Tetrahedron. Vol. 30, pp. 1499 to 1501. Pergamon Press 1974. Printed in Great Britain

STUDIES OF THE STRUCTURE OF TARTARIC ACID BEFORE 1874

M. J. T. ROBINSON*

The Dyson Perrins Laboratory, University of Oxford, England

(*Received in the UK* 8 *February* 1934)

The early history of tartaric[1,2] acid is representative of almost all aspects of the history of organic chemistry in the century prior to van't Hoff's and Le Bel's great papers on stereochemistry. This brief account of the tartaric acids in intended to show, using a single set of stereoisomers as illustrations, how the methods of isolation and characterisation of compounds, the determination of functional groups, and the concepts of chemical structure, developed with increasing rapidity and culminated in the elucidation of the structural origins of stereoisomerism.

Although tartar (potassium hydrogen tartrate), readily available from the fermentation of grape juice, is one of the few pure organic compounds known since antiquity, there appear to be no early records of its conversion into other organic compounds, even other salts of tartaric acid during two millenia. In the seventeenth century tartar was converted into other salts, including sodium potassium tartrate (Rochelle salt). This was prepared from tartar and 'natron' (impure sodium carbbonate), substances readily available for at least two thousand years, by Elie Seignette, son of an apothecary of La Rochelle. The process remained a profitable family secret for many years and was rediscovered and published by Boulduc (1731).

The beginning of rapid progress in organic chemistry in general and the study of tartaric acid in particular began in 1770 when Retzius published Scheele's isolation of tartaric acid. Although Pott (1757) had obtained crude tartaric acid from tartar and sulphuric acid, and Cavendish (at an uncertain date before 1770) had independently used but not published a method almost identical to Scheele's, the credit for the discovery rightly belongs to Scheele. He dramatically changed the whole approach to the isolation of involatile organic compounds by developing a *general* and *rational* method for the isolation of organic acids *via* sparingly soluble calcium or lead salts, applying it to tartaric acid in the first instance. This convenient source of the new organic acid led (a) to extensive studies of its chemistry, notably its salts and double salts (Berthollet, 1776), some of which became very important later, (b) to the development of the use of charcoal in the purification of discoloured organic compounds, tartaric acid being the first example (Lavitz, 1786), and (c) to the industrial production of tartaric acid for use in medicine and the textile industry.

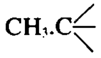
As a result of the large scale production of ordinary tartaric acid Kestner (1818) noticed crystals of the previously unrecognised racemic tartaric acid amidst the ordinary acid. The new acid was at first mistaken for oxalic acid but its similarity to ordinary tartaric acid was recognized by Gay Lussac (1826), who coined the name 'racemic' which much later came to be used as an adjective for all racemic compounds.

The recognition of the close relationship of the two acids was the result of new techniques, notably combustion analysis, which demonstrated the identity of composition of the acids and corresponding derivatives, apart from water of crystallisation in some cases, while polarimetry brought out the most distinctive, albeit subtle, difference, the optical activity of the ordinary dextrorotatory (+)-acid and the inactivity of the new racemic acid (Biot, 1832). The pair of acids was an important early example of isomerism, a word introduced by Berzelius (1830), who concluded after a careful comparison that the two acids were chemically identical. In seeking for the origin of the subtle physical differences between the acids Berzelius in 1830 asked Mitscherlich, the discoverer of isomorphism and a very experienced crystallographer, to investigate the acids and their salts crystallographically, including the double sodium ammonium salts. Although Mitscherlich soon obtained interesting results he became so puzzled that publication was delayed until 1842, by which time de la Provostaye (1841) had published an independent and very detailed study. Most of the corresponding salts of the two acids were crystallographically similar but readily distinguishable. The sodium ammonium salts, however, were apparently *identical* (apart from optical activity), although the original acids could be recovered unchanged from the salts.

Pasteur began his work on tartaric acid in 1848 and soon met with spectacular success, largely a result of an unusual breadth of interests and an ability to combine evidence from very varied sources. He combined an obscure report that ordinary, (+)-tartrate salt crystals show hemihedral faces (Hankel, 1843; Pasteur refers to this in his notebooks but never again), an observation missed by Mitscherlich and by de la Provostaye, with Herschel's neglected correlation of the handedness of quartz crystals with the sign of their optical rotation (1820). In addition Pasteur was convinced that hemihedral faces were not accidental, as many crystallographers believed, but reflected the asymmetry of the ultimate molecular components of crystals, following Häuy. Pasteur reasoned that crystals of symmetrical, optically inactive compounds should not have hemihedral faces and expected that this would be the difference, missed by Mitscherlich, between the sodium ammonium (+)-tartrate and racemate. He soon realised his mistake when he found that the racemate salt consisted not of symmetrical crystals but of a mixture of left and right handed hemihedral crystals, which he separated manually, whereas tartrate crystals all showed the same handedness. At one stroke he had discovered the relationship between (+)-tartaric and racemic acids and a method for 'resolving' the latter. He went on to discover how to interconvert the optically active and racemic forms, isolated the fourth (meso) and last stereoisomeric form, and recognised the generality of the differences in (diastereomeric) interactions between one chiral compound and the enantiomeric forms of another. Pasteur thought he had isolated all the stereoisomeric forms of tartaric acid and from this single example concluded wrongly that *all* optically active compounds should have (+)-, (−)-, racemic, *and* meso forms. He also believed that laboratory synthesis would give only meso forms because optical activity was a characteristically 'vital' effect, a notion that was falsified almost immediately by Perkin and Duppa's synthesis of racemic tartaric acid (see below). Having no structural theory as a basis, however, Pasteur could not be certain how many forms of tartaric acid were possible and other 'isomers' of tartaric acid, such as metatartaric acid, were reported.

