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.

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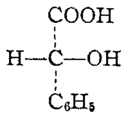
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF NEW YORK UNIVERSITY]

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

BY KURT MISLOW

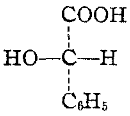
(−)-Mandelic acid has been chemically related to (−)-ethyl α-methylbenzyl ether. This result, together with previously published data, permits unequivocal assignment of (−)-mandelic acid to the D-series of α-hydroxy acids. The ether here reported has a considerably higher rotation than that of the ether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

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(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).

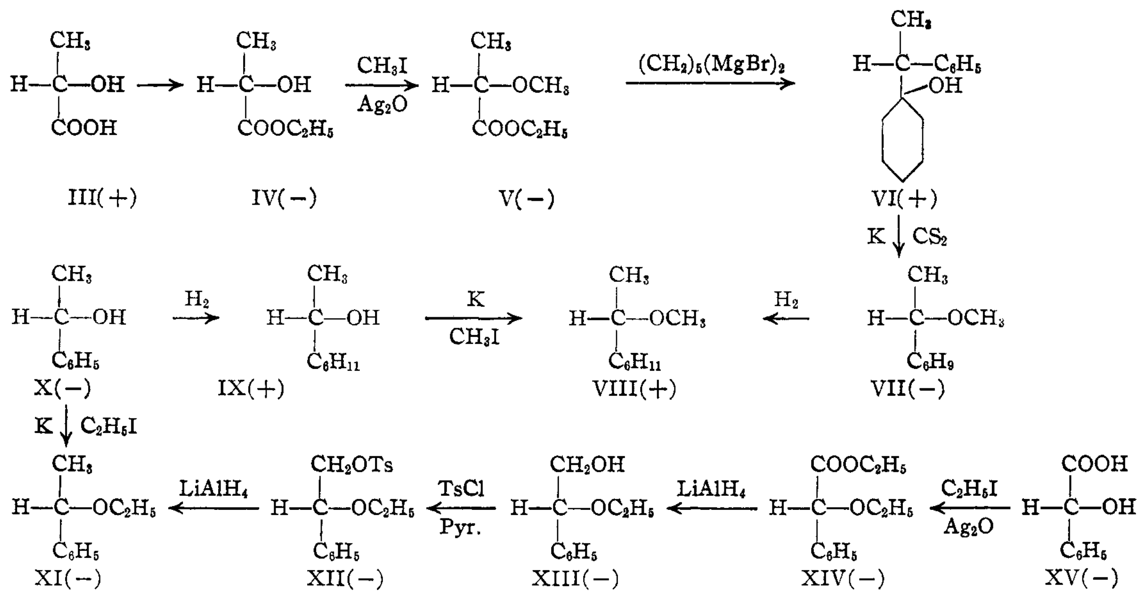
(13) McKenzie, *J. Chem. Soc.*, 753, 964 (1899).

(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).



an alcohol with $[\alpha]_D$ +66.4°. Optically pure β-ethoxyphenethyl alcohol might thus be expected to have $[\alpha]_D$ *ca.* 96°. A sample of alcohol, $[\alpha]_D$ −24.3°, which was prepared by diluting active alcohol, $[\alpha]_D$ −79.0°, with inactive alcohol, would accordingly be 25% active and would, upon tosylation and reduction of the tosylate, yield ethyl α-methylbenzyl ether with an optical purity not greater than 25%. According to the observed rotation of the product, α_D −46.32° (l = 2), the fully active ether should therefore have a rotation at 598 mμ of at least *ca.* 92° (l = 1). This rotation would be higher than the highest rotation thus far reported for the ether, α_D *ca.* 74° (l = 1).[18] This result is of considerable interest, since the rotation of the optically pure ether is an important part of the frame of reference used in several studies of the Walden inversion.[17,19] The high rotation of the ether here obtained might be explained by assuming that little, if any, racemization occurred in reaction sequence XV to XI. On the other hand, the method heretofore used to prepare this and similar "optically pure" ethers, from the *alkali alcoholate* and alkyl halide (*e.g.*, X to XI[17]), might have led to partial stereochemical equilibration of the alcohol[20] prior to etherification, with resulting loss of optical activity. These observations are in harmony with those of Hughes, Ingold and Scott,[19] who came to similar conclusions on the basis of the inconsistent results they obtained in the methylation of phenylmethylcarbinol. Further investigation of these anomalies is contemplated.

