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THE SCOPE OF ORGANIC CHEMISTRY[1]

THE chemistry of the compounds of carbon covers a wide field, wider than that covered by any other element. Its scope embraces all living matter, as well as the vast number of non-living substances which are produced through the agency of life. Moreover, it includes a very great number of compounds unrelated to life or to living processes which have been built up by the chemist in the laboratory by methods he has devised.

Already some two hundred thousand definite compounds have been tabulated in Richter's "Lexicon" and in the supplements thereto, and this number is increased yearly by several thousands through the agency of a band of zealous workers scattered over the globe. It may well be asked what is the good of continuing to increase this already astonishing number; and is the expenditure of time, labor and energy justified which lead to the discovery of some new fact having, apparently, no useful application to any department of human activity? The answers to these questions are quite clear and definite. You must acquire a knowledge of the simple before you can attack the complex with any hope of success. The element carbon has been used by nature as the basis of organized life because the capacity of carbon to combine with itself is shared by no other element, and it is upon this capacity that nature has relied in order to build up the tissues and reserve materials which form the living world around us. Moreover, since the compounds of carbon containing a moderate number of atoms of the element are usually crystalline or capable of becoming crystalline, and there are obvious disadvantages attaching to the use of potentially crystalline substances as the basis of living matter, it has been found necessary to employ the more complex carbon derivatives containing many hundreds of elemental atoms, which by reason of their high molecular complexities no longer possess, or seem capable of acquiring, a crystalline structure, but belong to the class of jelly-like or colloidal substances. Until we can determine how a small number of carbon atoms combine one with the other we can not hope to obtain any insight into the manner in which the more complex natural substances are built up, or any information regarding the way in which they are utilized to bring about the changes occurring during animal and vegetable metabolism.

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[1] Address of the president of Section B—Chemistry—British Association for the Advancement of Science, Oxford, August, 1926.

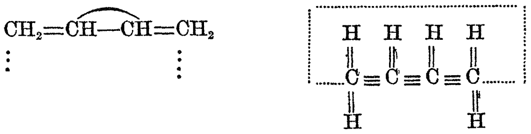
STRUCTURE

The science of structural organic chemistry is only just fifty years old. It was born when the genius of van't Hoff gave to the world the clue upon which the three dimensional formula we now use is based. It is, therefore, no inconsiderable achievement to have gained in so short a time a knowledge of many of the reactions and properties of the more simple complexes of carbon in combination with oxygen, nitrogen and other elements. But much yet remains to be done before we can attack with any real hope of success the problems which the chemistry of nature presents. It is true that the knowledge already gained has led to the synthetic preparation of quite a number of natural products, many of which are of service in relation to human needs. Many of the alkaloids, coloring matters like indigo and alizarine, camphor and a large number of natural products, have yielded the secrets of their structures and have been produced by laboratory methods and, where necessary, on the factory scale. But the synthesis of such compounds has not provided much insight into the mechanism leading to their production in nature, and indeed the reason for their occurrence in the plant is not understood. They are, moreover, crystalline substances which either occur in the plant as such or are formed by the hydrolytic fission of some more complex plant materials. Their homogeneity is, therefore, not open to doubt, and their degradation into known fragments and the rebuilding of these fragments into the original substances, although by no means easy, is nevertheless comparatively simple when the difficulties attending the investigation of more complex natural products are taken into account. Even so, some of the simpler type, for example, strychnine, still resist the attack of the chemist.

THE ELECTRONIC THEORY

It is clear that our knowledge of the finer mechanism of reactions is slight, and that great as has been the advance made through the discovery of van't Hoff, we are still at a loss to explain or predict the shades which determine whether one particular type of reaction will be more, or less, facile than another. The chief trouble seems to be that the electronic theories, which are quite satisfactory in themselves, are not yet developed so fully that they can include any quantitative statement relating to the changes in the free energy of systems. Yet it is evident that any theory of organic structure must conform to the modern physical conceptions of matter. The principle of shared electrons is primarily justified by its success in explaining the linking of atoms, *i.e.,* valency, and by its successful interpretation of the theory of coordination and "onium" salt formation. The subsidiary hypothesis of electron displacement also provides a means by which an explanation can be supplied to account for the ease of formation, stability and general reactions of conjugated systems, thus placing the hypothesis of Thiele on a sounder theoretical basis.

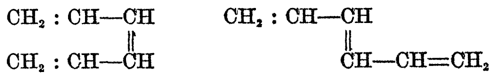
BUTADIENE



(Thiele.) (Electronic formula.)

