REMARKS

ON THE

SYNTHESIS OF ORGANIC BODIES.

BEING A PART OF THE PRESIDENTIAL ADDRESS DELIVERED

By SIR HENRY E. ROSCOE, F.R.S., M.P., D.C.L., PH.D.,

Before the British Association for the Advancement of Science, at Manchester, on August 31st, 1887.

AMONGST the tetrad class of elements, carbon, the distinctive element of organic compounds, finds its place; and the remarkable fact that the number of carbon compounds far exceeds that of all the other elements put together receives its explanation. For these carbon atoms not only possess four means of grasping other atoms, but these four-handed carbon atoms have a strong partiality for each other's company, and readily attach themselves hand in hand to form open chains or closed rings, to which the atoms of other elements join to grasp the unoccupied carbon hand, and thus to yield a dancing company in which all hands are locked together. Such a group, each individual occupying a given position with reference to the others, constitutes the organic molecule. When, in such a company, the individual members change hands, a new combination is formed. And as in such an assembly the eye can follow the changing positions of the individual members, so the chemist can recognise in his molecule the position of the several atoms, and explain by this the fact that each arrangement constitutes a new chemical compound possessing different properties, and account in this way for the decompositions which each differently constituted molecule is found to undergo.

Chemists are, however, not content with representing the arrangement of the atoms in one plane, as on a sheet of paper, but attempt to express the position of the atoms in space. In this way it is possible to explain certain observed differences in isomeric bodies which otherwise baffled our efforts. To Van t'Hoff, in the first instance, and more recently to Wislicenus, chemistry is indebted for work in this direction, which throws light on hitherto obscure phenomena, and points the way to still further and more important advances.

It is this knowledge of the mode in which the atoms in the molecule are arranged, this power of determining the nature of this arrangement, which has given to organic chemistry the impetus which has overcome so many experimental obstacles, and given rise to such unlooked for results. Organic chemistry has now become synthetic. In 1837 we were able to build up but very few and very simple organic compounds from their elements; indeed, the views of chemists were much divided as to the possibility of such a thing. Both Gmelin and Berzelius argued that organic compounds, unlike inorganic bodies, cannot be built up from their elements. Organic compounds were generally believed to be special products of the so-called vital force, and it was only intuitive minds, like those of Liebig and Wöhler, who foresaw what was coming, and wrote in 1837 strongly against this view, asserting that the artificial production in our laboratories of all organic substances, so far as they do not constitute a living organism, is not only probable but certain. Indeed, they went a step farther, and predicted that sugar, morphine, salicine, will all thus be prepared, a prophecy which, I need scarcely remind you, has been after fifty years fulfilled, for at the present time we can prepare an artificial sweetening principle, an artificial alkaloid, and salicine.

In spite of these predictions, and in spite of Wöhler's memorable discovery in 1828 of the artificial production of urea, which did in reality break down for ever the barrier of essential chemical difference between the products of the inanimate and of the animate world; still, even up to a much later date, contrary opinions were held, and the synthesis of urea was looked upon as the exception which proves the rule. So it came to pass that for many years the artificial production of any of the more complicated organic substances was believed to be impossible. Now the belief in a special vital force has disappeared like the *ignis fatuus*, and no longer lures us in the wrong direction. We know now that the same laws regulate the formation of chemical compounds in both animate and inanimate nature, and the chemist only asks for a knowledge of the constitution of any definite chemical compound found in the organic world in order to be able to promise to prepare it artificially.

But the progress of synthetic organic chemistry, which has of late

been so rapid, was made in the early days of the half-century only by feeble steps and slow. Seventeen long years elapsed between Wöhler's discovery and the next real synthesis. This was accomplished by Kolbe, who in 1845 prepared acetic acid from its elements. But then a splendid harvest of results gathered in by chemists of all nations quickly followed, a harvest so rich and so varied that we are apt to be overpowered by its wealth, and amidst so much that is alluring and striking we may well find it difficult to choose the most appropriate examples for illustrating the power and the extent of modern chemical synthesis.

