# EMIL FISCHER

# Syntheses in the purine and sugar group

*Nobel Lecture, December 12, 1902*

Although I am pleased to accept the honouring invitation of the Royal Swedish Academy of Sciences to report on my work to such a select audience, yet I cannot suppress certain misgivings as to the form and theme of my lecture; in its practical achievements my science, chemistry, is indubitably very popular, but is anything but popular in its methods, abstractions and language. I must therefore ask you to accept what I have to offer with the kind forbearance which this hospitable country willingly grants every foreigner.

The abundance of substances of which animals and plants are composed, the remarkable processes whereby they are formed and then broken down again have claimed the attention of mankind of old, and hence from the early days they also persistently captivated the interest of chemists. Yet noteworthy successes were not achieved by science in this most difficult field until the 18th century when men like Sigismund Marggraf in Berlin, Lavoisier in Paris and this country's great son, Carl Wilhelm Scheele studied it. But even then the study of those substances seemed so difficult and necessitated such unusual methods that it was resolved at the beginning of the 19th century to separate it altogether from mineral chemistry and carry it on as a special branch of our science.

Strange to relate, organic chemistry, as the new discipline was termed, did not remain for long within its original terms of reference. It found the exploration of new avenues more worthwhile. It replaced the animal and vegetable substances by many artificial products such as the hydrocarbons and cyano compounds, wood tar and coal tar, wood alcohol, etc. and by pressing into its service the synthetic methods of inorganic chemistry it appropriated the fundamental problems of our science at the same time.

Wöhler's famous synthesis of urea in 1828 was the starting-point for the glorious evolution which for many decennia gave organic chemistry a leading part in the development of chemical theories.

But this era seems to be drawing to a close. The almost obvious view that the one-sided study of carbon compounds cannot suffice to elucidate the nature of chemical processes in all its aspects has again won some measure of acceptance, and general chemistry, in closer association with physics, has been diverted back into the paths which it was following at the beginning of the 19th century under the guidance of Berzelius, Gay-Lussac and Davy.

A necessary consequence of this reorientation must be the reversion of organic chemistry to the great problems of biology.

I shall attempt to explain to you with the aid of two examples, the purines and the carbohydrates, what organic chemistry is capable of as the loyal ally of physiology with refined methods of analysis and synthesis.

Currently the name "purines" is a generic term for a large class of nitrogenous organic compounds, some being certain animal excretions and others the active constituents of important stimulating beverages.

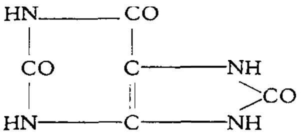
The oldest member of the group is known by the rather unattractive name of uric acid and was discovered in this country 126 years ago simultaneously by Scheele and his famous friend Torbern Bergman as a constituent of urinary calculus and urine. To the physician it is familiar as the cause of painful afflictions, e.g. gout. It appeals to zoologists as the main excrement of snakes and as the reservematerial of insects. And finally the enlightened farmer knows it to be a valuable constituent of guano.

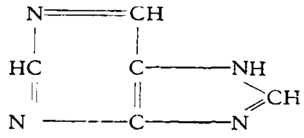
Its chemical history is particularly rich because it was involved in the famous studies by Liebig and Wöhler, by A. Strecker and by A. von Baeyer without its chemical nature being ultimately determined.

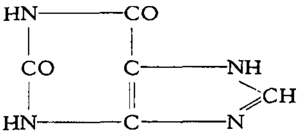
Rather closely related to uric acid in composition and external characteristics are four other substances occurring in the bodies of animals, xanthine, hypoxanthine, adenine and guanine, the first three of which were discovered in the muscular substance and the last in guano. Thanks to the progress of physiological chemistry we now know that these four substances are important constituents of the cell nucleus and therefore have great biological significance.

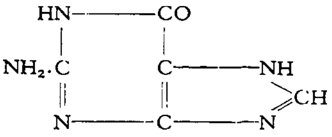
These animal products are joined by three substances from the vegetable kingdom, caffeine, theobromine and theophylline. As the name immediately suggests, the first is contained in coffee but occurs also and even in larger amounts in tea and constitutes the pleasant stimulating principle of these two staple stimulating beverages. Theobromine has the same effect in cocoa. Both substances are also valuable medicines because they promote heart action and diuresis. They are hence factory-produced in appreciable quantities by the extraction of tea and cocoa.

