SYNTHESES IN THE SUGAR GROUP.

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Until quite recently the sugars of the formula, $C_6H_{12}O_6$, were considered as the simplest members of the group. As long as the synthesis had not been applied products of animal and vegetable life were the only sources for the small number of sugars. In 1886 we knew four sugars of the formula $C_6H_{12}O_6$, viz.:

Grape sugar, or glucose.
Fruit sugar, or laevulose.
Galactose.
Sorbinose.

Closely connected with these is arabinose which Scheibler, its discoverer, held to be an isomere of glucose, while Kiliani[1] in 1887 characterized it as a compound, $C_5H_{10}O_5$. A few other substances had in former times been erroneously incorporated into the sugar series. Of these inosite and dambose, which are identical, have been recognised by Maquenne[2] as derivatives of hexamethylene, while others, such as phlorose[3], corcose[3] and cerebrose[4] are no longer considered as being chemical individuals.

Of the four remaining sugars the rare sorbinose has been but sparingly examined. According to the latest communications of Kiliani and Scheibler[5] it seems to have the same constitution as laevulose.

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* *Ber. d. Chem. Ges.*, **23**, *2114* (*Abstract.*)

[1] *Ber. d. Chem. Ges.*, **20**, *339.*

[2] *Compt. rend.*, **104**.

[3] *Ber. d. Chem. Ges.*, **21**, *988.*

[4] *Thierfelder, Zeitschr. für physiol. Chem.*, **14**, *209.*

[5] *Ber. d. Chem. Ges.*, **21**, *3276.*

On the other hand the structure of the three other important sugars was essentially known before my own researches began.

The formulæ now in use for glucose and galactose :

$CH_2(OH).CH(OH).CH(OH).CH(OH).CH(OH).COH$; and for laevulose :

$CH_2(OH).CH(OH).CH(OH).CH(OH).CO.CH_2(OH)$ are derived from the following facts :

Sodium amalgam changes glucose and laevulose into mannite; while galactose under the same conditions furnishes dulcite. But mannite and dulcite are to be considered as the hexatomic alcohols of normal hexane, because they are able to take up six acetyl groups and to furnish normal hexyl iodide with hydriodic acid. Furthermore glucose and galactose when subjected to moderate oxidation by means of chlorine or bromine water yield the monobasic gluconic and galactonic acids and, on continued oxidation, the bibasic saccharic and mucic acids. They consequently contain the aldehydic group.

Zincke[6] and V. Meyer[7] objected to this conclusion, upon the basis that ketones also with the group $CO.CH_2(OH)$, as for instance acetylcarbinol, may be transformed into oxyacids. This objection is not justified, because the formation of gluconic and galactonic acids takes place in acid solution, while the transition of acetylcarbinol into lactic acid has been effected only by alkaline oxidizers. In this latter case the carbinol may at first be transformed into the aldehyde, methylglyoxal, which then, under the influence of alkali must at once change to lactic acid.

Unlike the two aldehydes, laevulose is but very slowly attacked by cold bromine water and under the influence of more severe oxidizers it decomposes into products less rich in carbon[8].

All three sugars combine like the ordinary aldehydes or ketones with hydrocyanic acid. By saponification of the cyanhydrines formed, three different acids, $C_7H_{14}O_8$, are produced which are changed into heptylic acids when boiled with hydriodic acid.

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[6] *Ber. d. Chem. Ges.*, **23**, *636* and *Ann. Chem. (Liebig)*, **216**, *318*.

[7] *Ber. d. Chem. Ges.*, **23**, *2344*.

[8] *Kiliani, Ann. Chem. (Liebig)*, **205** *175*.

Under these conditions glucose and galactose furnish normal heptylic acid, while laevulose is transformed into methylbutylacetic acid.

This method devised by Kiliani[9], I consider to mark the greatest progress in the study of the sugar group during several decades. By its aid the old formula for glucose was confirmed and the ketonic formula given above for laevulose put beyond ambiguity. In the same manner Kiliani found the structure of arabinose[10] to be $CH_2(OH).\ CH(OH).\ CH(OH).\ CH(OH).\ COH$.

The addition of hydrocyanic acid implies the first successful step toward synthesis of compounds richer in carbon out of natural sugars.

Another support for the formula of glucose and galactose has been found recently in the observation that they form hydrazones[11] and oximes [12] just as the simple aldehydes do.

The only objection against the aldehyde formula which is maintained up to date, concerns the indifference of sugars towards fuchsine-sulphurous acid[13]. But this objection loses its importance if we consider that heretofore no simple oxyaldehyde of the fatty series has been tested by this reagent. For the time being it seems therefore not justifiable to replace the aldehyde formula by any other, especially as it explains all simple metamorphoses of the two compounds.