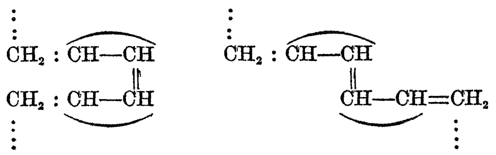
In the formula for butadiene shown above the dotted line indicates the interchange of an electron between the two end carbon atoms of the system; it is to be assumed that this condition provides a point of attack and leads to the 1:4 addition which is characteristic of this substance. Evidence has been sought in order to substantiate this view, and with this object an extended investigation on the properties of hexatriene has been undertaken.

Hexatriene contains a three-conjugated system, and must, in accordance with stereo-chemical theory, exist in two forms, which may be represented diagrammatically thus:



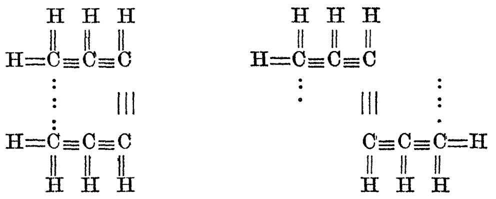
(cis.) (trans.)

In accordance with the Thiele hypothesis these would be conjugated thus:

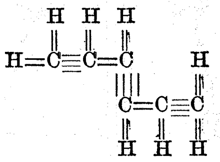


and there should thus be no difference in the behavior of the two forms towards additive reagents such as bromine.

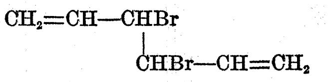
On the other hand, if these two forms are expressed in terms of the electronic hypothesis thus:



The cis form, in which the two terminal atoms are near together, might be expected to share the electron, as shown by the dotted line, whilst the trans form, having the terminal carbon atoms too remote from one another to enable this interchange to take place, would react in the form



There can be no doubt that the hexatriene prepared by van Romburgh is the trans form. This, as its discoverer showed, adds on bromine in the positions 3:4 to give



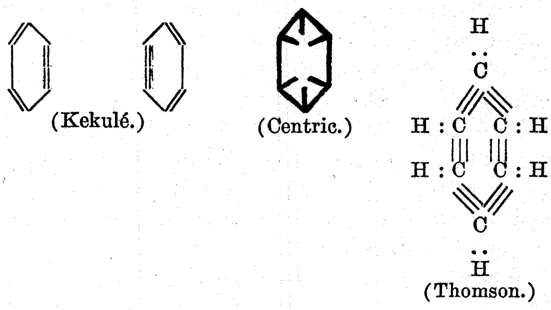
$$\begin{array}{l} CH_2{=}CH{-}CHBr \\ \qquad\quad | \\ \qquad\quad CHBr{-}CH{=}CH_2 \end{array}$$

It is, therefore, not a conjugated system in the sense that butadiene is a conjugated system.

We have now succeeded in isolating cis-hexatriene, and are studying the action of bromine on it. If, as is to be anticipated, the addition takes place in the 1:6 positions, direct evidence will be available in favor of the electronic hypothesis. The work is, however, exceedingly difficult because, unlike those of the trans series, the cis compounds are liquids and therefore difficult to identify. Moreover, they are unstable and readily polymerize to resins on keeping. There is no doubt, however, that these difficulties will be overcome.

In the same way the Thomson[2] formula for benzene provides an expression for the intermediate state as postulated by Kekulé, and renders the so-called centric formula, which is meaningless, now unnecessary.

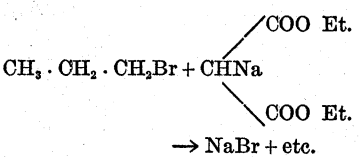
BENZENE



(Kekulé.) (Centric.) (Thomson.)

There can be no question that the distribution of electrons among the carbon atoms and other atoms of organic molecules must determine the reactions of the complexes involved, and future research will no doubt lead to an advance in our knowledge concerning the causes which promote or retard this distribution.