Next, as a contrast to our picture, let us for a moment glance back again to the state of things fifty years ago, and then notice the chief steps by which we have arrived at our present position. In 1837 organic chemistry possessed no scientific basis, and therefore no classification of a character worthy of the name. Writing to Berzelius in that year, Wöhler describes the condition of organic chemistry as one enough to drive a man mad. "It seems to me," says he, "like the tropical forest *primaeval*, full of the strangest growths, an endless and pathless thicket in which a man may well dread to wander." Still clearances had already been made in this wilderness of facts. Berzelius in 1832 welcomed the results of Liebig and Wöhler's research on benzoic acid as the dawn of a new era; and such it really was, inasmuch as it introduced a novel and fruitful idea, namely, the possibility of a group of atoms acting like an element by pointing out the existence of organic radicals. This theory was strengthened and confirmed by Bunsen's classical researches on the cacodyl compounds, in which he showed that a common group of elements which acts exactly as a metal can exist in the free state, and this was followed soon afterwards by isolation of the so-called alcohol radicals by Frankland and Kolbe. It is, however, to Schorlemmer that we owe our knowledge of the true constitution of these bodies, a matter which proved to be of vital importance for the further development of the science.

Turning our glance in another direction we find that Dumas, in 1834, by his law of substitution, threw light upon a whole series of singular and unexplained phenomena by showing that an exchange can take place between the constituent atoms in a molecule. Laurent indeed went farther, and assumed that a chlorine atom, for example, took up the position vacated by an atom of hydrogen and played the part of its displaced rival, so that the chemical and physical properties of the substitution product were thought to remain substantially the same as those of the original body. A singular story is connected with this discovery. At a *soirée* in the Tuileries, in the time of Charles X, the guests were almost suffocated by acrid vapours which were evidently emitted by the burning wax candles, and the great chemist Dumas was called in to examine into the cause of the annoyance. He found that the wax of which the candles were made had been bleached by chlorine, that a replacement of some of the hydrogen atoms of the wax by chlorine had occurred, and that the suffocating vapours consisted of hydrochloric acid given off during the combustion. The wax was as white and as odourless as before, and the fact of the substitution of chlorine for hydrogen could only be recognised when the candles were destroyed by burning. This incident induced Dumas to investigate more closely this class of phenomena, and the results of this investigation are embodied in his law of substitution.

But the debt which chemistry, both inorganic and organic, thus owes to Dumas' law of substitution is serious enough, for it proved to be the germ of Williamson's classical researches on etherification, as well as those of Wurtz and Hofmann on the compound ammonias, investigations which lie at the base of the structure of modern chemistry. Its influence has been, however, still more far-reaching, inasmuch as upon it depends in great measure the astounding progress made in the wide field of organic synthesis.

It may here be permitted me to sketch in rough outline the principles upon which all organic syntheses have been effected. We have already seen that as soon as the chemical structure of a body has been ascertained its artificial preparation may be certainly anticipated, so that the first step to be taken is the study of the structure of the naturally occurring substance which it is desired to prepare artificially by resolving it into simpler constituents, the constitution of which is already known. In this way, for example, Hofmann discovered that the alkaloid *conine*, the poisonous principle of hemlock, may be decomposed into a simpler substance well known to chemists under the name of pyridine. This fact having been established by Hofmann, and the grouping of the atoms approximately determined, it was then necessary to reverse the process, and, starting with pyridine, to build up a compound of the required constitution and properties, a result recently achieved by Ladenburg in a series of brilliant researches. The

well-known synthesis of the colouring matter of madder by Graebe and Liebermann, preceded by the important researches of Schunck, and that of indigo by Baeyer, are other striking examples in which this method has been successfully followed.

Not only has this intimate acquaintance with the changes which occur within the molecules of organic compounds been utilised, as we have seen, in the synthesis of naturally occurring substances, but it has also led to the discovery of many new ones. Of these, perhaps, the most remarkable instance is the production of an artificial sweetening agent termed saccharin, 250 times sweeter than sugar, prepared by a complicated series of reactions from coal-tar. Nor must we imagine that these discoveries are of scientific interest only, for they have given rise to the industry of the coal-tar colours, the value of which is measured by millions sterling annually, an industry which Englishmen may be proud to remember was founded by our countryman Perkin.

Another interesting application of synthetic chemistry to the needs of everyday life is the discovery of a series of valuable febrifuges, amongst which I may mention antipyrin as the most useful. An important aspect in connection with the study of these bodies is the physiological value which has been found to attach to the introduction of certain organic radicals, so that an indication is given of the possibility of preparing a compound which will possess certain desired physiological properties, or even to foretell the kind of action which such bodies may exert on the animal economy.

But it is not only the physiological properties of chemical compounds which stand in intimate relation with their constitution, for we find that this is the case with all their physical properties. It is true that at the beginning of our period any such relation was almost unsuspected, whilst at the present time the number of instances in which this connection has been ascertained is almost infinite. Amongst these, perhaps the most striking is the relationship which has been pointed out between the optical properties and chemical composition. This was in the first place recognised by Pasteur in his classical research on racemic and tartaric acids in 1848; but the first to indicate a quantitative relationship and a connection between chemical structure and optical properties was Gladstone in 1863. Great instrumental precision has been brought to bear on this question, and consequently most important practical applications have resulted. I need only refer to the well known accurate methods now in everyday use for the determination of sugar by the polariscope, equally valuable to the physician and to the manufacturer.