Thus the formulæ for the three kinds of sugar are derived from observations seemingly ample enough to serve as a basis for syntheses. But it was different in regard to the methods which were in use for the recognition and isolation of these compounds. Whosoever has tried to obtain glucose or laevulose in a pure state, from salt solutions only, by the methods formerly in use, will agree that it is quite impossible in that way to isolate such an artificial product from a mixture with other organic compounds and to characterize it as a chemical individual.

This want of suitable methods I experienced vividly myself

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[9] *Ber. d. Chem. Ges.*, **18**, *3066* ; **19**, *221*, *767*, *1128*.

[10] *Ber. d. Chem. Ges.*, **20**, *339*.

[11] *Fischer, Ber. d. Chem. Ges.*, **20**, *824*.

[12] *Rischbieth, Ber. d. Chem. Ges.*, **20**, *2673*.

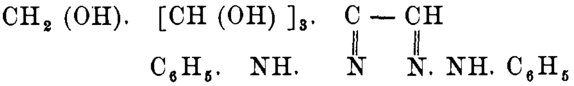
[13] *V. Meyer, Ber.d. Chem. Ges.*, **13**, *2343*.

when seven years ago I attempted *for the first time the synthesis of a sugar* from the bromine compound of acroleine. At that time I obtained by decomposition of the bromide with baryta water a syrup which showed the ordinary sugar reactions. But all endeavors to obtain a pure preparation from the raw product were without sucess. Only four years later this was obtained after a useful agent for this purpose had been found in phenylhydrazin[14].

The reaction between this base and sugars is easily shown as follows: Adding to a warm aqueous ten per cent. solution of glucose, a solution of phenylhydrazin in dilute acetic acid, the mixture at once assumes a yellow color. Heating on the water bath leads in ten or fifteen minutes to a deposit of fine yellow needles, which finally fill the entire liquid like a pulp. These needless have the composition $C_{18}H_{22}N_4O_4$, and are called glucosazone. They are formed by combination of one molecule of sugar and two of phenylhydrazin.

But the formation of this substance takes place in two phases.[15] At first, the sugar combines, like common aldehydes, with one molecule of the base to an hydrazone of the formula: $CH_2\,(OH).\,[CH\,(OH)\,]._3\ {}^*CH\,(OH).\,CH : N.\,NH.\,C_6H_5$.

This compound is easily soluble in water and consequently passes unnoticed in the experiment. On heating this hydrazone with an excess of hydrazin, it suffers a peculiar oxidation. The alcoholic group marked * in the above formula, is transitorily changed into a carbonyl group which latter then fixes in known manner a second molecule of phenylhydrazin. Thus the glucosazone results, the structure of which is given by the formula:



$$CH_2\,(OH).\ [CH\,(OH)\,]_3.\ \underset{\underset{C_6H_5.\,NH.\,N}{\|}}{C} - \underset{\underset{N.\,NH.\,C_6H_5}{\|}}{CH}$$

We are forced to look at the reaction in this way by the behavior of laevulose, which permits the entrance of the hydrazin groups in an inverted sequence. In this case also the first step

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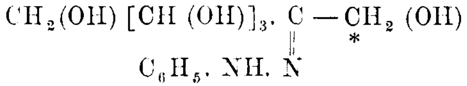
[14] *Ber.d. Chem. Ges.*, **17**, *579.*

[15] *Ber.d. Chem. Ges.*, **20**, *822.*

consists in the formation of an hydrazone easily soluble in water and non-crystallizable.



$$\begin{array}{rcl} CH_2(OH)\,[CH\,(OH)]_3. & C & -\underset{*}{CH_2}\,(OH) \\ & \| & \\ C_6H_5.\,NH. & N & \end{array}$$

Then again the alcoholic group marked * becomes oxidized, a second molecule of phenylhydrazine enters and allows the formation of a glucosazone identical with the one obtained from glucose.

The same reaction is shown by all natural sugars which reduce Fehling's solution, including lactose and maltose. It also obtains for the artificial sugars, or generally speaking, for all aldehydes and ketones which in neighboring position contain an oxidizable alcoholic group, that is, a primary or secondary alcoholic group.

The hydrazones of natural sugars are generally easily soluble in water; this is true for glucose, laevulose, galactose, sorbinose, lactose, maltose, arabinose, xylose and rhamnose.

Mannose[16] forms an exception. Its phenylhydrazone is very difficultly soluble in water, consequently it is precipitated from a cold solution of the sugar upon addition of phenylhydrazin acetate. Using a 10 per cent. mannose solution, a separation of almost colorless, fine crystals begins within one to two minutes and soon the entire liquid is filled with them. The optical isomeres of mannose behave similarly, as do also different artificially obtained sugars with seven, eight and nine carbon atoms.