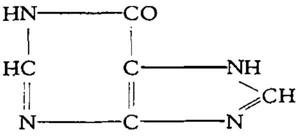
It was long suspected that all these substances were chemically related to each other and also to uric acid but it could not be proved prior to the syste-

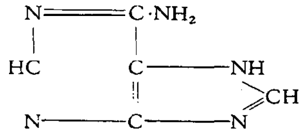

Uric acid

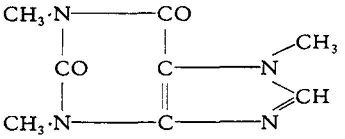

Purine

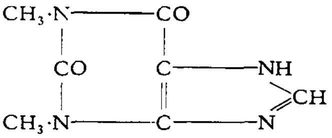

Xanthine

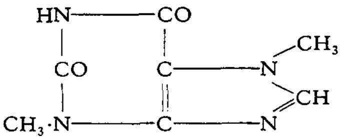

Guanine

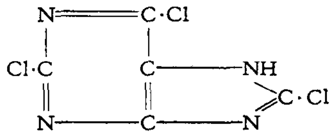

Hypoxanthine


Adenine


Caffeine


Theophylline


Theobromine

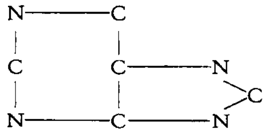

Trichloropurine

matic, i.e. synthetic, treatment of the entire group which we shall now consider.

To this end I would ask you to glance at the accompanying set of formulae, structural formulae as they are termed which may be elucidated as follows:

All theoretical considerations of chemistry are nowadays based on the concept of atoms which aggregate to form smaller or larger complexes, so-called molecules. Molecules are imagined to be constructed rather like a building with the atoms acting as bricks. This molecular building is referred to as its structure and the individual cases are depicted by such formulae. In the formulae the atoms are designated by the letters C for carbon, H for hydrogen, N for nitrogen and O for oxygen. The lines between them are intended to show how these atoms are interlinked to form the complete molecule.

It will readily be seen on comparing these formulae that they contain a common atomic group, a nucleus as it is called and which I have termed the purine nucleus. It consists of five carbon atoms and four nitrogen atoms so arranged that two cyclic groups with two common atoms are formed as shown by the following diagram:



The simplest combination of this skeleton is the hydrogen compound purine, which is therefore considered to be the fundamental form of the class and is as it were the parent from which all the other members can be derived. The addition of an oxygen atom to purine yields hypoxanthine, a second oxygen atom gives xanthine, and a third produces uric acid which is consequently also known by the rational name of trioxypurine.

Replacing a hydrogen atom in purine by the amide NH, forms adenine, and if a further oxygen atom is added, the result is guanine. Lastly, the nitrogen atoms in vegetable products are also linked with the $CH_3$ or methyl group.

To determine the structure of the molecule the chemist proceeds in a similar way to the anatomist. By chemical actions he breaks the system down into its components and continues with this division until familiar substances emerge. Where this decomposition has taken different directions, the structure of the original system can be inferred from the decomposition products. Usually, however, the structure will only be finally elucidated by the reverse method, by building up the molecule from the decomposition products or similar substances, i.e. by what is termed synthesis. The most varied analyses and syntheses have been carried out on the members of the purine group. Consequently transitions abound between all these compounds and in particular it has become possible to synthesize them all from the inexpensive uric acid.

In the focus of these syntheses is trichloropurine. It is formed from uric acid by the action of phosphorus chloride which detaches the three oxygen atoms by means of three hydrogen atoms and replaces them by chlorine. The three chlorine atoms which it contains are very mobile and can hence be replaced in the most versatile ways by hydrogen, oxygen, and groups containing nitrogen or sulphur, thus forming not only the natural compounds referred to here but a far greater number of related synthetic substances. Such is the privilege of organic synthesis; where it is successful in penetrating such a field it far surpasses narrowly restricted Nature, a fact strikingly exemplified by the purine group. So far twelve naturally occurring members are known and perhaps this number will increase as a result of the progressive study of vegetable and animal substances. Nevertheless it is very unlikely that more than double that number will ever be found in Nature. In contrast, synthesis has so far produced no less than 146 members of this group and the methods applied would readily enable twice or three times that number to be synthesized.

For the moment, however, such mere multiplication of the forms would only be of secondary importance. It is more worth while at any rate to utilize for other higher purposes the results available so far.

