

SYNTHESES IN THE SUGAR GROUP.

BY EMIL FISCHER.

(Concluded.)

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Analysis and synthesis meet at this point, since i-mannite is identical with synthetical α -acrite, and it was an easy matter to prove that α -acrose, regenerated from the osazone is nothing else than i. fructose.¹ In order to conclude the synthesis of natural sugars it remains only to search for the transition of the middle inactive series into the side series.

The fundamental work of *Pasteur* taught us two methods for the transformation of inactive substances into optically active ones: partial fermentation by bacilli, or splitting by crystallization of the salts. With sugars, only the first way is applicable. Here, yeast is to be preferred to mold ferments and splitting ferments as used by *Pasteur* and others. An aqueous solution of synthetical α -acrose ferments actively in a short time with beer yeast. In one to two days the fermentation is completed. The liquid, previously inactive, then rotates strongly to the right and furnishes a d-glucosazone, since the yeast left behind in it the *laevo-fructose*.² It may seem surprising, that a sugar of strongly dextro-rotary power is enumerated here as a laevo compound. But the signs d. and l. are not intended to express in every case the power of rotation, which changes without regularity, but rather the *chemical* nexus of these compounds. The letter d. has been chosen for the group of natural sugars because most of them turn towards the right. But in consequence it has also to be maintained for fruit sugar, which, in spite of its power of rotation to the left, belongs to the same geometrical series as the d-mannose.

¹*Ber. d. chem. Ges.*, **23**, 384 and 387.

²*Ber. d. chem. Ges.*, **23**, 389.

The action of beer yeast upon i-mannose is quite analogous, the dextro part ferments and l-mannose remains behind.³

In both cases the yeast uses up that part of the inactive substance to which it clings by force of past evolution.

But this method only leads to the less interesting sugars of the *l* series. In order to obtain the natural products of the *d* series synthetically, chemical methods are required, which lead on to the end by the following reactions.⁴

Careful oxidation of i-mannite with nitric acid furnishes i-mannose which by means of bromine water is transformed into i-mannonic acid. This latter is split by means of the strychnia—or morphia—salt into *d*- and *l*-mannonic acids, from which result by reduction, the optically active mannoses and mannites. Then the way leads from *d*-mannose and its glucosazone to *d*-fructose.

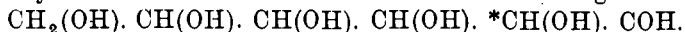
In the mannite series there remains now only the synthesis of glucose and its derivatives and isomers, which have been enumerated in the glucose group of the table above. We mentioned that glucose is stereo-isomeric with mannose. [The older assumption of glucose as the aldehyde of mannite was proved to be erroneous by the discovery of mannose. But I have furthermore convinced myself of this fact by a new research of the reduction of grape sugar by sodium amalgam. Working in the old way, allowing the sugar solution to remain over the amalgam, the operation lasts for weeks and then really furnishes mannite, however in a quantity proportionally small. But if the detrimental action of the alkali is prevented by frequent neutralization with sulphuric acid, and if by continuous agitation the action of the amalgam is accelerated, the reaction is accomplished as swiftly as with mannose and other aldehydic sugars. Using quantities of 10 grms., twelve to fifteen hours finish it; no mannite is then obtained, at least its quantity is so trifling that I was unable to isolate it. Instead, a syrup results which is easily soluble in alcohol and which most likely contains a hexatomic alcohol, stereo-isomeric with mannite. (Compare also, C. Scheibler, *Ber. d. chem. Ges.*, **16**, 3010.)]

Glucose and mannose both furnish an identical glucosazone and

³*Ber. d. chem. Ges.*, **23**, 382.

⁴*Ber. d. chem. Ges.*, **23**, 389.

consequently the isomery between the two depends upon asymmetry of that ⁵carbon atom marked * in the following formula :



Thus it might be expected that a reciprocal transformation of the two compounds was feasible. These easily decomposed sugars, however, do not admit of the experiment. The pertaining acids do, however, by heating them with quinoline.⁶

I chose this tertiary basis because it cannot form amido-like compounds, and because it is so easy to remove it again from the mixture of reaction.

