SYNTHESES IN THE SUGAR GROUP.

By Emil Fischer.

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On heating dulcite with dilute nitric acid Carlet[1] obtained a liquid which strongly reduced alkaline copper solution, and which turned yellow with alkalies.

Gorup-Besanez[2] studied this process more thoroughly a year later with mannite. As an oxidizer he used platinum sponge and atmospheric oxygen and thus obtained an amorphous, fermentable sugar, the so called mannitose, which, however, was said to differ from the natural compound by optical inactivity.

Twenty-three years later the interesting experiment of Gorup-Besanez was repeated with better facilities by Dafert.[3] He concluded that manitose is a mixture of fruit sugar with other unknown products, the isolation of which he found to be impossible.

Aided by the new reagent I studied anew the oxidation of mannite in 1887. Using dilute nitric acid, I obtained, along with fruit sugar, a second sugar, which in contrast to the then known compounds, furnished a difficultly soluble hydrazone. This is the previously mentioned mannose. A further research which I undertook together with Dr. Hirschberger, lead to the surprising result that it possesses the same structure as glucose, that it is the real aldehyde of mannite, while glucose belongs to a stereoisomeric series.[4] Mannose was thus originally an artificial product, but it soon was found in plants. Tollens and Gans[5] obtained it by hydrolysis of salep mucous, and R. Reiss[6] as a product of

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[1] Jahresbericht für Chemie, **1860**, 250.

[2] *Ann. Chem. Pharm.*, **118**, 257.

[3] *Ber. d. chem. Ges.*, **17**, *227*, and Zeitschrift des Vereins für Rübenzucker-Industrie, 1884.

[4] *Ber. d. chem. Ges.*, **22**, *374*.

[5] *Ann. Chem. Pharm.*, **249**, *256*.

[6] *Ber. d. chem. Ges.*, **22**, *609*; **22**, *3218*.

decomposition of the so called reserve cellulose. This latter is found in sundry palm fruits, particularly in the corocos nut (Steinnuss). The shavings which result in the manufacture of buttons from this nut offer a cheap and ample raw material for obtaining this sugar.

The knowledge of mannose has been of particular influence in the study of the sugar group ; the observation that mannonic acid, formed from this sugar, is the optical isomere of arabinose carbo acid, furnished the key for the understanding of the mannite group. I shall recur later to this point.

As with dulcite and mannite we find also that the simpler polyatomic alcohols erythrite and glycerol, when cautiously oxidized, furnish sugar-like products. Dr. Tafel and myself have called these erythrose and glycerose[7], and we have isolated them as beautifully cyrstallizing osazones. Our publication caused a reclamation on the part of Grimaux[8] who says, that he had reported upon the preparation of glycerol aldehyde and its property of fermenting with beer yeast, a year previous, in the protocoll of the meeeting of the Chemical Society of Paris. But he did not succeed in isolating the product nor in proving that it was glycerol aldehyde for want of suitable methods.

In regard to all this I must draw attention to a much older, almost forgotten notice of I. van Deen[9] from the year 1863. He observed that a substance is formed from glycerol by nitric acid as well as by electrolysis, which strongly reduces alkaline copper solution and which admits of fermentation. His statement that this substance is a crystallizable sugar has been disputed from different sides, but no one has contradicted the formation of this reducing substance. Since now our own experiments as well as those of Grimaux confirm the data of van Deen in this direction, he must be considered the first observer of glycerose.

Although the proof that this is a derivative of glycerol of the formula $C_3H_6O_3$ has only been furnished by us by means of ana-

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[7] *Ber. d. Chem. Ges.*, **20**, *1088*.

[8] *Compt. Rend.*, **104**, *1276* ; *Ber. d. Chem. Ges.*, **20**, *3384*.

[9] *Jahresbericht f. Chem.*, **1863**, *501* ; also *Tydschrift voor Geneeskunde*, **4** *and* **5**.

lysis of the osazone even this result does not yet decide the question, whether this product is the aldehyde or the ketone of glycerol, since both must furnish the same osazone. On the contrary we were only able to conclude much later that glycerose is to be considered a mixture of both by the following observations: Dilute alkali transforms the substance into sugars containing along with other products α-acrose (of which we treat later) which requires for its formation glycerol aldehyde.[10]

Furthermore glycerose combines with hydrocyanic acid forming an intermediary cyanhydrin, which on saponification gave us trioxyisobutyric acid, which can only form from the ketone, *i. e.* the dioxyaceton.[11]

The easiest manner of obtaining glycerose is that of oxidation of glycerol with bromine and sodium carbonate. This mode is particularly adapted for a lecture experiment. To this end dissolve 10 grms. glycerol and 35 grms. crystallized soda in 60 grms. warm water, cool to the temperature of the room and add 15 grms. bromine. This latter dissolves on shaking and the development of CO_2 begins at once. The reaction is only finished in half an hour, but already in two minutes the formation of glycerose can be proven. Take out a sample of the liquid, saturate it with SO_2 until discolored, so as to destroy hypobromic acid, then saturate with alkali and finally add Fehling's solution. Now, on heating, coloration to red and separation of cuprous oxide takes place.