Among the purine substances there are two valued drugs, caffeine and theobromine, which so far had to be prepared by extraction from tea and cocoa. Their production is not altogether insignificant for their value may be estimated at more than one million marks a year. Now that these drugs can be made synthetically from inexpensive uric acid the mind readily turns to exploiting the synthesis on an industrial scale: it is no secret that several factories in Germany are seriously tackling the problem. Synthetic theophylline has already appeared on the market and I have no doubt that synthetic theobromine and caffeine will very soon follow. But further discussion would scarcely be worthwhile if all that mattered were to lower the price of certain drugs. When it is considered that caffeine is the most active constituent of the two most widespread stimulants, coffee and tea, the matter takes on quite a different complexion. It is common knowledge that for a long time efforts have been made to replace those still rather costly substances by cheaper ones. The clearest proof is the large number of coffee substitutes which appear on the market. Nevertheless all these substitutes lack the best feature of coffee and tea, i.e. the pleasant stimulating effect that originates from the caffeine content. This shortcoming could readily be overcome by the addition of synthetic caffeine as soon as it has become cheap enough, and when once this step has been taken, an improvement in the taste and aroma of those substitutes will not fail to follow. It is even possible to produce the true aroma of coffee or tea artificially, too, by synthesis; with the exercise of a little imagination the day can be foreseen when beans will no longer be required to make good coffee: a small amount of powder from a chemical works together with water will provide a savoury, refreshing drink surprisingly cheaply. The layman usually receives with scepticism such prophecies by the chemist and in this specific instance his scepticism will not be weakened by the knowledge that a constituent of guano would be used to prepare the synthetic drink.

In our age, however, such prejudices on the part of the public do not normally persist for very long. Who, nowadays, still considers that the magnificent dyes colouring our garments and furnishings are derived from unsightly coal tar, or that sweet-tasting saccharin is prepared from the same material ? The point is that chemical transformations are so thorough that the end-product retains nothing at all of the properties of the original substance. The manufacture of caffeine from uric acid is therefore nothing worse than the processes which occur when manure used to nourish plants is converted into appetizing fruits or into wonderfully scented flowers.

Physiology has been ahead of industry in exploiting the chemical elucidation of the purine group. As mentioned earlier, xanthine, hypoxanthine, adenine and guanine are constituents of the cell nucleus which, in the morphological sense, is undoubtedly the most important part of the living cell. Consequently they belong to that group of chemical substances with which the vital functions are directly associated. The knowledge of their chemical constitution and of their transformation into one another will make it easier for physiological research to follow their creation and utilization in the cell and even now it has been possible to demonstrate experimentally that they are an important source for the formation of uric acid in the organism. In addition this immediately provides a fresh viewpoint for practical medicine in that where patients with a tendency to uric acid diathesis have to be cured by an appropriate diet, substances rich in purines will in future have to be avoided in the choice of foods. Many further and similar conclusions can be inferred from the chemical elucidation of the purines and in all probability will greatly benefit biological research.

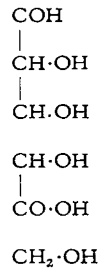
Although for the chemical economy of the cell the purines are qualitatively very valuable, they are quantitatively not very important. In this respect they come far behind the second class of organic compounds which I intend discussing today, i.e. the carbohydrates. Not only are these the first organic products formed in plants from the carbon dioxide in the air but in abundance, too, they surpass all substances that are current in the living world. Their study also dates back to the early beginnings of organic chemistry and has persistently been conducted with such lively enthusiasm that the present state of knowledge in this group may even be used as a yardstick for the discipline as a whole. Nevertheless more than a century elapsed from the elucidation of their elementary composition by Lavoisier before science prepared them by artificial means. The reason for this slow progress lies firstly in the peculiar difficulties which those substances pose for experimental treatment, and secondly in their great profusion of forms which also necessitates a rather complex systematology. A distinction is made between two classes of carbohydrates in particular, the monosaccharides and the polysaccharides. Grape sugar, found in grapes and in other sweet-tasting fruit, may serve as an instance of the former. Starch, the main constituent of all vegetable nutriment, and cellulose, the main constituent of wood or of the other solid frameworks of plants, can be quoted as polysaccharides.