The ductility of the carbon to carbon bonds which have now been clearly demonstrated enables us to impart strains to certain parts of an organic molecule at will, and it is reasonable to assume that such strain when once set up will be shared as far as possible equally by all the atoms of the system involved. If this distribution is, as Robinson postulates, effected by a restricted flow[3] of electrons from one atom to another in the molecule we have, at any rate, a definite picture of the process which the mind can grasp; and if the distribution leads ultimately—as is to be surmised—to the establishment of polar characteristics at different parts of the molecule, which will determine reactivity at those points, we are in a fair way to reconcile the views of various contending schools and to reach a general hypothesis acceptable to all chemists, and which may even satisfy the physicists. It seems that, despite the organic chemist's proneness and ability to distort the molecules with which he deals, nature has provided a means by which a certain degree of molecular equilibrium can be attained. Nevertheless, it will be by the investigation of the conditions leading to the setting up of strain and of the effect produced thereby that we shall gain the most information regarding the chemistry of carbon structures in the near future. The course of a reaction in organic chemistry which involves an equation such as the following



$$CH_3 \cdot CH_2 \cdot CH_2Br + CHNa\left\langle\begin{array}{l} COO\ Et. \\ COO\ Et. \end{array}\right. \rightarrow NaBr + etc.$$

is determined by the tendency to form NaBr—the organic residues have to make the best they can of the situation, and the manner in which they will combine with themselves or react each with the solvent is dependent on the influence of many factors. Undoubtedly there will be a tendency to produce the most stable system and the one whose formation involves the greatest loss of free energy, but there must be a possible mechanism, and this involves the polar factors. Even these can not force a group into a position in which there is no room for it, and therefore the effect of polarity must always be dependent on steric conditions. No doubt polar conditions determine the order of priority of a number of possible arrangements, but it is the steric condition

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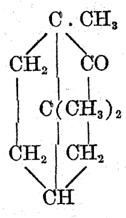
[2] See also H. Kauffmann ("Die Valenzlehre," 1911, p. 539).

[3] Robinson considers that an electron may leave its "moorings" on one of the atoms which holds it but never on both.

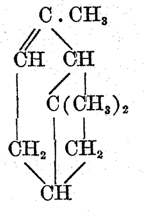
that determines which of these arrangements shall be followed.

Strainless Systems

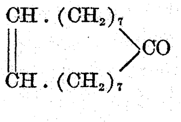
It is reasonable to assume that the organic substances that occur in nature as such are produced by means which involve the least expenditure of energy, and that they are, therefore, strainless. Among such natural products there are many containing carbon rings belonging to ring systems which can not normally be produced without distorting the carbon tetrahedral angles of the component carbon atoms, and thus imparting intramolecular strain to the compounds formed. Nevertheless, it is interesting to note the means adopted by nature to relieve this strain and thus to confer equilibrium and stability on quite unlikely ring systems. Ring systems stabilized in this way are found frequently among terpenes; two, namely, camphor and pinene, need only be mentioned to illustrate the general method. In camphor the bridged ring is stabilized by the presence of two dimethyl groups, and in pinene, where the junction of the inner ring has to take effect in the position 3, the presence of a double bond on the shoulder of the external ring is necessary. Still more remarkable examples are afforded by more complex natural ring systems. For instance, there is a substance named civetone, which is extracted from certain glands of the civet cat. There is no doubt as to its structure, which has been shown to contain a 17-membered ring, thus:



(Camphor.)

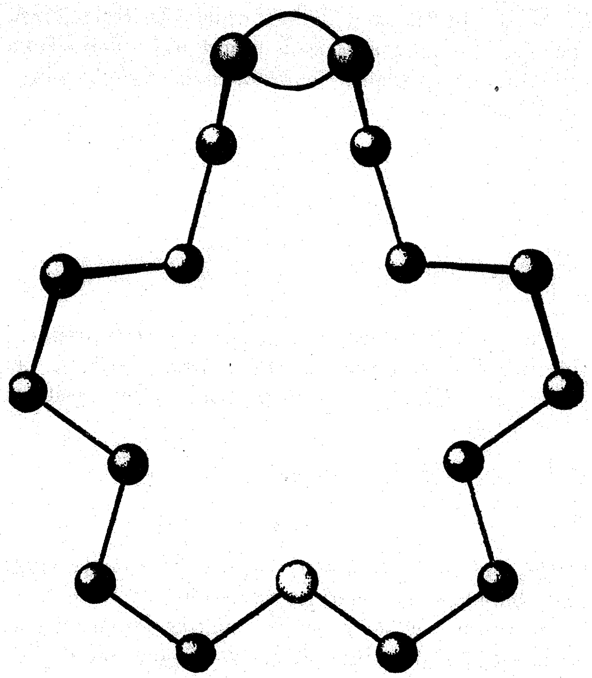


(Pinene.)



$$\left.\begin{matrix}CH\,.\,(CH_2)_7\\ \| \\ CH\,.\,(CH_2)_7\end{matrix}\right\rangle CO$$

The evidence of structure being derived both from a study of the degradation products of the substance as well as by its recent synthesis. If this compound is set up on the tetrahedral models, thus



it will be found to form a triplanar figure which is strainless; the condition being produced by the presence of the double bond in the position shown.

