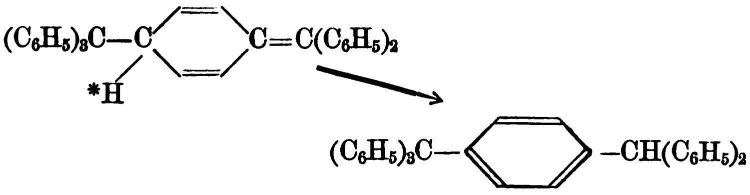


(I.)



(II.)

By analogy, it seems hardly likely that the hydrogen atom marked with an asterisk in the Jacobson formula would remain fixed in its present position when by a similar wandering to the para-carbon atom it could allow the compound to revert to the benzenoid type.



That such a wandering must be possible is shown by the conversion of the Jacobson compound into that of Ullmann and Borsum by the action of acids; but it seems strange that a compound of the Jacobson formula should exist in the free state at all.

Against the Heintschel formula, it has been alleged by Tschitschibabin[1] that it should be easily isomerized into a compound having the structure (B); whereas in practice no such change takes place.

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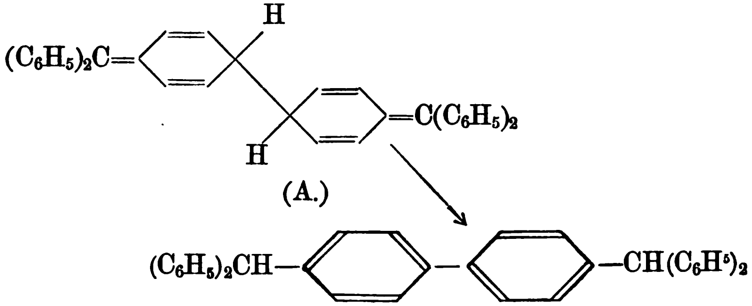
[1] Tschitschibabin, *Ber.*, 1905, **38**, 771.



(A.)

(B.)

From the foregoing summary it will be seen that the arguments both in favour of and against the quinonoid structure for triphenylmethyl are based very largely upon considerations of what a compound ought to do if it has a structure analogous to some other compound, the latter body being as yet undiscovered in practice. As far as the relevant evidence is concerned, it certainly goes to show that the quinonoid formula is a step in advance of either the triphenylmethyl hypothesis or the hexaphenyl-ethane view.

5. *The Tautomerism Hypothesis.*

We have now exhausted the possibilities of static formulæ to explain the behaviour of triphenylmethyl; and it is evident that the results have not been completely satisfactory. All the three views which we have discussed in the foregoing sections have certain advantages; and each has its own drawbacks. It thus becomes clear that, if we are to make any further progress towards a solution of the problem, we must contrive some means of uniting the advantages of the various formulæ; while at the same time we must endeavour to minimize their weak points. In order to do this it is obvious that we must turn to modern dynamic ideas and represent triphenylmethyl as a series of equilibrium mixtures of isomerides.

Gomberg[1] has developed this line of thought; and if his results do not represent the truth, it seems probable that they come very close to it. At the present time we cannot assume

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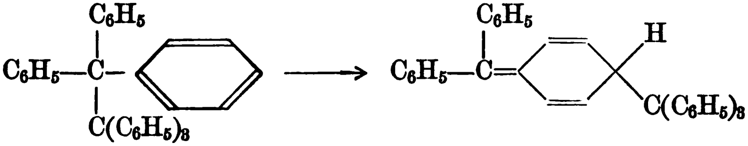
[1] Gomberg, *Ber.*, 1907, 40, 1880.

that the problem is completely solved; but we are evidently very near to the solution.

Gomberg's later views took their rise in the fact that there are two varieties of triphenylmethyl which differ from each other in colour; the solid form of the substance is colourless; but in solution this is changed into a yellow compound. Schmidlin[1] states that he has obtained the two forms of the substance in solution. Now, Gomberg assumes in the first place that there are two tautomeric forms of triphenylmethyl, $C_{38}H_{30}$; and in the second place that the radicle triphenylmethyl, $(C_6H_5)_3C$, can exist as such and is also capable of tautomerization. Let us now take up the possible constitution of the solid, colourless modification. This we may suppose to be hexaphenylethane. It is evident that we may assume tautomeric change in this compound, leading us to the following structure:—



This alteration of the benzenoid into the quinonoid form would be accompanied by a change of the substance from colourless to yellow; and since all ordinary solvents seem to be capable of yielding yellow solutions of triphenylmethyl, we may assume that this change from the benzenoid to the quinonoid form takes place under the action of most solvents during the process of solution.

We must now go a step further and deal with the behaviour of triphenylmethyl dissolved in a medium of high dissociating power, liquid sulphur dioxide. It has been proved by Walden[2] that a solution of the hydrocarbon in this solvent possesses a fairly high conductivity, and that the molecular conductivity increases with the dilution; in other words, the substance behaves just like an ordinary ionized salt. From this behaviour, Gomberg deduces that tautomerization is not the only change which triphenylmethyl undergoes as it is dissolved; but that in addition it is dissociated into two ions which we may

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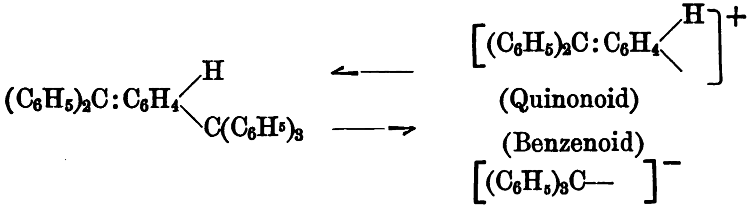
[1] Schmidlin, *Ber.*, 1908, 41, 2471.

[2] Walden, *Zeit. Phys. Chem.*, 1903, 43, 443; Gomberg and Cone, *Ber.*, 1904, 37, 2403.

represent as below. The anion is supposed to have the benzenoid structure, while the kation is quinonoid.



On this view, the action of iodine upon triphenylmethyl solutions is explicable. The iodine in solution is supposed to interact with both the anion and the kation, yielding one molecule of benzenoid triphenylmethyl iodide and one molecule in the quinonoid form; but since the latter seems to be incapable of existence in the free state, it is assumed that it undergoes intramolecular change at once and produces a benzenoid molecule. When we turn to the action of oxygen upon triphenylmethyl in solution, however, we have a somewhat different state of affairs, since only the anion unites with oxygen. (This follows from the fact that the peroxide formed has the benzenoid structure, whereas the action of oxygen upon the quinonoid ion would give rise to a highly complicated product which is not observed among the reaction products). We are thus led to the further assumption that in the process of peroxide formation the first step is the oxidation of the benzenoid ions; as these are removed from the solution, equilibrium is disturbed; and, in order to re-establish it, some of the quinonoid ions must re-tautomerize into the benzenoid form. They in turn are removed by the oxygen; and the process continues until all the triphenylmethyl is exhausted.

The same tautomerization process can be invoked to explain why triphenylmethyl gives a yellow solution with ethers, esters and ketones, while the solid double compounds which crystallize out from these solutions are colourless. In this case the benzenoid ions may be assumed to unite with the quadrivalent oxygen of the ethers, etc.; and in order to take their place some of the quinonoid ions are converted into benzenoid ones.

According to Gomberg, then, we can explain all the important properties of triphenylmethyl on the basis of the following hypotheses: (1) tautomerization of solid triphenylmethyl to a quinonoid substance having the Jacobson formula; (2) partial dissociation of this compound into positive and negative ions in all solvents; (3) mutual interconvertibility of these ions by tautomeric change. Gomberg further assumes that solid triphenylmethyl is actually a free radicle, $—C(C_6H_5)_3$.

6. *Conclusion.*

We have now examined in turn the principal hypotheses which have been put forward at various times to account for the peculiar properties of triphenylmethyl; and it must be admitted that even yet there appears to be some doubt as to whether we have arrived at the solution of the problem. The substance in its general behaviour is so unlike the majority of organic compounds that at first sight the tri-valent carbon hypothesis appeared to have some points in its favour; but, as we have seen, the arguments against it are strong. It seems clear that the quinonoid view, however it be expressed, is the most probable of all; and, in its final form as put forward by Gomberg, it seems to present the maximum of advantages. In certain respects triphenylmethyl appears to resemble the quinhydrone type of compound, and it may be that further researches in that branch of the subject may throw light upon the curious behaviour of this enigmatic body.

CHAPTER XI

ASYMMETRIC SYNTHESES AND NEW METHODS OF PRODUCING OPTICALLY ACTIVE COMPOUNDS

If we pass a current of carbon dioxide into water in which sticks of magnesium have been immersed, some of the gas is reduced to formaldehyde[1]; and by acting upon the latter with calcium hydrate solution,[2] we can produce fructose—

$$CH_2OH.(CH.OH)_3.CO.CH_2OH$$

A similar operation is probably carried out in the natural synthesis of fructose in plants, where the starting materials are also water and carbon dioxide; but the process in the latter case is evidently subject to some influence which is absent in our ordinary laboratory reactions, for the naturally occurring fruit sugar is optically active, while that prepared in the laboratory has no action upon the plane of polarization. The question now suggests itself, in what way does the mechanism of the reaction vary in such a manner as to produce results so similar up to a certain point, and yet so distinct from one another?

It is at once obvious that we cannot consider the organism of the plant merely as a peculiar kind of beaker in which the reaction takes place; for if this were so, there would be no difference between the two reaction products. Evidently, then, the plant tissues play some part other than merely containing the interacting substances; they absorb water and carbon dioxide at their surfaces, bring the two compounds together, and then in some way assist them to react with one another so as to form fructose. The accepted view is that the plant tissues combine with both the carbon dioxide and the water in the first place to form some unstable substance, and then

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[1] Fenton, *Trans. Chem. Soc.*, 1907, **91**, 687.

[2] Loew, *J. pr. Chem.*, 1886, **33**, 321.

eliminate fructose as a decomposition product. If we accept this view, the problem before us becomes clear at once. In the case of our laboratory reaction, we are dealing throughout with a purely symmetrical set of substances, and there is no possibility of optically active products being formed. But in the case of the plant we have a mass of optically active bodies which make up the sap and tissues of the organism; these fasten upon the water and carbon dioxide, combine with them, forming more complex *but still optically active* compounds, which on decomposition eliminate optically active products.

In recent years many attempts, some successful and others unavailing, have been made to parallel this process by means of our ordinary laboratory reactions. To do this, we must take as our starting-point some optically active body which will play the part of the active constituents in the plant; to this optically active nucleus we must then add a new chain of atoms, when we shall have a parallel to the unstable intermediate product in the plant; and now, when we split off the new chain from the original active nucleus, we must find that it in turn is active if our artificial reaction is to resemble the natural one. Perhaps a concrete example will make the matter clearer. Let us take an optically active acid, X.COOH, and combine it with amidobenzaldehyde. We shall then have the compound—

$$X.CO.NH.C_6H_4.CHO$$

To this we then attach a molecule of hydrocyanic acid to form the cyanhydrin—

$$X.CO.NH.C_6H_4.CH(OH).CN$$

This represents the intermediate unstable product in the plant; and it will be noticed that a new asymmetric carbon atom (marked with an asterisk) has been produced in the compound. On hydrolyzing the nitrile group, we shall obtain the corresponding acid, in which the new asymmetric carbon still remains—

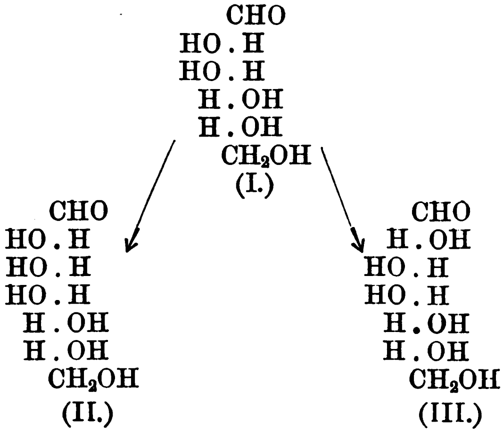
$$X.CO.NH.C_6H_4.\overset{*}{C}H(OH).COOH$$

If we now wish to represent the breakdown of the unstable plant product, we need only split off the original active acid group from this, and we shall have left behind the "new chain of atoms"—

$$NH_2 . C_6H_4 . \overset{*}{C}H(OH) . COOH$$

Should this prove to be active, the parallel between plant synthesis and laboratory reaction will be complete.

As far back as 1889,[1] evidence bearing indirectly upon this question had been obtained from researches in the sugar group. For example, it had been shown that dextro-mannose (I.), which, when submitted to the cyanhydrin reaction, should theoretically yield an equimolecular mixture of the compounds (II.) and (III.), actually in practice produces only one of the isomers.



$$\begin{array}{c} CHO \\ HO . H \\ HO . H \\ H . OH \\ H . OH \\ CH_2OH \\ (I.) \end{array}$$

$$\begin{array}{c} CHO \\ HO . H \\ HO . H \\ HO . H \\ H . OH \\ H . OH \\ CH_2OH \\ (II.) \end{array} \qquad \begin{array}{c} CHO \\ H . OH \\ HO . H \\ HO . H \\ H . OH \\ H . OH \\ CH_2OH \\ (III.) \end{array}$$

In this case, therefore, the original asymmetric nucleus has governed the progress of the reaction to such an extent as to preclude the formation of one isomer. We are, however, unable to carry the matter further in this particular example, as we have no means of splitting off the original mannose molecule without destroying the "new chain" in the process.

Having now shown what is being sought in this branch of the subject, it may be well to give at this point a formal definition of the term "*asymmetric synthesis.*" In an asymmetric synthesis an active compound is taken as a starting-point, to which a new radicle is added in such a way as to form a new asymmetric carbon atom; the originally active portion of the

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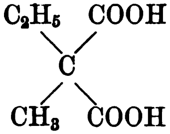
[1] Fischer and Hirschberger, *Ber.*, 1889, **22**, 365; Fischer, *Ber.*, 1894, **27**, 3208; Fischer, *Annalen*, 1892, **270**, 68.

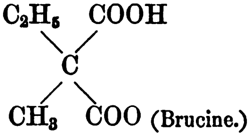
molecule is then split off, and the remainder must be optically active if the synthesis is successful.