Of distinct interest, relative to the reaction of lithium aluminum hydride with the *p*-toluenesulfonate of β-ethoxyphenethyl alcohol, is the fact that ethyl phenethyl ether, the product of a possible rearrangement,[21] was not isolated.

Experimental[22]

(−)-β-Ethoxyphenethyl Alcohol (XIII).—The resolution of mandelic acid was most conveniently accomplished through crystallization of the morphine salt from ethanol.[13] It was found that a single recrystallization of the precipitated salt afforded (−)-mandelic acid which was 75–85% optically pure. A vigorously stirred suspension of 28.5 g. (0.19 mole) of mandelic acid, $[\alpha]^{26}_D$ −130° (*c* 3.24, water), in 153 g. (0.60 mole) of ethyl iodide was treated with 87.5 g. (0.38 mole) of silver oxide.[13] The resulting suspension was refluxed two hours, filtered, and the residue washed with benzene. The filtrate was stripped of solvent *in vacuo*; the residue of mixed[13] esters weighed 34.7 g. A solution of 25.4 g. of the mixed esters in 150 ml. of ether was added, over a period of 30 minutes, to a solution of 5.0 g. of lithium aluminum hydride in 150 ml. of ether. After an additional 30 minutes of refluxing, the reaction mixture was decomposed with dilute sulfuric acid, the aqueous layer extracted with ether, and the combined ethereal layers washed with 10% sodium carbonate solution and dried over potassium carbonate. Distillation afforded 5.5 g. (24.2% based on mandelic acid) of a colorless oil, b.p. 84° (2 mm.), $[\alpha]^{29}_D$ −79.0° (*c* 2.06, benzene), n^{25}_D 1.5105. The residue remaining after the distillation proved to be a high boiling, low melting solid, presumably phenylglycol. When the experiment was repeated with mandelic acid, $[\alpha]^{28}_D$ +109° (*c* 3.17, water), a 54% yield of the alcohol, $[\alpha]^{20}_D$ +66.4° (*c* 10.98, benzene), was obtained. Optically inactive alcohol (XIII), prepared in the same manner, had n^{28}_D 1.5098, d^{25}_4 1.029; M_D calcd., 47.95; found, 48.27.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.16, 72.33; H, 8.50, 8.61.

(−)-β-Ethoxyphenethyl *p*-Toluenesulfonate (Tosylate) (XII).—A solution of 17.6 g. (0.106 mole) of β-ethoxyphenethyl alcohol (XIII), $[\alpha]^{28}_D$ −24.3° (*c* 3.33, benzene), and 26.8 g. (0.141 mole) of *p*-toluenesulfonyl chloride in 20 ml. of anhydrous ether, protected from moisture by Drierite tubes, was cooled to −15° in an ice–salt-bath. While the mixture was stirred and kept at −15°, 17.6 g. (0.223 mole) of reagent pyridine, which had previously been distilled from and stored over barium oxide, was added over a period of 20 minutes. The resulting suspension was kept in the refrigerator for four days. The mixture, which at that time had set to a semi-solid slurry, was diluted with water and made strongly acid. The organic layer was separated, the aqueous layer extracted with ether and the combined organic layers twice extracted with water. The ether was stripped *in vacuo* at room temperature and the residual oil-dried over Drierite. There was thus obtained 32.2 g. (95%) of tosylate, $[\alpha]^{25}_D$ −10.8° (*c* 2.03, benzene), n^{25}_D 1.5402, d^{25}_4 1.179.

Anal. Calcd. for $C_{17}H_{20}O_4S$: S, 10.01. Found: S, 10.16.