Biochemistry

In its earliest days the science of organic chemistry dealt only with those compounds which were derived from natural sources, and it was regarded as certain that such substances could only be produced through the agency of life and by no other means Since then this theory has been shown to be wrong by the preparation in the laboratory of many substances identical with those formed during the operation of life processes. Nevertheless, the more complex substances which nature utilizes in building up her animal and vegetable structures still show no signs of yielding the secrets of their constitutions, or the mechanism by which they are produced. Indeed, although we can imitate in the laboratory certain natural operations such as the hydrolysis of starch to glucose, we are still quite ignorant of the means by which glucose is converted, by the appropriate enzyme, into alcohol and carbon dioxide, neither can we imitate this process in the laboratory.

When once the chemist has passed beyond the crystalline and the distillable he enters a region full of difficulties, because he has few means either of purifying the materials with which he has to deal, or of determining their homogeneity when they have been purified. These are the real difficulties which confront the biochemist when he approaches his subject from the structural side of organic chemistry. Biochemistry is in the unique position of being both a descriptive or observational science as well as one of the experimental sciences. From the biological side it has at its disposal the wealth of knowledge acquired by the physiologists and pathologists, and from the chemical side it is in touch with the recorded experience of several generations of organic chemists. If biochemistry is to justify its name it must carry out its function of bringing into line the discoveries of the physiologists with organic chemical structure, for by this means only will it be possible to gain an insight into the chemistry of natural processes which it is the object of biochemistry to discover. It is far from my object to disparage the wonderful work which has been done and is being done by physiologists and pathologists in their attack on the mechanism of normal and abnormal life processes. Their record speaks for itself. But too little is being done to approach the problems from the purely organic chemical side, and too few of the people engaged in biochemical research have an adequate knowledge of organic chemistry or the methods of the organic chemist. The number of organic chemists who are cooperating with biologists in their attack on natural processes is too few. Indeed, the very difficult question arises here as to how best to organize methods for dealing with problems which are essential borderland problems between two great sciences. I do not propose on this occasion to discuss the vexed question of the chemical engineer, but actually the analogy between this hybrid and the biochemist is fairly close. Is the biochemist to be a biologist with a knowledge of chemistry, or is he to be a chemist with a knowledge of biology? I refer, of course, to the method of training required for a man or woman who proposes to take up biochemical research during the fourth year. Given twenty years and the requisite capacity it is, of course, possible for a man to acquire sufficient acquaintance with both sciences to render him an effective worker in the borderland field, altogether here again the temperament which promotes enthusiasm for research in the experimental sciences and that which leads to initiative in the descriptive sciences is not usually found in the same individual. As knowledge increases the need for specialization must also increase, because the time factor, that is the time during which it is possible for a student to undergo training, can not be prolonged beyond a certain period. Even at the present time it is an open question whether it is possible to give a student a special training in more than one science and in the sciences subsidiary thereto in the time available, and this problem will become more acute as knowledge increases. It has been suggested that we should revert to the older method by which a student was instructed in, say, three sciences without any special training in any one of them, and doubtless this method was a good one for the requirements of those times. But the day of the universalist is past, and general scientific culture has become a luxury of the leisured classes. It is only by the aid of the specialist that, nowadays, we can hope to obtain advances in knowledge either in the sciences or in the sciences applied to industry.

It seems that the best method to attack problems in the borderland subjects is by cooperation between two types of trained investigators. In the case of biochemistry, for example, by the provision of trained students of two kinds, the one trained in physiology but with a sufficient knowledge of organic chemistry to promote sympathy with and knowledge of the chemist's point of view, and the other trained as an organic chemist with a similar knowledge of the methods and requirements of the physiologist. The former would be a trained physiologist who would devote his final year to organic chemistry, the latter an organic chemist who would devote his final year to a study of physiology. This is, of course, no new idea, but is one which is being carried out in at least one institution in this country in connection with other borderland subjects. But it is the absence of any real attempt to approach biochemical problems from the chemical side that renders it particularly desirable that the need for some such scheme should be emphasized. It is true that the fault is largely on the side of the organic chemists who, for the most part, seem appalled by the difficulties attaching to the study of natural processes. The difficulties are indeed great, but not insurmountable. We are far from gaining any insight into the meaning of life, but it is not unlikely that we shall, in the near future, obtain some information regarding the mechanism of the action of the enzyme, the important agent in the non-living transformation of living matter into chemical products. It may be that organic chemists are waiting to see how Willstätter, who has already made great progress in enzyme chemistry, will surmount the difficulties confronting him, and it may well be that this great organic chemist will introduce new methods of attack which will open up fresh fields for investigation.