We must next review the various attempts which have been made to solve this problem. The first of any interest is that made by Cohen and Whitely,[1] in which they took as their starting material mesaconic acid. This they esterified with lævo-menthol, and in this way obtained an active ester. They next reduced this to methyl-succinic menthyl ester, and finally split off the menthyl group. If the synthesis had been an asymmetric one, the remaining methyl-succinic acid should have been active; it was not.

It is unnecessary to refer in detail to Fischer and Slimmer's unsuccessful method,[2] in which helicin was the starting-point; or to Cohen and Whitely's second unsuccessful attempt to produce optically active bodies in this way.[3] The first true asymmetric synthesis was carried out by Marckwald[4] in the following ingenious way. He took methyl-ethyl-malonic acid (I.), which contains no asymmetric carbon atom, and from it made the acid brucine salt (II.). When this salt is heated until no more carbon dioxide is liberated, the brucine salt of valerianic acid (III.) is left, and it will be noticed that this acid contains a new asymmetric carbon atom. Marckwald found that when he liberated the valerianic acid from the salt (III.) it had a slight optical rotatory power, which could only be due to the new asymmetric carbon atom.



(I.)



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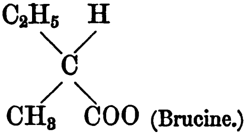

(III.)

By this research it was proved that asymmetric synthesis was not an impossible achievement, and since that time several such syntheses have been carried out.

McKenzie[5] has produced a mandelic ester in which the

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[1] Cohen and Whitely, *Proc. Chem. Soc.*, 1901, **16**, 226.

[2] Fischer and Slimmer, *Sitzungsber. d. K. Akad. Wiss. Berlin*, 1902, 597; *Ber.*, 1903, **36**, 2575.

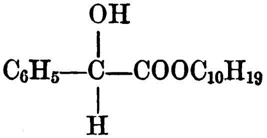
[3] Cohen and Whitely, *Trans. Chem. Soc.*, 1901, **79**, 1305.

[4] Marckwald, *Ber.*, 1904, **37**, 349, 1868, 4696.

[5] McKenzie. *Trans. Chem. Soc.*, 1904, **85**, 1249; 1906, **89**, 365.

lævo-form predominates over the dextro-form. Choosing as his starting substance benzoyl-formic acid (I.), he esterified this with lævo-menthol, producing the ester (II.). This he reduced by means of aluminium amalgam, and thus obtained mandelic lævo-menthyl ester (III.)—

$C_6H_5 . CO . COOH$ (I.) $C_6H_5 . CO . COOC_{10}H_{19}$ (II.)



$$C_6H_5\text{—}\overset{\overset{\Large OH}{|}}{\underset{\underset{\Large H}{|}}{C}}\text{—}COOC_{10}H_{19}$$

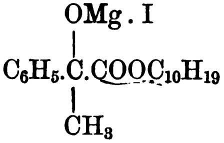
(III.)

On examination, (III.) was found to be a mixture of *d*-mandelic-*l*-menthyl ester with *l*-mandelic-*l*-menthyl ester; the latter slightly preponderated in the mixture, so that on getting rid of the menthol, the asymmetric synthesis would be complete. This method has been applied to the preparation of active lactic from pyruvic acid.[1]

Using benzoyl-formic menthyl ester again as his starting-point, the same author[2] applied the Grignard reaction, with the following result:—

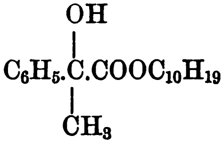
$C_6H_5.CO.COOC_{10}H_{19}$

(I.)



$$C_6H_5.\overset{\overset{\Large OMg.I}{|}}{\underset{\underset{\Large CH_3}{|}}{C}}.COOC_{10}H_{19}$$

(II.)



$$C_6H_5.\overset{\overset{\Large OH}{|}}{\underset{\underset{\Large CH_3}{|}}{C}}.COOC_{10}H_{19}$$

(III.)

From the menthyl ester (I.) the compound (II.) was obtained by the action of magnesium methyl iodide; this intermediate compound was then decomposed with water to form (III.); from which in turn, by the action of acid, a mixture of externally compensated and lævo-methyl-phenyl-glycollic acid was produced. Since the one antipode predominated over the other, the asymmetric synthesis had been successfully accomplished.

McKenzie and Wren[3] have been able to synthesize both

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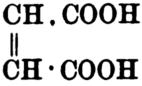
[1] McKenzie, *Trans. Chem. Soc.*, 1905, **87**, 1373; McKenzie and Wren, *ibid.*, 1906, **89**, 688.

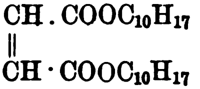
[2] McKenzie, *Trans. Chem. Soc.*, 1904, **85**, 1249.

[3] McKenzie and Wren, *Trans. Chem. Soc.*, 1907, **91**, 1215.

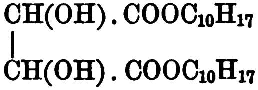
lævo and dextro forms of tartaric acid in the following manner. Fumaric acid was esterified with lævo-borneol, the ester was dissolved in glacial acetic acid and oxidized with potassium permanganate. The result was a tartaric ester in which there was a slight excess of the lævo form.



$$\begin{array}{l} CH.COOH \\ \| \\ CH\cdot COOH \end{array}$$



$$\begin{array}{l} CH.COOC_{10}H_{17} \\ \| \\ CH\cdot COOC_{10}H_{17} \end{array}$$

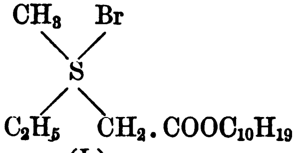


$$\begin{array}{l} CH(OH).COOC_{10}H_{17} \\ | \\ CH(OH).COOC_{10}H_{17} \end{array}$$

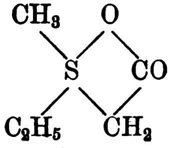
By using dextro-borneol they obtained the dextro-tartaric-dextro-borneol ester in excess over the lævo-tartaric-dextro-borneol ester. When menthol was substituted for borneol, it gave a greater yield of the lævo-tartaric ester.

Only two other attempts in this direction need be dealt with here. In the nitrogen series, Scholtz[1] has endeavoured to carry out an asymmetric synthesis by the action of optically active halogen alkyl derivatives upon racemic bases; E. and O. Wedekind[2] have also made experiments of the same type, but in neither case was a true asymmetric synthesis accomplished.

Smiles[3] investigated a case of asymmetric synthesis of tetravalent sulphur, but found that when methyl-ethyl-sulphide interacted with lævo-menthyl-bromacetate an ester (I.) was produced which, on hydrolysis with hydrochloric acid, gives the externally compensated thetine (II.). The two antipodes are therefore formed in equal quantity, and no asymmetric synthesis takes place.



(I.)



(II.)

We must now leave the question of asymmetric synthesis and consider some other recently discovered methods of producing optically active compounds.

In his study of the tartaric acids, with which modern stereochemistry may be said to have begun, Pasteur contrived three methods by which optically active substances could be

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[1] Scholtz, *Ber.*, 1901, **34**, 3015.
[2] E. and O. Wedekind, *Ber.*, 1908, **41**, 456.
[3] Smiles, *Trans. Chem. Soc.*, 1905, **87**, 450.

obtained from externally compensated mixtures. One method depended upon the spontaneous separation of the crystals of the two antipodes; another upon the selective action of fungi; and the third upon the formation of salts with an active substance and the racemic compound as the two components. No greater tribute to Pasteur's genius can be found than the fact that for nearly fifty years, in spite of almost incessant research in this field, no substitutes for these three methods had been invented. Modifications may have been introduced, such as substituting hydrazone formation for salt formation,[1] but no fundamentally different method was contrived until a few years ago.

We may now examine in turn the methods which recent workers have brought forward. As regards the question of spontaneous separation of the antipodes, no advance seems possible. The study of transition temperatures has, of course, rendered the use of this mode of separation much more certain in its results than it used to be, but in actual experimental details it remains as Pasteur left it. Numerous attempts have been made[2] to modify it by using optically active solvents instead of symmetrical ones, but none of these have been successful; and it appears improbable that resolution can be accomplished in this manner. It has been shown,[3] however, that if a saturated solution of a *dl*-compound be sown with crystals isomorphous with those of one antipode, that antipode will predominate in the crystals formed. The seed crystal need not necessarily be itself optically active.

Turning now to the biochemical method of separation by the aid of fungi, though no modification of this has been introduced which would enable us to obtain one component of a racemic substance by a less wasteful method than the original Pasteur one, Bertrand[4] has applied the sorbose bacterium

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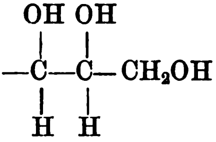
[1] Erlenmeyer, junr., *Ber.*, 1903, **36**, 976; Erlenmeyer, junr., and Arnold, *Annalen*, 1904, **337**, 307; Neuberg, *Ber.*, 1903, **36**, 1192; Neuberg and Federer, *Ber.*, 1905, **38**, 801.

[2] Tolloczko, *Zeit. phys. Chem.*, 1896, **20**, 412; Cooper, *ibid.*, 1898, **26**, 711; *Amer. Chem. J.*, 1900, **23**, 253; Kipping and Pope, *Proc. Chem. Soc.*, 1898, **14**, 113; cf. Wedekind, *Ber.*, 1908, **41**, 457, footnote; Jones, *Proc. Cam. Phil. Soc.*, 1907, **14**, 27.

[3] Ostromisslensky, *Ber.*, 1908, **41**, 3035; Kipping and Pope, *Trans. Chem. Soc.*, 1909, **95**, 103.

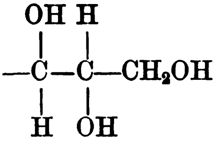
[4] Bertrand, *C. r.*, 1896, **122**, 900; 1898, **126**, 762; *Bull. soc. chim.*, 1898, III. **19**, 347, 947, 999.

(*Bacterium xylinum*) in a somewhat different manner. This bacterium has the faculty of oxidizing certain hydroxyl-compounds, attacking secondary hydroxyl groups which lie in the *a*-position to a primary hydroxyl, and transforming them into carbonyl groups. It is found, however, that the configuration of the sugar submitted to the bacterium has a considerable effect upon the action, for only those sugars are attacked which have the group (I.), those having the group (II.) at the end of the chain being uninfluenced by the ferment. It will be seen that in (I.) the two hydroxyl groups are adjacent, while in (II.) a hydrogen atom and a hydroxyl group lie together.



$$\begin{array}{ccccl} & \mathrm{OH} & & \mathrm{OH} & \\ & | & & | & \\ - & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\ & | & & | & \\ & \mathrm{H} & & \mathrm{H} & \end{array}$$

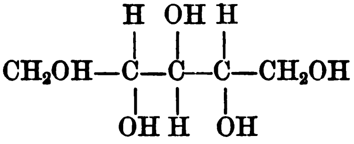
(I.)



$$\begin{array}{ccccl} & \mathrm{OH} & & \mathrm{H} & \\ & | & & | & \\ - & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\ & | & & | & \\ & \mathrm{H} & & \mathrm{OH} & \end{array}$$

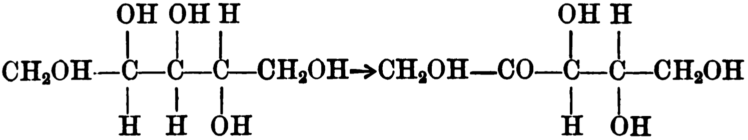
(II.)

For example, xylite is unattacked by the sorbose bacterium, since it does not contain the grouping (I.)—



$$\begin{array}{lcccccl} & \mathrm{H} & & \mathrm{OH} & & \mathrm{H} & \\ & | & & | & & | & \\ \mathrm{CH_2OH}- & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\ & | & & | & & | & \\ & \mathrm{OH} & & \mathrm{H} & & \mathrm{OH} & \end{array}$$

while arabite, which contains the grouping (II.) is oxidized to the corresponding keto-compound—



$$\begin{array}{lcccccccccl} & \mathrm{OH} & & \mathrm{OH} & & \mathrm{H} & & & \mathrm{OH} & & \mathrm{H} & \\ & | & & | & & | & & & | & & | & \\ \mathrm{CH_2OH}- & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \rightarrow \mathrm{CH_2OH}-\mathrm{CO}- & & \mathrm{C} & - & \mathrm{C} & -\mathrm{CH_2OH} \\ & | & & | & & | & & & | & & | & \\ & \mathrm{H} & & \mathrm{H} & & \mathrm{OH} & & & \mathrm{H} & & \mathrm{OH} & \end{array}$$

Coming now to chemical methods of separating one antipode from another, we shall find that in the last few years a very considerable number of new lines have been struck out in this branch of the subject.

The Pasteur method of separating antipodes by means of the salt formation was in its essence a purely static one. In order to resolve a racemic base into its antipodes, a salt was made in whose preparation an active acid was used. The two salts would then be, say, *d*-acid-*d*-base and *d*-acid-*l*-base; and since they were now no longer optical antipodes, they could be separated from one another by utilizing their differences in solubility. This was a purely physical method, in which the chemical reaction played, *per se*, no part in the actual sifting of one compound from the other.

Fischer[1] attacked the matter from quite a different standpoint. For him, the chemical reaction, instead of being a subsidiary part of the separation, became the actual machinery of resolution. Taking the case of the hydrolysis of cane-sugar, he applied an *asymmetric* hydrolyzer, and hoped in this way that a selective hydrolysis might be achieved. Unfortunately, his experiments with dextro- and lævo-camphoric acids, as well as others with camphor-sulphonic acids,[2] were alike unsuccessful; no selective hydrolysis could be observed, both agents hydrolyzing the sugar with the same velocity. More interesting results were obtained by Fischer[3] in studying the action of enzymes on glucosides. Selective hydrolysis takes place in this case, and thus a separation of isomers is possible.

