

EMIL FISCHER'S WORK ON THE CHEMISTRY OF HEXOSES

BY

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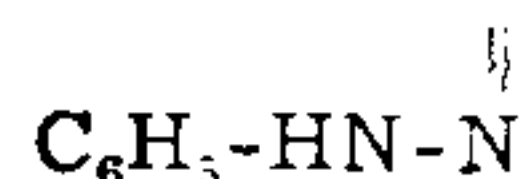
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THIS is a very brief note on Emil Fischer's work on the hexoses; it is just 50 years ago that Emil Fischer published his first paper on the structure of hexoses.

Upto the year 1880, our knowledge of the sugar group was very meagre and consisted of a chaos of isolated facts. Zincke (1876) assigned the ketonic structure to glucose ($\text{CH}_2\text{OH}-\text{CHOH}-\text{CHOH}-\text{CHOH}-\text{CO}-\text{CH}_2\text{OH}$) and fructose ($\text{CH}_2\text{OH}-\text{CHOH}-\text{CHOH}-\text{CO}-\text{CHOH}-\text{CH}_2\text{OH}$), but Kiliani (1886) corrected this view by the application of cyanohydrin reaction and represented these compounds thus: Glucose— $\text{C}^6\text{H}_2\text{OH}-\text{C}^5\text{HOH}-\text{C}^4\text{HOH}-\text{C}^3\text{HOH}-\text{C}^2\text{HOH}-\text{C}^1\text{HO}$. Fructose— $\text{CH}_2\text{OH}-\text{CHOH}-\text{CHOH}-\text{CHOH}-\text{CO}-\text{CH}_2\text{OH}$.

Kiliani was also responsible for showing arabinose to be a pentose (1886) and galactose (1885) to be a straight chain pentahydroxyaldehyde, isomeric with glucose. But Kiliani's success was short lived: he could not follow it up in view of the almost insurmountable experimental difficulties; sugars crystallise with difficulty even when pure; when other substances are present, the task of isolating a sugar from the mixture is hopeless. Such was in brief the state of sugar chemistry when Emil Fischer started his researches on hexoses in 1887, and brought them to a successful conclusion within less than a decade. There were three factors which contributed to the remarkable achievements of Fischer in this extremely difficult field of work. Firstly he possessed in himself rare skill, patience and insight which are seldom combined in one individual. The second factor which ensured his success was the doctrine of the asymmetric carbon atom propounded by Van't Hoff and Le Bel in 1874. Fischer made it the theoretical basis and the guiding principle in these astonishingly successful researches which in turn vindicated the truth of the new doctrine of molecular configuration. The third factor which assisted this experimental skill and theoreti-

cal insight was his discovery of phenylhydrazine in 1875. This substance acted as a magician's wand in Fischer's hands. Fischer found that hexoses first react with one molecule of phenylhydrazine to give a phenylhydrazone which is usually soluble and escapes detection, but with an excess of the base (2 molecules), the hydrozone is converted into an osazone: $\text{C}^6\text{H}_2\text{OH}-\text{C}^5\text{HOH}-\text{C}^4\text{HOH}-\text{C}^3\text{HOH}-\text{C}^2-\text{C}^1\text{H}=\text{N}-\text{NHC}_6\text{H}_5$. The