By a process termed hydrolysis all polysaccharides can be converted into the simpler monosaccharides. Both starch and cellulose hydrolyse to form grape sugar. With starch, for example, hydrolysis comes about under the action of the gastric and intestinal juices when vegetable food is consumed. A more potent chemical treatment is required to effect the same conversion with cellulose. This substance is best hydrolysed by strong sulphuric acid and yields the reputed wood sugar which, it is not infrequently claimed inpopular lectures, would one day solve the subsistence problem.

Conversely monosaccharides can be transformed into the more complex poly-compounds by a process termed dehydratation.

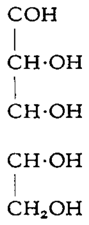
Some 50 monosaccharides are at present known, ten of them occurring in Nature. The others, as you will soon see, were prepared artificially and the methods applied would be sufficient to produce hundreds more such substances. Since all these products are able to combine in bewildering variety and varying quantitative ratios to form polysaccharides, it will readily be appreciated what a plethora of forms there are.

Before the synthesis of this class of substances had been mastered, six monosaccharides, commonly termed sugars, had been found in the animal and vegetable kingdoms and their structure, too, had been elucidated with a sufficient degree of accuracy by decomposition of the molecule. The first in practical importance and in chronological sequence was grape sugar which has already been referred to and which is known by the scientific name of glucose. The insider will at once appreciate from the structural formula that in addition to a chain of six carbon atoms it contains five alcohol groups and one aldehyde group, and that hence it is the aldehyde of a hexavalent alcohol. Surprisingly the same structural formula is also valid for various other



$$\begin{array}{l} \mathrm{COH} \\ | \\ \mathrm{CH\cdot OH} \\ | \\ \mathrm{CH.OH} \\ \\ \mathrm{CH\cdot OH} \\ | \\ \mathrm{CO\cdot OH} \\ \\ \mathrm{CH_2\cdot OH} \end{array}$$

Glucose or
galactose



$$\begin{array}{l} \mathrm{COH} \\ | \\ \mathrm{CH\cdot OH} \\ | \\ \mathrm{CH\cdot OH} \\ \\ \mathrm{CH\cdot OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

Arabinose
and xylose

sugars, e.g. galactose. This phenomenon will be explained later. While these two important sugars contain six carbon atoms, two others are found in Nature which contain only five carbon atoms, i.e. arabinose and xylose.

Their structure is quite similar to that of grape sugar except that the carbon atom at the bottom with its attached hydrogen and oxygen atoms is missing.

As is reasonable to expect in view of the importance of the problem there has in the past been no lack of attempts to synthesize these compounds. But success remained extremely scant, for only a single one of the many artificial products reported in the older chemical literature and regarded as sugar-like substances has stood the critical test of modern methods of examination. And that is the sweet syrup which the Russian chemist Butlerov obtained 40 years ago from formaldehyde – nowadays more widely known as a disinfectant – by the action of lime water. Yet, as shown by more detailed study, this product, too, is a complex mixture and contains only a tiny amount of a substance, closely related to grape sugar, which will shortly be discussed. The route chosen by Butlerov thus did not lead directly to its ultimate goal : success had to be sought under simpler conditions, and those I found in the relationships of grape sugar to glycerol. Outwardly the similarity is already apparent from the sweet taste which they have in common. Chemically the relationship is not quite so great, as glycerol has only three carbon atoms, i.e. half as many as sugar. Neither does it contain an aldehyde group, but it is a polyvalent alcohol. Consequently, by reason of analogy, there were grounds to expect that it would be converted, by gentle oxidation, into an aldehyde, which should correspond in some way to natural sugar. Experiment bore out this expectation. Under the action of dilute nitric acid, glycerol does indeed change into a product exhibiting the typical properties of the sugars. To indicate this similarity as well as the origin of the substance, it was called glycerose.

Here you will realize, ladies and gentlemen, the central position occupied by glycerol in organic chemistry. Discovered by your countryman, Scheele, 140 years ago as a constituent of fat, glycerol, as you will soon see has become the gate through which synthesis gained access to the natural sugars. And how wonderful are the changes of this sweet liquid! Under the action of strong nitric acid it yields the terrible explosive nitroglycerin which, through Dr. Nobel's brilliant technical utilization of it, has become the powerful aid to human work. Conversely, under the action of dilute nitric acid it changes into the new sugar-like substance just mentioned.

