

In this experiment approximately equal amounts of chloride and pyridine were used, without precautions in regard to cooling. As the time of existence of color seemed to increase from benzene to xylene, mesitylene and cymene were used to ascertain whether the progression would continue. This is seen not to be the case.

The addition of various organic bases to the colored solution gave colorless precipitates, some possessing sharp melting-points. Lack of time alone has prevented the investigation of these compounds, which, it is hoped, will be continued this year.

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### ON FISCHER'S CLASSIFICATION OF STEREO-ISOMERS.<sup>1</sup>

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FISCHER divides optically active substances into two enantiomorphous families. For example, ordinary glucose and levulose (fructose) are classed as members of one family because of their intimate genetic relationship; the two antipodal substances are classed together as members of the opposite family because of a similar relationship. The chemical relationships are indicated by the letters *d* and *l* prefixed to the names of compounds. Thus, ordinary glucose and its corresponding fructose (levulose) are designated, respectively, *d*-glucose and *d*-fructose, notwithstanding the levo-rotation of the latter.

The substances so correlated include, as yet, only the monosaccharides and their derivatives. In other cases the symbols *d* and *l* denote dextro- and levo-rotation. The reform proposed in the following pages, and the importance of avoiding possible confusion, will justify my employing in this paper the Greek  $\delta$  and  $\lambda$  as family-symbols in place of the customary but misleading *d* and *l*.<sup>2</sup>

The great value of Fischer's classification to systematic stereochemistry is self-evident. The subdivision, however, as established by him in the celebrated memoirs<sup>3</sup> on the configuration of the

<sup>1</sup> Presented before the New York Section of the American Chemical Society on November 10, 1905.

<sup>2</sup> In cases in which misunderstanding is possible, it would be well to prefix the rotation-symbols  $\div$  or  $\ominus$  to the family-symbols, designating ordinary levulose, for instance,  $\ominus\delta$ -fructose. [On the symbols *d* or *l* might be used, these *l*- $\delta$ -fructose. *Editor.*]

<sup>3</sup> Ber. 24, 1836 and 2683 (1891); *Ibid.* 27, 382 and 3208 (1894); etc.

monosaccharides, is inconsistent. Thus, ordinary xylose, which is placed in the  $\lambda$ -family, changes, not into a  $\lambda$ -lyxose, as might be expected, but into the lyxose placed in the  $\delta$ -family.

The chaos that such inconsistencies are liable to produce is well illustrated by a controversy that ensued some three years ago, when Salkowski and Neuberg<sup>1</sup> succeeded in transforming  $\delta$ -glucuronic acid biochemically into  $\lambda$ -xylose, and interpreted the reaction as the first-known direct transformation of a compound of the  $\delta$ -family into one of the  $\lambda$ -family. Some  $\delta$ -compounds are intimately associated in nature with  $\lambda$ -compounds, and such transformations would show them to be actually biochemical relatives, even though according to Fischer's classification there is no relationship between them and their associated occurrence in nature is apparently accidental. It may be said, however, as Wohl pointed out, that natural xylose was classed by Fischer among the  $\lambda$ -compounds because its genetic relationship to  $\lambda$ -gulose happened to have been discovered before its formation from  $\delta$ -lyxose was known: had accident (!) reversed the order of discovery, the xylose would have taken a place among the sugars of the  $\delta$ -family.<sup>2</sup> Whatever, then, the possibilities of Salkowski and Neuberg's method as such, the theoretical value of the transformation actually effected appeared capable of two very different, yet equally justifiable, estimates. In the same connection, Fischer's classification was examined by W. Küster,<sup>3</sup> who arrived at the conclusion that the designation of natural xylose as a relative of the artificial  $\lambda$ -glucose is entirely conventional, arbitrary, and that a perfectly consistent classification of the sugars and their derivatives is impossible. Again, the impossibility of a consistent classification is asserted by Salkowski and Neuberg in their reply to Küster's criticism.<sup>4</sup>

A careful re-examination of the subject has led me to a different view, and I propose to show in the present paper that while Fischer's subdivision is partially based on a faulty principle and is, consequently, faulty in a number of cases, the errors are readily corrected, and the result is a system of stereochemical classification entirely free from self-contradiction.

