[CONTRIBUTION FROM NEW PRODUCT DEVELOPMENT LABORATORY, GENERAL ELECTRIC COMPANY]

Sodium Poly-(hydroxymethyl)-phenates

BY R. W. MARTIN

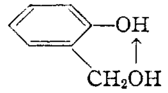
Sodium phenate and sodium *m*-cresylate form tris-(hydroxymethyl) derivatives by reaction with formaldehyde while sodium 3,5-xylenate forms a bis-(hydroxymethyl) derivative. Neutralization of the xylenate product gives the corresponding phenol but neutralization of the phenate and *m*-cresylate products gives tetra-(hydroxymethyl)-dihydroxydiphenylmethanes.

Because of their low solubility in concentrated alkaline solution, the sodium salts of the bis-(hydroxymethyl) derivatives of substituted phenols, such as *p*-cresol, are readily isolated.[1] Although Granger[2] reported the reaction of *m*-cresol and 3,5-xylenol with three moles of formaldehyde in the presence of sodium hydroxide, the isolation of the more soluble sodium salts of tris-(hydroxymethyl)-phenols in pure form has not previously been described.

Herein reported is the preparation of the sodium salts of the hydroxymethyl derivatives of phenol, *m*-cresol and 3,5-xylenol by the reaction of alkaline solutions of the phenols with three moles of formaldehyde. The salts are precipitated by pouring the reaction mixtures into a water miscible solvent. Equivalent weight determinations indicate the formation of tris-(hydroxymethyl) derivatives of phenol and *m*-cresol but a bis-(hydroxymethyl) derivative of 3,5-xylenol. The structure of the compound prepared from phenol was confirmed by a sodium analysis, equivalent weight determination, and by the synthesis of a number of derivatives.

The liberation of phenol alcohols from their salts by acidification has been frequently employed.[3,4,5] No difficulty is experienced in obtaining the free phenol from the bis-(hydroxymethyl) derivative of sodium 3,5-xylenate but the expected phenols are not obtained by neutralizing sodium tris-(hydroxymethyl)-phenate and *m*-cresylate. Instead, the phenate gives two crystalline solids, apparently isomeric. One of these compounds is 3,3′,5,5′-tetra-(hydroxymethyl)-4,4′-dihydroxydiphenylmethane and the other is probably 3,3′,5,5′-tetra-(hydroxymethyl)-2,4′-dihydroxydiphenylmethane. Similarly, the cresylate gives a substance whose analysis agrees with a tetra-(hydroxymethyl)-dicresylolmethane.

The formation of the diphenylmethanes can best be explained by the loss of a mole of water and a mole of formaldehyde (the loss of formaldehyde was shown experimentally) between two moles of the tris-(hydroxymethyl)-phenols, presumably formed as intermediates. Such a condensation has been previously reported only at elevated temperatures.[6] Hultzsch[7] believes that phenol alcohols are stabilized by the formation of proton bridges between the hydroxymethyl and phenolic groups as shown for saligenin:



However, three hydroxymethyl groups could not be effectively stabilized by bridging with a single phenolic group. According to Hultzsch, this explains why all efforts to obtain tris-(hydroxymethyl)-phenol have been unsuccessful.

Experimental

Reaction of Sodium Phenate with Formaldehyde.—One mole of phenol was dissolved in 1.1 moles of 50% sodium hydroxide solution. The solution was cooled to 25–30°, at which temperature it solidified. Formalin (270 ml. of 40% by volume) was added to the sodium phenate and the solution was stirred to dissolve the sodium phenate. External cooling was employed during the first 1–2 hours of reaction so that the temperature never exceeded 40°. The reaction mixture was allowed to stand several days at room temperature or maintained at 40° for 24 hours. The reaction mixture was then poured into three liters of ethanol, giving a white granular precipitate. After standing for 2 hours, the precipitate of sodium tris-(hydroxymethyl)-phenate was filtered, rinsed with acetone and ether and then dried in a vacuum desiccator; yield 165 g.; theory, 206 g.

Reaction of Sodium *m*-Cresylate with Formaldehyde.—The procedure for the reaction of sodium *m*-cresylate with formaldehyde was similar to the above except that to prevent resinification the reaction period was limited to 24 hours at room temperature. Isopropyl alcohol proved to be the best precipitating agent.

Reaction of Sodium 3,5-Xylenate with Formaldehyde.—With a maximum reaction period of 2 hours, the procedure described for sodium phenate gave a 20% yield of sodium bis-(hydroxymethyl)-3,5-xylenate.

Equivalent Weight of Salts.—A weighed sample of the salt was dissolved in water and titrated with 0.1 *N* hydrochloric acid, using brom phenol blue as the indicator.

