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Studies of *C*-Substituted Tartaric Acid. I. The Preparation of Optically Active 2-Methyltartaric and 2, 3-Dimethyltartaric Acid

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Two racemic forms of 2-methyltartaric acid were prepared, and their optical resolutions were performed. Four optically active isomers were obtained. 2, 3-Dimethyltartaric acid was also prepared and separated into two isomeric optically inactive forms. The isomer with the higher melting point could be resolved into two optically active isomers, but the other, with the lower melting point, could not. The former was, therefore, assigned to the racemic configuration, and the latter, to the meso configuration.

Optically active 2-methyltartaric and 2, 3-dimethyltartaric acid are interesting substances to study from the stereochemical point of view in their relation to tartaric acid. Moreover, in a previous publication$^{1)}$ from our laboratory, it was reported that a Raney nickel catalyst treated with aqueous solutions of these optically active hydroxy carboxylic acids has an asymmetric hydrogenation activity in the hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate, and that an especially high asymmetric activity is obtained with optically active 2-methyltartaric acid (B) under optimum conditions. However, preparations of optically active 2-methyltartaric and 2, 3-dimethyltartaric acid have never been described.

In the present work, optically active 2-methyltartaric and 2, 3-dimethyltartaric acid will be prepared.

The two racemic forms of 2-methyltartaric acid (I), the melting points of which are 146°C (Ia) and 161°C (Ib), were prepared from ethyl α-acetoxyacetoacetate by a modification of Schmidt's procedure,$^{2)}$ and their optical resolutions were performed with brucine by the method of the differential solubility of the diastereomers in water. The optical rotation values of the four isomers were as follows:

(A) From the racemic form with the lower melting point (2-methyltartaric acid A)$\cdots$(Ia):

(+) isomer $[\alpha]_D^{20}$ +8.90° (*c* 3.7, water)
(−) isomer $[\alpha]_D^{20}$ −8.94° (*c* 3.7, water)

(B) From the racemic form with the higher melting point (2-methyltartaric acid B)$\cdots$(Ib):

(+) isomer $[\alpha]_D^{20}$ +5.88° (*c* 3.2, water)
(−) isomer $[\alpha]_D^{20}$ −5.60° (*c* 3.2, water)

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1) Y. Izumi, S. Tatsumi, M. Imaida, Y. Fukuda and S. Akabori, This Bulletin, in press.

2) O. T. Schmidt and W. Perkow, *Chem. Ber.*, **83**, 484 (1950).

2, 3-Dimethyltartaric acid (II) has two optically inactive modifications, the meso (IIa) and the racemic forms (IIb). This acid was synthesized from diacetyl and hydrogen cyanide, and the separation into two components, the meso and racemic form, was performed by means of the differential solubility of their barium salts in water. The melting points of the free meso and racemic acid are 180 and 187°C respectively. The optical resolution of the racemic form was performed in an aqueous solution with brucine, and the optical rotation values of the two isomers were as follows:

(+) isomer $[\alpha]^{20}_{D}$ +13.4° (*c* 4.0, water)

(−) isomer $[\alpha]^{20}_{D}$ −13.4° (*c* 4.0, water)

Experimental*

The Preparation of 2-Methyltartaric Acid (I) and Separation into Two Racemic Forms (Ia and Ib).—A mixture of 28.2 g. of ethyl α-acetoxyacetoacetate in 100 ml. of ethanol and 13 g. of potassium cyanide in 50 ml. of water was cooled to 0—5°C in an ice water bath; 200 ml. of N hydrochloric acid was then vigorously stirred, drop by drop, into the mixture. The flask was tightly stoppered, and the mixture was warmed in a water bath at 50—60°C for 4 hr. and then left to stand overnight at room temperature. After the reaction mixture had been cooled in an ice water bath, it was poured into 400 ml. of concentrated hydrochloric acid; the mixture was then allowed to stand for two days. The acidic solution was refluxed for an hour and concentrated in vacuo. During the concentration inorganic salts were removed by filtration. The residue was dissolved in a small amount of water and concentrated again in vacuo.