However, glycerose still differs strongly in its composition from the natural sugars, for it contains only half as much carbon and many conservative chemists therefore had their misgivings at first about assigning it to the sugar group. But this expulsion was short-lived, for glycerose soon provided a new, and this time unassailable, proof for its close relationship with the old sugars, i.e. under the action of dilute alkali it undergoes a change which we term polymerization in conformity with Berzelius' proposition. Two molecules combine to form a single system and the new product, which has been given the name acrose, is a sugar with six carbon atoms and maximum similarity to the natural substances. It lacks only one property of the latter, i.e. the capacity to rotate polarized light, but a small modification was sufficient to add even this quality and convert the synthetic product freely into grape sugar or the related natural substances.

The total synthesis of the latter has thus been achieved although at first only in a roundabout way via glycerol. Nevertheless it was not long before the process was shortened, for acrose was also found in the above-mentioned sweet syrup formed from formaldehyde in accordance with Butlerov's observation, and now, starting from the simplest materials of organic chemistry or even from inorganic carbon dioxide, it is possible to form the most important natural sugars via readily comprehensible operations.

On the basis thus acquired, synthesis proceeds further still to synthetic sugars with a higher carbon content in the following manner:

As demonstrated by Kiliani, natural sugars are capable, via their aldehyde group, of fixing hydrocyanic acid which was discovered by Scheele, and -

oh, wonder of wonders ! – from the sweet substance and the violent poison a new, harmless substance is formed which has the property of the fruit acids, e.g. tartaric acid. On further treatment with suitable reducing agents it loses oxygen and changes into a new sugar containing one carbon atom more than the starting material. The same procedure can then be repeated and again leads to a new, still higher member of the group. In this way I have already successfully synthesized sugars with up to nine carbon atoms, and with time, trouble and money to spare it will be possible for someone to climb a further few rungs up this ladder.

The upward expansion of the group inevitably awakened the desire to find the simplest members too. According to the new hypothesis there should exist below glycerose a further sugar with two carbon atoms, the aldehyde of glycol. This product, too, could be prepared by simple, synthetic processes, and its properties leave no doubt that it is the simplest of the monosaccharides. In particular it is polymerized by dilute alkali in the same way as glycerose, when it yields the last missing sugar with four carbon atoms.

The series is now complete from the simplest to the ninth member, and chemical parlance must adapt itself to the expanded factual knowledge.

In conformity with a proven principle of our nomenclature the sugars are now described according to their carbon content by the Greek numerals to which is added the conventional sufffix "ose". Pentose, heptose, and nonose, which are now part of the accepted word stock, were formed in this way and the old sugars appear in modern nomenclature as hexoses.

Earlier only fleeting attention was paid to the observation that grape sugar and galactose, which differ considerably from one another in their external characteristics, have the same structure. The older theory had no explanation for this type of isomerism. The chemists of the day contented themselves with calling such substances physically isomeric, and this discrepancy was not accounted for until the molecule was studied in spatial terms. As a result, the further study of the sugars is linked very closely to the development of so-called stereochemistry, a branch of chemistry originating particularly from the study of those substances which, like the sugars, rotate the plane of polarized light. Its first beginnings are to be found in L. Pasteur's celebrated studies of tartaric acids. Natural tartaric acid is contained in wine and rotates polarized light to the right. Pasteur found its optical opposite, i.e. laevo-tartaric acid, and his speculative mind successfully attributed the cause of this rotation to the asymmetrical structure of the molecule. He compared the two acids with the right and the left hands or, tantamount to the same analogy, with an object and its mirror image.

It was only after organic chemistry had made the important advance constituted by the structural theory that this geometrical concept yielded results for our science when in 1874, simultaneously and independently of each other, Le Bel and Van't Hoff attributed the asymmetry of the molecule to the individual carbon atom.

Nowadays numerous observations from the most varied fields of organic chemistry, but most especially the experimental knowledge of the sugar group, testify to the correctness of their hypothesis.

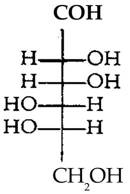
In the sugar molecule several such asymmetrical carbon atoms, i.e. linked with four different substances, are present in quite large numbers. The hexoses, to which grape sugar belongs, contain not less than four, and here the conclusions of the theory relating to the number of isomers are particularly interesting. Since each individual asymmetric carbon atom gives rise to a dextro and a laevo form, calculation shows that not less than sixteen geometrically different substances with the structure of grape sugar must exist. This hence afforded an excellent opportunity to compare broadly the results of speculation with reality. The outcome has been a complete triumph for the theory. Of the sixteen predicted forms no less than twelve are nowadays known, constituting six optical pairs, and the four still missing members will indubitably be obtained by means of the same experimental methods.