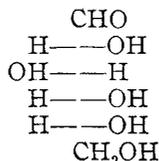
<sup>1</sup> Z. physiol. Chem. 36, 261 (1902).

<sup>2</sup> See E. O. von Lippmann: "Die Chemie der Zuckerarten," 3d ed. (1904), pp. 366 and 1714.

<sup>3</sup> Z. physiol. Chem. 37, 221 (1903).

<sup>4</sup> Ibid. 37, 464 (1903).

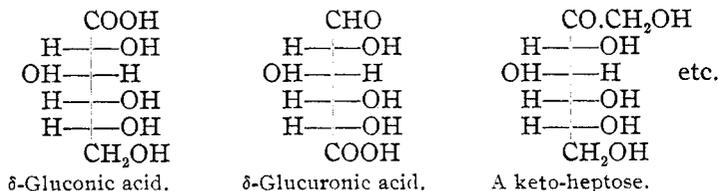
But first of all, in the interest of economy of space, I will take the liberty of employing here a stereochemical notation which seems to me more concise and transparent than any hitherto proposed.<sup>1</sup> Ordinary glucose, for instance, whose projection-formula, as simplified by Victor Meyer, is



will be represented by the symbol



and the same symbol will stand for all other compounds with different terminal groups and stereochemically similar to glucose, such as



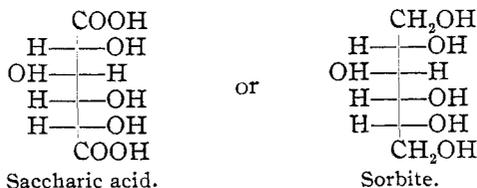
Similarly, compounds like fructose, arabinose, etc., will be represented by the symbol



On the other hand, symbols like



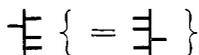
for



<sup>1</sup> Compare Lespieau and Maquenne's notation; Lespieau: Bull. soc. chim. [3] 13, 105 (1895), and L. Maquenne: Les Sucres et leurs principaux dérivés, Paris, 1900.

will represent compounds whose molecules consist of two chemically similar halves.

Fischer blends the assignment of each compound to the  $\delta$ - or the  $\lambda$ -family with the assignment of a single stereochemical formula to the compound. Thus, after on the one hand choosing the formula



to represent the dextro-rotatory saccharic acid and choosing this acid for founding the  $\delta$ -family, and after, on the other hand, showing that corresponding to the two glucoses and the two guloses are the two pairs of enantiomorphous formulas:



he concludes that the glucose yielding that saccharic acid and the gulose derived from the same acid should be represented, respectively, by formulas I and III and belong to the same stereochemical family, viz., the  $\delta$ -family.

In the latter part of Fischer's conclusion is the fundamental error. While the assignment of formulas is entirely correct, that latter part of the conclusion is based on an assumption that may be formulated as follows: Two aldoses can produce the same dibasic acid only if they belong to the same stereochemical family. That this, however, is erroneous as a general proposition, may be readily seen from the fact that the two enantiomorphous galactoses—plainly belonging to the opposite families—yield the same mucic acid. Similar cases are presented by the pairs of enantiomorphous aldoses yielding allomucic, xylotrioxyglutaric, ribotrixyglutaric, and mesotartaric acids. True, all these acids are optically inactive by intramolecular compensation. But their example is sufficient warning that *the testimony of a symmetrically constituted compound, whether active or inactive, cannot be relied upon to prove the stereochemical family-relationship of two compounds with dissimilar end-groups.*

Fischer's simultaneous assignment of single formula to aldose and of aldose to family are based mainly on the following forms of relationship: I, genetic relationship, as just seen, of two sugars

to the same dicarboxylic acid; 2, transformation of two sugars into the same osazone; 3, mutual transmutability of two sugars through their corresponding aldonic acids; 4, transformation of a sugar with  $n$  into one with  $n+1$  asymmetric carbon atoms by Kiliani's method; 5, transformation of a sugar with  $n$  into one with  $n-1$  asymmetric carbon atoms by Wohl's method (or the more recent method of Ruff). Now, accepting Fischer's assignment of formulas, and discarding, for the reason just stated, the first of these relationships, the formulas themselves (and hence the sugars labeled by them) may be grouped into two enantiomorphous families as shown in the accompanying table, which embodies practically all the known chemical relationships. Couples of aldoses like 10 and 11, 4 and 5, 2 and 3, are obviously  $\alpha$ -isomeric: the members of each couple are mutually transformable through their aldonic acids, yield the same osazones, are derived from the same simpler aldoses (*e. g.*, 10 and 11 from 5) by the cyanhydrin reaction, yield the same simpler aldoses by Wohl's or Ruff's method, yield the same ketoses, etc.