In order to remove the free hydrochloric acid, the above operation was then repeated. The residual syrup was taken up in 150 ml. of water and decolorized with charcoal; when it was neutralized with a 3% barium hydroxide solution, a great deal of the barium salt of Ia was precipitated. After it had been stored overnight in a refrigerator, the salt was collected by filtration, washed several times with hot water, and dried in air at 80°C. Yield, 15 g. The salt was dissolved in 50 ml. of N hydrochloric acid, and the resulting solution was then evaporated to dryness in vacuo. The residue was extracted with four 20-ml. portions of acetone. The acetone extracts were combined and evaporated to a syrup. The syrupy product was cooled and crystallized by the addition of a small amount of petroleum ether. Recrystallization from dry ethyl acetate gave pure, white, crystalline Ia. Yield, 5.5 g. M. p. 146°C.

Found: C, 36.73; H, 4.89. Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91%.

The mother liquor of the barium salt of Ia was concentrated to half its volume and then left to stand for 2 hr. in an ice box. A small amount of crystalline precipitate was filtered off, and the filtrate was treated with 10 ml. of 6 N hydrochloric acid and then evaporated to dryness. The residue was extracted with acetone and then treated as above.

In this way, four grams of white crystalline Ib were obtained. M. p. 161°C.

Found: C, 36.53; H, 4.93. Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91%.

The Optical Resolution of Ia.—Forty-nine grams of Ia and 118 g. of brucine were dissolved in 1000 ml. of boiling water; the resulting solution was allowed to stand overnight in a refrigerator. The needle-like crystals of the brucine salt which precipitated were collected by filtration; six recrystallizations of this salt from ten parts of boiling water gave 61 g. of the pure brucine salt of Ia. M. p. 236—237°C, $[\alpha]^{20}_{D}$ −21.9° (*c* 0.4, in water). This salt was then suspended in 100 ml. of cold water and decomposed with 225 ml. of a N sodium hydroxide solution. The precipitated brucine was removed by filtration, and the alkaline filtrate was washed twice with 50 ml. of chlorofoum, neutralized with 20 ml. of concentrated hydrochloric acid, and then evaporated to a syrup. To the residual syrup a small amount of water was added, and the resulting solution was decolorized with charcoal and evaporated to dryness in order to remove the free hydrochloric acid. The residue was extracted several times with 20 ml. of acetone. These acetone extracts were then combined and evaporated to a syrup. The syrupy product was dried over sulfuric acid in a vacuum desiccator. In this way, white, hygroscopic crystals of (−)-Ia were obtained. Recrystallization from dry ethyl acetate gave 14.9 g. of optically pure (−)-Ia. M. p. 115—116°C, $[\alpha]^{20}_{D}$ −8.94° (*c* 3.7, water).

Found: C, 36.53; H, 5.02. Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91%.

The mother liquor of the brucine salt of (−)-Ia was concentrated to a paste. After it had been stood for a week in a refrigerator, the brucine salt of (+)-Ia was collected. Optically pure (+)-Ia was obtained from this salt by the procedure described above. Yield, 8.0 g. M. p. 115°C, $[\alpha]^{20}_{D}$ +8.90° (*c* 3.7, water).

Found: C, 36.57; H, 4.94. Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91%.

The Optical Resolution of Ib.—Thirty-eight grams of Ib and 91.5 g. of brucine were dissolved in 1000 ml. of boiling water, and the resulting solution was treated as in the resolution of Ia. Forty grams of the pure brucine salt of (+)-Ib were, thus obtained. M. p. 234—235°C, $[\alpha]^{20}_{D}$ −16.5° (*c* 0.4, water). When the brucine salt was decomposed with alkali, 8.2 g. of optically pure (+)-Ib were obtained. M. p. 130—131°C, $[\alpha]^{20}_{D}$ +5.88° (*c* 3.2, water).

Found: C, 36.53; H, 4.88. Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91%.

From the mother liquor of the brucine salt of (+)-Ib, 5.1 g. of optically acitive (−)-Ib were obtained by the procedures described above. M. p. 129°C, $[\alpha]^{20}_{D}$ −5.60° (*c* 3.2, water).

Found: C, 36.63; H, 4.79. Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91%.