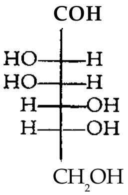
In the light of the theory it has also been possible to derive from the actual observations the geometrical structure or, as it is commonly termed, the configuration, of the molecule for the individual members of this group, and a small modification of the customary structural formulae has been found a convenient form of representing these results of stereochemical research.

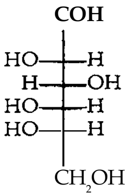
Below are shown the modern formulae for the configurations of the twelve known hexoses and of the four isomers still to be found. The four asymmetrical carbon atoms have been left out and are only intimated in the points of intersection between the vertical line and the four horizontal lines. The position of the letters H and OH which signify hydrogen and hydroxyl, then gives an idea of the geometrical arrangement at each asymmetrical carbon atom. To the insider these formulae reveal with the conciseness and, one may say, with the precision of a mathematical expression, the actually examined relationships between the substances, and furthermore they allow him to foresee a long series of modifications which in all probability are confirmed by later observations. As similar formlae are known for the pen-

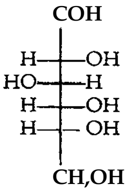
### Aldohexoses

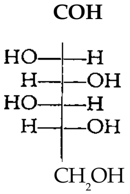
*(a) Mannitol series* :

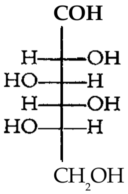

*l*-Mannose

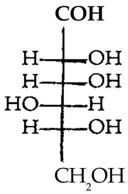

*d*-Mannose

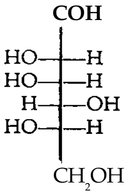

*l*-Glucose


*d-Glucose*

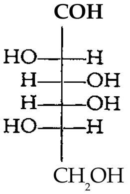

*l*-Idose

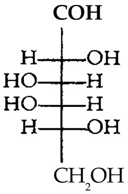

*d*-Idose

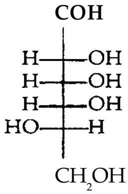

*l*-Gulose

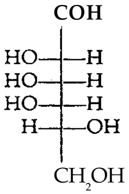

*d*-Gulose

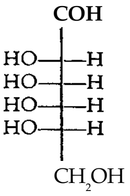
*(b) Ddcitol series* :

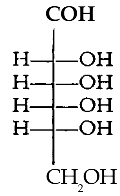

*l*-Galactose

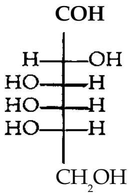

*d*-Galactose

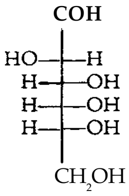

*l*-Talose


*d*-Talose









toses and tetroses, it may be claimed that for the time being the systematology of the monosaccharides has been concluded with these results.

In the meantime synthesis in this field has turned to new problems. Of the simple derivatives of grape sugar the physiologist is best acquainted with glucuronic acid since the animal organism uses it to neutralize poisonous substances, such as phenol, chloral and turpentine. Its configuration, its relationship to grape sugar and its conjectural formation in the animal stomach can readily be elucidated synthetically. Glucosamine, a peculiar nitrogenous substance first derived from lobster shells but which is now known to be widespread throughout the animal kingdom, proved more difficult. Its synthesis, which I successfully accomplished only in recent weeks, showed it to be an intermediate between grape sugar and the cc-amino acids, so providing one of the longest sought-for bridges between the carbohydrates and the proteins.

Of more general interest are also the results relating to the glucosides, substances which occur widely in the vegetable kingdom and which may be regarded as compounds of the sugars with various other substances. Suitable examples are amygdalin, a constituent of bitter almonds, or salicin, formerly used medicinally as an antipyretic. Until 1879 its preparation was also one of Nature's privileges. In that year the American chemist, Michael, successfully synthesized a few of them but his process was restricted to a small number and moreover was so laborious that it has since only rarely been used.