A further step in this direction was taken by Marckwald and McKenzie.[4] Since the reaction of salt-formation is ionic, it takes place almost instantaneously, and spacial influences appear to have very little bearing upon it. On the other hand, a comparatively slow reaction, like esterification, which seems to require the formation of an unstable intermediate product, should lend itself better to selective action. Marckwald and McKenzie proceeded on this assumption, and carried out a series of experiments in which they esterified a racemic acid with an active alcohol, interrupting the process before all the acid was esterified. In this way, if one antipode reacted more rapidly than the other with the alcohol, an excess of its ester would be formed. This was found actually to be the case Lævo-menthol reacts more readily with dextro- than with lævo-mandelic acid, so that if the esterification process be interrupted when half the acid is esterified the ester will contain some *l*-mandelic-*l*-menthyl ester mixed with an excess of *d*-mandelic-*l*-menthyl ester. By saponifying the mixed esters and repeating the process several times one antipode could

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[1] Fischer, *Zeit physiol. Chem.*, 1898, **26**, 83.

[2] Caldwell, *Proc. Roy. Soc.*, 1904, **74**, 184.

[3] Fischer, *Zeit. physiol. Chem.*, 1898, **26**, 83.

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

be separated completely from the other. The same authors[1] applied the inverse method of completely esterifying the racemic mandelic acid with active menthol and then fractionally hydrolyzing the mixed esters with insufficient alkali. The ester of the type *d*-acid-*l*-menthol is hydrolyzed at a different rate from the type *l*-acid-*l*-menthol, so that the reaction product contains an excess of one acid over the other. By removing the unhydrolyzed esters the mixture of acids is left; and this was found to be optically active.

Marckwald and Meth[2] have applied a similar method to the case of amide formation. They have shown that if, when a racemic acid is converted into an amide by heating it with an active amine, the process be interrupted before all the acid is converted into amide the unconverted acid is optically active. Racemic mandelic acid, for example, when heated with lævo-menthylamine to 160° or 170° for ten hours, yields about 36 per cent. of amide. The remaining 64 per cent. of the acid had a specific rotation of $[\alpha]_D = -5{\cdot}1°$. It appears that the relative velocities of amide formation from lævo-menthylamine with dextro- and lævo-mandelic acids are in the ratio 1 : 0·682.

Marckwald and Paul[3] have utilized another property of non-antipodic isomers. They take a racemic acid, form a salt with an active base in the usual manner, and then heat the salt to a high temperature for some time. Now, while two optical antipodes have exactly equal velocities of racemization, two salts of the types *d*-acid-*d*-base and *l*-acid-*d*-base will racemize at different speeds; so that when the reaction product is isolated and the acids regenerated they will be found to be optically active. In many cases, however, this method yields no results, doubtless owing to the slight difference between the racemization velocities of the two isomers.

We may now turn to some other attempts which have been made to obtain optically active substances from inactive compounds. We have already seen that it has not been found possible to separate one antipode by crystallization from an optically active solvent. There still remains the possibility

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[1] See also McKenzie and Thompson, *Trans. Chem. Soc.*, 1905, **87**, 1004.

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

[3] Marckwald and Paul, *Ber.*, 1905, **38**, 810; 1906, **39**, 3654.

that if we start with an inactive substance containing no asymmetric carbon atom and so modify it, as in asymmetric synthesis, that an asymmetric carbon atom is formed in it, and if, further, we carry out the production of this new asymmetric carbon atom in an *active solvent*, we might find that the solvent had had an influence upon the reaction and caused the one antipode to be formed in excess of the other. Kipping[1] has put this idea to the test in the following way. He reduced pyruvic acid to lactic acid in a strong glucose solution; and also synthesized benzoin from benzaldehyde and potassium cyanide, using as solvent a solution of camphor in alcohol. In neither case was the reaction product active.

Hitherto we have dealt exclusively with the chemical side of the problem, but it may not be amiss to say a few words on some experiments which have treated the matter from a physical point of view, and have led in some cases to results of considerable interest.

Pasteur appears to have been the first to attempt to produce optically active substances by use of a strong magnetic field. His experiments were unsuccessful, as were those of Boyd.[2] It appears that an ordinary magnetic field is not truly asymmetrical; and in order to introduce the required asymmetry some addition must be made to the play of forces involved. Meyer[3] contrived the following system in order to overcome this difficulty. In his apparatus, a magnetic field is obtained in the usual way, and through it is passed a ray of light. When this ray of light is polarized before being passed through the field, the system becomes asymmetrical. Meyer placed a glass beaker in the path of the ray, and in the beaker he reduced benzoylformic to mandelic acid. The results, however, were negative; the mandelic acid formed being the ordinary externally compensated variety. Though this experiment failed, the method appears to be based upon sound principles, for Cotton[4] has shown that *d*-circularly polarized light is differently absorbed by the dextro- and lævo-forms of tartaric acid. Absorption cannot be carried on without a loss of energy, so that obviously a

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[1] Kipping, *Proc. Chem. Soc.*, 1901, **16**, 226; E. and O. Wedekind, *Ber.*, 1908, **41**, 456.

[2] Boyd, "Dissertation." Heidelberg, 1896.

[3] Meyer, *Chem. Zeit.*, 1904, **28**, 41.

[4] Cotton, *Ann. Chim. Phys.*, 1896, VII., **8**, 373.

reaction, carried out under polarized light, favours the formation of one antipode rather than the other. Henle and Haakh[1] have pointed out that results could be expected from such a method only if the reaction producing the asymmetric carbon atom were one which is influenced by light action; but their experiments in this line were unsuccessful. Unfortunately, the only apparatus at present at the command of the chemist does not allow us to influence reactions in this manner; and until we have more powerful instruments at our disposal it is unlikely that syntheses in this way will yield any great results.

In conclusion, we may sum up the matter simply. The task of producing a laboratory parallel to plant syntheses has been accomplished; we may not have actually produced the same substances as the plant forms within its organism, but we have certainly utilized analogous methods, and obtained similar results.

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[1] Henle and Haakh, *Ber.*, 1908, **41**, 4261.

CHAPTER XII

SOME THEORIES OF ADDITION REACTIONS

WHEN two compounds interact with one another there are two possible courses: in the one case from the two original molecules we may have two or more new molecules formed; while in the second case the two molecules coalesce to form a single substance. The latter type of interaction is what we understand by the term "addition reaction."

The importance of addition reactions from the point of view of theory has been very widely recognized, as is testified by the flood of hypotheses which have been put forward in this branch at one time or another. We cannot attempt to give a complete sketch of the various views which have been suggested, and must content ourselves with brief accounts of several recent attempts to formulate the principles underlying the practical side of the subject. The relation between stereochemical influences and the products of addition reactions lies outside the province of the present volume; and we shall confine our attention to the purely structural side of the question.

There is very little connection between the views which different authors have brought forward to deal with the addition question, and consequently it is difficult to arrange the various theories in anything resembling logical sequence. The most simple arrangement seems to be to begin with the more general views, and deal later with those of more restricted scope; and this plan will be followed in the rest of the chapter.

The most general view of all has been taken by Michael.[1] According to him, addition is caused by the affinity of the two interacting molecules for each other, and takes place in the manner which produces the most "chemically saturated" compound. But, as he points out, this "neutralization" of affinity

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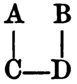
[1] Michael, *J. pr. Chem.*, 1888, II. **37**, 524; 1899, **60**, 286, 409; 1903, **68**, 487; *Ber.*, 1906, **39**, 2138.

depends very largely upon the character of the atoms forming the two interacting molecules. For instance, suppose that the two molecules—

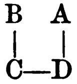
$$A—B \qquad C—D$$

are capable of reacting together. Let us first consider the affinity of A for C and for D. If the affinity of A for C is greater than that of A for D, then we should expect to find A attaching itself to C, and leaving B to attach itself to D, thus forming the compound—



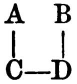
$$\begin{matrix} A & & B \\ | & & | \\ C & — & D \end{matrix}$$

But this leaves out of account the attraction of B for C. If this were greater than the attraction of B for D, then we should expect the formation of the compound—



$$\begin{matrix} B & & A \\ | & & | \\ C & — & D \end{matrix}$$

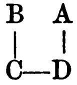
It is obvious that the actual result of the reaction will depend upon the relative intensity of the forces between A and C and between B and C, coupled with the relative intensity of the forces between A and D and between B and D. Let us represent the forces between A and C by *ac* and those between B and C by *bc*, also those between A and D by *ad* and those between B and D by *bd*. Then the forces which are favouring the formation of the first type—



$$\begin{matrix} A & & B \\ | & & | \\ C & — & D \end{matrix}$$

(I.)

will be represented by $ac + bd$, while those favouring the formation of—



$$\begin{matrix} B & & A \\ | & & | \\ C & — & D \end{matrix}$$

(II.)

will be represented by $bc + ad$. The amounts of the two compounds formed during the progress of the reaction will therefore be to one another in the ratio of $ac + bd : bc + ad$. This is termed Michael's "Distribution Principle."

The consideration of a concrete case will make the matter clearer. Suppose we take propylene, $CH_3 . CH : CH_2$, and allow it to react with hydriodic acid. Two possible products may result; for in the one case the iodine atom may attach itself to the middle carbon atom, while in the other it may be attracted by the end carbon atom.

(I.)	(II.)	
$CH_3 . CHI . CH_3$	$CH_3 . CH_2 . CH_2I$	(300:1)

It has been found that about three hundred times more of (I.) is formed than (II.). This is due to the great chemical difference between the hydrogen and iodine atoms of hydriodic acid. But if we lessen this difference between the two atoms by substituting a chlorine atom for hydrogen (using iodine chloride instead of hydriodic acid), we shall find that the iodine atom now attaches itself to the end of the chain rather than to the central atom, the amounts of the compound (I*a*.) and (II*a*.) being formed in the ratio of three to one—

(I*a*.)	(II*a*.)	
$CH_3 . CHCl . CH_2I$	$CH_3 . CHI . CH_2Cl$	(3:1)

The directing influences at work may be still further neutralized if we employ bromine chloride instead of iodine chloride. In this last case there is great similarity between the two atoms, and, as a result, the two possible end-products are formed in very nearly equal proportions (1.4:1.0)—

(I*b*.)	(II*b*.)	
$CH_3 . CHCl . CH_2Br$	$CH_3 . CHBr . CH_2Cl$	(1.4:1)

It will be seen that the "Markownikoff Rule"[1] is only a particular application of the "Distribution Principle," and that its applicability depends to some extent upon the constitution of the molecule containing the double bond.

We must now turn to the views of Vorländer.[2] If we take an $\alpha\beta$-unsaturated ketone and allow it to react with an acid, the first substance formed is a coloured, unstable substance.

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[1] See p. 58, footnote.

[2] Vorländer and Mumme, *Ber.*, 1903, **36**, 1470; Vorländer and Hayakawa, *ibid.*, 3528; Vorländer, *Annalen*, 1903, **341**, 1; 1906, **345**, 155.

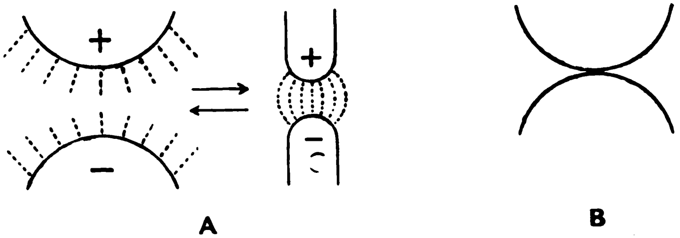
This series of bodies Vorländer designated as Type 𝔄. These compounds may undergo a change, being converted into white stable substances which Vorländer classes together under the heading Type 𝔅. According to Vorländer, these two series of substances differ from each other in the following way.

If we consider different states of unsaturation as the outcome of the different capacities of the elements and radicles for positive or negative electricity (of course this is merely used as an analogy), then in the case of the addition of two oppositely charged compounds there are two possibilities—

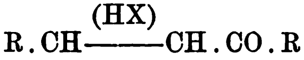
A. There may be no complete neutralization of the electric charges. In this case the electricity which was originally spread over the surface of the substances becomes concentrated into a comparatively small area by the attraction of the opposite charge on the second substance, and consequently strain is set up.

B. The compounds unite together and become discharged.

The figures below illustrate this graphically.

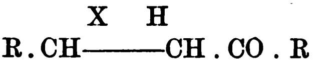


Let us take the case of the addition of an acid HX to the ketone R.CH:CH.CO.R as an example. In compounds of Class 𝔄 the acid HX has simply attached itself to the ketone to form a kind of double compound, which he represents thus—

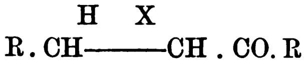


$$\mathrm{R.CH}\overset{(\mathrm{HX})}{\text{————}}\mathrm{CH.CO.R}$$

Here no separation of HX into H and X occurs. But in the case of the stable bodies, Type 𝔅, this dissociation of the acid molecule does actually take place, so that we may write the formula of these bodies thus—



$\overset{X}{R.CH}\text{———}\overset{H}{CH}.CO.R$ or



$\overset{H}{R.CH}\text{———}\overset{X}{CH}.CO.R$

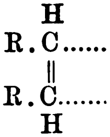
Now, in order that any addition-compound be formed there must exist between the two interacting molecules of acid and ketone a difference which Vorländer terms a difference in "potential." The amount of this difference we can estimate by measuring the velocity with which the two substances unite; for the greater the difference in potential between them, the more rapidly will they unite with each other. The rapidity of formation of the coloured, unstable products is almost instantaneous, while the rate of formation of the stable type is quite measurable. From this we may conclude that the strain in the case of the formation of the unstable bodies is greater than that in the production of the stable isomers.

Vorländer expresses his view somewhat as follows. If we consider the case of two substances about to interact, the difference in potential between them may be called h. When the unstable compound is formed, only a very little energy is used up, and the difference in potential between the two components sinks to h_a, the rest of the original energy being utilized in holding the two components loosely together. Since there is little change of potential throughout the system, such reactions can take place rapidly even at low temperatures. In the case of the stable compounds, however, the difference in potential h is much reduced, say to h_b. On Vorländer's view, time is required to bring about this change in potential, and also to overcome certain reaction difficulties, so that the rate of addition is slow. Further, the two types of addition products, owing to the difference in potential between them, have quite different properties. Vorländer groups the whole series of addition reactions according to their results, and in this way obtains the following series: (1) Compounds of Type 𝔄; (2) double salts; (3) complex salts; (4) compounds of Type 𝔅.