The Preparation of 2, 3-Dimethyltartaric Acid (II) and Its Separation into Meso (IIa) and Racemic Forms (IIb).—Into a solution of 520 g. of sodium cyanide in 1000 ml. of water, 800 ml. of concentrated hydrochloric acid was stirred vigorously, drop by drop, below 15°C in a hood. After the addition of hydrochloric acid, 74 ml. of a 20% aqueous potassium carbonate solution was added slowly. Then 344 ml. of diacetyl was stirred in drop by drop under sufficient

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* All melting points are uncorrected.

cooling, and the reaction mixture was maintained at 15—20°C for 2 hr. Then 2.4 l. of concentrated hydrochloric acid were added cautiously (the temperature of the solution rose up to 40°C with foaming). After the reaction mixture had been kept at room temperature overnight, it was refluxed for 7 hr. Inorganic salt and tar were removed by suction from the cooled hydrolyzed solution, and the filtrate was concentrated to about 800 ml. in vacuo. On the addition of 300 ml. of acetone, inorganic salt was precipitated; this was filtered off, and the solution was concentrated again. The above treatment was repeated several times in order to remove the inorganic salts, and the residual syrup was dissolved in 1.5 l. of ethanol and was esterified with blowing dry hydrogen chloride gas into the solution. The alcohol was distilled off in vacuo, and the diethyl ester of II was collected at 110—115°C (4 mmHg). Yield, 240 g.

Two hundred and forty grams of diethyl ester were refluxed with 1000 ml. of 10% hydrochloric acid for 5 hr. The hydrolyzate was decolorized with charcoal and then concentrated to a syrup. The syrupy residue was taken up in 200 ml. of water and concentrated again. The above treatment was repeated in order to remove the free hydrochloric acid, and then the residue was dissolved in 2 l. of water and neutralized slowly to pH 5.0 with a barium hydroxide solution. A great deal of the barium salt of IIa was immediately precipitated. The barium salt was collected by suction, washed with a large quantity of hot water, and dried in air at 80°C. Yield, 160 g. When the mother liquor of the barium salt of IIa was adjusted to pH 8.0, a small amount of an additional salt appeared; this was removed by filtration. The filtrate was concentrated in vacuo, and the barium salt of IIb precipitating from the solution was collected successively by suction. It was washed with a small amount of water and dried in air at 80°C. Yield, 120 g.

IIa and IIb from their barium salts were prepared essentially as described in the preceding paragraph.

From 160 g. of the barium salt of IIa, 70 g. of IIa were obtained. M. p. 180°C.

Found: C, 40.31; H, 5.64. Calcd. for $C_6H_{10}O_6$: C, 40.45; H, 5.66%.

Similarly from 120 g. of the barium salt of IIb, 53 g. of IIb were obtained. M. p. 187°C.

Found: C, 41.00; H, 5.60. Calcd. for $C_6H_{10}O_6$: C, 40.45; H, 5.66%.

The Optical Resolution of IIb.—Sixty grams of IIb and 145 g. of brucine dihydrate were dissolved in 1300 ml. of boiling water. The resulting solution was treated by the method described for the resolution of Ia; 15.5 g. of optically pure (+)-IIb were thus obtained. M. p. 158°C, $[\alpha]_D^{20}$ +13.4° (*c* 4.0, water).

Found: C, 40.72; H, 5.60. Calcd. for $C_6H_{10}O_6$: C, 40.45; H, 5.66%.

From the mother liquor of the brucine salt of (+)-IIb, 13 g. of optically pure (−)-IIb were obtained. M. p. 160°C, $[\alpha]_D^{20}$ −13.4° (*c* 4.0, water).

Found: C, 40.38: H, 5.43. Calcd. for $C_6H_{10}O_6$: C, 40.45; H, 5.66%.

Summary

1) The optical resolutions of the two racemic forms of 2-methyltartaric acid, the melting points of which are 146 and 161°C, were performed using brucine as a resolving reagent; four optically active isomers were obtained.

2) 2, 3-Dimethyltartaric acid was prepared from diacetyl and hydrogen cyanide and was separated into meso (m. p. 180°C) and racemic forms (m. p. 187°C); the racemic form was then resolved into two optically active isomers.

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