But now the question may well be put, Is any limit set to this synthetic power of the chemist? Although the danger of dogmatising as to the progress of science has already been shown in too many instances, yet one cannot help feeling that the barrier which exists between the organised and unorganised worlds is one which the chemist at present sees no chance of breaking down.

It is true that there are those who profess to foresee that the day will arrive when the chemist, by a succession of constructive efforts, may pass beyond albumen, and gather the elements of lifeless matter into a living structure. Whatever may be said regarding this from other standpoints, the chemist can only say that at present no such problem lies within his province. Protoplasm, with which the simplest manifestations of life are associated, is not a compound, but a structure built up of compounds. The chemist may successfully synthesise any of its component molecules, but he has no more reason to look forward to the synthetic production of the structure than to imagine that the synthesis of gallic acid leads to the artificial production of gall-nuts.

Although there is thus no prospect of our effecting a synthesis of organised material, yet the progress made in our knowledge of the chemistry of life during the last fifty years has been very great, and so much so, indeed, that the sciences of physiological and of pathological chemistry may be said to have entirely arisen within this period.

Fifty years ago, too, the connection existing between the laws of life, vegetable and animal, and the phenomena of inorganic chemistry, was ill understood. The idea that the functions of living beings are controlled by the same forces, chemical and physical, which regulate the changes occurring in the inanimate world, was then one held by only a very few of the foremost thinkers of the time. Let me now briefly trace a few of the more important steps which have marked the progress of this branch of science during this period. Certainly no portion of our science is of greater interest, nor, I may add, of greater complexity, than that which, bearing on the vital functions both of plants and of animals, endeavours to unravel the tangled skein of the chemistry of life, and to explain its principles according to which our bodies live, and move, and have their being. If, therefore, in the

less complicated problems with which other portions of our science have to deal, we find ourselves, as we have seen, often far from possessing satisfactory solutions, we cannot be surprised to learn that with regard to the chemistry of the living body—whether vegetable or animal—in health or disease we are still further from a complete knowledge of phenomena, even those of fundamental importance.

It is of interest here to recall the fact that nearly fifty years ago Liebig presented to the Chemical Section of this Association a communication in which, for the first time, an attempt was made to explain the phenomena of life on chemical and physical lines, for in this paper he admits the applicability of the great principle of the conservation of energy to the functions of animals, pointing out that the animal cannot generate more heat than is produced by the combustion of the carbon and hydrogen of his food.

"The source of animal heat," says Liebig, "has previously been ascribed to nervous action or to the contraction of the muscles, or even to the mechanical motions of the body, as if these motions could exist without an expenditure of force (equal to that) consumed in producing them." Again he compares the living body to a laboratory furnace, in which a complicated series of changes occur in the fuel, but in which the end-products are carbonic acid and water, the amount of heat evolved being dependent, not upon the intermediate, but upon the final products. Liebig asked himself the question, does every kind of food go to the production of heat; or can we distinguish, on the one hand, between the kind of food which goes to create warmth, and, on the other, that by the oxidation of which the motions and mechanical energy of the body are kept up? He thought that he was able to do this, and he divided food into two categories; the starchy or carbohydrate food is that, said he, which by its combustion provides the warmth necessary for the existence and life of the body. The albuminous or nitrogenous constituents of our food, the flesh meat, the gluten, the casein out of which our muscles are built up, are not available for the purposes of creating warmth, but it is by the waste of those muscles that the mechanical energy, the activity, the motions of the animal are supplied. "We see," said Liebig, "that the Esquimaux feeds on fat and tallow, and this burning in his body keeps out the cold." The Gaucho, riding on the pampas, lives entirely on dried meat, and the rowing man and pugilist, trained on beefsteaks and porter, require little food to keep up the temperature of their bodies, but much to enable them to meet the demand for fresh muscular tissue, and for this purpose they need to live on a strongly nitrogenous diet."

Thus far Liebig. Now let us turn to the present state of our knowledge. The question of the source of muscular power is one of the greatest interest, for, as Frankland observes, it is the corner-stone of the physiological edifice and the key to the nutrition of animals.