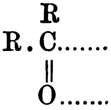
The difference between the two systems 𝔄 and 𝔅 is especially marked, when we take into consideration the nature of the solvent. In the case of 𝔄 the dielectric constant of the solvent will exercise a very marked influence; but in the case of 𝔅, since the compounds are in actual contact, the solvent will have no effect.

In the foregoing theories the question of addition was treated from a broad standpoint, but now we must come to more restricted fields. 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 theory, with which we are about to deal, that it became a classic almost as soon as it was published; and was not forced to undergo the process of cud-chewing which is usually the most that can be expected when a new theory is under consideration.

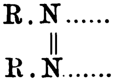
The Thiele theory[1] is based upon the following assumption. If we imagine the case of a double bond between two atoms, it is supposed that the whole of the affinity of the atoms is not used up, but that in addition to that which is utilized in joining the two atoms together there is a slight excess on each atom. This slight excess of valency Thiele designates by the name *Partial Valency*, and to its presence he attributes the additive power which unsaturated compounds display. To represent the partial valencies, Thiele employs a dotted line, thus—



$$\begin{array}{rl} & \text{H} \\ \text{R}\,.\, & \text{C}\ldots\ldots \\ & \| \\ \text{R}\,.\, & \text{C}\ldots\ldots \\ & \text{H} \end{array}$$



$$\begin{array}{rl} & \text{R} \\ \text{R}\,.\, & \text{C}\ldots\ldots \\ & \| \\ & \text{O}\ldots\ldots \end{array}$$



$$\begin{array}{rl} \text{R}\,.\, & \text{N}\ldots\ldots \\ & \| \\ \text{R}\,.\, & \text{N}\ldots\ldots \end{array}$$

Now, when we come to the consideration of such a system as

$$\text{R.CH:CH.CH:CH.R}$$

we find that it shows one peculiar property in connection with addition reactions. Since it contains two double bonds, it might be expected to take up four atoms of hydrogen or bromine at once, or at least to take up two atoms of bromine or hydrogen at one of the double bonds. In other words, we should expect to find one molecule of bromine attacking it first with the formation of the compound—

$$\text{R.CHBr.CHBr.CH:CH.R}$$

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[1] Thiele, *Annalen*, 1899, **306**, 87.

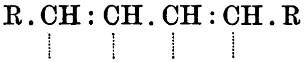
to which another bromine molecule might be added, giving the tetrabromo-compound—

$$\mathrm{R.CHBr.CHBr.CHBr.CHBr.R}$$

In practice, however, the first molecule of bromine does not attack either of the double bonds; it attacks them both at once, with the formation of the compound—

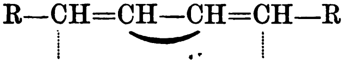
$$\mathrm{R.CHBr.CH:CH.CHBr.R}$$

in which both of the original double bonds have disappeared, giving rise to a new double bond in the centre of the molecule. If we write out the scheme of partial valencies for the original substance—



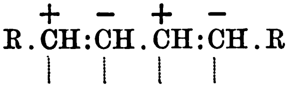
$$\mathrm{R.\underset{\vdots}{C}H:\underset{\vdots}{C}H.\underset{\vdots}{C}H:\underset{\vdots}{C}H.R}$$

it is evident that only the two at the ends of the system have the faculty of attracting bromine, the two middle partial valencies failing to act. In order to express this behaviour Thiele writes the formula in the following way, in which the two central partial valencies are supposed to have neutralized one another:—



$$\mathrm{R{-}\underset{\vdots}{C}H{=}\underbrace{CH{-}CH}{=}\underset{\vdots}{C}H{-}R}$$

We can make this behaviour clear by supposing that the carbon atoms of the chain are charged alternately with positive and negative forces, the two central atoms will then neutralize one another, leaving the ends still charged—

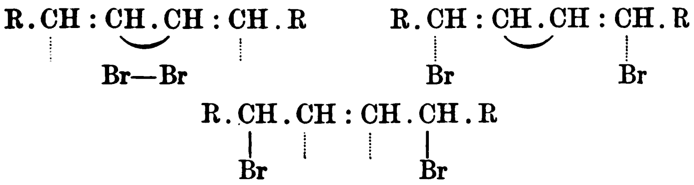


$$\mathrm{R.\underset{\vdots}{\overset{+}{C}}H:\underset{\vdots}{\overset{-}{C}}H.\underset{\vdots}{\overset{+}{C}}H:\underset{\vdots}{\overset{-}{C}}H.R}$$

$$\mathrm{R.\underset{\vdots}{\overset{+}{C}}H:\underbrace{CH.CH}:\underset{\vdots}{\overset{-}{C}}H.R}$$

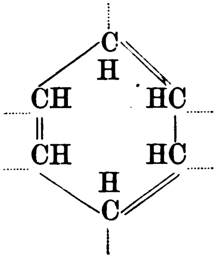
Such a system Thiele terms a *Conjugated Double Bond.*

If addition takes place in the case of a conjugated double bond, obviously the two new atoms will attach themselves at the ends of the chain in the position indicated by the free partial valencies. But this does not end the matter, for no sooner has addition taken place than the conjugation is destroyed, and hence a new double bond will be formed between the central atoms of the system—

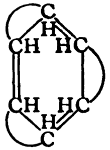


$$R.CH:CH.CH:CH.R + Br{-}Br \qquad R.CH:CH.CH:CH.R \qquad R.CH(Br).CH:CH.CH(Br).R$$

The most striking application of the Thiele theory, however, is found in the case of the benzene ring. If we write down the Kekulé formula for benzene, and fill in the partial valencies in the usual way, we arrive at the following figure:—



An examination of this system will show that it forms *a closed series of conjugated double bonds.* In other words, it can be written as shown below, and no free partial valencies exist in the system. Hence the impossibility of producing addition products with benzene under ordinary conditions.



Though the theory of partial valencies has very widespread application, it is not absolutely accurate, for several cases are known in which it is not in accordance with the results of experiment. We may mention one or two of these, without laying too much stress upon them.

Harries[1] has shown that unsaturated aldoximes or ketoximes may be reduced to unsaturated amines. Thiele himself mentions a case observed by Bredt and Kallen[2] in which hydrocyanic

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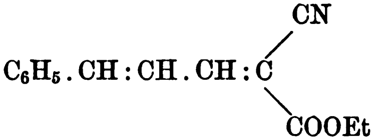
[1] Harries, *Annalen*, 1903, **330**, 185.

[2] Bredt and Kallen, *Annalen*, **293**, 338.

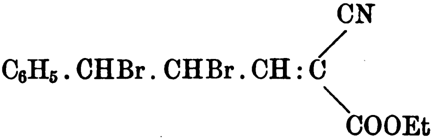
acid adds on to cinnamylidene-malonic acid by simple addition to the double bond next the carboxyl radical. Hinrichsen and Lohse observed that when cinnamenyl-cyanacrylic ester (I.) is allowed to react with bromine it yields a bromide of the formula (II.) shown below—

(I.)



$$C_6H_5.CH:CH.CH:C\begin{matrix}\diagup CN\\ \diagdown COOEt\end{matrix}$$

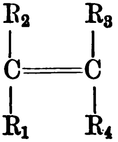
(II.)



$$C_6H_5.CHBr.CHBr.CH:C\begin{matrix}\diagup CN\\ \diagdown COOEt\end{matrix}$$

Several other similar instances are known, and it appears that, though in the main the partial valency theory is most useful, in some cases it is necessary to take into account the influence exerted upon the addition reaction by substituents near the double bond.

This part of the subject has been investigated by Bauer,[1] who was able to substantiate Nef's view [2] that addition reactions may be influenced in this way. Bauer showed that if we accumulate phenyl, carboxyl, or carbethoxyl groups or bromine atoms in the neighbourhood of a double bond, bromine is not easily taken up by the double linking. For instance, if we take the general formula—



$$\begin{matrix}R_2 & & R_3\\ | & & |\\ C & = & C\\ | & & |\\ R_1 & & R_4\end{matrix}$$

and make R_1 a carboxyl group, bromine will be added on, unless the other R groups are bromine atoms, or bromine atoms with some methyl groups. Methyl groups alone do not hinder the addition. Thus we get addition of bromine in the case of acrylic acid, α- and β-bromacrylic acids, crotonic and isocrotonic acids, dimethylacrylic acid, tiglic acid and trimethylacrylic

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[1] Bauer, *Ber.*, 1904, **37**, 3488.

[2] Nef, *Annalen*, 1898, **298**, 208.

acid. No addition of bromine takes place in the cases of tribromacrylic and dibromcrotonic acids.

If we replace R_1 and R_4 by carboxyl groups, addition of bromine remains possible as long as R_2 and R_3 are not either bromine atoms or methyl groups. Thus bromine will attack maleic, fumaric, mesaconic, or bromomaleic acid, but it will not attack the double bonds of dimethylfumaric, dibromofumaric, or bromo-mesaconic acid.

If R_1 is a phenyl radical, and the other three Rs methyl groups, the compound takes up a molecule of bromine. If R_1 and R_4 are phenyl groups, and one of the remaining Rs is a hydrogen atom, the compound will react with bromine; but if in addition to the two phenyl groups we introduce two bromine atoms, the additive power ceases. Thus while addition takes place in the case of stilbene, methyl-stilbene, or bromo-stilbene, it fails in the case of dibromostilbene.

If for R_1 and R_2 we substitute phenyl groups, while the other two Rs are hydrogen atoms or alkyl groups, we enter a new phase; for now we have first an addition reaction, and then a spontaneous loss of hydrobromic acid, leaving us with a bromo-substituted unsaturated compound. In this way behave diphenyl-ethylene, diphenyl-propylene, diphenyl-methyl-propylene; but no addition of bromine takes place in the cases of diphenyl-bromo-ethylene, diphenyl-bromo-propylene, or tetraphenyl-ethylene.

In a later paper[1] Bauer showed that, when placed near a double bond, the phenyl group had a certain effect upon the addition of bromine, the carbethoxyl group had more, while the nitrile group had the strongest influence of the three.

It was also found that the influence of the phenyl group was weakened by nitration, a nitro-group in the meta-position having least effect, and one in the ortho-position the most influence.

Bauer showed further that the addition of bromine to the double bond is a reversible reaction, equilibrium being attained at different stages according to the effect of the substituents introduced into the molecule.

It is a curious fact that substituents which influence the

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[1] Bauer, *J. pr. Chem.*, 1905, II. 72, 201; Bauer and Moser, *Ber.*, 1907, 40, 918.

addition of bromine have a parallel effect upon the dissociation constant of acids, the effect of a phenyl group in the one case, for instance, being less than that of a cyanide radicle, and the same holding good in the case of the dissociation constants.

Somewhat similar results have been obtained by Klages[1] in the course of his researches on the reduction of styrolene derivatives.

It will be noticed that in all the foregoing views the question is treated purely from a static standpoint; the double bond is regarded more or less as a kind of hook which can fix itself upon any atom wandering in the neighbourhood. Stewart's view differs from the others in that it concerns itself more with the dynamics of intramolecular change than with the purely static side.

In the first place, we may give a brief account of the chemical evidence upon which this view is based. Stewart[2] first showed that the reactive power of the carbonyl group in acetoacetic ester greatly exceeded that of the carbonyl radicle in acetone. Later[3] he proved that the carbonyl radicle of acetone dicarboxylic ester was even more reactive than that of acetoacetic ester. On the other hand, the carbonyl groups in læevulinic ester and in acetonylacetone were much less reactive than those of acetone. Acetylacetone proved to be more reactive than either. Pinacoline was the least reactive of all the ketones examined.

Taking acetone as the highest substance in the "slight reactivity" class we can arrange the two sets of compounds thus—

	Low Reactivity.		*High Reactivity.*
Decrease. ↓	Acetone	Increase. ↓	(Acetone)
	Lævulinic ester		Acetoacetic ester
	Acetonylacetone		Acetylacetone
	Pinacoline		Acetone dicarboxylic ester

And when we examine the "reactive" group we find that all the substances which it contains are tautomeric bodies, which are capable of yielding sodium derivatives, and whose methylene hydrogen atoms are easily replaced by halogens. In other

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[1] Klages, *Ber.*, 1903, **36**, 3584; 1904, **37**, 1721, 2301.

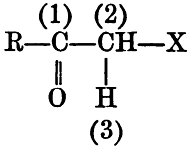
[2] Stewart, *Trans. Chem. Soc.*, 1905, **87**, 185.

[3] Stewart, *Proc. Chem. Soc.*, 1905, **21**, 78.

words, not only is the carbonyl group in each of them very reactive, but the hydrogen atoms of the neighbouring methylene group share this activity. On the other hand, none of the "weakly reactive" group are strongly tautomeric, and their hydrogen atoms are not acidic to any great extent.

Now, in the case of the substance acetoacetic ester, for instance, it is obvious that the hydrogen atoms in the methylene group must be very closely related to the oxygen atom of the carbonyl group; for if they were not, it is difficult to understand how the sodium derivative of such substances is derived from the hydroxylic form of the compound. Without actually supposing that the hydrogen atom wanders freely between the carbon and oxygen atoms, as in the Laar hypothesis, it must be admitted that the oxygen atom exercises some influence upon the hydrogen atoms, and *vice versâ*. This influence will be most strongly marked in the case of acetone dicarboxylic ester, but it will be perceptible even in simple ketones.

Let us next consider the effect which this influence will have upon the various atoms in the molecule. If we take the case of the grouping—



$$\begin{matrix} & (1) & & (2) & \\ R- & C & - & CH & -X \\ & \| & & | & \\ & O & & H & \\ & & & (3) & \end{matrix}$$

it is obvious that the affinity of the carbon atom (1) is occupied in part by the group R, part by the carbon atom (2), and the remainder is devoted to saturating the affinity of the oxygen atom. Similarly, the affinity of the carbon atom (2) is distributed between the group X, the carbon atom (1), and the hydrogen atoms. But since there is some relation between the oxygen atom and the hydrogen atom (3), some of the affinity of these two atoms must be used up in mutual attraction, and the more tautomeric the compound is, the more affinity will thus be employed.*

Regarded in this way, the molecule would represent a closed system, the affinities of whose atoms are mutually saturated.