In the same manner the change of mannite into laevulose can be shown.[12]

The purest glycerose, comparatively, is obtained by action of bromine vapor upon the lead compound of glycerol[13]; but the greater part of the product thus gained consists of dioxyaceton. The preparation of pure glycerol aldehyd has so far remained an unsolved problem of no inferior interest.

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[10] *Ber. d. Chem. Ges.*, **20**, *3385*.

[11] *Ber. d. chem. Ges.*, **22**, *106*.

[12] Dissolve 5 grms. mannite and 12 grms. soda in 40 grms. water. After cooling add 5 grms. bromine.

[13] *Ber. d. chem. Ges.*, **21**, *2635*.

All the experiments so far reported upon were merely antecedents for the synthesis of natural sugars. The final aim of the research has gradually forced them into existence. In approaching now this final aim, I have at first to draw your attention to some historical data.

The thought of preparing glucose artificially is as old as organic synthesis itself.

Liebig and others have often pointed to the importance of this problem and many a note of the older literature puts it beyond doubt that earnest endeavor to realize this idea was made. But if we adhere to the principle that in working at such tasks, only the actual success signalizes an advance of science, then the history of sugar synthesis begins only 29 years ago with the discovery of methylenitane by Butlerow.[14] He obtained it by cautious addition of lime water to a hot solution of trioxymethylene, the polymere of formaldehyd. He describes it as a faintly yellow syrup of sweet taste, which shows the ordinary sugar reactions, but being optically inactive and seemingly not fermentable with beer yeast. He believes it possible as a preliminary step to express the composition of the product by the formula $C_7H_{14}O_6$, but he remarks that the analyses of the syrup yielded varying results. Butlerow was by no means in doubt about the importance of his observation, for he concludes his short but memorable paper with this sentence: "And if so we can say that here we have the first example of the total synthesis of a body of sugar like nature."

General attention seems only to have been attracted by this experiment of Butlerow after A. von Baeyer[15] had applied it as the basis of his well known hypothesis in regard to the formation of sugar in plants. Now the experiment was repeated from different sides, but without yielding noticeable results.

The work of Oskar Löw[16] shows an advance of this remarkable synthesis. By means of a modification of A. W. von Hofmann's method, he furnished an easy and productive method for the

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[14] *Ann. Chem. Pharm.*, **120**, *295*; *Compt. Rend.*, **53**, *145*.

[15] *Ber. d. chem. Ges.*, **3**, *67*.

[16] *Journ. für prakt. Chem.*, **33**, *321*.

preparation of formaldehyd[17], thus offering to himself and others the possibility of studying its condensation in a larger measure. He then showed that the transformation of the aldehyd into sugar by lime water takes place even at ordinary temperature He called the sweet syrup thus prepared formose, with the formula $C_6H_{12}O_6$. He pronounced it to be different from methylenitane, which at the utmost contained but twenty per cent. formose, in addition to the products of decomposition of this sugar. Unfortunately, Löw, in his conclusions, overstepped the limit of his observations, and thus his statement that formose differs from methylenitane and is to be considered as the first artificial sugar called forth vigorous contradiction, especially from Tollens.

As methylenitane formose neither ferments with yeast, nor furnishes laevulinic acid with hydrochloric acid, the formula $C_6 H_{12} O_6$ which Löw choose was not sufficiently proven, since the analyses of such a syrup are not decisive and furthermore the only crystalline derivative of formose, the osazone should (according to Löw's analyses) not possess the formula $C_{18} H_{22} N_4 O_4$, but that of $C_{18} H_{22} N_4 O_3$. If the former had been correct, formose ought to have been represented by the formula $C_6 H_{12} O_5$ and thus would have been considered as an isomere of rhamnose. This contradiction in Löw's work led me to repeat his and Butlerow's experiments and to scrutinize them with the aid of phenylhydrazin[18].

Then it appeared that methylenitane and formose are essentially the same, *i. e.*, mixtures of different sugar like compounds.