Gluconic acid heated with quinoline to 140°C. is partly transformed into mannonic acid ; conversely this latter, under similar conditions, yields a considerable quantity of gluconic acid. These observations recall the known reciprocal conversion of racemic acid and mesotartaric acid.

Now, since gluconic acid is transformed by nascent hydrogen into glucose, the total synthesis of this latter is realized.

Exactly the same process leads from l-mannonic acid to the compounds optically isomeric with gluconic acid and grape sugar. They are enumerated in the above table as l-gluconic acid and l-glucose. The preparation of l-gluconic acid from l-mannonic acid by heating with quinoline signifies its synthesis, but this procedure is so circumstantial and yields so little that the acid would perhaps not have been found, unless it had been met with and studied on another path. Curious to say this l-gluconic acid forms abundantly from arabinose by aggregation of hydrocyanic acid. Along with it is formed arabinose carboacid, isolated by Kiliani. The simultaneous formation of two stereoisomeric products on addition of hydrocyanic acid to aldehydes, which here was observed for the first time, is very remarkable, theoretically as well as practically. According to expectation l-gluconic acid is deceptively similar to the d-compound and both acids unite in aqueous solution to a third inactive substance which forms independent salts as well as other inactive derivatives.

⁶*Ber. d. chem. Ges.*, **22**, 374.

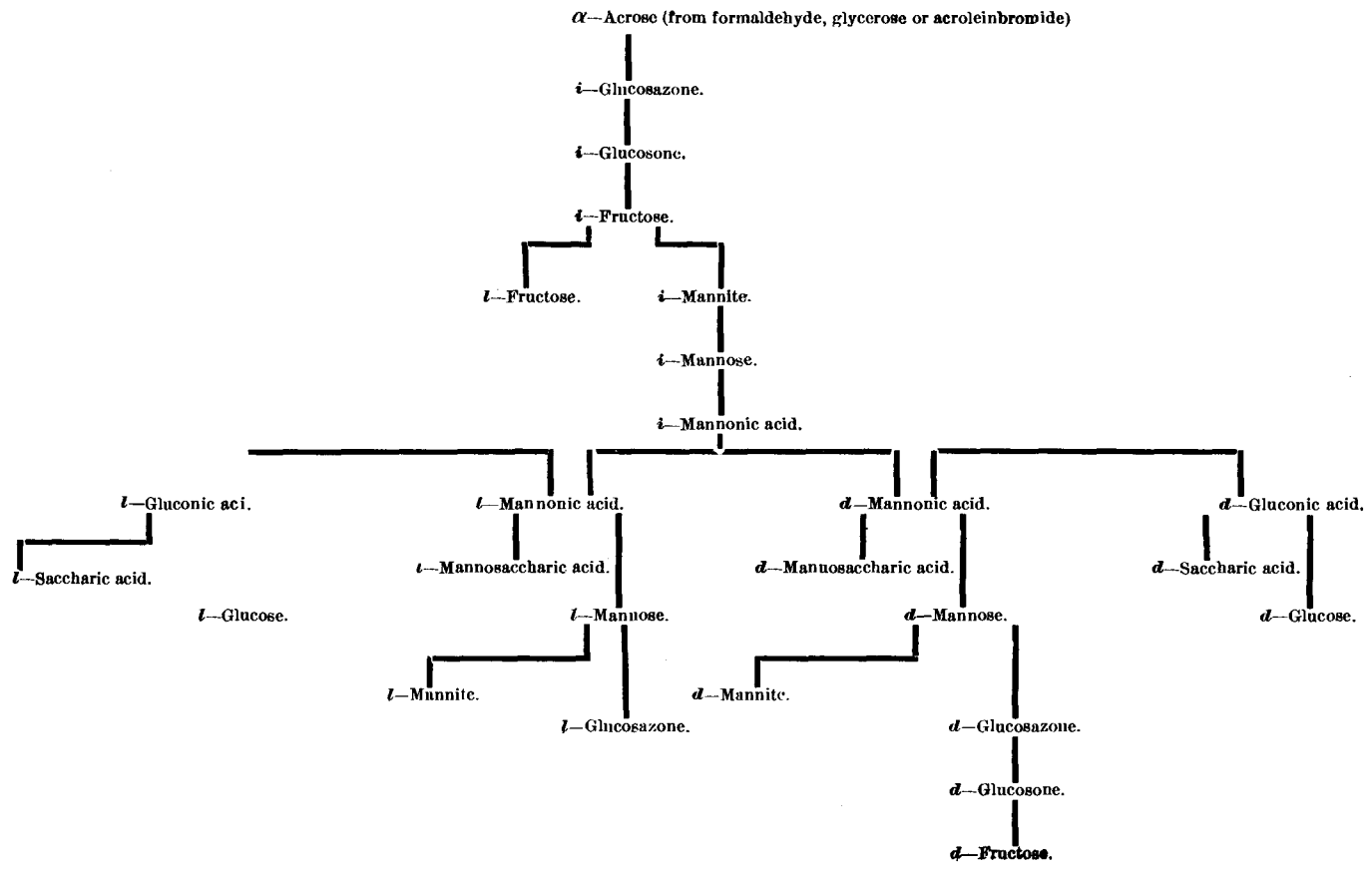
^{*}*Ber. d. chem. Ges.*, **23**, 799.