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* Tautomeric is perhaps not the correct word; what is meant is that the affinity-exchange between the two atoms will be greatest in the case where the methylene hydrogen atoms are most strongly acidic.

But if we take into account the intramolecular motions of atoms, the case at once assumes a different aspect. It is obvious that the influence exerted by the hydrogen atom (3) upon the oxygen atom will not be constant, but will vary according to the distance between these atoms. If we assume, as is usually done, that the atoms within a molecule vibrate in closed paths about relatively fixed centres, it is evident that the hydrogen atom will be now approaching, now retreating from the oxygen atom. Every approach will entail a rearrangement of the affinity of the two atoms, and another rearrangement of affinity will take place during their retreat from each other. Stewart considers that this *rearrangement of affinity* of these two atoms is the cause of their chemical activity. In a closed or stable system of forces the introduction of a new element is difficult; but if a system be in a state of unstable or continually varying equilibrium it is more readily amenable to change.

Now, in tautomeric compounds, since the oxygen and hydrogen atoms exert great influence upon each other, this redistribution of affinity will be much more strongly marked than in the case of substances like acetone, whose hydrogen atoms are only very weakly acidic; and when we replace the hydrogen atoms of acetone by methyl groups we shall still further lessen the possible influence upon the oxygen atom, which serves to make clear the very low reactivity of the carbonyl group in pinacoline. Support is lent to Stewart's views by the evidence of the absorption spectra of the above-mentioned ketonic compounds which were examined by Stewart and Baly.[1]

We must now turn to the question of the α-diketones and quinones, which also contain very reactive carbonyl groups. When the reactivity of the carbonyl group in pyruvic ester was determined by Stewart's method,[2] it was found to be more active than any of those previously dealt with. Now, in this case, we can hardly suppose that there is any great attraction between the hydrogen atoms of the methyl radicle and the oxygen of the carbonyl group: the chemical behaviour of the substance gives us no right to draw any such

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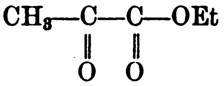
[1] Stewart and Baly, *Trans. Chem. Soc.*, 1906, **89**, 489; cf. Stewart and Baly, *Trans. Chem. Soc.*, 1906, **89**, 618.

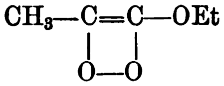
[2] Stewart, *Trans. Chem. Soc.*, 1905, **87**, 185.

conclusion; and the spectroscopic evidence, as far as it can be considered relevant in a purely chemical question, tends to disprove the existence of any such mutual influence. We are therefore forced to a new point of view.

If we assume that instead of a mutual attraction between the oxygen and hydrogen atoms we have a similar attraction between the oxygen atoms of the two carbonyl groups in pyruvic ester, we should be able to explain how in that substance a redistribution of affinity is going on which to some extent will resemble that in acetoacetic ester. But we may go even further in this case, and assume that as an extreme form of the intramolecular vibration we have *almost* a rearrangement of bonds such as is expressed in the following formula:—

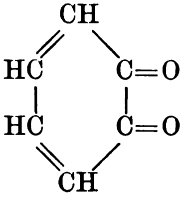


$$CH_3-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-OEt$$

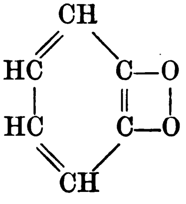


$$\begin{array}{l} CH_3-C=C-OEt \\ \qquad\;\; | \quad\; | \\ \qquad\;\, O-O \end{array}$$

In pyruvic ester it is doubtful whether this change ever takes place; we have only spectroscopic evidence in support of it, not chemical. But there is a parallel case in which we can bring actual chemical evidence in support of this attraction between the two oxygen atoms. Willstätter and Müller,[1] by oxidizing catechol with silver oxide, have succeeded in isolating ortho-benzoquinone in two isomeric forms, to one of which they ascribe the dicarbonyl formula (I.), while the other they suppose to have the structure (II.)—



(I.)



(II.)

It is well known that the para-positions of the benzene ring are closely related to each other, more closely than the ordinary structural formulæ indicate; and in the case of the quinones, this connection is very strongly marked in the

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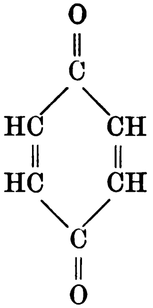
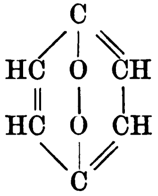
[1] Willstätter and Müller, *Ber.*, 1908, 41, 2580.

reactions of the two carbonyl radicles. Now, quinone itself is a tautomeric body which reacts as if it had either of the two structures shown below—



(I.)



(II.)

Hence it is obvious that in this case we actually have a change taking place which converts the compound (I.) into the compound (II.), and *vice versâ.* This change is perfectly analogous to that which we have already written down in the case of pyruvic ester, though in that compound we had no chemical evidence for the two formulæ such as we have in the case of quinone. The conversion of the quinone (I.) into the quinone (II.) and its reverse would produce that redistribution of affinity upon the oxygen atoms which we have postulated as the cause of the chemical activity in carbonyl groups; and the vibrations of the benzene ring itself suffice to explain why this conversion takes place, for in one phase we should expect to find the carbonyl groups near to each other, while in another phase they may be far apart, and therefore unable to exert much influence upon each other.

Analogous ideas have been applied by Baly[1] to the case of the colour of some nitrogen compounds, but as we are dealing purely with the chemical side of the question here we need not enter into any discussion of this physical property.

Forster[2] suggests that we might regard the oxygen atom as changing its valency in these cases, so that the extreme

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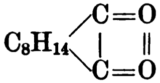
[1] Baly, Edwards and Stewart, *Trans. Chem. Soc.*, 1906, **89**, 514; Baly, Marsden and Stewart, *ibid.*, 966.

[2] Forster, private communication to the author.

phase of the vibration in the case of camphor-quinone, for example, might be written thus—



and this view appears to have much to recommend it.

By means of the foregoing hypothesis, then, we are enabled to give some explanation of a series of apparently quite disconnected facts: the reactivity of aliphatic ketones and diketones, the tautomeric power of these substances, the sensitiveness of the hydrogen atoms in the grouping —CO . CH_2 . CO—, the extreme chemical reactivity of the quinones; and by a slight extension of the hypothesis we could explain also the ease with which the α-hydrogen atoms of acids are replaced by halogens.

The foregoing brief account of the various theories of addition reactions only serves to throw into relief the insufficiency of our present views on this subject. On the one hand, we have ideas which are so vague as to convey very little meaning, while on the other we have mechanical hypotheses which are too inelastic to cover anything but a very narrow field. The most useful of all the suggestions hitherto put forward, Thiele's partial valencies, deals rather with the facts themselves than with any explanation of them, and takes little account of subtle differences in reactivity. The field is tempting to the theorist, however, and perhaps before long we may have some view which will combine the advantages of all the present hypotheses without their drawbacks.

CHAPTER XIII

UNSATURATION

When we examine the matter closely, we find that the foundations of theoretical organic chemistry are a series of labels by means of which we endeavour to conceal our ignorance of the fundamental phenomena of the subject. Of these labels, none is used more indefinitely and at random than the word "Unsaturation." It seems not without some interest, therefore, to examine the various phenomena which are usually ascribed to the presence of this property, and to see how far we can attain to some clear idea of what we mean by the word.

In the first place, let us ask ourselves what we mean by an unsaturated compound. The picture which is formed in our mind by these words usually represents two molecules uniting together, and one of these we are accustomed to call an unsaturated substance. But before going further we are faced by a difficulty, for there seems no reason why we should consider one of the two molecules unsaturated and the other saturated. For example, if a molecule of bromine unites with a molecule of ethylene, we call ethylene an unsaturated hydrocarbon, but we do not regard the bromine molecule as unsaturated in the same sense. If we examine the matter more closely, however, the difference between the two cases becomes clear. When ethylene takes up an atom of bromine the ethylene molecule is not completely disrupted; part of it remains as it was, for the two carbon atoms are still united, and each bears the same number of hydrogen atoms as before. With the bromine molecule, however, no trace of the original structure remains. Evidently our idea of an unsaturated compound must be extended; it is no longer sufficient to say that it is "a molecule capable of uniting with another molecule"; but we must add, "without a disruption of its original structure." This definition covers practically every case which has any claims to be considered; and we may therefore adopt it and proceed to inquire if we can distinguish further between the various classes of substances which come within the definition.

The simplest type of an unsaturated compound with which we can deal is a component of a double salt. Here the amount of unsaturation is very slight, for we may decompose the saturated body (double salt) into its components again by a mere lowering of temperature.

The second class of unsaturated compounds includes those in which the addition of new atoms takes place at one atom only, as, for example, trimethylamine, dimethyl-sulphide, dimethyl-pyrone, etc. In this case the least possible change in the general structure of the molecule takes place during the addition reaction.

The third class of unsaturated compounds contains those bodies which are capable of uniting with two atoms, but in which addition takes place at two adjacent atoms. The ethylene series, the ketones, and the nitriles are instances of this type.

There is another class of bodies which, while resembling the last-mentioned one, in so far as their capability of adding on only one pair of atoms is concerned, differs from it in the manner of addition; for, instead of the two new atoms attaching themselves to two adjacent atoms, as in the ethylene class, in this new series they attach themselves to non-adjacent carbon atoms. The polymethylenes are a case in point.

Finally, we come to the acetylene class, in which we are able to unite four new atoms to two of the carbon atoms of the unsaturated compound.

Thus we have divided unsaturated bodies into the following five classes:—

1. Components of molecular compounds.
2. Compounds of mono-valent iodine, divalent sulphur, selenium, tellurium, oxygen, etc., trivalent nitrogen, phosphorus, antimony, etc.
3. Compounds containing groups like C : C , C : N , C : O.
4. Cyclic compounds.
5. The acetylenes.

Of course, it is quite easy to multiply the possibilities by combining in one molecule representatives of each class, as in the case of mesityl oxide, for instance; but if we reduce the question to its simplest form, the above series will serve as a mode of classification.

Before entering into a consideration of these classes, however, we must deal with two other points which arise. What we call an unsaturated substance may be unsaturated with regard to one agent, and quite saturated towards another.[1] For instance, if we take the substances in Class 3, though all of them are unsaturated with respect to nascent hydrogen, they differ in their behaviour towards bromine, ammonia, or water. Again, it is sometimes found that a compound may behave as a saturated or an unsaturated substance according to the conditions under which reactions are carried out. For example, in sunlight benzene forms addition products much more easily than in the dark. Thus there are fine differences for which we have no corresponding technical terms.

It would occupy too much space were we to enter into any detailed examination of the differences in physical properties between saturated substances and the unsaturated bodies from which they have been prepared. There is hardly a single physical property which remains common to the two groups. Melting-point, boiling-point, refractive index, optical rotatory power, absorption spectrum, magnetic rotation, crystalline form, electrical conductivity, and a host of other properties are all changed by the addition of as many atoms as the unsaturation requires.

The chemical effects of unsaturation are hardly less marked. Leaving out of consideration the chemical difference implied in the fact that the unsaturated compound is capable of adding on more atoms, while the saturated one is not, there are many other differences which the presence or absence of unsaturation in the molecule brings into view. For example, if we take a saturated aliphatic acid and the corresponding unsaturated substance in which the double bond lies next the carboxyl group, the saturated acid will esterify with much greater ease than the unsaturated one.[2] Again, unsaturation may call into

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[1] See Vorländer, *Annalen*, 1902, **320**, 66.

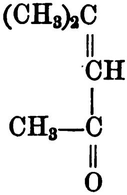
[2] Sudborough and Roberts, *Trans. Chem. Soc.*, 1905, **87**, 1840; Sudborough and Thomas, *ibid.*, 1907, **91**, 1033.

being a peculiar type of isomerism, of which the best example is found in the case of maleic and fumaric acids. Further, in the case of the acetylene series, the presence of unsaturation so alters the chemical characters of the hydrogen atoms that they become replaceable by metallic atoms; while, if we accumulate acetylenic linkages in a compound, it may become so unstable as to decompose with explosive violence. These few examples will suffice to illustrate the very varied influences exerted on the properties of compounds by unsaturation.

We may now turn to the question of the relative stability of various unsaturated compounds. In the first place, it is obvious that the amount of energy which is used up in saturating the component of a double salt cannot be very great; for if it were so, the double salt would not be decomposed again into its components with the ease which is found in practice. In the second class, we obtain saturated compounds by calling into existence some latent affinities on the sulphur or nitrogen atoms. Now, these new salts—sulphonium, ammonium, phosphonium, or whatever they be—can, in many cases, be broken down into the unsaturated substance again by very simple means. For instance, merely by heating the quaternary ammonium salts we can obtain the amido-compounds from which we started. Thus, though we have here a set of substances more stable than the double salts, still the increase in stability is not very great. When we come to the groups 3, 4, and 5, the change from the saturated to the unsaturated body can only be brought about by chemical means, so that in their case we have passed into a new stage of the question.

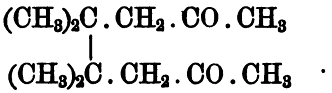
There is another way in which we can look at the matter, and, for the sake of simplicity, we may confine our investigation in the rest of this chapter to the cases of the carbon compounds. If we take an ethylene derivative and compare it with the isomeric polymethylene, we find that the former is much more readily attacked by reagents than the latter; in other words, the ethylene type is more unsaturated than the polymethylene. Thus, while ethylene compounds are almost instantaneously oxidized by permanganate, the polymethylenes are not so rapidly destroyed. The acetylene series is even more sensitive to oxidizing agents than the ethylenes.