Let us examine by the light of modern science the truth of Liebig's view—even now not uncommonly held—as to the functions of the two kinds of food, and as to the cause of muscular exercise being the oxidation of the muscular tissue. Soon after the promulgation of these views, J. R. Mayer, whose name as the first expositor of the idea of the conservation of energy is so well known, warmly attacked them, throwing out the hypothesis that all muscular action is due to the combustion of food, and not to the destruction of muscle, proving his case by showing that if the muscles of the heart be destroyed in doing mechanical work the heart would be burnt up in eight days. What does modern research say to this question? Can it be brought to the crucial test of experiment? It can; but how? Well, in the first place we can ascertain the work done by a man or any other animal; we can measure this work in terms of our mechanical standard, in kilogramme-mètres or foot-pounds. We can next determine what is the destruction of nitrogenous tissue at rest and under exercise, by the amount of nitrogenous material thrown off by the body. And here we must remember that these tissues are never completely burnt, so that free nitrogen is never eliminated. If now we know the heat-value of the burnt muscle, it is easy to convert this into its mechanical equivalent, and thus measure the energy generated. What is the result? Is the weight of the muscle destroyed by ascending the Faulhorn, or by working on the treadmill sufficient to produce on combustion heat enough when transformed into mechanical exercise, to lift the body up to the summit of the Faulhorn or to do the work on the treadmill? Careful experiment has shown that this is so far from being the case that the actual energy developed is twice as great as that which could possibly be produced by the oxidation of the nitrogenous constituents eliminated from the body during twenty-four hours. That is to say, taking the amount of nitrogenous substance cast off from the body, not only whilst the work was being done but during twenty-four hours, the mechanical effect capable of being pro-

duced by the muscular tissue from which this cast-off material is derived would only raise the body halfway up the Faulhorn, or enable the prisoner to work half his time on the treadmill.

Hence it is clear that Liebig's proposition is not true. The nitrogenous constituents of the food do doubtless go to repair the waste of muscle, which, like every other portion of the body, needs renewal, whilst the function of the non-nitrogenous food is not only to supply the animal heat, but also to furnish by its oxidation the muscular energy of the body.

We thus come to the conclusion that it is the potential energy of the food which furnishes the actual energy of the body, expressed in terms either of heat or of mechanical work.

But there is one other factor which comes into play in this question of mechanical energy, and must be taken into account; and this factor we are as yet unable to estimate in our usual terms. It concerns the action of the mind upon the body, and, although incapable of exact expression, exerts none the less an important influence on the physics and chemistry of the body, so that a connection undoubtedly exists between intellectual activity or mental work and bodily nutrition. In proof that there is a marked difference between voluntary and involuntary work, we need only compare the mechanical action of the heart, which never causes fatigue, with that of the voluntary muscles, which become fatigued by continued exertion. So, too, we know well that an amount of drill which is fatiguing to the recruit is not felt by the old soldier, who goes through the evolutions automatically. What is the expenditure of mechanical energy which accompanies mental effort is a question which science is probably far removed from answering. But that the body experiences exhaustion as the result of mental activity is a well-recognised fact. Indeed, whilst the second law of thermodynamics teaches that in none of the mechanical contrivances for the conversion of heat into actual energy can such a conversion be complete, it is perhaps possible, as Helmholtz has suggested, that such a complete conversion may take place in the subtle mechanism of the animal organism.

The phenomena of vegetation, no less than those of the animal world, have, however, during the last fifty years been placed by the chemist on an entirely new basis. Although before the publication of Liebig's celebrated report on chemistry and its application to agriculture, presented to the British Association in 1840, much had been done, many fundamental facts had been established, still Liebig's report marks an era in the progress of this branch of our science. He not only gathered up in a masterly fashion the results of previous workers, but put forward his own original views with a boldness and frequently with a sagacity which gave a vast stimulus and interest to the questions at issue. As a proof of this I may remind you of the attack which he made on, and the complete victory which he gained over, the humus theory. Although Saussure and others had already done much to destroy the basis of this theory, yet the fact remained that vegetable physiologists up to 1840 continued to hold to the opinion that humus, or decayed vegetable matter, was the only source of the carbon of vegetation. Liebig, giving due consideration to the labours of Saussure, came to the conclusion that it was absolutely impossible that the carbon deposited as vegetable tissue over a given area, as for instance over an area of forest land, could be derived from humus, which is itself the result of the decay of vegetable matter. He asserted that the whole of the carbon of vegetation is obtained from the atmospheric carbonic acid, which, though only present in the small relative proportion of 4 parts in 10,000 of air, is contained in such absolutely large quantity that if all the vegetation on the earth's surface was burnt, the proportion of carbonic acid which would thus be thrown into the air would not be sufficient to double the present amount.