Phenol Derivative. *Anal.* Calcd. for $C_9H_{11}O_4Na$.: equiv. wt., 206. Found: equiv. wt., 204, 209, 206, 210. *m*-Cresol Derivative. *Anal.* Calcd. for $C_{10}H_{13}O_4Na$: equiv. wt., 220. Found: equiv. wt., 228. 3,5-Xylenol Deriv. *Anal.* Calcd. for $C_{10}H_{13}O_3Na$: equiv. wt., 204.2. Found: equiv. wt., 205, 204.2, 204.5.

Sodium Analysis.—A weighed sample of sodium tris-(hydroxymethyl)-phenate was ignited in a platinum boat with sulfuric acid. The sodium was weighed as sodium sulfate.

Anal. Calcd. for $C_9H_{11}O_4Na$: Na, 11.16. Found: Na, 10.9, 10.7.

Reaction of Sodium Tris-(hydroxymethyl)-phenate with Methyl Iodide.—A mixture of 0.1 mole of sodium tris-(hydroxymethyl)-phenate, 0.15 mole of methyl iodide and 100 ml. of methanol was maintained under pressure at 50° for approximately 16 hours. The methanol and excess methyl iodide were removed by heating on a steam-bath and the residue was poured into warm water. The water solution was extracted with several portions of *t*-amyl alcohol at 70°. After distilling off the amyl alcohol under a high vacuum, a tan sirup was obtained; yield 14.45 g.; theory, 19.8 g.

Anal. Calcd. for $C_9H_{10}O_3OCH_3$: methoxyl, 15.66. Found: methoxyl, 15.33, 15.70

Acetate Ester of Tris-(hydroxymethyl)-anisole.—Ten grams of tris-(hydroxymethyl)-anisole was refluxed 15 minutes with 100 ml. of pyridine and 100 ml. of acetic anhydride. The reaction mixture was poured into ice-water

---

(1) F. Ullmann and K. Brittner, *Ber.*, **42**, 2540 (1909).

(2) F. S. Granger, *Ind. Eng. Chem.*, **24**, 442 (1932).

(3) K. Auwers, *Ber.*, **40**, 2524 (1907).

(4) O. Manasse, *ibid.*, **27**, 2409 (1894).

(5) M. Koebner, British Patent 558,987.

(6) F. Hanus, E. Fuchs and E. Ziegler, *J. prakt. Chem.*, **153**, 327 (1939).

(7) K. Hultzsch, *Kunststoffe*, **39**, 192 (1949).

and the ester was extracted with ether. After evaporating the ether, the ester was distilled, boiling range 170–180° (1–2 mm.). The product was a light tan oil which very slowly crystallized to a waxy material, melting point 52–56°.

Anal. Calcd. for $C_{16}H_{20}O_7$: sapn. equiv., 108; C, 59.26; H, 6.22. Found: sapn. equiv., 107, 106.4; C, 59.53, 59.57; H, 5.96, 6.01.

2,4,6-Tris-(acetoxymethyl)-phenyl Acetate.—Twenty-one grams of sodium tris-(hydroxymethyl)-phenate was suspended in 350 ml. of pyridine. To this suspension was added 100 ml. of acetic anhydride. The reaction mixture was stirred a few minutes, heated to 110° for ten minutes and then poured into 1500 ml. of cold water saturated with sodium chloride. The ester was extracted from the salt solution with ether, giving a 70% yield of crude ester. The ester was distilled, boiling range 200–203° (1.4–1.7 mm.). Bruson and MacMullen[8] report a boiling range of 200–205° (1–2 mm.).

Anal. Calcd. for $C_{17}H_{20}O_8$: sapn. equiv., 88; C, 57.92; H, 5.73. Found: sapn. equiv., 85.9, 92; C, 57.95, 57.99; H, 5.67, 5.82.

Oxidation of Tris-(hydroxymethyl)-anisole.—Ten grams of tris-(hydroxymethyl)-anisole was dissolved in 100 ml. of 10% sodium hydroxide solution and treated with potassium permanganate in the cold until a slight excess had been added. The excess permanganate was reduced by adding a little alcohol and the manganese dioxide formed during the oxidation was filtered off. The clear filtrate was acidified with concentrated hydrochloric acid and extracted with ether. The ether was evaporated giving a white powder. After recrystallizing once the acid had a neutralization equivalent of 85.7, calculated for methoxytrimesic acid, 80.1. The acid was refluxed with an excess of methanol containing 3% hydrogen chloride. An ester was obtained melting at 83–85° which showed no depression in melting point when mixed with an authentic sample of the trimethyl ester of methoxytrimesic acid. Beilstein[9] gives a melting point of 86° for trimethyl methoxytrimesate.