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(18) Extrapolated from values reported by Kenyon and Phillips (ref. 17) for other wave lengths.

(19) Holmberg, *Ber.*, **45**, 997 (1912); Ward, *J. Chem. Soc.*, 453 (1927); Kenyon, Phillips and Taylor, *ibid.*, 173 (1933); Hughes, Ingold and Scott, *ibid.*, 1201 (1937); Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937).

(20) Doering and Aschner, THIS JOURNAL, **71**, 838 (1949).

(21) Cram, 118th American Chemical Society Meeting, Chicago, 1950, Abstracts 49N, 50N.

(22) Microanalyses by W. Manser.

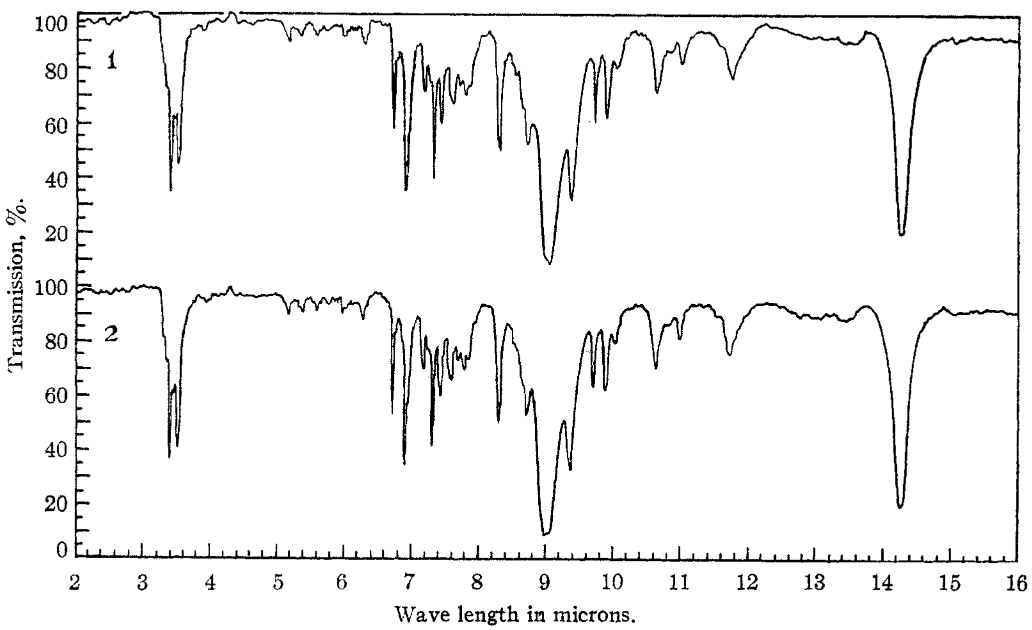

Fig. 1.

(−)-Ethyl α-Methyl Benzyl Ether (XI).—A solution of 32.0 g. (0.100 mole) of tosylate (XII), $[\alpha]^{25}_{\mathrm{D}}$ −10.8° (c 2.03, benzene), in 30 ml. of ether was added to a solution of 4.0 g. (0.105 mole) of lithium aluminum hydride in 20 ml. of ether. The addition took 40 minutes; the reaction was vigorous enough to require intermittent external cooling. The resulting suspension was refluxed another 40 minutes, poured over cracked ice and acidified with sulfuric acid. The product was worked up in the usual manner; on distillation there was obtained 7.3 g. (49%) of impure ether (XI), b.p. 65.5° (11 mm.), α^{25}_{D} −38.45° (l = 2, no solvent), n^{25}_{D} 1.4920, with a disagreeable odor. The residue from the distillation consisted of 7.6 g. of a high boiling oil with a very offensive odor. The distillate was shaken with hot concentrated potassium hydroxide, dried, and redistilled to give the desired ether, b.p. 77° (18 mm.), α^{22}_{D} −46.32° (l = 2, no solvent), n^{25}_{D} 1.4842, with a pleasant, fruity odor. The infrared spectrum is shown in Fig. 1 (curve 1).[23]