That this conclusion of Liebig's is correct needed experimental proof, but such proof could only be given by long continued and laborious experiment, and this serves to show that chemical research is not now confined to laboratory experiments lasting perhaps a few minutes, but that it has invaded the domain of agriculture as well as of physiology, and reckons the periods of her observations in the field not by minutes, but by years. It is to our English agricultural chemists Lawes and Gilbert that we owe the complete experimental proof required. And it is true that this experiment was a long and tedious one, for it has taken forty-four years to give the definite reply. At Rothamsted a plot was set apart for the growth of wheat. For forty-four successive years that field has grown wheat without addition of any carbonised manure; so that the only possible source from which the plant could obtain the carbon for its growth is the atmospheric carbonic acid. Now, the quantity of carbon which on an average was removed in the form of wheat and straw from a plot manured only with mineral matter was 1,000 pounds, whilst on

another plot, for which a nitrogenous manure was employed, 1,500 pounds more carbon was annually removed; or 2,500 pounds of carbon are removed by this crop annually without the addition of any carbonaceous manure. So that Liebig's prevision has received a complete experimental verification.

May I, without wearying you with experimental details, refer for a moment to Liebig's views as to the assimilation of nitrogen by plants—a much more complicated and difficult question than the one we have just considered—and compare these with the most modern results of agricultural chemistry? We find that in this case his views have not been substantiated. He imagined that the whole of the nitrogen required by the plant was derived from atmospheric ammonia; whereas Lawes and Gilbert have shown by experiments of a similar nature to those just described, and extending over a nearly equal length of time, that this source is wholly insufficient to account for the nitrogen removed in the crop, and have come to the conclusion that the nitrogen must have been obtained either from a store of nitrogenous material in the soil or by absorption of free nitrogen from the air. These two apparently contradictory alternatives may, perhaps, be reconciled by the recent observations of Warrington and of Berthelot, which have thrown light upon the changes which the so-called nitrogenous capital of the soil undergoes, as well as upon its chemical nature, for the latter has shown that under certain conditions the soil has the power of absorbing the nitrogen of the air, forming compounds which can subsequently be assimilated by the plant.

Touching us as human beings even still more closely than the foregoing, is the influence which chemistry has exerted on the science of pathology, and in no direction has greater progress been made than in the study of micro-organisms in relation to health and disease. In the complicated chemical changes to which we give the names of fermentation and putrefaction, the views of Liebig, according to which these phenomena are of a purely chemical character, have given way under the searching investigations of Pasteur, who established the fundamental principle that these processes are inseparably connected with the life of certain low forms of organisms. Thus was founded the science of bacteriology, which in Lister's hands has yielded such splendid results in the treatment of surgical cases, and in those of Klebs, Koch, and others has been the means of detecting the cause of many diseases both in man and animals, the latest and not the least important of which is the remarkable series of successful researches by Pasteur into the nature and mode of cure of that most dreadful of maladies, hydrophobia. And here I may be allowed to refer with satisfaction to the results of the labours on this subject of a committee, the formation of which I had the honour of moving for in the House of Commons. These results confirm in every respect Pasteur's assertions, and prove beyond a doubt that the adoption of his method has prevented the occurrence of hydrophobia in a large proportion of persons bitten by rabid animals, who, if they had not been subjected to this treatment, would have died of that disease. The value of his discovery is, however, greater than can be estimated by its present utility, for it shows that it may be possible to avert other diseases besides hydrophobia by the adoption of a somewhat similar method of investigation and of treatment. This, though the last, is certainly not the least of the debts which humanity owes to the great French experimentalist. Here it might seem as if we had outstepped the boundaries of chemistry, and have to do with phenomena purely vital; but recent research indicates that this is not the case, and points to the conclusion that the microscopist must again give way to the chemist, and that it is by chemical rather than by biological investigation that the causes of diseases will be discovered, and the power of removing them obtained. For we learn that the symptoms of infective diseases are no more due to the microbes which constitute the infection than alcoholic intoxication is produced by the yeast cell, but that these symptoms are due to the presence of definite chemical compounds, the result of the life of these microscopic organisms. So it is to the action of these poisonous substances formed during the life of the organism, rather than to that of the organism itself, that the special characteristics of the disease are to be traced; for it has been shown that the disease can be communicated by such poisons in entire absence of living organisms.

If I have thus far dwelt on the progress made in certain branches of pure science, it is not because I undervalue the other methods by which the advancement of science is accomplished—namely, that of the application and of the diffusion of a knowledge of Nature—but rather because the British Association has always held, and wisely held, that original investigation lies at the root of all application, so that to foster its growth and encourage its development has for more than fifty years been our chief aim and wish.