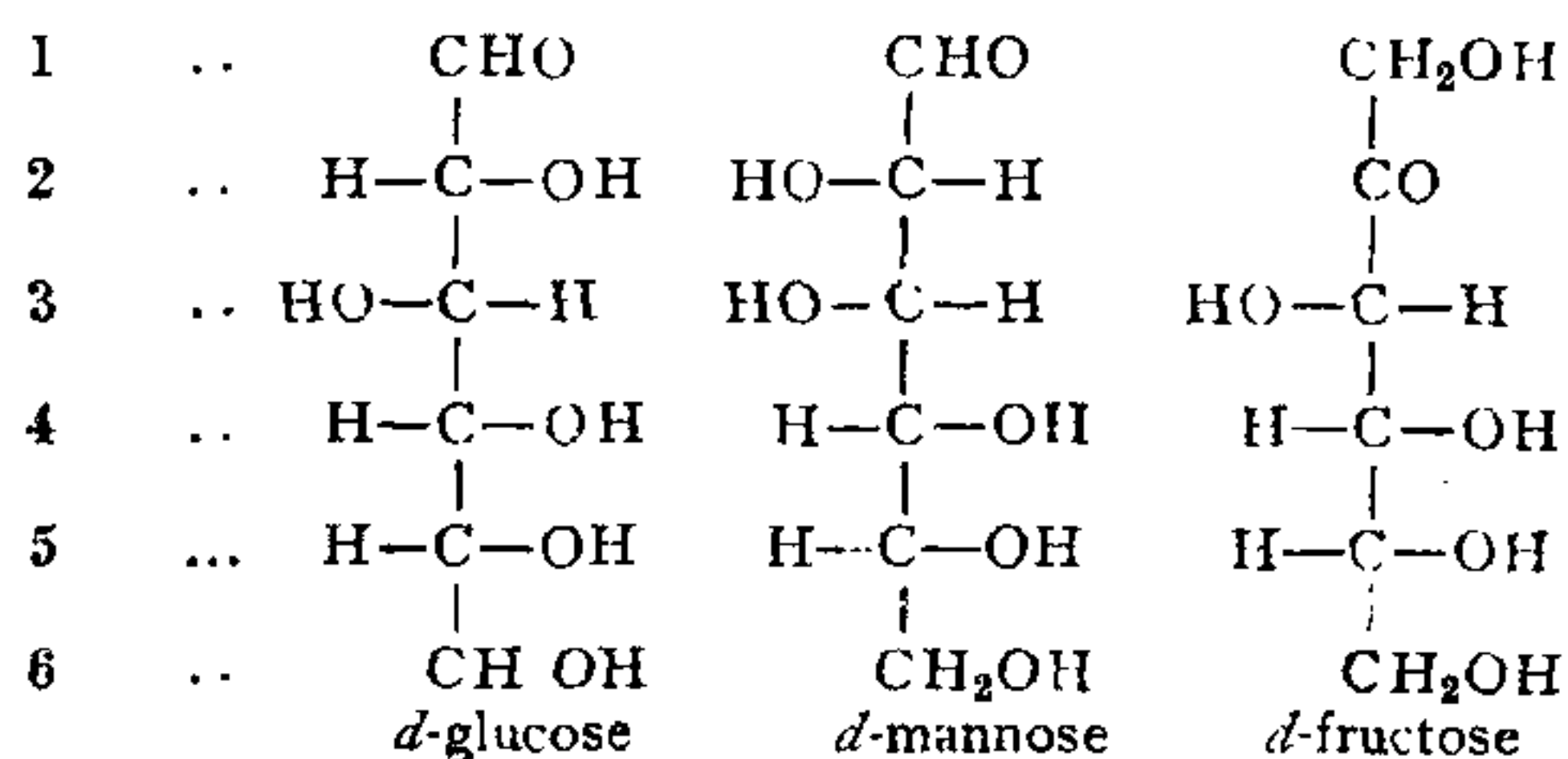
osazones, being insoluble in water and easily crystallisable from organic solvents, were thus found by Fischer to be very suitable for detecting and identifying sugars by their melting points. Fischer (1887) further found that several sugars give identical osazones, namely, glucose, mannose, and fructose give one and the same derivative (glucosazone). The osazones on hydrolysis and subsequent reduction yield ketoses. The Kiliani structural formula of glucose contains 4 asymmetric carbon atoms, numbered 2, 3, 4 and 5 and this formula according to Van't Hoff and Le Bel theory, should exist in 16 optically active forms in 8 opposite pairs. Sugars producing the same osazone thus had identical structure on all but the first two carbon atoms, numbered 1 and 2.

Another even more important application of osazones was in the complete synthesis of glucose, fructose and mannose in their enantiomorphous forms. Starting from α -acrose (*dl.* fructose) which he had obtained separately from formaldehyde, acrolein dibromide and glycerose, Fischer was able to achieve the synthesis of the above-mentioned sugars by a series of difficult operations, which consisted in resolving the sugars and the corresponding acids into their enantiomorphous forms by Pasteur's methods, reducing the sugar acids (lactones) into the corresponding sugars in acid solution, transforming a sugar acid into

an isomeric one by heating it at 140° C. with pyridine or quinoline by means of an epimeric change, in which the configuration of the carbon atom adjacent to the carboxyl group becomes inverted. This enabled Fischer (1889 and 1890) to produce *l*-glucose, *d*-talose, and *d*-idose through *l*-mannonic, *d*-galactonic, and *d*-gulonic acids respectively.

No less than 16 isomeric aldohexoses are possible which possess the structural formula of a straight chain pentahydroxyaldehyde,