Reaction of Sodium Tris-(hydroxymethyl)-phenate with Acidified Bromate–Bromide Solution.—Five grams of sodium tris-(hydroxymethyl)-phenate was dissolved in a large excess of *N* bromate–bromide solution. The solution was diluted with a liter of water and acidified with concentrated hydrochloric acid. After standing one hour the solution was treated with sodium bisulfite and filtered. A very small yield (0.5 g.) of tribromophenol was obtained, melting point 93°, by recrystallizing the precipitate from alcohol–water. The melting point reported for tribromophenol is 92.5–93.5°.[10] The compound showed no depression in melting point when mixed with an authentic sample of tribromophenol.

***p*-Toluenesulfonate.**—A solution of 12.8 g. of sodium tris-(hydroxymethyl)-phenate in 47 ml. of $^1/_3$ *N* sodium hydroxide was shaken mechanically for two hours with a solution of 11 g. of *p*-toluenesulfonyl chloride in 50–60 ml. of benzene, a grayish-white paste separating early in the reaction. The water and benzene were then decanted, the paste dissolved in acetone and precipitated by pouring the solution into a large volume of water. The aqueous layer was decanted and the product washed with ether. The product was redissolved in acetone and the solution decolorized with activated carbon. The acetone was evaporated, first on a steam-bath, and then in a vacuum desiccator to give a fluffy white powder. The powder melted to a viscous sirup between 70–75° but a thin melt was not obtained until a temperature of 120–130° was reached. The material appeared to resinify on heating. The sulfur has been calculated assuming that the product is tris-(hydroxymethyl)-phenyl *p*-toluenesulfonate.

Anal. Calcd. for $C_{16}H_{18}O_6S$: S, 9.47. Found: S, 9.65, 9.83.

Reaction of Sodium Tris-(hydroxymethyl)-phenate with *p*-Chlorophenol.—One hundred grams of *p*-chlorophenol was dissolved in 75 ml. of acetic acid and 50 ml. of concentrated hydrochloric acid and the solution was heated to 80°. To the hot solution was added, in 2–3 ml. portions, a solution containing 4.2 g. of sodium tris-(hydroxymethyl)-phenate dissolved in 25 ml. of water. When the addition of the phenate solution was complete the solution was heated to remove the acids and the excess *p*-chlorophenol was removed by steam distillation. The residue was purified by repeated precipitation from an ether solution by the addition of petroleum ether. The product was then dried and analyzed for chlorine. The calculated chlorine content is based on a product in which each hydroxymethyl group of tris-(hydroxymethyl)-phenol has condensed with a mole of *p*-chlorophenol. The somewhat low chlorine content of the product probably indicates some self-condensation of the hydroxymethyl phenol.

Anal. Calcd. for $C_{27}H_{18}O_4Cl_3$: Cl, 20.63. Found: Cl, 18.76, 18.76.

Neutralization of Sodium Bis-(hydroxymethyl)-3,5-xylenate.—An acetone suspension of 6.1 g. of the sodium salt precipitated after reaction of formaldehyde with sodium 3,5-xylenate was added to 1.8 g. of acetic acid. Upon diluting the acetone solution with water, tan crystals separated. Recrystallization from acetone–petroleum ether gave glistening snow-white plates. Heated slowly the material fuses around 147° but if dropped on a melting point block previously heated to the desired temperature the compound melts at 166°. Auwers[11] has reported a compound having an analysis checking with theory for a bis-(hydroxymethyl) derivative of 3,5-xylenol and melting at 133–138°. Based on the blue coloration with ferric chloride reported by Auwers for his product and also given by the compound reported above it is believed that the compounds are identical except for purity. Auwers felt that the hydroxymethyl groups were located at the 2- and 4-positions relative to the phenolic group.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 65.39, 65.28; H, 7.50, 7.26.

Neutralization of Sodium Tris-(hydroxymethyl)-phenate.—To a suspension of 258 g. of sodium tris-(hydroxymethyl)-phenate in two liters of acetone was added a solution containing 72 g. of glacial acetic acid dissolved in 500 ml. of acetone. The reaction mixture was stirred vigorously during the addition of the acid and for 30 minutes thereafter. The solution was filtered to remove sodium acetate and unreacted sodium tris-(hydroxymethyl)-phenate. The filtrate was decolorized with activated charcoal, filtered and evaporated to a small volume at room temperature. Approximately 500 ml. of diethyl ether was added and the solution set aside to crystallize. About 46 g. of white, crystalline material melting at 144° was obtained along with less than a gram of material melting at 130–132°. No other crystalline products were obtained. Both compounds were slightly soluble in cold water, fairly soluble in hot water, readily soluble in the lower alcohols, ketones and esters but practically insoluble in benzene or petroleum ether. They quickly resinify in the presence of mineral acids, when boiled in water or when heated dry above their melting points.