The table represents, not the monosaccharides alone, but, in general, any system of stereochemical molecules (with dissimilar halves) uniformly built up from a pair of enantiomorphous molecules with single asymmetric carbon atoms.<sup>1</sup> It must, however, be observed that the same arrangement would result if instead of starting from the simplest pair of enantiomorphous

<sup>1</sup> The formulas to the right of the dividing line (the  $\delta$ -family) all have the hydroxyl of the basal asymmetric carbon atom turned to the right. This is in accordance with the fact that if the corresponding compounds were all

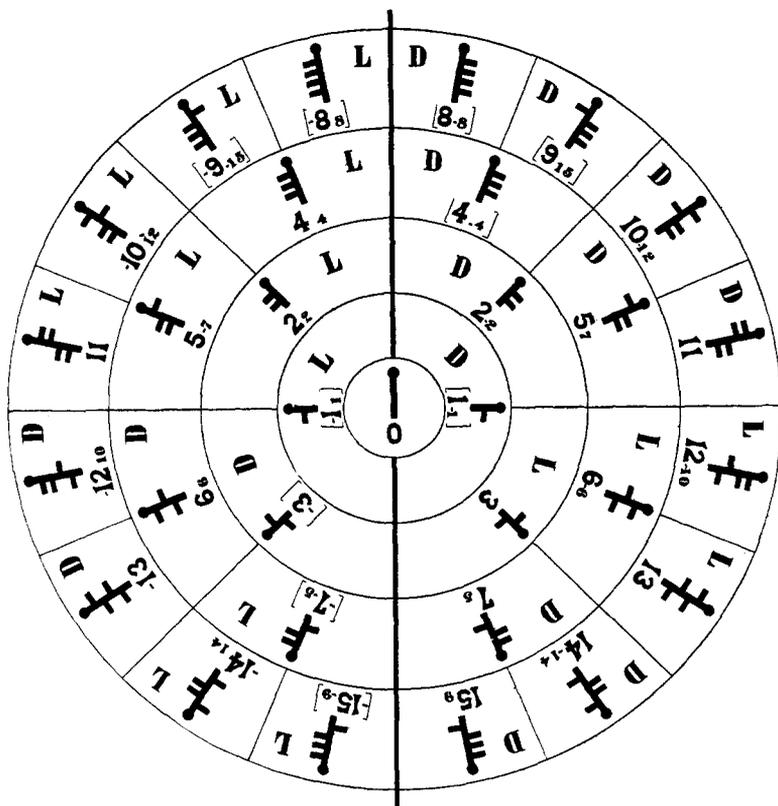
actually built up by Kiliani's method from  $\delta$ -glycerose,  $\begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array}$ , the HCOH group of the latter would go to form part of the more complex molecules without suffering a change of configuration:  $\begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array} \rightarrow \begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array}$  and  $\begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array}$ , etc. In the  $\lambda$ -family the hydroxyl in question is of course invariably turned to the left.

Every sugar marked in the table by an even number (2, 4, -6, etc.) must yield the same dibasic acid and the same alcohol as one of the sugars of the opposite family, because in all even-numbered sugars the hydroxyls of the first and last asymmetric carbon atoms are turned in the same direction. This may be illustrated by an instance. The acid  $\begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array}$  is derivable

from the sugars  $\begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array} = \begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array}$  and  $\begin{array}{c} \bullet \\ | \\ \text{---} \\ | \\ \bullet \end{array}$  (-14 and 14), but these sugars belong to

the opposite families, as shown by their basal hydroxyls being turned in the opposite directions.

CLASSIFICATION OF STEREOISOMERS.