From l- and i-gluconic acids we obtain by reduction the optical isomeres of glucose (enumerated in the above table as l- and i-glucose) ; by oxidation l- and i-saccharic acids are formed.

Leaving the nitrogenized products aside, we now know no less than 26 bodies of the mannite series which may be subdivided into the fructose, mannose and glucose groups.

One might feel tempted to use this rich material as a touchstone for the consequences of Le Bel-van't Hoff theory. Let it suffice to say that all compounds fit into the general frame of this theory, but that, most likely, our views in regard to the union of isomeric substances with asymmetric carbon atoms has to be modified.

All members of the mannite series are joined by transitions, all of them are to be obtained by direct synthesis. The following table gives a systematic view of this latter, beginning with α -acrose.



Thus we are now enabled, starting from one of the simplest of carbon compounds, formaldehyde, to prepare the two most important natural sugars.

But upon the basis thus gained the synthesis leads further on to sugars containing a greater number of carbon atoms. Any one of the previously mentioned "oses" can be transformed into an acid, richer in one carbon atom, by aggregation of hydrocyanic acid. The lactone of any such acid, when treated with sodium amalgam, will be reduced to a corresponding sugar, and starting from this latter, the modus of building up a higher compound can be repeated in a similar manner.

In this way Passmore and myself have obtained from mannose a compound $C_6H_{18}O_9$, and thus far we are unable to see the limit of this mode of procedure.

The older nomenclature is not sufficing for the denotation of these numerous synthetical products. I have therefore proposed a new one¹, which temporarily meets the want.

The sugar is named according to the number of carbon atoms which it contains: Triose, tetrose, pentose, hexose, heptose, octose, nonose and the different isomeric products receive a prefix, indicating their derivation. This nomenclature seems to collide with² Scheibler's proposal to call sugars: $C_{12}H_{22}O_{11}$ (the so called saccharoses) bioses, and sugars: $C_{13}H_{24}O_{12}$ trioses. In reality the two proposals are easily combined in forming the words, hexobiose and hexotriose. For the general distinction of aldehyde and ketone sugars, Armstrong's names, aldose and ketose, seem well fitted.

The greatest hindrance to suitable names for the now known optically isomeric sugars is offered by the words heretofore in use, laevulose and dextrose. It will be good to drop them altogether in spite of the famous authorship of Berthelot and Kekulé. Instead of dextrose, the old name glucose may be used, and for laevulose I have used above the non-ambiguous name fructose, to which Liebermann drew my attention.

¹*Ber. d. chem. Ges.*, **23**, 934.

²*Ber. d. chem. Ges.*, **18**, 646.