The analysis and melting point of the higher melting compound corresponded to that for 3,3′,5,5′-tetra-(hydroxymethyl)-4,4′-dihydroxydiphenylmethane, previously reported by Seebach[12] who found a melting point of 145°.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.71; H, 6.30. Found: C, 63.69, 63.35; H, 6.04, 5.98.

The compound was esterified by refluxing with an excess of acetic anhydride containing about 2% of fused sodium acetate. The ester was recrystallized several times from alcohol–water, melting point 86–87°. Seebach reported a melting point of 87° for the hexaacetate of 3,3′,5,5′-tetra-(hydroxymethyl)-4,4′-dihydroxydiphenylmethane.

Anal. Calcd. for $C_{29}H_{32}O_{12}$: C, 60.81; H, 5.64, sapn. equiv., 95.4. Found: C, 60.96, 61.06; H, 5.61, 5.68; sapn. equiv., 95, 96, 95.7, 97.1.

The analysis of the compound melting at 130–132° also corresponded with the calculated values for a tetra-(hydroxymethyl)-dihydroxydiphenylmethane. The structure of this compound was not established experimentally, but it is believed to be an isomer of the higher melting compound, probably 3,3′,5,5′-tetra-(hydroxymethyl)-2,4′-dihydroxydiphenylmethane.

---

(8) H. A. Bruson and C. W. MacMullen, THIS JOURNAL, **63**, 270–272 (1941).

(9) Beilstein's, "Handbuch der organischen Chemie," 4th Edition, Edwards Bros., Inc., Ann Arbor, Mich., 1942, Vol. X, p. 581.

(10) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 210.

(11) K. Auwers, *Ber.*, **40**, 2524 (1907).

(12) F. Seebach, *ibid.*, **73**, 1338 (1940).

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.71; H, 6.30. Found: C, 63.95, 63.35; H, 6.28, 6.32.

Neutralization of Sodium Tris-(hydroxymethyl)-*m*-cresylate.—Sodium tris-(hydroxymethyl)-*m*-cresylate was treated with acetic acid diluted with acetone in a manner analogous to that described above for sodium tris-(hydroxymethyl)-phenate. A light tan crystalline compound was obtained which showed no sharp melting point due to very rapid resinification. The analysis of the compound corresponded with that for a tetra-(hydroxymethyl)-dihydroxydicresylmethane.

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.20; H, 6.98. Found: C, 65.19, 64.95; H, 6.98, 7.07.

Elimination of Formaldehyde from Sodium Tris-(hydroxymethyl)-phenate.—Ten grams of sodium tris-(hydroxymethyl)-phenate was suspended in 100 ml. of aldehyde-free ethanol and 2.5 g. of acetic acid was added. The reaction mixture was stirred vigorously for five minutes and then filtered. The filtrate was diluted with water and 10 ml. of a 10% solution of dimedone was added. A copious precipitate formed immediately which was filtered off and recrystallized. The recrystallized product was identified as the reaction product of formaldehyde and dimedone by a mixed melting point with an authentic sample of dimedone-formaldehyde compound.

PITTSFIELD, MASS. RECEIVED DECEMBER 6, 1950

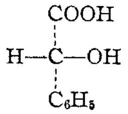
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF NEW YORK UNIVERSITY]

The Relative Configuration of (*levo*)-Mandelic Acid[1]

BY KURT MISLOW

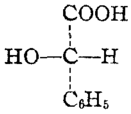
(−)-Mandelic acid has been chemically related to (−)-ethyl α-methylbenzyl ether. This result, together with previously published data, permits unequivocal assignment of (−)-mandelic acid to the D-series of α-hydroxy acids. The ether here reported has a considerably higher rotation than that of the ether prepared by the ethylation of phenylmethylcarbinol.

The problem of the relative configuration of mandelic acid has not so far been solved; the question has been one of assigning to (−)-mandelic acid either of the configurations I or II, and hence, by definition[2]



$$\begin{array}{c} COOH \\ | \\ H—C—OH \\ | \\ C_6H_5 \end{array}$$

I



$$\begin{array}{c} COOH \\ | \\ HO—C—H \\ | \\ C_6H_5 \end{array}$$

II

and in analogy to the lactic acids,[3] the corresponding denotation D or L. Such a correlation would be of importance in problems of Walden inversion and optical activity, as well as in certain aspects of biochemistry.