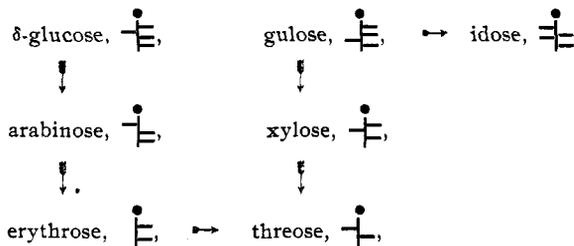


Acids.	Sugars.	Alcohols.
0. Oxalic.	0. Glycolose; dioxyacetone.	0. Ethyleneglycol.
1,-1. Tartronic.	1. Glycerose; erythrulose.	1,-1. Glycerol.
2,-2. Mesotartaric.	2. Erythrose; araboketose.	2,-2. Mesoerythrite.
3. Tartaric.	3. Threose; xyloketose.	3. Erythrite.
4,-4. Ribtrioxyglutaric.	4. Ribose.	4,-4. Adonite
5,7. Trioxyglutaric.	5. Arabinose; fructose.	5,7. Arabite.
6,-6. Xylotrioxylglutaric.	6. Xylose; sorbinose.	6,-6. Xylite.
7,5. =5,7.	7. Lyxose; tagatose.	7,5. =5,7.
8,-8. Allomucic	8. Allose.	8,-8. ....
9,15. Talomucic.	9. ?	9,15. Talite
10,-12. + Saccharic.	10. Glucose.	10,-12. —Sorbite.
11. Mannosaccharic.	11. Mannose	11. Mannite.
12,-10. —Saccharic.	12. Gulose.	12,-10. + Sorbite.
13. Idosaccharic.	13. Idose.	13. Idite.
14,-14. Mucic.	14 Galactose.	14,-14. Dulcite.
15,9. =9,15.	15. Talose.	15,9. =9,15.



compounds we started from two enantiomorphous pairs of  $\alpha$ -isomeric compounds with two asymmetric carbon atoms (2,3 and  $-2, -3$ ). In other words, the fact that the glyceroses have not yet been isolated and correlated with the more complex sugars cannot affect the classification: the known aldotetroses lead to the same result.

The *D*'s and *L*'s in the table exhibit Fischer's classification, and it is seen at a glance that the principle whose unreliability was pointed out above has led to error in the case of the guloses, their  $\alpha$ -isomeric idoses, their kindred xyloses and threoses<sup>1</sup> (12,  $-12$ , 13,  $-13$ , 6,  $-6$ , and 3,  $-3$ , respectively), and all the corresponding aldonic acids, as well as in the case of the sorbinoses (6,  $-6$ ), the xyloketoses (3,  $-3$ ), and other derivatives of unsymmetric structure. Thus natural xylose, whose designation as a  $\lambda$ -compound would mark it as a relative of  $\lambda$ -glucose, is really a  $\delta$ -compound, *i. e.*, a relative of natural  $\delta$ -glucose; and the same is true of its kindred gulose, idose, threose, etc. The set of relationships in question are as follows:



Conversely, the antipodal xylose, gulose, idose, threose, etc., are seen to be really relatives of the artificial  $\lambda$ -glucose. Plainly, a change in the designation of all such compounds will definitely eliminate a number of current misapprehensions, which partially defeat the very object of the classification. At all events, the transformation effected by Salkowski and Neuberg, important as it certainly is from a physiological point of view, does not by any means constitute a transformation of a  $\delta$ -compound into a  $\lambda$ -compound, although it does point clearly to a biochemical relationship between  $\delta$ -galactose and  $\lambda$ -arabinose.

The numbers marking the formulas in the table<sup>2</sup> indicate the derivation of dicarboxylic acids and polyatomic alcohols from

<sup>1</sup> Ruff (with Kohn); Ber. 34, 1370 (1901).