The gradual discovery of the chemical structure of tartaric acid depended on the work of many chemists in the 1850's and 1860's and resulted from combining three strands of argument. These were (a) a rational synthesis of succinic acid from ethylene, (b) the establishment of the relationship between succinic and tartaric acids, and (c) accumulating evidence that tartaric acid has two alcoholic hydroxyl groups and two acidic carboxyl groups.

Maxwell Simpson,[7] as part of an extensive study of aliphatic polyhalides and polycarboxylic acids, converted ethylene into dibromoethane and thence through succinonitrile into succinic acid. This established the carbon skeleton of succinic acid. The relationship between succinic and tartaric acids was first demonstrated synthetically by Perkin and Duppa.[8] They dibrominated succinic acid *via* the acid chloride (the first use of this 'ingenious' method, as Kekulé called it,[9] for facilitating substitution in carboxylic acids) and hydrolysed the dibromosuccinic acid by heating its silver salt with water. Their papers make it clear that they had expected to obtain tartaric acid. Kekulé achieved the same transformation independently.[9] Pasteur[10] was at first incredulous when he heard of the synthesis but he examined a sample of Perkin and Duppa's product and found it to be the racemic acid, and not the meso isomer he had expected. The combined work of Simpson, Perkin and Duppa, and Pasteur is memorable as the first total synthesis of a chiral organic compound. Tartaric and succinic acids were also related to one another through the reduction of tartaric acid by Schmitt,[11] using hydriodic acid, and by Dessaignes,[12] using phosphorus triiodide, almost simultaneously with Perkin and Duppa's synthesis. It is clear that all these authors regarded tartaric acid as a di-alcohol and a di-acid.

The structure of tartaric acid could not be regarded as settled, however, while doubts remained about its basicity. As early as 1850 Kolbe[13] established that the constitution of the 'acetyl' radical was  $\mathrm{CH_3.C}\!\begin{smallmatrix}\diagup\\ -\\ \diagdown\end{smallmatrix}$ (using modern atomic weights; the oxygen atom in the modern acetyl radical, $CH_3.CO$– was added later) and therefore that the characteristic grouping in simple organic acids is $-CO_2H$, although the type formulae he used obscured this. Kolbe went on to study acids such as lactic, concluding that it was diatomic but monobasic, i.e., its type formula should have two replaceable 'typical' hydrogen atoms, one in a monobasic (carboxylic) acid group and the other in an alcoholic hydroxyl group (1859).[14] Schmitt,[11] working in Kolbe's laboratory at Marburg, first referred to tartaric acid as 'dioxybernsteinsäure', implying the correct constitutional formula in modern terms, and Wislicenus explicitly called this "die Kolbe'sche Formel" (1864).[15] The first complete (and correct!) con-

$$\begin{array}{l}
CH_2{=}CH_2 \rightarrow BrCH_2.CH_2Br \rightarrow NC.CH_2.CH_2.CN \rightarrow HO_2C.CH_2.CH_2.CO_2H \rightarrow \\
\hspace{26em}\downarrow \\
ClCO.CH_2.CH_2.COCl \rightarrow (ClCO.CHBr.CHBr.COCl) \rightarrow HO_2C.CHBr.CHBr.CO_2H \\
AgO_2C.CHBr.CHBr.CO_2Ag \rightarrow (\pm)\text{-}HO_2C.CHOH.CHOH.CO_2H \rightarrow \\
{}^{-}O_2C.CHOH.CHOH.CO_2{}^{-}.Na^{+}.NH_4{}^{+} \rightarrow (+)\text{-}HO_2C.CHOH.CHOH.CO_2H
\end{array}$$

SCHEME. The synthesis of (+)-tartaric acid, the first total synthesis of a chiral natural product (Simpson, Perkin and Duppa, Kekulé, and Pasteur).

stitutional formula for tartaric acid had been given by Couper,[16] but without any indication how he came to this conclusion, in his remarkable paper in which he explained the structure of organic compounds on the basis of carbon–carbon bonds.