Here the precipitation of the hydrazone is by far the best means for the recognition as well as for isolation and purification of the sugar, since this latter may easily be regenerated from its hydrazone by splitting this with hydrochloric acid in the following way. To finely pulverized mannose phenylhydrazone add four times its quantity of fuming HCl of Sp. Gr. 1.19 at ordinary temperature. On vigorously shaking, a clear brown liquid is rapidly obtained, the hydrochloride forming. After 1 to 2 minutes the splitting of the hydrazone becomes noticeable, since the crystallization of phenylhydrazine hydrochloride begins. In 10 to 15 minutes the reaction is completed and then the separation of the sugar from the filtered liquid offers no difficulty.

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[16] *Ber. d. Chem. Ges.*, **20**, *832;* **21**, *1805.*

The osazones, which are almost insoluble in water, have proved to be still more valuable for the developement of work in the sugar group. They crystallize with comparative ease and precipitate even from most dilute solutions. In addition, they differ in solubility, melting point and in optical behavior, and they are now consequently used for recognizing natural sugars.

The derivatives of these latter, as well as the important marks of difference are put down in the following table :

Glucosazone, $C_{18}H_{22}N_4O_4$. Is formed from glucose, laevulose, mannose, glucosamine and isoglucosamine. Almost insoluble in water, difficultly soluble in hot alcohol. Melting point near 205° C. The solution in glacial acetic acid turns the plane of polarization to the left.

Galactosazone, $C_{18}H_{22}N_4O_4$. From galactose. Almost insoluble in water, a little more soluble in alcohol than the preceding. Melting point near 193° C. No noticeable action on polarized light when dissolved in glacial acetic acid.

Sorbinosazone, $C_{18}H_{22}N_4O_4$. From sorbinose. Almost insoluble in water, easily soluble in hot alcohol. Melting point 164° C.

Lactosazone, $C_{24}H_{32}N_4O_9$. From lactose. Soluble in 80 to 90 parts of hot water. Melting point near 200° C. Dilute sulphuric acid changes it into its anhydride $C_{24}H_{30}N_4O_8$, which is almost insoluble in water.

Maltosazone, $C_{24}H_{32}N_4O_9$. From maltose. Soluble in about 75 parts of hot water. Melting point near 206° C. Does not furnish an anhydride.

Arabinosazone, $C_{17}H_{20}N_4O_3$. From arabinose. Sparely soluble in hot water, easily soluble in hot alcohol. Melting points near 160° C. Its alcoholic solution shows no action upon the polarized light.

Xylosazone, $C_{17}H_{20}N_4O_3$. From xylose. Deceptively similar to arabinosazone, but, in alcoholic solution strongly turns polarized light to the left.

Rhamnosazone, $C_{18}H_{32}N_4O_3$. From rhamnose (isodulcite). Almost insoluble in water, easily soluble in hot alcohol. Melting point near 180° C.

As before stated, the osazones are formed by a process of oxidation. The reconversion into sugars is consequently much more difficult than with the hydrazones. But for the investigation of synthetical sugars which could only be isolated in the form of osazones, a way to effect this conversion had inevitably to be obtained. After many vain experiments I have found a way in the following two reactions :

Zinc dust and acetic acid reduce the osazones to nitrogenized, basic products. The glucosazone thus forms a compound, $C_6H_{13}NO_5$, which is isomeric with the glucosamine discovered by Ledderhose and which consequently was called isoglucosamine.[17] It forms a beautifully crystallizing acetate and has the structural formula :

$$CH_2(OH).\ CH(OH).\ CH(OH).\ CH(OH).\ CO.\ CH_2.\ NH_2.$$

Its formation from the osazone is a very remarkable process. One hydrazine group is split off entirely; in the other one the nitrogen chain is broken by the nascent hydrogen, aniline being formed. The other nitrogen atom remains united with carbon of the sugar molecule, in form of an amido group. If the base is treated with nitrous acid in the cold, it loses its amido group and is easily transformed into fruit sugar.[18]

But this treatment which furnishes such good results for the glucosazone, is not applicable in other cases, simply because the corresponding bases do not crystallize and cannot therefore be isolated from the mixture of the reaction.

Far more serviceable is the second method. Fuming hydrochloric acid splits the osazones of the sugar group into phenylhydrazine and the so called osones.[19] Considering the glucosazone the process takes place according to the following equation :

$$\underset{\text{Glucosazone.}}{C_6H_{10}O_4(N_2H.C_6H_5)_2} + 2H_2O \quad \underset{\text{Glucosone.}}{C_6H_{10}O_6} + 2C_6H_5.\ N_2H_3.$$

But the practical performance of this reaction requires very close attention. The following experiment shows the condi-

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[17] *Ber. d. Chem. Ges.*, **19**, *1920.*