A somewhat interesting point arises when we combine in one molecule two different types of unsaturation, and then endeavour to find out which of them is the more readily saturated. For example, if we take the case of mesityl oxide, we have in one molecule the double bond between two carbon atoms, and the other double bond between a carbon and an oxygen atom—



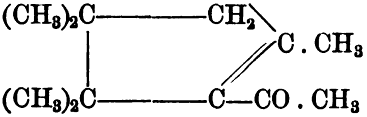
$$(CH_3)_2C{=}CH{-}C({=}O){-}CH_3$$

These two double bonds are of different types, and hence we should expect to find some differences between their chemical activities. In the first place, of course, we find that the one bond will react with halogen acids, which do not attack the carbonyl group. But if we leave out of account such differences and confine ourselves to the action of those reagents which are capable of reacting with both linkages, the results are sufficiently striking. If we reduce mesityl oxide by means of weak alkaline reagents, such as sodium amalgam or aluminium amalgam, the carbonyl group remains intact, while the double bond is opened up. Two molecules of the ketone unite together to form a saturated diketone—



$$\begin{array}{l}(CH_3)_2C\,.\,CH_2\,.\,CO\,.\,CH_3\\ \quad\;\;|\\ (CH_3)_2C\,.\,CH_2\,.\,CO\,.\,CH_3\end{array}$$

(In the case of aliphatic ketones this diketone further condenses to a cyclic compound, in this instance desoxy-mesityl oxide—



while in the aromatic series the reaction may be stopped at the first stage.)

When we use, as a reducing agent, sodium in aqueous ether, the reaction takes quite a different course, for here both the carbonyl and the ethylene linkages are attacked simultaneously, giving the saturated alcohol—

$$(CH_3)_2CH . CH_2 . CH(OH) . CH_3$$

No method has yet been discovered by which we can reduce the carbonyl group of mesityl oxide without destroying the ethylene linkage as well.

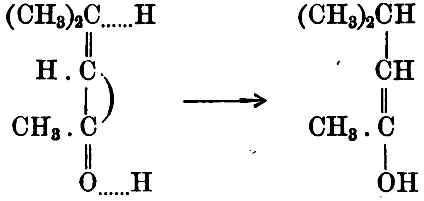
But if we take the case of another ketone, such as—

$$CH_2 : CH . CH_2 . CO . CH_3$$

we shall find no difficulty whatever in reducing it with sodium in alcohol or aqueous ether to the unsaturated alcohol—

$$CH_2 : CH . CH_2 . CH(OH) . CH_3$$

If we examine the structures of the two substances we find that in the case of mesityl oxide we have a conjugated double bond, while in that of the second ketone we have two unconjugated linkages; thus in the case of mesityl oxide we cannot attack one bond without tampering with the other, while in the second case we can reduce either separately. If we examine the progress of the reaction which we should expect from Thiele's hypothesis in the case of mesityl oxide, we find that in the first place, hydrogen adds on to the two end partial valencies, as shown below—

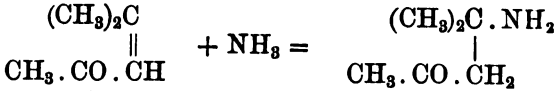


But this new body is merely the enolic form of the ketone—

$$(CH_3)_2CH . CH_2 . CO . CH_3$$

into which it will rearrange itself at once. Thus it is easy to understand why the carbonyl group is never attacked first when it is conjugated with another double bond of a different nature.

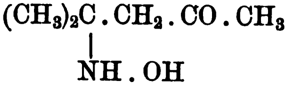
Again, ammonia is an agent which is capable of acting both upon carbonyl groups and on ethylenic linkages, but if we allow it to react with mesityl oxide it attacks only the double bond between the carbon atoms and leaves intact the carbonyl radicle—



$$\begin{array}{r} (CH_3)_2C \\ \| \\ CH_3.CO.CH \end{array} + NH_3 = \begin{array}{r} (CH_3)_2C.NH_2 \\ | \\ CH_3.CO.CH_2 \end{array}$$

Mesityl oxide. Diacetonamine.

The matter becomes a little clearer when we consider the action of hydroxylamine upon mesityl oxide.[1] If the action 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—



$$\begin{array}{l} (CH_3)_2C.CH_2.CO.CH_3 \\ \quad\quad\;\; | \\ \quad\quad NH.OH \end{array}$$

But if, on the other hand, we take hydroxylamine hydrochloride and after exactly neutralizing it with sodium carbonate 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.

The influence of the conjugated double bond makes itself felt also in the cases of propenyl and allyl methyl ketones. Blaise[2] has examined these two isomeric substances, and finds that when treated with one molecule of hydroxylamine in a neutral solution they are both converted into oximes—

$$CH_3.CH:CH.CO.CH_3 \rightarrow CH_3.CH:CH.C(NOH).CH_3$$
$$CH_2:CH.CH_2.CO.CH_3 \rightarrow CH_2:CH.CH_2.C(NOH).CH_3$$

But if we treat them with *two* molecules of hydroxylamine the results are different; allyl methyl ketone reacts as in the last case, giving the oxime shown above, while propenyl methyl

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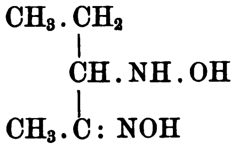
[1] Harries and Lellmann, *Ber.*, 1897, **30**, 230, 2726; Harries and Jablonski, *ibid.*, 1898, **31**, 1371; Harries, *Annalen*, 1904, **330**, 191.

[2] Blaise, *Bull. soc. chim.*, 1905, III. **33**, 42.

ketone reacts with two molecules of hydroxylamine to give the hydroxylamineoxime derivative shown below—



$$\begin{array}{l} CH_3.CH_2 \\ \quad\quad | \\ \quad\quad CH.NH.OH \\ \quad\quad | \\ CH_3.C : NOH \end{array}$$

Thus the conjugation of the ethylene and carbonyl bonds increases the activity of the ethylenic linkage in this case also. Blaise showed that exactly similar results were obtained with semicarbazide, the allyl ketone forming a semicarbazone, while the propenyl ketone, in virtue of its conjugated bonds, took up a second molecule of semicarbazide to form a semicarbazide-semicarbazone.

Posner[1] has studied the matter very fully in order to find what effect various groups exert when placed near the ethylenic double bond. In the first place, he proved that the ethylenic linkage alone was capable of taking up hydroxylamine and mercaptans, so that this addition capacity does not depend entirely upon the proximity to the carbonyl group. When unsaturated acids were used, he found that the activity of the double bond was weakened if the carboxyl group was placed in its vicinity. Thus neither maleic nor fumaric acid can be induced to combine with hydroxylamine except to form the usual salts; phenyl-isocrotonic acid, on the other hand, in which the ethylene linkage is not conjugated with the double bond of a carboxyl group, takes up a hydroxylamine molecule with special ease. $\alpha\beta$-unsaturated monocarboxylic acids give with hydroxylamine α-oximino-acids, whilst $\alpha\beta$-unsaturated ketones form β-hydroxylamine derivatives.

Thus we cannot say definitely that the ethylenic linkage is more or less active than the carbonyl bond; for the matter is influenced in different ways by the reagent employed, the solvent used and the relative position of the two double bonds in the molecule. In other words, "unsaturation" is not a definite, measureable thing which we can predict in any case from the behaviour of the "unsaturated" substance in other

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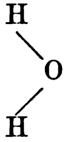
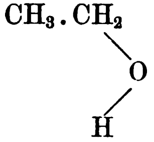
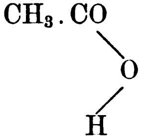
[1] Posner, *Ber.*, 1901, **34**, 1395; 1902, **35**, 799; 1903, **36**, 4305; 1905, **38**, 646; 1906, **39**, 3515; 1907, **40**, 218; Posner and Oppermann, *ibid.*, 1906, **39**, 3705.

circumstances; it is rather something kinetic, something which is extremely sensitive to external forces, and which in its turn can play a part in influencing the chemical action of groups which it does not apparently affect directly.

As an example of this latter property we may quote the case of the Vorländer Rule.[1] Vorländer has pointed out that we can consider both acids and alcohols as derived from water by substitution. In the case of acetic acid we substitute an acetyl group for one of the hydrogen atoms of water, while ethyl alcohol is formed from water by the substitution of an ethyl group for a hydrogen atom.







When we examine the chemical behaviour of the hydrogen atom in each case, we find that in the acids it has a much greater activity than in the alcohols. The origin of this difference obviously lies in the difference between the acyl and alkyl groups to which the hydroxyl radicle is united. The question is commonly dealt with by labelling the acyl group "electro-negative," and treating the label as an explanation. But, as Vorländer pointed out, this case is only one example of a general rule. If we represent non-metallic elements by E, and write down the following series:—

1 2 3 4
H.E.E:E
1 2 3
H.E:E
1 2 3 4 5
H.E.E.E:E

we shall find that the hydrogen atom in the first line has a greater reactivity than those in the second and third lines; in the first case the double bond between two E atoms lies in the 3:4 position to the labile hydrogen atom, while, where the double bonds are in the 2:3 or 4:5 positions the hydrogen atom is not specially active. For example, the labile hydrogen atoms in oximes, acids, phenols, diazo-compounds, and sulphinic

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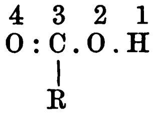
[1] Vorländer, *Ber.*, 1901, **34**, 1633.

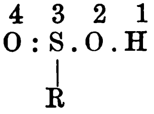
acids are all situated as in the first type with respect to the double bond—

$\overset{4}{\mathrm{R}}.\overset{3}{\mathrm{CH}}:\overset{2}{\mathrm{N}}.\overset{1}{\mathrm{O}}.\mathrm{H}$

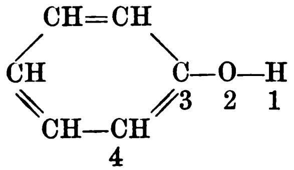


$\overset{4}{\mathrm{O}}:\underset{\mathrm{R}}{\overset{3}{\mathrm{C}}}.\overset{2}{\mathrm{O}}.\overset{1}{\mathrm{H}}$

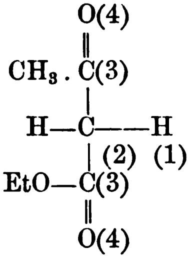
$\mathrm{R}\text{—}\overset{4}{\mathrm{N}}:\overset{3}{\mathrm{N}}.\overset{2}{\mathrm{O}}.\overset{2}{\mathrm{H}}$

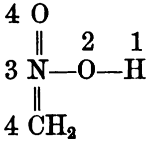


$\overset{4}{\mathrm{O}}:\underset{\mathrm{R}}{\overset{3}{\mathrm{S}}}.\overset{2}{\mathrm{O}}.\overset{1}{\mathrm{H}}$

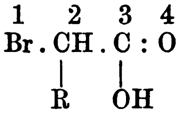


In acetoacetic ester and nitro-methane the hydrogen atoms are doubly influenced—

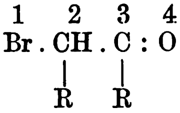




Further, when an acid or a ketone is brominated, the halogen atom enters the nucleus in the position required by this rule, *i.e.* it replaces the hydrogen atom in the α-position to the carbonyl group—



$\overset{1}{\mathrm{Br}}.\underset{\mathrm{R}}{\overset{2}{\mathrm{CH}}}.\underset{\mathrm{OH}}{\overset{3}{\mathrm{C}}}:\overset{4}{\mathrm{O}}$



$\overset{1}{\mathrm{Br}}.\underset{\mathrm{R}}{\overset{2}{\mathrm{CH}}}.\underset{\mathrm{R}}{\overset{3}{\mathrm{C}}}:\overset{4}{\mathrm{O}}$

There seems to be another influence at work in the case of acidic hydrogen atoms; and as the matter appears to have escaped notice hitherto, it may be well to call attention to it in this connection.[1] An examination of the formulæ of most substances which are capable of yielding metallic derivatives

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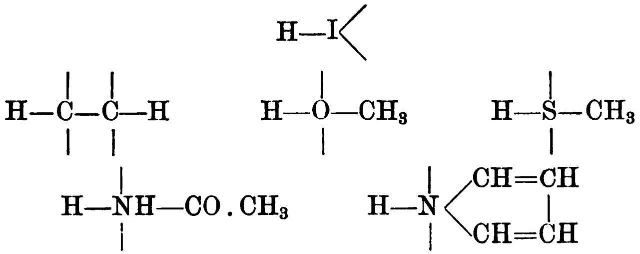
[1] Smiles, *Trans. Chem. Soc.*, 1900, 77, 160.

will show that the atom to which the labile hydrogen is attached is capable of exerting a valency higher than that which it exhibits in the acidic compound. For example, in the following substances the oxygen and sulphur atoms are divalent, while both oxygen and sulphur are capable of acting as quadrivalent elements; carbon in acetylene acts as a divalent atom, though its maximum valency is four; the nitrogen atoms shown below are trivalent, but nitrogen can act as a pentad; iodine can act either as a mono- or a trivalent element. The formulæ are written with lines to show the extra valencies.



$$H{-}I \qquad H{-}C{-}C{-}H \qquad H{-}O{-}CH_3 \qquad H{-}S{-}CH_3 \qquad H{-}NH{-}CO.CH_3$$

It will be seen that this is of more general application than the Vorländer Rule, for it holds in the case of substances such as ethylates, whose formation takes place though there is no double bond in the molecule such as is required by Vorländer's view.

We must now turn to another point of view. Hitherto we have regarded unsaturation from the standpoint of addition reactions, but we may now extend this a little. Suppose that we have two isomeric substances, each capable of taking up four bromine atoms, are these two bodies equally saturated or are they not? The question of unsaturation thus resolves itself into one of stability. We cannot distinguish between the bodies by the *amount* of bromine they take up, so we seek some other criterion. Now, in the case of two substances, one of which has a pair of conjugated double bonds, while in the other the bonds are not so related, the second substance takes up the four bromine atoms at once, but the first one takes them up two by two. The action is thus more precipitate in the second instance, and we should be tempted to consider the first substance as the less unsaturated of the two. In fact, as Thiele put it, the conjugated double bonds partially saturate one another.

Further, when an unsaturated acid is brought into conditions which allow it to undergo isomeric change, it is almost always converted into the form which contains the ethylenic bond conjugated with that of the carboxyl group. Evidently, then, this grouping must be the most exothermic, and therefore the most saturated.