In both cases the main product is a sugar which really has the formula $C_6 H_{12} O_6$ as an expression. Its osazone melts near 144°, and has the normal composition $C_{18} H_{22} N_4 O_4$. For this compound (which, by the way, shows but a very slight similarity to glucose) the well chosen name of "formose" may be maintained.

On this occasion also was observed another sugar, of much more interest, which is contained in small quantity in the product of condensation of formaldehyde. Its osazone showed great similar-

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[17] Compare: *Tollens, Ber. d. Chem. Ges.*, **19**, *2133.*

[18] *Ber. d. Chem. Ges.*, **21**, *989.*

ity, in melting point and solubility, with glucosazone. Later on it was identified with α-acrosazone.[19]

Immediately after publication of this last observation, O. Löw[20] reported upon a new method of condensation of formaldehyde. On warming its dilute watery solution with lead and magnesium oxide, he obtained a syrupy sugar, which was directly fermentable. But even this product, which Löw calls methose is nothing else than α-acrose, as the more minute study of the osazone showed. But in this case it is formed in greater quantity, as in the case of condensation with lime, and for this reason the raw product is directly fermentable.

In the meantime (1887) the discovery of the acroses[21] was made, which gave to all my work a determined direction. As we have already seen, acrolein bromide is transformed by bases into a product of the nature of sugar.

For a lecture experiment it suffices to agitate a few drops of the bromide with strongly diluted, cold sodic hydrate solution, and to test the filtrate of the separated resin with Fehling's solution. The study of this phenomenon led Dr. Tafel and myself to the discovery of the acroses. They are formed in considerable quantity only by very cautious decomposition of the bromide, by means of cold baryta water. The formation of sugar then takes place according to the equation :

$$2C_3H_4OBr_2+2Ba(OH)_2=C_6H_{12}O_6+2BaBr_2$$

The isolation of the sugar can only be perfected by its transformation into the osazone. We were thus enabled to prove that this reaction furnishes, along with other still unknown products, two isomeric sugars, $C_6H_{12}O_6$, which were distinguished as α-and β-acrose.

The preparation of these two compounds from glycerose[22] is far easier, since even dilute alkali in the cold condenses it to sugar. It is merely necessary to take the solution of glycerose, as shown

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[19] *Ber. d. chem. Ges.*, **22**, *359.*

[20] *Ber. d. chem. Ges.*, **22**, *475.*

[21] *Ber. d. chem. Ges.*, **20**. *1093, 2566.*

[22] *Ber. d. chem. Ges.*, **20**, *3384.*

to be prepared by the action of bromine and soda upon glycerol, to just supersaturate it by means of caustic soda solution and to allow it to rest for two days at 0°. Thus all glycerose will be transformed into sugar. The process corresponds to the empirical equation : $2\ C_3H_6O_3=C_6H_{12}O_6$.

Here also several sugarlike compounds are formed, of which only the two acroses were isolated in form of osazones.

The α-acrose, which here also is only formed in small quantity, is generated most likely according to the aldol formation from equal molecules of glycerol aldehyd and dioxyaceton.

$$CH_2(OH).CH(OH).COH + CH_2(OH).CO.CH_2(OH)=CH_2(OH).CH(OH).CH(OH).CH(OH).CO.CH_2(OH).$$

The reaction takes place under conditions which are also given in the plant, and consequently it is much more interesting, from a physiological standpoint than the formation of sugar from acrolein bromide. The same remark obtains still more fully for the above mentioned transformation of formaldehyd into α-acrose.

The properties of α-acrosazone attract closer attention, since it is deceptively similar to glucosazone, from which it differs essentially only by its optical inactivity. The surmise, therefore, which later on developed into certainty, that α-acrose is the inactive form of glucose or laevulose was soon suggested. Nevertheless, it required the work of years to pass from acrose to natural sugars.

The first and greatest difficulty was offered by the re-transformation of α—acrosazone into the sugar. It was only accomplished in a satisfactory manner, after the above method had been found, by which we pass from glucosazone, by way of the osone, to laevulose.

If this method be applied to acrosazone a sweet syrup results, which ferments with beer yeast, forms laevulinic acid with HCl, and is transformed by sodium amalgam into a beautifully crystallizing hexatomic alcohol, the α-acrit.[23] This latter showed such a remarkable similarity to mannite that we suspected it to be its inactive form.

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[23] *Ber. d. chem. Ges.*, **22**, *97*.

Thus the way for the synthesis of natural sugars seemed to be opened. Another obstacle arose, however, in the difficulty of obtaining the raw material. If we consider that a kilo. of glycerol, in consequence of the manifold operations and the partially scant yield, furnishes but 0. 2 grms. of acrit, we understand that only the rise of a factory for the manufacture of acrose could have helped us. Thus we were forced to break off our work at this point and look for another method.