Optically inactive ether (XI) was prepared from (±)-phenylmethylcarbinol according to the procedure of Kenyon and Phillips.[17] The product had b.p. 78° (20 mm.), n^{25}_{D} 1.4850, d^{25}_{4} 0.9131; M_{D} calcd., 46.42; found, 47.18. The infrared spectrum is shown in Fig. 1 (curve 2).[23]

Hydrogenolysis of β-Ethoxyphenethyl Bromide.—The bromide, prepared from 1,2-dibromoethyl ether[24] and phenylmagnesium bromide,[14] had b.p. 78° (2 mm.), 122° (18 mm.) (repd.[14] 129–133° (18 mm.); 96–100° (15 mm.)[25]), n^{25}_{D} 1.5317 (repd.[14] n^{25}_{D} 1.5317), d^{25}_{4} 1.288; M_{D} calcd., 54.18; found, 55.08. A solution of 24.2 g. of bromide in 20 ml. of ether was added to a solution of 4 g. of lithium aluminum hydride in 20 ml. of ether. The addition required five minutes, after which refluxing was continued for one-half hour. The addition of a few milliliters of dilute hydrochloric acid at this point caused an almost explosively violent decomposition, requiring vigorous stirring and external cooling. When this reaction had subsided, the product was poured over ice, worked up in the usual manner, and distilled. A few drops of low-boiling forerun gave a positive Baeyer test, and from their characteristic odor and b.p. 41° (18 mm.) were tentatively identified as styrene. The main fraction consisted of 4.0 g. (25%) of ethyl α-methylbenzyl ether, b.p. 74° (18 mm.), n^{25}_{D} 1.4850.

Attempted Preparation of β-Ethoxyphenethyl Bromide from the Alcohol and the Tosylate.—A solution of 25.6 g. of the alcohol in 75 ml. of anhydrous ether was added to a solution of 18 g. of phosphorus tribromide in 50 ml. of ether. The mixture was refluxed for two hours; the product, on distillation through a one-foot helix-packed column, yielded 6.6 g. of a colorless liquid, b.p. 75° (2 mm.), n^{25}_{D} 1.5221, d^{25}_{4} 1.207.

Anal. Calcd. for $C_{10}H_{13}OBr$: Br, 34.88. Found: Br, 25.39.

During the distillation, schlieren formation was observed as the distillate was collected, albeit the temperature stayed constant. A repetition of the experiment, in which the reaction mixture was refluxed 20 hours, yielded similar inconclusive results. The product had b.p. 74° (2 mm.), n^{25}_{D} 1.5173, d^{25}_{4} 1.155.

Anal. Calcd. for $C_{10}H_{13}OBr$: Br, 34.88. Found: Br, 20.19.

The product was similarly impure when phosphorus tribromide was added to an ice-cold solution of the alcohol in pyridine. The following experiment was equally fruitless. A suspension of 9.7 g. (0.030 mole) of tosylate and 3.5 g. (0.034 mole) of sodium bromide in 10 ml. of diethylene glycol was stirred and heated in an oil-bath at 140° for 90 minutes. The resulting mixture was diluted with water and extracted with ether. The extracts were worked up to give 3.0 g. of a product, b.p. 72.5° (2 mm.) which was arbitrarily collected in four successive fractions of about 0.8 g. each. The fractions, in the order in which they were collected, had n^{25}_{D} 1.5118, 1.5213, 1.5264, 1.5245. The residue, n^{25}_{D} 1.5430, consisted of 2.7 g. of a brown oil.

The impure products described in this section were not investigated further.

NEW YORK, N. Y.

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[23] A Baird Model B infrared spectrophotometer with 0.1 mm. cells was employed. The samples were made up to 5% solutions in carbon tetrachloride.

[24] Swallen and Boord, THIS JOURNAL, **52**, 651 (1930).

[25] De Kok, *Rec. trav. chim.*, **53**, 1133 (1934).