We may now sum up, as far as possible, the various points which we have treated in the foregoing pages. We have shown, in the first place, that unsaturation is not an intrinsic property of any molecule. It depends largely upon the nature of the outside reagent; in order to have unsaturation we must have two substances, each specially fitted to interact with the other. In fact, the addition reactions of organic chemistry appear to be an extreme case of the ordinary reactions of salt formation, such as takes place in the case of ammonia and acid. Secondly, the influence of the other (non-reacting) parts of the molecule may play a very considerable part in any addition reaction, so that we cannot ascribe the same meaning to every double bond that we write down. For example, the ethylenic bond in maleic acid must be chemically quite different from that in mesityl oxide. Thirdly, just as unsaturation can be influenced by neighbouring unsaturations, it can in turn exert an influence upon groups of atoms in its vicinity. And, finally, if we have a series of unsaturations in a molecule they can be made to rearrange themselves to form a more stable system.

It has thus been shown that the term "unsaturation" covers a very wide and ill-defined field. Our knowledge of the whole problem is very scanty at best, and we are handicapped (and likely to remain so) owing to the fact that no one has the faintest idea of what really lies at the back of the various phenomena which we catalogue under this name.

CHAPTER XIV

CONCLUSION *

It often happens that we meet with a series of apparently related facts, and we are anxious to put forward some plausible explanation which will make the connection between them clear. Under these conditions we may proceed on either of two alternative lines. For instance, on the one hand we may put forward some general idea which, without troubling about details, will allow us to regard the matter from a broad point of view; or, on the other, we may set up some mechanical model which will, as far as possible, reproduce the phenomena we set out to explain.

At the first glance, the former method seems the more likely to lead near the truth; but consideration will show us that this is not the case. Suppose that our general idea covers all the facts known at a given time, and is quite comprehensible when considered in relation to these facts. Then let us imagine that some new facts are discovered which do not quite agree with the general idea. As a result, the general idea is widened to include these facts, and thus it becomes more vague than it was before. After this process has continued for a time, the general idea is widened insensibly, until it ceases to have any definite meaning. It eventually becomes a mere rag-bag of views or an amorphous mass which can be squeezed to fit any vessel. Naturally, also, it has ceased to have any value from the scientific point of view—it can no longer stimulate us in research, nor can it aid us in our classification of facts.

With a mechanical hypothesis, on the other hand, we have something definite, which either does or does not fit the facts. If it fits them, well and good; but as soon as it ceases to agree

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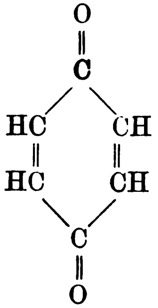
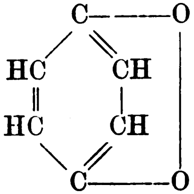
* This chapter was written at the suggestion of Professor Collie, who is partly responsible for some of the ideas expressed in it.

with our data we discover the inadequacy, and can discard the mechanical model, replacing it by another which is more in accord with our increased knowledge. We cannot, as in the case of the general idea, expand it and make it more vague, but we can expand it while retaining its definiteness.

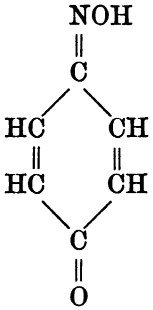
The difference between the two methods can be seen by comparing the system of "energetics" put forward by Ostwald and others with the modern structural (mechanical) theories of organic chemistry. It is quite certain that no application of the purely "energetic" view to organic chemistry could ever have carried the science to the point at which it now stands.

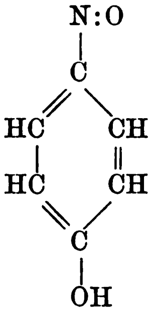
In the first chapter of this volume the question of the real meaning of our modern structural formulæ was touched upon, and it was pointed out that Kekulé and Couper differed with regard to this matter. Up to the present time, there is no doubt that the Kekulé view has prevailed to a great extent. Our formulæ for organic compounds are reaction-formulæ; they represent merely the behaviour of the substance when treated with various reagents, and it is simply on this account that our ordinary structural formulæ are now failing to meet the demands which are made upon them by recent work. If we take the case of quinone as an example, we find that its formula is written in either of two ways—





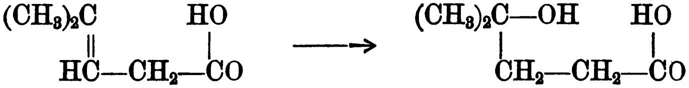
each of which is a representation of its method of reacting with a certain reagent. But neither of these formulæ allows us to foresee the fact that quinone monoxime will react as if it were nitroso-phenol—





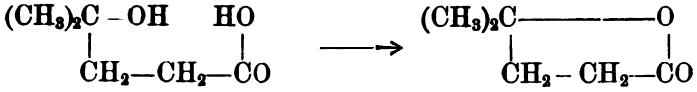
The number of facts of this type which have accumulated in recent years is very considerable, and the result of this increase in knowledge has been somewhat remarkable. Instead of attempting to bring their formulæ into harmony with the facts, organic chemists have been content to drag behind them a lengthening chain of implications, which they read into a formula; *e.g.* in the case of acetone and ethyl acetate we do not distinguish in our formulæ between the two carbonyl groups, 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, which to a more experienced chemist is implicitly expressed in the formula which misleads the student.

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—



$$\mathrm{(CH_3)_2C{=}HC{-}CH_2{-}CO{-}HO} \longrightarrow \mathrm{(CH_3)_2C(OH){-}CH_2{-}CH_2{-}CO{-}HO}$$

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 deduce that the next step in the process would be such an abstraction of a water-molecule—

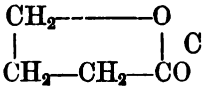


$$\begin{array}{ll}(CH_3)_2C-OH \quad HO & \\ CH_2-CH_2-CO & \end{array} \longrightarrow \begin{array}{l}(CH_3)_2C-O \\ CH_2-CH_2-CO\end{array}$$

The formation of this compound is actually what does take place, so that in this case our implications 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 deduce 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.)



$$\begin{array}{l}CH_2-O \\ CH_2-CH_2-CO\end{array}$$

(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 another carbon atom we find that the reaction follows yet another course—

$$CH_2:CH.C(CH_3)_2.COOH \longrightarrow CH_3.CHOH.C(CH_3)_2.COOH \longrightarrow CH_3.CH:C(CH_3)_2 + CO_2 + H_2O$$

Thus, our formulæ have ceased to be true reaction formulæ, and merely serve to mislead us if we attempt to draw any general conclusions from them.

But this by no means ends the confusion to which our modern formulæ have given rise. It is evident that, treated as mere reaction formulæ, they do not fulfil our requirements; but there is another side to the question upon which they are quite as unsatisfactory. Until, say, twenty years ago, the relation between chemical constitution and physical properties had not been very thoroughly investigated, and it was immaterial whether or not we could bring the two sides of the subject into harmony with our structural formulæ. Now, however, that is all changed. The study of the physical properties of chemical compounds has made vast strides, even within the last two decades, and the mass of material now at our disposal in this branch of the subject is continually increasing. At the same time, no attempt has been made (except in a few cases like Baeyer's carbonium[1] bond) to broaden the basis of our structural formulæ, so as to allow us to merge into them both the physical and chemical behaviour of substances. Instead, we have the usual train of implications, which are not expressed in the formulæ we write down, but are left to be inserted mentally.

Within the last few years, also, several authors have pointed out a connection between the *reactivities* of substances and certain of their physical properties. Such a relation has been shown by Brühl and Schröder in the case of refractive index,[2] by Kauffmann[3] in that of magnetic rotation, and by Stewart and Baly[4] in absorption spectra. In these cases we are dealing with some "reaction-property," so that the matter certainly deserves consideration along with the ordinary chemical reactions.

When all is said and done, however, it cannot for the moment be considered desirable that we should get rid of our present style of formulæ; they represent so much, and are undoubtedly more convenient than any substitute at present conceivable. What is required is that we should endeavour to bring them into harmony with reactions on the one side, and with physical evidence on the other. If this could be done we should see our way much more clearly in the subject, and should not be misled by as many false analogies as at present is the case.

To-day we are apparently standing on the verge of a new view of things, which may conceivably carry us as far in advance of present-day structural chemistry as the Couper and Kekulé formulæ carried the chemistry of the Type Theory; and though it is impossible to say exactly what the new view will be, it is not beyond our power to show the foundations upon which it must rest, and the problems which it must solve if it is to constitute a real advance upon our present position. We

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[1] Baeyer, *Ber.*, 1905, **38**, 569.

[2] Brühl and Schröder, *Zeit. physikal. Chem.*, 1904, **50**, 1; 1905, **51**, 18, 513.

[3] Kauffmann, *J. pr. Chem.*, 1903, II. **67**, 334.

[4] Stewart and Baly, *Trans. Chem. Soc.*, 1906, **89**, 489.

shall endeavour to present a sketch of these in the remainder of this chapter.

It will be remembered that the chief basis upon which our modern views of chemical structure were laid was the recognition of Frankland's doctrine that atoms had a constant valency. For many years this view sufficed for chemists, but in the more advanced thought of the present day, doubts have arisen as to its truth; and it seems very probable that in a few years' time it will cease to be regarded with quite the same definiteness as now.

In one of the foregoing chapters it was pointed out that when we write a double bond between two atoms, we do not always mean the same thing. Thus 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, ethylene 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; while 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 "valency-force," which gives rise to 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 if we take bromo-benzene, the bromine atom is held to the carbon atom of the nucleus more firmly than is the case 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.[1] Flürscheim[2] has carried out

[1] When the above paragraph was written in 1908, I was under the impression that this was common knowledge. Dr. Flürscheim desires me to mention, however, that he published a paper on the point in 1906 (*Ber.*, 39, 2016).—A.W.S.

[2] Flürscheim, *J. pr. Chem.*, II. 1902, 66, 329; see also Werner, *Ber.*, 1906, 39, 1278.

some experiments by means of which he shows that this variation in the value of the single bond is quite a general property.

It may be supposed by some that if we accept these ideas we shall be taking a retrograde step, and plunging ourselves into a web of inconsistencies; but surely it is not so! At the time of Frankland, chemists had not acquired those ideas of chemical structure which we now possess, and which we cannot abandon without having something better to take their place; consequently, it was necessary for the science to go through a stage in which valency was regarded as a fixed, unalterable force; without this guiding principle the work of the last forty years would have been impossible. But we have now reached a stage when we can look back and enlarge our views without running the risk of losing hold of what we have acquired. Instead of regarding a "bond" as a fixed unit, we can afford to regard it rather as the sum of an almost infinite number of small forces; so that we can subtract from or add to its strength within limits without bringing it out of the category of a "bond" or valency. For example, if the force employed in uniting two atoms together by means of a single bond be termed "F^2," then the quantity F will be negligible in comparison with the force of the single bond. But it is quite conceivable that this small force F would be sufficient to cause a difference of *reactivity* according as it were added to or subtracted from the force F^2. Thus the two forces expressed by—

$$F^2 + F \text{ and } F^2 - F$$

would not differ appreciably in their capacity for uniting two atoms, and certainly would not be so different as to allow the first atom to unite with two others; yet at the same time they would be sufficiently different to produce a change in reactivity of an atom attached to another by one or other of them.

There is another point of view which we must examine. If we are going to broaden the basis upon which our chemistry rests, we must be prepared to include the physical[1] as well as the chemical properties of substances in our classification: and naturally for an explanation of the physical properties of

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[1] The relations between chemical constitution and physical properties have been fully dealt with by Dr. Smiles in his book on this subject. Those interested in the question should consult especially the concluding chapter of his volume.

substances we must go to the physicists, and from them we can borrow as much of their theory as seems likely to help us in our own branch of science. Within the last few years, physics has been to some extent rejuvenated by the conception of the electron; and it may not be amiss to give a brief account of the modern electrical theory of matter in order to point out how it might be applicable to our own subject.[1]

According to the modern view of matter, the atom consists of a "positive sphere" (*i.e.* a sphere throughout which positive electricity is uniformly distributed), within which lie a number of electrons. Excluding radio-active bodies from our consideration, it may be said that the electrons in an atom are of two kinds. The first type, "fixed electrons," are those which remain always attached to the positive sphere; the other class, "detachable electrons," are more or less free to wander from atom to atom. Now, when a detachable electron leaves one atom and makes its way towards another, it is supposed to carry with it the end of a "tube of force," or "Faraday tube"; so that when it penetrates into the second atom, and remains there, the two atoms become united by this tube of force.

It is evident that what the chemist calls valency, the physicist would regard as an accumulation of tubes of force. Thus the weakening or strengthening of a bond could be regarded either as a reduction or increase in the number of Faraday tubes joining two atoms together, or as a decrease in the strength of the tube of force uniting the one atom to the other.

Since Faraday tubes are supposed to be mutually repellent, this hypothesis furnishes us with a new way of regarding Baeyer's Strain Theory. It is obvious that in a double bond between carbon atoms, the Faraday tubes will be more numerous and closely packed than in the case of the single bond. They will thus be more strongly repelled from the line joining the centres of the two carbon atoms, and a state of strain will be set up just as Baeyer postulated. The same holds good in the case of the acetylene derivatives also.[2]

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[1] Nelson and Falk (*School of Mines Quarterly*, 1909, **30**, 179) have developed this line of thought in their paper on "The Electron Conception of Valency in Organic Chemistry," and have shown how isomerisms of different types may all be expressed in terms of electronic motion.

[2] Dr. Flürscheim has called my attention to a paper of his (*J. pr. Chem.*, II.

On the physical side, it has been shown that the properties of matter are very largely due to the movements of the electrons within the positive sphere; while on the chemical side, as we have seen, the reactivity and valency of atoms depends upon the detachable electrons which they contain. It is obvious that these two phenomena are not independent; but that, on the contrary, a very close relationship must exist between them. Further, physicists have shown us that some atoms are capable of shedding electrons more readily than others; which may aid us in our correlation of physical and chemical properties.

Thus it becomes clear that any future advance on the theoretical side of organic chemistry must take into account the following branches of the subject:—

I. The arrangement of atoms in space.
II. The mode of linkage of the atoms within the molecule.
III. The influence which two non-adjacent atoms in a chain can exercise upon each other.
IV. The difference between ionic and non-ionic reactions.
V. Those physical properties of organic compounds which are due to electronic motions.