In order to show what fortunate accidents sometimes lead to success I shall have to return to the natural sugars.

Mannose is the aldehyd of mannit and is consequently transformed by bromine water into the monobasic mannonic acid : $C_6 H_{12}O_7$. It had to be considered that such a simple reaction could not be troublesome. But the other products of oxidation prevent the acid from crystallizing. The same is to be said of the corresponding salts and thus in order merely to purify this acid a new method had to be discovered. Here also phenylhydrazin was of assistance. It forms with the acids of the sugar group, when warmed in aqueous solution, well crystallizing hydrazides[24], from which by splitting with baryta water the acid is easily regenerated. The aqueous solution of the thus purified mannonic acid[25] when evaporated is transformed into the well-crystallizing lactone : $C_6 H_{10}O_6$. A compound of the same composition had been found some years previously by Kiliani[26] when aggregating hydrocyanic acid to arabinose. Both lactones are remarkably similar, but they turn the polarized ray in a different sense and, in aqueous solution combine with each other to a third, inactive compound[27].

Evidently they offer an analogue to dextro and laevo tartaric acids and offer the first example of this kind of isomerism in the sugar group.

In order to convey the same phenomenon to the mannose, it is only necessary to transform the three lactones into sugar. This

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[24] Fischer & Passmore, *Ber. d. chem. Ges.*, **22**, *2728*.

[25] Fischer & Hirschberger, *Ber. d. chem. Ges.*, **22**, *3219*.

[26] *Ber. d. chem. Ges.*, **19**, *3034*.

[27] *Ber. d. chem. Ges.*, **23**, *370*.

is attained in a very simple manner by reduction with sodium amalgam in cold solution acidulated by sulphuric acid. This new reaction[28] which was of the greatest consequence in the whole research, is also easily to be demonstrated. To a cold ten per cent. aqueous solution of 3 grms. mannonic acid lactone I add alternately dilute sulphuric acid and sodium amalgam, so that the reaction remains always an acid one. If the action of the amalgam be increased by strong agitation, the experiment takes hardly more than five minutes. The liquid separated from mercury reduces Fehlings' solution vigorously and gives with phenylhydrasin acetate in the cold after a few minutes a precipitate of mannosephenylhydrazone.

In the same manner the arabinose carbo acid furnishes the isomeric laevomannose, while the third lactone permits an inactive sugar to result.

By further reduction the three sugars are transformed into three optically different mannits and thus nine compounds result which may be grouped into three optical series.

The following table, which represents all now known members of the mannit series in tabular form, contains the nine compounds in the mannose group where they are distinguished by the signs, *d*, *l* and *i* (dextro, laevo and inactive).

MANNITE SERIES.

l. Fructose.	i. Fructose. (α-Acrose.)	d. Fructose. (Fruit sugar.)
——	i. Glucosone.	d. Glucosone.
	MANNOSE GROUP.	
l. Mannonic acid. (Arabinose carbo-acid.)	i. Mannonic acid.	d. Mannonic acid.
l. Mannose.	i. Mannose.	d. Mannose.
l. Mannite.	i. Mannite. (α-Acrit.)	d. Mannite.
l. Mannosaccharic acid. (Meta-saccharic acid.)	*i. Mannosaccharic acid.	*d. Mannosaccharic acid.

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[28] *Ber. d. chem. Ges.*, **22**, *2204 and* **23**, *930.*

* The compounds marked * are new, but they will described as soon as possible.

GLUCOSE GROUP.

*l. Gluconic acid.	*i. Gluconic acid.	d. Gluconic acid.
*l. Glucose.	*i. Glucose.	d. Glucose. (Grape sugar.)

ALCOHOLS ABSENT.

*l. Saccharic acid.	*i. Saccharic acid.	d. Saccharic acid.

Immediately underneath these we find three further compounds, which stand to each other in the same optical relation, and which are named mannosaccharic acids. The compound of the left series is Kiliani's metasaccharic acid,[29] prepared from arabinose carbo-acid. The two isomeres are formed in the same manner from i and d. mannonic acid by oxidation with nitric acid. The table shows, furthermore, three sugars called fructose. The d. compound is the ordinary fruitsugar and the d. glucosone right underneath it we have seen to be formed from the ordinary glucosazone. The three other compounds of this group are products of synthesis. The new bodies of the glucose group, which also contains grape sugar, I shall recur to later.

Here we have arrived at a point where the analytical research meets the work of synthesis.

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[29] *Ber. d. chem. Ges.* **20**, *341 ; 2710.*

(*To be Continued.*)