Almost all of the numerous studies which were made of this problem led to the tentative assignment of (−)-mandelic acid (MA) to the D-series. In the main, these studies were based on a comparison of the properties of (−)-MA and D-(−)-lactic acid. The criteria which were employed included the relative solubility of the alkaloidal salts of α-hydroxy acids,[4] the stereospecificity of biochemical reactions,[5] the formation of quasi-racemic compounds,[6] and the application of the displacement rule[7] to D-(−)-lactic acid, (−)-MA and (−)-hexahydromandelic acid.[8-11] The most recent such study[12] is again based on optical comparisons.

The present investigation was undertaken in an attempt to correlate, by a *chemical* method, the configurations of (−)-lactic acid and (−)-MA. The latter acid was ethylated with ethyl iodide and silver oxide to (−)-ethyl α-ethoxyphenylacetate,[13] which was then reduced with lithium aluminum hydride to (−)-β-ethoxyphenethyl alcohol. It was found that β-ethoxyphenethyl bromide[14] could be reduced to ethyl α-methylbenzyl ether; accordingly attempts were made to convert β-ethoxyphenethyl alcohol to the bromide. All such attempts proved abortive. (−)-β-Ethoxyphenethyl alcohol was converted to the *p*-toluenesulfonate by a standard procedure; the ester upon reduction with lithium aluminum hydride yielded (−)-ethyl α-methylbenzyl ether. The identity of this product was proved by a comparison of its infrared spectrum with that of a sample of authentic ether.

This work completes a synthetic relationship between (−)-MA and (−)-lactic acid which is shown in formulas III to IX,[15] IX to X,[16] X to XI,[17] XI to XIV (present investigation) and XIV to XV.[13] The relative configuration of mandelic acid is thus established; (−)-MA accordingly belongs to the D-series (formula I) and (+)-MA to the L-series (formula II). Similarly, the relative configurations of all substances related chemically to mandelic acid but not heretofore to lactic acid (hexahydromandelic acid,[8] cyclohexylpropylcarbinol,[12] etc.) are now established.

Rotation of Ethyl α-Methylbenzyl Ether.—The ethylation and reduction of mandelic acid gave consistent results. Acid with $[\alpha]_D$ −130° (82% active on the basis of −158° as the rotation of pure (−)-MA[13]) gave an alcohol with $[\alpha]_D$ −79.0°; acid with $[\alpha]_D$ +109° (69% active) gave

---

[1] Presented before the Division of Organic Chemistry, 119th American Chemical Society Meeting, Boston, Mass., April, 1951.

[2] Freudenberg, in Freudenberg, "Stereochemie," Franz Deuticke, Leipzig and Vienna, 1932, pp. 662 ff.

[3] Wolfrom, Lemieux, Olin and Weisblat, THIS JOURNAL, **71**, 4057 (1949).

[4] Winther, *Ber.*, **28**, 3000 (1895).

[5] Freudenberg, *ibid.*, **47**, 2027 (1914); McKenzie and Harden, *J. Chem. Soc.*, 424 (1903); Lewkowitsch, *Ber.*, **15**, 1505 (1882); **16**, 1568 (1883).

[6] Timmermans, van Lansker and Jaffe, *Bull. soc. chim. Belg.*, **48**, 33 (1939); Fredga, in "The Svedberg," Almqvist and Wiksells, Uppsala, 1944.

[7] Kuhn, in Freudenberg, "Stereochemie," Franz Deuticke, Leipzig and Vienna, 1932, pp. 396 ff.

[8] Freudenberg, Brauns and Siegel, *Ber.*, **56**, 193 (1923).

[9] Clough, *J. Chem. Soc.*, 2808 (1925).

[10] Freudenberg and Markert, *Ber.*, **58**, 1753 (1925).

[11] Woods and Nicholas, *J. Chem. Soc.*, 1712 (1928).

[12] Kuna and Levene, *J. Biol. Chem.*, **118**, 315 (1937).

[13] McKenzie, *J. Chem. Soc.*, 753, 964 (1899).

[14] Lauer and Spielman, THIS JOURNAL, **53**, 1533 (1931).

[15] Levene and Harris, *J. Biol. Chem.*, **113**, 55 (1936).

[16] Levene and Stevens, *ibid.*, **89**, 471 (1930); Freudenberg, Todd and Seidler, *Ann.*, **501**, 199 (1933).

[17] Kenyon and Phillips, *J. Chem. Soc.*, 1676 (1930).