These difficulties have now fortunately been overcome by a new process of synthesis in which sugar is combined with alcohol or similar substances by the simple action of dilute hydrochloric acid. Since then glucosides of alcohol, of wood alcohol, of glycerol, and of lactic acid have become known in abundance and their study led to the surprising realization that there is no fundamental difference between the glucosides and the polysaccharides, the latter being nothing other than the glucosides of the sugars themselves. This fact is indicated not only by their behaviour on hydrolysis by acids or ferments, but even more strongly by the result of synthesis: by applying the same methods which yield glucosides it has also been possible to prepare dextrin-type substances, and recently in particular a series of synthetic disaccharides, one of which appears to be identical with natural melibiose. However scanty these achievements may appear compared with the profusion of polysaccharides, they are nevertheless adequate to prove in principle the possibility of synthesis. For all that there is still a long way to go before the most important polysaccharides, starch and cellulose, can be synthetically prepared; easier, more perfect methods will have to be sought to accomplish those syntheses. But even now we can be perfectly confident that the problem is not an impossibility.

The extreme limits of synthesis have been reached and it only remains for me to illustrate with the aid of a few examples how the knowledge that has been accumulated can be applied to solving biological problems.

Of the chemical aids in the living organism the ferments - mostly referred to nowadays as enzymes - are so pre-eminent that they may justifiably be claimed to be involved in most of the chemical transformations in the living cell. The examination of the synthetic glucosides has shown that the action of the enzymes depends to a large extent on the geometrical structure of the molecule to be attacked, that the two must match like lock and key. Consequently, with their aid, the organism is capable of performing highly specific chemical transformations which can never be accomplished with the customary agents. To equal Nature here, the same means have to be applied, and I therefore foresee the day when physiological chemistry will not only make extensive use of the natural enzymes as agents, but when it will also prepare synthetic ferments for its purposes.

The application of the new knowledge to the superb natural process without which the living world could not exist, i.e. the assimilation of carbon dioxide from the atmosphere by plants, seems even more interesting. This leads as we know to the formation of sugar, Nature's first organochemical product, from which all other constituents of the plant and animal body are formed. As mentioned earlier this transformation can also be accomplished with purely chemical resources, although only in a very roundabout way. But there still remains one distinction between the natural and the artificial synthesis. Above all, the latter invariably yields a mixture of dextro- and laevo-rotatory sugars which must first be separated by special operations. Nature, in contrast, produces exclusively the dextro sugar. Formerly this contrast seemed so wonderful that the direct preparation of optically active substances was regarded quite simply as the privilege of the living organism. The experimental knowledge gained with the sugar group has provided a simple explanation for that biological phenomenon, however, and in the light of the new conception it does not appear at all impossible to reproduce that asymmetrical synthesis artificially in the same way as it occurs in the natural formation of sugars.

And so, progressively, the veil behind which Nature has so carefully concealed her secrets is being lifted where the carbohydrates are concerned. Nevertheless, the chemical enigma of Life will not be solved until organic chemistry has mastered another, even more difficult subject, the proteins, in the same way as it has mastered the carbohydrates. It is hence understandable that the organic and physiological chemists are increasingly turning their attention to it and I, too, have been concerned with it for a number of years. It is true that on this hard ground the fruit ripens far more slowly and the total amount of work that has to be done here is so enormous that in contrast the elucidation of the carbohydrates seems child's play. As against that, however, better methods and a far richer stock of resources are now available, added to which the prize beckoning at the end attracts quite a number of competitors. That is not without its implications for the success of research, since mass production methods which dominate modern economic life have also penetrated experimental science. The days have long since gone when one man such as Berzelius could have a command of, and promote, all branches of chemistry. The circle within which the individual research worker, especially as an experimenter, can distinguish himself is continually shrinking in size. Consequently the progress of science today is not so much determined by brilliant achievements of individual workers, but rather by the planned collaboration of many observers.

Imbued with this conviction, gentlemen of the "Vetenskapsakademien", I feel that the high distinction which you are conferring on me applies less to my person than to the branch of science which I represent. As you honoured last year the great strides made by general chemistry, so this year you have sought to honour the achievements of organic chemistry, a sentiment quite in keeping with the long-standing pursuit of our science in this country. True to Berzelius' great tradition your Academy has fostered all branches of chemistry with the same measure of affection and with a success apt to make many other civilized peoples jealous of Sweden. To be allowed to report on my studies before such a competent body of scientists, is such a great honour that I request you to accept my warmest gratitude in return.