1907, **76**, 190) in which, starting from somewhat different premises, he arrives at similar conclusions.

BIBLIOGRAPHY

WITHIN the last decade the literature of organic chemistry has become increased and specialized to a much greater extent than before, and it may be useful to give in this place a brief account of some of the more recent works in various branches of the subject.

Beilstein's "Handbuch der Organischen Chemie," which is now complete in nine volumes, is too well known to need any description; and the same may be said for Richter's "Lexikon der Kohlenstoffverbindungen," to which three supplements have been published. The former work was completed in October, 1906; while the third supplement to the "Lexikon" is complete up to 1904. New editions of both works are in preparation.

As regards practical methods, Lassar-Cohn's "Arbeitsmethoden für organisch-chemische Laboratorien" has now reached its fourth edition (1906–7), which exceeds the third edition (1903) by no fewer than 607 pages. The index of the new edition is much superior to that in the older volume. A new work on somewhat similar lines: "Die Methoden der organischen Chemie; ein Handbuch für die Arbeiten im Laboratorium" has been brought out by Weyl. The first volume and part of the second have been published (1909–10).

The historical side of the subject is treated by Schorlemmer in his "Rise and Development of Organic Chemistry," but this only carries the matter up to the year 1894; later developments are to be found in Ladenburg's "Entwicklungsgeschichte der Chemie" (1907), Meyer's "Geschichte der Chemie" (1905), Armitage's "History of Chemistry" (1906), or Hilditch's "Short History of Chemistry" (1910). The history of modern theories in organic chemistry has been dealt with by Pattison Muir in his "History of Chemical Theories and Laws," and also by Hilditch in his "Short History." The Chemical Society's "Memorial Lectures," as well as the obituary notices in the *Berichte der deutschen chemischen Gesellschaft* may be consulted by those who are interested in the personal side of chemical development.

The number of annual summaries of work published continues to increase. By the side of the "Jahresbericht der Chemie" and Meyer's "Jahrbuch der Chemie," we have now the Chemical Society's Annual Reports; while a "Jahrbuch der organischen Chemie" has been begun by J. Schmidt (vol. i., 1907).

Turning to the modern text-books on the subject of organic chemistry, the most important is, of course, Meyer and Jacobson's "Lehrbuch der organischen Chemie" (vol. i., 1893; vol. ii. part 1, 1902; part 2, 1903). It is unfortunate that this work is not yet complete, the volume on the heterocyclic substances being still lacking. A new edition of the first volume is in preparation, part of it (dealing with the aliphatic substances and their mono-derivatives) having already appeared (1907). A tenth edition of the Richter-Anschütz "Organische Chemie" has appeared (vol. i., 1903; vol. ii., 1905), and the first volume of the eleventh edition was published in 1909. The German edition of Roscoe and Schorlemmer was completed some years ago. Among more recent works J. Schmidt's "Kurzes Lehrbuch der organischen Chemie" deserves special mention.

In recent years several volumes of essays on various branches of organic chemistry have appeared. Of these, Lachman's "Spirit of Organic Chemistry" is the most original. It contains an historical account of the development of various outstanding researches, such as those on rosaniline dyes, the sugars, maleic and fumaric acids, Perkin's reaction and aceto-acetic ester. A French collection, published under the title "Récents Progrès de la Chimie," has reached its third volume (vol. i., 1904; vol. ii., 1906; vol. iii., 1908), and contains much that is of interest to the organic chemist. Cohen's "Organic Chemistry for Advanced Students," and Keane's "Modern Organic Chemistry" (1907) probably should also be included in this category. In his "Neuere Anschauungen auf dem Gebiete der organischen Chemie" (1908) Henrich has dealt with the development of the more important modern theories.

We must now mention some monographs on special subjects. Since 1896 a collection of pamphlets has been issued by Ahrens under the title "Sammlung chemischer und chemisch-technischer Vorträge; and recently a somewhat analogous series has appeared under the name "Die Wissenschaft." We need not deal with these in detail here, as we shall have occasion later to mention the numbers which specially concern us.

Under the head of stereochemistry we find that in the last ten or fifteen years a perfect flood of text-books and pamphlets has been issued, which testifies to some extent to the interest taken in this branch of chemistry. The most complete work of reference on the subject is Bischoff and Walden's "Handbuch der Stereochemie" (1894), with its two supplementary volumes, Bischoff's "Materialen der Stereochemie" (1904). In these are abstracts of practically every paper that has been published on the subject up to 1902, the abstracts being grouped according to the year of publication, and very well indexed. Werner's "Lehrbuch der Stereochemie" (1904) and Stewart's "Stereochemistry" (1907) are the most complete text-books on the subject. Smaller works are Hantzsch's "Grundriss der Stereochemie" (1904), van't Hoff's "Lagerung der Atome in Raume" (1908), Mamlock's "Stereochemie" (1908), and Wedekind's booklet, "Stereochemie," in the Sammlung Göschen (1906). Landolt's "Optical Rotating Power of Organic Substances" (1902) deals with one section of the subject in great detail. Among the numerous pamphlets we need only mention the following: Wedekind and Fröhlich, "Zur Stereochemie des fünfwertigen Stickstoffs" (1907); Meyerhoffer, "Gleichgewichte der Stereomeren" (1906); Jones, "Stereochemistry of Nitrogen" (British Association Report, 1904); Ladenburg "Ueber Racemie" (Ahrens Sammlung, 1903); Schmidt, "Einfluss der Kernsubstitution auf die Reaktionsfähigkeit aromatischer Verbindungen" (Ahrens Sammlung, 1902); Scholtz, "Einfluss der Raumerfüllung auf den Verlauf chemischer Reaktionen" and "Die optisch-aktiven Verbindungen des Schwefels, Selens, Zinns, Siliziums und Stickstoffs" (Ahrens Sammlung, 1898 and 1907).

Three other papers in the Ahrens Sammlung deserve mention. Marckwald, in one of them, gives a sketch of the "Benzoltheorie" to 1897; while a second is devoted by Goose to the "Beziehung der Benzolderivate zu den Verbindungen der

Fettreihe" (1898). W. Wislicenus, in the same series, gave a pamphlet, "Ueber Tautomerie" (1897); while the same subject is treated by Lowry in the British Association "Report on Dynamic Isomerism" (1904).

The literature of the terpenes is an ever-increasing one. Heusler's "Die Terpene" was published in 1896, and is now, to a great extent, out of date, as is also Scholtz's pamphlet, "Die Terpene," in the Ahrens Sammlung (1896). Gildemeister and Hoffman's "Ethereal Oils" (1900) deals only with the occurrence and commercial side of the question, and does not trench upon the problem of terpene constitutions. In Meldola's work on "The Chemical Synthesis of Vital Products" (1904), the occurrence and syntheses of many terpene derivatives are described. A very complete account of all the alicyclic series is given by Aschan in his work, "Die Chemie der alicyklischen Verbindungen" (1905), while the terpenes themselves are very fully described by Semmler in his work on "Die ætherischen Oele" (1906). In both of the two last works the authors have given very clear and complete accounts of terpene structures. The chemistry of camphor has been dealt with by Lapworth in the 1900 British Association Report on "The Constitution of Camphor," and by Aschan in "Die Konstitution des Kamphers" (1903), which was afterwards incorporated in his "Chemie der alicyklischen Verbindungen." Wallach has republished his papers on the terpenes in a volume "Studien ueber die Terpene" (1909); and a condensed description of this class of compounds has been written by Barthelt (1909).

The chemistry of the alkaloids has not produced any extensive literature apart from the papers in the journals. The older books, such as Guareschi's "Die Alkaloide," are out of date, to a very great extent, as regards the constitutions of the alkaloids, though they are still useful as far as descriptions of physical and chemical properties are concerned. Scholtz's pamphlet on "Die künstliche Aufbau der Alkaloide" (Ahrens Sammlung, 1897) contains a good account of the state of the subject at that period. Later, Pictet's "Vegetable Alkaloids" (1904) brought the subject more up to date. We are most indebted, however, to J. Schmidt, who has brought out from time to time small volumes upon the state of alkaloid chemistry. Three of these have already been published: "Ueber die

Erforschung der Konstitution wichtiger Pflanzenalkaloide" (1900); "Die Alkaloidchemie in den Jahren 1900–1904"; "Die Alkaloidchemie in den Jahren 1904–1907." It is probable that the series will be continued. The pharmacological side of the subject is dealt with by Fränkel in his "Arzneimittel Synthese" (1906).

With regard to the sugars, Tollens' "Kurzes Handbuch der Kohlenhydrate" (1895); Lippmann's "Chemie der Zuckerarten" (1895); or Maquenne's "Les sucres et principaux dérivés" may be consulted. Fischer's papers have been reprinted under the title "Untersuchungen über Kohlenhydrate und Fermente" (1909).

Fischer has republished his papers on the purines under the title, "Untersuchungen in der Puringruppe" (1882–1906), and those on the polypeptides in a volume called "Die Aminosäuren, Polypeptide und Proteine" (1906). The following works have appeared dealing with the problems of the proteins and albumins: Mann, "Chemistry of the Proteids" (1906); Schryver, "Chemistry of the Albumens" (1906); Schulz, "Allgemeine Chemie der Eiweissstoffe" (Ahrens Sammlung, 1906). A new series of monographs on biochemistry has recently been issued under the editorship of Plimmer and Hopkins. Up to the present, the following volumes have been published:—Bayliss, "The Nature of Enzyme Action;" Plimmer, "The Chemical Constitution of the Proteins;" Schryver, "The General Character of the Proteins;" Osborne, "The Vegetable Proteins;" Armstrong, "The Simple Carbohydrates and the Glucosides." Other volumes are announced dealing with "The Development of Biological Chemistry" (Hopkins); "The Carbohydrates and Polysaccharides" (Ling); "The Fats" (Leathes); "Colloids" (Hardy); and "Alcoholic Fermentation" (Harden).

The diazo-compounds have been described by Hantzsch in his pamphlet "Die Diazoverbindungen" (Ahrens Sammlung, 1903); by Morgan in the British Association Report of 1902 on that subject; and lastly, by Cain in his recent volume "The Chemistry of the Diazo-compounds (1908).

Organic dyestuffs have been dealt with by Nietzki in his "Chemie der organischen Farbstoffe" (1901), and later in his pamphlet "Die Entwicklungsgeschichte der künstlichen organischen Farbstoffe" (Ahrens Sammlung, 1902). Cain and Thorpe have recently brought out a work on "Synthetic Dyestuffs and Intermediate Products from which they are derived." A small but comprehensive volume in the Sammlung Göschen, Bucherer's "Die Teerfarbstoffe," gives a condensed account of these substances. The constitutions and properties of the naturally occurring dyes have been described by Rupe in his "Chemie der natürlichen Farbstoffe" (Vol. I., 1900; Vol. II., 1909).

The Ahrens Sammlung contains also some treatises on more or less isolated questions of chemical interest, such as Hjelt, "Ueber die Laktone" (1903); Wedekind, "Die Santoningruppe" (1903); and Schmidt, "Ueber die Pyrazolgruppe" (1899); "Die Halogenalkylate und quaternären Ammoniumbasen" (1899); "Die Nitrosoverbindungen" (1903); and "Ueber Chinone und chinoide Verbindungen" (1906).

The relation between colour, fluorescence, and chemical structure has been dealt with by Kauffmann in three pamphlets belonging to the same series: "Ueber den Zusammenhang zwischen Farbe und Konstitution bei chemischen Verbindungen" (1904); "Die Beziehungen zwischen Fluoreszenz und chemischer Konstitution" (1906); "Die Auxochrome" (1907); but for a full account of these and allied subjects, Smiles' volume, "The Relations between Chemical Constitution and some Physical Properties" (1910) should be consulted.

Finally, we may turn to those works in which the reactions of the laboratory are classified and regarded from the point of view of their value in synthetic work. Posner, in his "Synthetischen Methoden der organischen Chemie," has inverted the usual order of text-books; for instead of classifying reactions according to the compounds which they produce, he classifies compounds according to the nature of the reaction which gives rise to them. Lassar Cohn, in his "Allgemeine Gesichtspunkte der organischen Chemie," has collected together many instances in which reactions cannot be carried through conveniently in the ordinary manner, and he shows how by resorting to various artifices the required product may be obtained. The Grignard reaction and its various applications have been described in detail by Schmidt in "Die organischen Magnesiumverbindungen und ihre Anwendung zu Synthesen" (Ahrens Sammlung, 1905); and by McKenzie in the 1907 British Association Report on the subject. The whole question of recent synthetic chemistry has been dealt with by Schmidt in his work, "Die synthetisch-organische Chemie der Neuzeit" (*Die Wissenschaft*, 1908).

In concluding this notice of the current literature of organic chemistry, it may be well to point out one or two branches which still remain unexhausted. In the first place, there is room for a second work on the lines of Lachman's "Spirit of Organic Chemistry," as a perusal of that volume generally stimulates in the reader a desire for further essays of the same type. Secondly, it seems possible that a very interesting account of modern research in organic chemistry might be written by taking up in turn the chief workers of the last two decades and showing how from one investigation they were led to another. Of course the Memorial Lectures of the Chemical Society and the obituary notices of the deutschen chemischen Gesellschaft cover some of this ground; but in them we have no account of many of the most important researches of the last ten years, owing to the fact that the investigators are still alive. Then, a third book might be written to show the connection between organic chemistry and chemical industries. To a great extent, the specialization in pure chemistry on the organic side at the present day is caused by the difficulty which the ordinary chemist encounters when he endeavours to get into touch with the commercial side of the subject. A book which would bridge this gap would be of considerable service. Finally, one may suggest that a most useful volume might be written by any one who would go to the original literature and endeavour to deal critically with the constitutions attributed to the commoner classes of organic substances. In comparing text-books with original papers, one is often struck by the way in which a tentative suggestion put forward in a paper becomes dogmatic in tone when transferred to a text-book; and any one who would assess for us the value of the actual experimental evidence in favour of, say, the presence of a carbonyl radicle in a carboxyl group, would be doing work of much interest and of very considerable importance.

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