Kolbe's conclusions about the constitution of hydroxyacids was accepted by many chemists but Wurtz[17] maintained that the atomicity and basicity of some hydroxyacids were numerically equal, i.e., the 'typical', or as we would say hydroxylic hydrogens were all characteristically acidic. This view was supported by the preparation of 'hyperbasic' salts of tartaric acid by, e.g., Schiff.[18] These salts were all prepared under unusual conditions and involved heavy metals, as in the di-lead and cadmium–antimony salts. The uncertainty induced by these 'hyperbasic' salts is clearly shown by Kekulé, who agreed with Kolbe about the constitution of hydroxy-acids. In Volume I of his *Lehrbuch*, published in 1861 very soon after Kolbe's paper on lactic acid, Kekulé did not differentiate between two kinds of 'typical' hydrogens and their replacements in, e.g., lactic acid. In Volume II (1866), however, the type formulae for tartaric acid and its derivatives make the distinction *except* for the 'hyperbasic' salts, for which he slips back into the older style of formulae.[19]

The problem seems to have been settled to most chemists satisfaction by more detailed characterisation of the hydroxyl groups in diethyl tartrate by Wislicenus and by Perkin. Wislicenus prepared a diacetate and was satisfied from its properties that it was an ester and not a mixed anhydride, some of which were known.[15] Perkin made a much more detailed study specifically aimed at determining whether two or four hydrogen atoms in tartaric acid were acidic in character.[20] In particular he prepared mono- and di-acyl derivatives of diethyl tartrate and showed that these behaved as esters. He found that diethyl tartrate and its mono-acyl, but *not* the di-acyl, derivatives reacted with sodium like ordinary alcohols. He also found that partial hydrolysis by alkali converted diethyl benzoyltartrate successively into the monoethyl ester and then into benzoyltartaric acid. He concluded that tartaric acid is a dibasic acid and a dihydric alcohol, and that the 'hyperbasic' salts, being insoluble and unpurifiable substances prepared at high temperatures, were of uncertain constitution and not useful evidence.

Thus the constitution of tartaric acid was settled about seven years before van't Hoff and Le Bel made their great discoveries and solved the problem of the origin of the stereoisomerism of tartaric acid.

Acknowledgement—The problem of who should be credited with determining the constitution of tartaric acid was raised by Sir Robert Robinson, and turned out to have no simple answer. I thank him for having encouraged me to look into the early history of tartaric acid, which illuminates through the chemistry of one compound how great was the contribution made by van't Hoff and Le Bel to the understanding of organic chemistry.

REFERENCES

[1] References to early work on tartaric acid and its derivatives may be obtained through Refs 2–5

[2] J. R. Partington, *A History of Chemistry* Macmillan, London, 1964

[3] R. P. Multhauf, *The Origins of Chemistry* Oldbourne, London, 1966

[4] H. P. Hartley, *Studies in the History of Chemistry* Clarendon Press, Oxford, pp. 85–86, 1971

[5] J. D. Bernal, *Science and Industry in the Nineteenth Century* Routledge and Kegan Paul, London, 1953

[6] L. Pasteur, *The Asymmetry of Naturally Occurring Compounds* (two lectures given to the Chemical Society of Paris, 1860), (translated by G. M. Richardson), in *The Foundations of Stereochemistry* American Book Company, New York, 1901

[7] M. Simpson, *Proc. Roy. Soc.* **10**, 574 (1860)

[8] W. H. Perkin and B. F. Duppa, *Chem. News* 244 (1860); *J. Chem. Soc.* **13**, 102 (1861).

[9] A. Kekulé, *Ann. Chem. Pharm.* **117**, 120 (1861)

[10] L. Pasteur, *Ann. Chim.* **61**, 484 (1860)

[11] R. Schmitt, *Ann. Chem. Pharm.* **114**, 134 (1860)

[12] V. Dessaignes, *Compt. rend.* **50**, 759 (1860)

[13] H. Kolbe, *Ann. Chem. Pharm.* **75**, 216 (1850)

[14] A. S. Couper, *Phil. Mag.* **16**, 104 (1858)

[15] J. Wislicenus, *Ibid.* **125**, 175 (1864)

[16] A. S. Couper, *Phil. Mag.* **16**, 104 (1858)

[17] A. Wurtz, *Compt. rend.* **45**, 306 (1857); **46**, 1228 (1858)

[18] H. Schiff, *Ann. Chem. Pharm.* **125**, 129 (1863); **104**, 325 (1857)

[19] A. Kekulé, *Lehrbuch der Organischen Chemie* Enke, Stutigart, 1861–1887

[20] W. H. Perkin, *J. Chem. Soc.* **5**, 138 (1867)