The preferences of the new nomenclature are very obvious in the following table, which contains all now known simple sugars:

Trioses: Glycerose (mixture of glycerolaldehyde and dioxycetone).

Tetroses: Erythrose (most likely a mixture of aldose and ketose).

Pentoses: Arabinose (aldose).

Xylose.

Methylpentose: Rhamnose (aldose).

Hexoses: d-l-i. Glucose } (aldoses) } Mannite series.
 d-l-i. Mannose }
 d-l-i. Fructose (ketose) }

Galactose (aldose of dulcete series).

Sorbinose.

Formose } (unknown constitution).
 β -acrose }

Methylhexose: Rhamnohexose (aldose).

Heptoses: Mannoheptose,
 Glucoheptose,
 Galaheptose,
 Fructoheptose,
 Methylheptose: Rhamnoheptose } (aldoses).
 Octoses: Mannoctose,
 Glucoctose,
 Nonoses: Mannononose,

Glycerose and erythrose have been explicitly dealt with before. Amongst the pentoses we find arabinose and xylose⁹. The first is an aldehyde with normal carbon chain, and belongs to the l-mannose series. The constitution of the second is not yet determined. Rhamnose must be considered as a methylpentose with normal carbon chain.

The number of hexoses we find considerably increased. Grape sugar and fruit sugar are to be seen here as d-glucose and d-fructose; along with them we find their optical isomeres.

Galactose and sorbinose stand as isolated as formerly. Formose and β -acrose are too scantily investigated as to judge about their constitution. It appears unlikely that they should contain a normal carbon chain.

⁹ Wheeler and Tollen's *Ann. Chem. Pharm.*, 254, 304.

Rhamnohexose (methylhexose) has been prepared synthetically from rhamnose by aggregation of hydrocyanic acid. The same is true for the following heptoses, octoses and nonoses, the origin of which is expressed by the prefixes. Most of these products surpass in their capacity of crystallization, and in beauty the derivatives of natural hexoses.

The most interesting of them is the mannononose, *because it ferments with beer yeast as easily as glucose*. This property is wanting to the octoses, heptoses and pentoses, but we find it existing with most hexoses and with glycerose. Yeast, therefore, seems to incline to the number three and its multiples.

In comparing this table with the one first given, which represented the sugar group of a few years ago (Journ. Am. Chem. Soc., **12**, 340), we recognize the extent of the newly gained territory.

Many of these artificial sugars will certainly be found some day in plants. Indications exist, since the heptatomic alcohol, which is generated from mannoheptose by reduction is identical with *perseit*, occurring in the fruits of *Laurus Persea*, which, according to newer researches of Maquenne¹⁰ has the formula $C_7H_{16}O_7$. But these observations are only of secondary importance; they are a mere by-products of the new methods. The centre of interest is offered by the synthesis of grape sugar and fruit sugar, since it is suited to open the understanding of one of the grandest and most remarkable physiological processes, that of formation of carbohydrates in the green plant. As far as our knowledge reaches, grape and fruit sugar are the first products of assimilation, and they thus form the carbon-bearing material from which the plant prepares all other organic compounds. Up to this day practically nothing is known about the process of natural formation of sugar. All attempts of explanation are mere hypotheses, the value of which may be disputed. If in spite of this, I shall now mention one, this is only done in order to point out the path on which, perhaps, the results of my researches may be utilized for physiological experiments.

According to the view of Baeyer, carbon dioxide is reduced at first within green leaves to formaldehyde. This latter, then,

¹⁰ *Compt. Rend.*, **107**, 583; and *Ann. Chim. Phys.* [6], **19**, 1.

by condensation is transformed into sugar. Since heretofore it has not been possible to prove the existence of quantities of formaldehyde notable in some degree in leaves, it may perhaps be more proper to search for other intermediate products, particularly for glycerose, according to the now known methods.