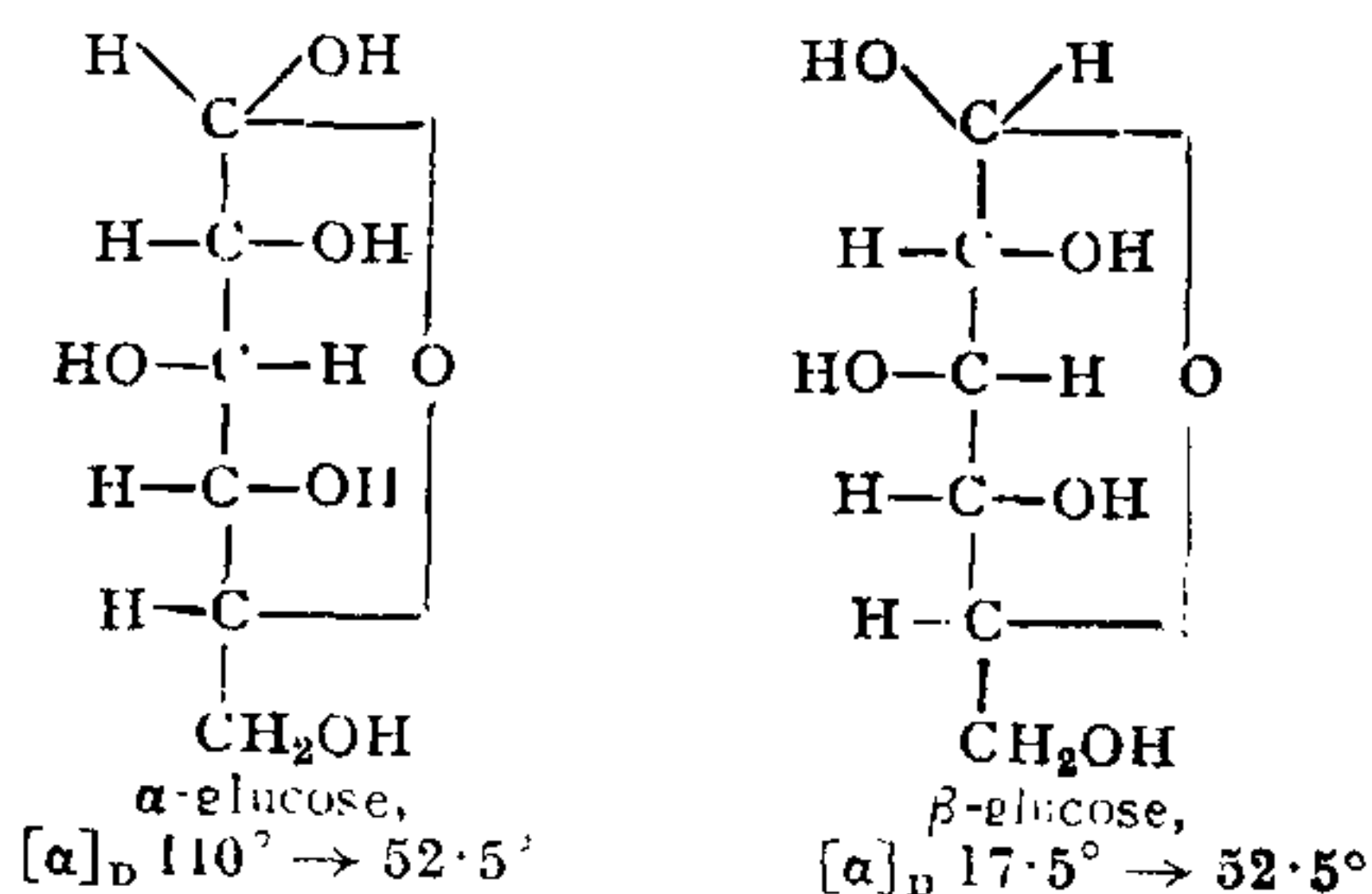
$\text{CH}_2\text{OH}\cdot\text{CHOH}\cdot\text{CHOH}\cdot\text{CHOH}\cdot\text{CHOH}\cdot\text{CHO}$. The principles which Fischer employed in elucidating the space configurations of the hexoses were dependent on the identity of the osazones of the different sugars, the oxidation of sugars to *meso* acids or reduction to *meso* alcohols, methods for building up or degrading sugars and transformations of sugar acids into their isomers by epimeric changes. Thus the projection formulæ of glucose, mannose and fructose obtained in this way are given below by way of illustration:



By the application of these methods and reasonings, Fischer synthesised and configured twelve out of the sixteen theoretically possible aldohexoses, and since then the remaining two pairs (allose and altrose) have been configured by Levene and Jacobs (1910).

This account of the chemistry of hexoses, illustrating as it does a remarkable combination of theory and practice, will be incomplete without reference to another advance which has proved highly fruitful in the whole domain of carbohydrates. In the foregoing account the aldehyde structure

of the sugars has been assumed. That sugars and their derivatives possess oxide ring structures was established by unequivocal evidence. From an assumed analogy with γ -lactones, Fischer assigned the butylene or 1:4 oxide ring to α - and β -methylglucosides and the parent sugars, but this structure was subsequently corrected by the work of Haworth (1925) which gives the pyranose formulation:



His discovery of γ -methyl-glucoside in 1914 led to the recognition of a different cyclic structure from that given in the foregoing formulation and laid the foundation of work associated with Purdie and the St. Andrews School. Just as phenylhydrazine had proved a valuable weapon in the hands of Fischer, this new development was made possible by the discovery of another weapon in the 'methylation process', and led to the recognition of five different oxide rings for *d*-glucose, giving ten isomerides of *d*-glucose, excluding the aldehyde form.

The evolution of a single straight chain pentahydroxyaldehyde formula into 16 optically active configurations and their subsequent possible expansion into 160 isomeric formulæ, having five different oxide ring structures, furnishes a most remarkable development of molecular structure and molecular configuration, based on the theoretical speculations of Kekule, Van't Hoff and Le Bel.

There is thus no doubt that this later development by Fischer will continue to inspire the prosecution of research in this field by several generations of chemists.