<sup>2</sup> Brackets mark *aldoses* that have not yet been isolated.

the aldoses. Thus aldose 11 ( $\delta$ -mannose) leads to an acid and an alcohol not derivable from any other aldose. The designation 5<sub>7</sub> shows that two different aldoses, 5 and 7, the lyxose and arabinose of the same  $\delta$ -family, yield the same (active) acid and alcohol. The designation 14<sub>-14</sub> shows that the two enantiomorphous galactoses, 14 and  $-14$ , yield the same (hence optically inactive) acid and alcohol. Finally, the designation 10<sub>-12</sub> indicates that two aldoses belonging to the opposite families yield the same saccharic acid and sorbite; the aldoses not being enantiomorphous, the acid and alcohol must obviously be optically active. The antipodal acid and alcohol are derived from the aldoses  $-12$  and 10, as indicated by the designation  $-12_{10}$ . How are such optically active compounds of mixed genealogy—say, ordinary dextro-rotatory saccharic acid—to be designated?<sup>1</sup> The combined symbol  $\delta$ - $\lambda$  might be misleading, since the symbol *d-l* has frequently been used in connection with racemic mixtures. The best way would probably be to denote the sense of the rotatory power by the signs + and — and to remind that the compounds belong to either of the families by the prefix *amphi*. Thus we would have +amphi-saccharic acid and —amphi-saccharic acid, —amphi-sorbite and +amphi-sorbite. A glance at the table shows that the cases in question are *the only ones* in which an active acid and alcohol are derived from two non-enantiomorphous sugars of opposite families. It is easy to foresee, however, that a number of similar cases will be encountered among the mono-saccharides with more than four asymmetric carbon atoms.

An important point to note in connection with our subject is that the rectification of the genealogy of the threoses leads directly to a similar rectification in the case of the active tartaric acids, in view of the immediate derivation of these, as well as of the active erythrites, from the threoses.<sup>2</sup> Ordinary tartaric acid,



which is generally believed to be a relative of ordinary  $\delta$ -glucose, really belongs to the family of  $\lambda$ -glucose and should be designated  $\lambda$ -tartaric acid. The direct oxidation which produces ordinary

<sup>1</sup> An independent classification of compounds of symmetrical structure is impossible.

<sup>2</sup> Ruff: Ber. 32, 3677 (1899); Maquenne and Bertrand: C. R. 132, 149 (1901).

tartaric acid from  $\delta$ -glucose is scarcely a more reliable criterion than would be a process of destructive distillation. In the same family with 10, *i. e.*,  $\delta$ -glucose, are the acids of 2<sub>-2</sub> and 3, *i. e.*, mesotartaric and levo-rotatory tartaric acids, and it is the latter, therefore, that should be designated  $\delta$ -tartaric acid. Similar changes are obviously required in the case of the active erythrites.

Neuberg and Silbermann have recently<sup>1</sup> transformed, by simple reactions, the aldehyde-glyceric acid,  $\text{CHO}.\text{CHOH}.\text{CO}_2\text{H}$ , produced by the action of caustic soda on nitrocellulose,<sup>2</sup> on the one hand into a mixture of levo-rotatory tartaric and mesotartaric acids, on the other hand into levo-rotatory glyceric acid. Levo-rotatory tartaric acid being, according to Fischer, tartaric acid, Neuberg and Silbermann now designate its other relative, levo-rotatory glyceric acid, among the  $\lambda$ -compounds. "Attention," say the authors, "may especially be called to the *peculiar* circumstance that starting from cellulose, indisputably a derivative of *d*-glucose, one thus passes, by way of nitrocellulose, aldehyde-glyceric acid, and *l*-glyceric acid, from the *d*-family of the carbohydrates into the *l*-family." From what has been said above it is plain that levo-rotatory glyceric acid, being a relative of levo-rotatory tartaric acid, belongs within the same stereochemical family as  $\delta$ -glucose (and, presumably, cellulose), and should be designated  $\delta$ -glyceric acid, so that the series of changes in question are neither a transformation of  $\delta$ -compounds into  $\lambda$ -compounds, nor in any way "peculiar." The aldehyde-glyceric (glyceruronic ?) acid, too, must be considered as a member of the  $\delta$ -family, and the same applies to the natural malic and aspartic acids and asparagine, in view of their well-known relationship to levo-rotatory tartaric acid.

I cannot conclude without cordially thanking Professor Morris Loeb, the head of this department, for much valuable help in connection with the present paper.

<sup>1</sup> Z. physiol. Chem. 44, 134 (1905).

<sup>2</sup> Will: Ber. 24, 400 (1891).