ANALYTICAL

Except for the substitution of gas for charcoal, it can not be said that the ordinary methods of analysis employed by the organic chemists have changed much since the days of Liebig. They have been modified, notably by Dennstedt, and more recently some have adopted the microchemical methods introduced by Pregl, but the older methods, for example, the long and tedious process for the estimation of halogens by the method of Carius, are still in vogue in many of our laboratories and are taught to the students. In any case the usual operation entailed by the estimation of carbon and hydrogen, nitrogen, sulphur and the halogen requires considerable time, which has not been materially shortened by the introduction of the less cumbersome methods due to Dennstedt. Pregl's methods, in which a very small quantity of material is used requiring the provision of a special type of balance, have been tried in many laboratories, and have found favor, it is understood, in several of them, more particularly abroad. But the general experience has been that the technical skill required to obtain good results is acquired only after long practice, and that whereas the methods are useful for gaining an indication of structure when the quantities of material at hand are so small as to necessitate their use, yet when a sufficient quantity of substance is available the older methods are more reliable and more easily carried out. It is interesting to note that the new methods which have been introduced by Professor ter Meulen, of Delft, are going to be described to us by Professor ter Meulen himself, who is fortunately with us at this meeting. Professor ter Meulen will give an account of his methods on Tuesday morning, and they will be shown in actual operation during the soirée on Tuesday evening. Chemists will then see that a great saving of time can be effected by methods which can not only be used to analyze the small quantities employed by Pregl, but also quantities of 0.1 gm., such as organic chemists have been accustomed to use in the past, and which have been shown to produce the most accurate results.

THE UTILIZATION OF FOREST PRODUCTS

The immense number of organic compounds distributed among the plants, trees and grasses which form the forests and jungles of the world, offer a wide field for research which has still much to yield. Our knowledge of the medicinal properties of organic substances and the various uses to which they could be put in the service of mankind did not come to us through any effort of the chemist, but as the outcome of a process of trial and error which is as old as the human race itself. These products were obtained from vegetable materials present in the forests, and as time went on they were extracted in a form possessing some degree of purity, and the plants containing those with specially valuable properties were cultivated for their production. As soon as a theory of organic structure was evolved upon which prediction could be based, these useful products were subjected to close investigation, and in several cases they were prepared by laboratory means. As an outcome several of them, such as indigo and alizarine, were found to be capable of production more economically by the chemical method than by the processes of life, and the natural substances were rapidly replaced by the artificial products. Others still resist all efforts to unravel their structures and remain still unsynthesized. Nevertheless it has been by a study of the chemical structure of natural products that much has been learned regarding the relation between chemical composition and physiological action, and although it may not have been found possible economically to prepare the natural substance itself, the clue revealed by the determination of structure has led to the production of other substances which have not only shown the properties of the natural compound in an enhanced form, but have also exhibited other valuable physiological effects. The determination of structure has, therefore, two objects—to prepare the natural substance and to ascertain the particular arrangement of the atoms in the molecule which confers on it the properties which determine its value. The determination of the structure of indigo led not only to the production of the blue natural indigo, but enabled indigoes of every shade of the spectrum to be prepared as commercial products. The determination of the structure of cocaine revealed the molecular complex which conferred on this substance its power to act as a local anesthetic, and has led to the production of a number of other substances possessing this valuable property, but without the special disadvantages attaching to the use of the natural substance. Examples of this kind are numerous and should be increased. A systematic examination of our forest products would undoubtedly lead to the discovery of many others and would provide opportunity for the investigation of many other important problems, such as, for example, the utilization of forest grasses as a source of power alcohol.

Systematic team-work research by organic chemists in close association with botanists is required, and now that the Forest Production Research Board of the Department of Scientific and Industrial Research is in active operation, no doubt this branch of its work will receive attention.

(To be concluded) J. F. THORPE

AGE: THE PIPER[1]

I HAVE chosen as my title "Age: the Piper," for I propose to show how we, the younger partners in this dance of life, must foot the measure piped by our

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[1] Address delivered at the Alumni Banquet of the Medical School, Western Reserve University, June 15, 1926.