And even of more interest seems this other question : chemical synthesis leads, as we have seen above, starting from formaldehyde, in the first place to optically *inactive* acrose. In contrast to this we have found in plants heretofore exclusively the *active* sugars of the d-mannite series. Are these the only products of assimilation? Is it a prerogative of the living organism to prepare optically active substances. Is here a particular cause active, a sort of vital force? I do not believe it, but incline towards the view that it is merely the imperfection of our knowledge which surrounds this process with the halo of a miracle.

Not one known fact exists, to directly deny that the plant at first prepares *inactive* sugars, just as chemical synthesis does, that then it splits these using the members of the d-mannite series to build up starch, cellulose, inuline, etc., etc., while the optical isomeres serve other purposes, still unknown to us.

This question will soon be answered by a closer study of the sugars occurring in plants, since the methods given facilitate this work greatly.

These considerations have brought us to the territory of limits between chemistry and physiology and thus I will touch another problem, the experimental treatment of which lies nearer to the biologist than to the chemist.

The natural carbohydrates next to the albuminoids are the most important food for the animal, particularly for herbivora, and we possess a great number of valuable observations in regard to the fate of these in the body of the animal.

May it not be possible to replace these natural carbohydrates entirely or partly by some of the artificial sugars and what then would be the consequence?

Mannose, standing so near to grape sugar and so easily fermentable by yeast, will be most likely, even for the higher organized animal a food ; and still this small change of material may cause corresponding changes in physiological processes.

After partaking of mannose will a new glycogen be produced by the liver, will a substitute for milk sugar be formed by the mammary gland, will the system of the diabetic be able to oxidize this sugar?

In offering as a food to the animal body a pentose, heptose or even the easily fermentable nonose, the physiological changes would become still more visible. We would find that the blood and the tissues were modified in their functions, the pig or the goose would produce another fat, the bee another wax.

This experiment should even be carried further.

The assimilating plant builds up from sugar not only the more complicated carbohydrates and the fats, but also with the auxiliary inorganic nitrogen compounds, the albuminoids. The mold and splitting organisms do this likewise.

Now, in nourishing the assimilating plant or those organisms by means of a differently composed sugar, they might be forced to even produce a different albumen. And then should we not expect that the change in building material would have as a consequence a change of architecture? Thus a chemical influence upon the formation of an organism would be gained, which would lead to most peculiar phenomena: to changes of form which would leave behind them everything heretofore attained by breeding and cross breeding.

Since the fundamental work done by Wöhler and Frerichs¹¹ hundreds of organic compounds have been incorporated into the animal body, in order to trace (often in the most tedious manner) their products of decomposition in the urine. But physiological chemists have used almost exclusively material of not the slightest similarity with natural food.

A wide field of work is opened to them in the use of these new sugars, the results of such work promises, by far, more remarkable results.

Biology stands here before a question which, as far as I know, was never put before and could not very well be put, since chemistry had not furnished the material for the experiment.

The question is worthy of the experimental test.

¹¹*Ann. Chem. (Liebig)*, **65**, 335.

For the chemist proper enough work remains to be done with the carbohydrates. The mannite group, it is true, is completely built up as few other chapters of organic chemistry are, but in the dulcite series the old state of affairs prevails.

Supposing this group should in the very nearest time be opened as perfectly as its isomeric group, we would, nevertheless, know only eight hexoses of the structure of grape sugar, not counting the inactive compounds which allow of splitting.

But modern theory anticipates no less than sixteen, and it is very likely, according to experience in the mannite series, that they are all able to exist.

It is even not too much to foretell that the preparation, according to the methods described, will not be over difficult, as soon as it is possible to transform the different tartaric acids into the optically isomeric trioxybutyric acids.

A problem of a different nature is put to synthesis by the example of the plant, which, starting from hexoses, produces in an apparently simple manner the more complicated carbohydrates. The beginning has already been made by the preparation of dextrin and of artificial dextrans; thus the chemical synthesis of starch, cellulose, inuline, gum, etc., is only a question of time.

It seems to me that organic synthesis which, thanks to the splendid methods which we inherited from the old masters, has, within the short period of sixty-two years, furnished: urea, the fats, many acids, bases and colors of the vegetable class, finally uric acid and sugars, need not shrink before any product of the living organism.