[18] *Ber. d. Chem. Ges.*, **20**, *2569.*

[19] *Ber. d. Chem. Ges.*, **22**, *87.*

tions for a successful operation. To finely powdered glucosazone the tenfold quantity of fuming HCl is added. It turns dark red, and a portion goes into solution with the same tint. It is thus transformed into its hydrochloride, which, however, is decomposed by water. If the mixture is rapidly heated to 40° C. and vigorously shaken a clear solution is obtained. This is kept for but one minute at 40° C. and then cooled down to 25° C. Now an ample crystallization of phenylhydrazine hydrochloride sets in which indicates the splitting of the osazone. At the same time the dark red tint of the liquid turns to a dark brown. In ten minutes the reaction is finished. The filtered liquid is freed from HCl and the glucosone is precipitated as an insoluble lead compound. It has not, so far, been made to crystallize, and, consequently, could not be analyzed, but its reactions, which correspond absolutely to those of glyoxal and with 1, 2-diketones, do not leave any doubt, that the compound is the aldehyde of fruit sugar and possesses the formula :

$$CH_2(OH).\ CH(OH).\ CH(OH).\ CH(OH).\ CO.\ COH.$$

The behavior towards phenylhydrazine is particularly characteristic. The cold aqueous solution upon addition of phenylhydrazine acetate becomes rapidly turbid, and in five to ten minutes a dense precipitate of glucosazone is formed.

The glucosone combines also with aromatic orthodiamines and forms well-crystallizing chinoxaline derivatives. Finally its transformation by means of nascent hydrogen is particularly interesting, since heating with zinc dust and acetic acid changes it entirely into fruit sugar.

This method thus leads from grape sugar by way of the osazone and osone to fruit sugar and it is to be expected that in this manner most of the still unknown ketone sugars will be prepared from all aldehyde sugars. If we want to return from the ketone sugars to the aldehyde sugars we have to go by way of the alcohol. Considering the last example, the transformation would be as follows : Fruit sugar is easily reduced to mannite by means of sodium amalgam. Careful oxidation with nitric acid forms out of this its aldehyde, the mannose, and further, from this, as I shall show, grape sugar.

In studying the sugars the osazones are capable of application to other purposes.

The formulæ $C_6H_{12}O_6$; $C_5H_{10}O_5$; $C_7H_{14}O_7$, etc., showing the same percentage composition, the analysis alone of these sugars will never allow to decide in regard to the number of carbon atoms; we are therefore forced to analyze a derivative. For this purpose the osazones are best fitted since, as a rule, they may be obtained in a very pure state. They have been utilized so far for the determination of the empirical formulæ of arabinose [20], sorbine[21] and xylose [22].

In still other cases the osazones offer a new means of determining the constitution of a sugar. In former times rhamnose (isodulcite) was considered to be a hexatomic alcohol and an analogue of mannite, although its reducing action upon alkaline copper sol. was known. But the use of the hydrazin test showed, in furnishing[23] an osazone, $C_6H_{10}O_3\ (N_2H.\ C_6H_5)_2$, that the anhydrous rhamnose is a sugar of the formula $C_6\ H_{12}\ O_5$, for which later on *the structural formula was found*[24] *to be* $CH_3.\ CH(OH).\ CH(OH).\ CH(OH).\ CH(OH).\ COH$.

Another example is offered by milk sugar, which, as we know, is an anhydride of equal molecules of glucose and galactose. Its faculty of forming an osazone proves that it still contains one group—CH(OH). COH. Since, furthermore, the osone which is formed from the osazone decomposes into galactose and glucosone when boiled with dilute acids, it follows that we find in sugar of milk the unchanged aldehydic group of the glucose molecule.[25]

This conclusion, which has been corroborated by the preparation of lactobionic acid[26] and by the hydrolysis of this latter, has led to a new conception of the constitution of milk sugar and of the closely related maltose.

Finally the hydrazones and osazones proved to be particularly valuable for the discovery of new sugars and of substances similar to sugars. These latter are obtained in a comparatively easy manner by moderate oxidation by polyatomic alcohols. As far as I know, it was Carlet[27] who made the first observation of this kind.

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[20] *Kiliani, Ber. d. Chem. Ges.*, **20**, *345*.
[21] *E. Fischer, Ber. d. Chem. Ges.*, **20**, *827*.
[22] *Tollens und Wheeler, Ann. Chem. (Liebig)*, **254**, *315*.
[23] *Fischer und Tafel, Ber. d. Chem. Ges.*, **20**, *1091*.
[24] *Fischer und Tafel, Ber. d. Chem. Ges.*, **21**, *2173*; see also *Maquenne, Compt. Rend.*, **109**, *603*.
[25] *Fischer, Ber. d. Chem. Ges.*, **21**, *2633*.
[26] *Fischer und Meyer, Ber. d. Chem. Ges.*, **22**, *361*.
[27] *Jahresbericht für Chemie* (*1860*), *250*.

(*To be continued.*)