# Studies of *C*-Substituted Tartaric Acid. III. The Preparation of Isomeric 1, 2-Dihydroxycyclohexane-1, 2-dicarboxylic Acids and the Optical Resolution of the Racemate

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1, 2-Dihydroxycyclohexane-1, 2-dicarboxylic acid is a kind of *C, C'*-dialkyltartaric acid. This hydroxy acid contains two asymmetric centers; hence, it exists in two optically inactive modifications. One is a racemic form which may be resolved into optically active forms, while the other is a meso form. The optically active and inactive forms, therefore, are interesting substances from the stereochemical point of view in relation to tartaric acid. Moreover, in a previous paper(1) from our laboratory, it was reported that a Raney nickel catalyst treated with an aqueous solution of this optically active hydroxy acid exhibits an asymmetric hydrogenation activity in the hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate. However, there have been no reports on the preparation of the two optically inactive or active forms of this hydroxy acid.

In the present work, 1, 2-dihydroxycyclohexane-1, 2-dicarboxylic acid was prepared from 1, 2-cyclohexanedione and was then separated into the meso (I) and racemic (II) forms on the basis of the different solubilities of their calcium salts in water. The purity of each salt was checked by a study of the infrared spectrum.(2) Subsequently, the optical resolution of II was performed in an aqueous solution with brucine. The optical rotation values of the optically active isomers were as follows: (+)-isomer, $[\alpha]_D^{20}$ $+31.0°$ (*c* 2, water); (−)-isomer, $[\alpha]_D^{20}$ $-30.5°$ (*c* 2, water).

## Experimental*

**The Preparation of 1, 2-Dihydroxycyclohexane-1, 2-dicarboxylic Acid.**—One hundred and twenty-nine grams of sodium cyanide was dissolved in 250 ml. of cold water in a 2 l. three-necked flask fitted with a stirrer and a dropping funnel. Into the cold solution, a 220 ml. portion of concentrated hydrochloric acid was added, drop by drop, with the temperature of the solution maintained below 20°C under a hood. After the addition of hydrochloric acid was complete, 3.6 g. of potassium carbonate was added, and then 115 g. of 1,2-cyclohexanedione(3) was added, drop by drop. The reaction mixture was stirred for 3 hr. at room temperature and then allowed to stand overnight. To the mixture, a 600 ml. portion of concentrated hydrochloric acid was added, after which the solution was kept for an hour at room temperature. Inorganic salts were removed by filtration, and the filtrate was refluxed for 5 hr. The hydrolyzed solution was decolorized with charcoal and then evaporated to dryness under reduced pressure. The residue was extracted with four 100 ml. portions of ethanol, and the white residue was discarded. The alcohol extracts were combined and evaporated to a syrup. This was dissolved in 3 l. of ethanol and esterified by blowing dry hydrogen chloride gas into the solution. The alcohol was distilled off in vacuo, and the diethyl ester of the acid was collected at 116—119°C/2 mmHg. Yield, 84 g.

Eighty-four grams of the ester were refluxed with 150 ml. of 12% hydrochloric acid for 5 hr. The hydrolyzate was then concentrated to a syrup under reduced pressure. This was taken up in 100 ml. of water and concentrated again. To remove free hydrochloric acid, water was added and the evaporation was repeated. The resulting viscous syrup was dissolved in 80 ml. of hot ethyl acetate, and then a 20 ml. portion of petroleum ether was added to the solution. After the mixture had stood overnight in a refrigerator, white crystals were collected by suction. Yield, 50 g.

Found: C, 47.31; H, 5.85. Calcd. for $C_8H_{12}O_6$: C, 47.06; H, 5.92%.

**Separation into the Meso (I) and Racemic (II) Forms.**—*The Preparation of Calcium Salts of I and II.*—Fifty grams of isomeric acids and 36 g. of calcium chloride dihydrate were dissolved in 2.8 l. of water. The resulting solution was adjusted to pH 5 with 10% sodium hydroxide, and then left to stand overnight at room temperature. The calcium salt which precipitated was collected by suction. In order to purify the salt, it was decomposed with hydrochloric acid and then neutralized with a sodium hydroxide solution. The decomposition and neutralization were repeated alternately three times, with the purity of the salt being checked on the basis of its infrared spectrum.(2) In this way, 18 g. of the pure calcium salt of I was obtained.

Found: C, 37.00; H, 4.70. Calcd. for $C_8H_{10}O_6Ca \cdot H_2O$: C, 36.91; H, 4.65%.

The mother liquor of the calcium salt of I was concentrated to dryness under reduced pressure. Four recrystallizations of the residue from boiling water gave 19 g. of the pure salt of II.

Found: C, 39.57; H, 4.20. Calcd. for $C_8H_{10}O_6Ca$: C, 39.66; H, 4.16%.

*The Preparation of I and II.*—Thirty grams of the

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1) Y. Izumi, S. Tatsumi and M. Imaida, This Bulletin, **39**, 1087 (1966).

2) S. Tatsumi, ibid., **39**, 2202 (1966).

* All melting points are uncorrected.

3) R. S. Schreiber, "Organic Syntheses," Vol. 32, 35 (1951).

calcium salt of I was dissolved in 120 ml. of 2 N hydrochloric acid, and then the resulting solution was evaporated to dryness under reduced pressure. The residue was extracted with four 50 ml. portions of acetone, and the white residue was discarded. The acetone extracts were combined and evaporated to dryness in vacuo, yielding 23 g. of crude I. Recrystallization from ethyl acetate - petroleum ether (4 : 1) gave 20 g. of pure I. M. p. 154°C.

Found: C, 47.14; H, 5.96. Calcd. for $C_8H_{12}O_6$: C, 47.06; H, 5.92%.

Thirty grams of the calcium salt of II was treated as has been described above. 18.5 g. of pure II was thus obtained. M. p. 180°C.

Found: C, 46.72; H, 5.97. Calcd. for $C_8H_{12}O_6$: C, 47.06; H, 5.92%.

**The Optical Resolution of II.**—Twenty grams of II and 39 g. of brucine were dissolved in 600 ml. of boiling water, and the resulting solution was allowed to stand overnight in an ice box. The crystals of the brucine salt which precipitated were collected by suction; six recrystallizations of this salt from ten parts of boiling water gave 16 g. of the pure brucine salt of II. This salt was suspended in 150 ml. of water and decomposed with 35 ml. of N sodium hydroxide. The precipitated brucine was removed by filtration, and the alkaline filtrate was washed with 20 ml. of chloroform, neutralized with concentrated hydrochloric acid, and then evaporated to a syrup. To this a small amount of water was added, and the resulting solution was decolorized with charcoal and evaporated to dryness. The residue was extracted several times with 10 ml. volumes of acetone. The acetone extracts were combined and again evaporated to a syrup. The syrupy product was dried over sulfuric acid in a vacuum desiccator. In this way, 4.4 g. of (+) II was obtained. Recrystallization from ethyl acetate - petroleum ether (3 : 1) gave 3.8 g. of optically pure (+)-II. $[\alpha]_D^{20}$ +31.0° (*c* 2, water).

Found: C, 47.11; H, 5.81. Calcd. for $C_8H_{12}O_6$: C, 47.06; H, 5.92%.

The mother liquor of the brucine salt of (+)-II was concentrated to dryness under reduced pressure. The brucine salt of (−)-II was collected and treated as has been described above. 2.0 g. of optically pure (−)-II were thus obtained. $[\alpha]_D^{20}$ −30.5° (*c* 2, water).

Found: C, 47.14; H, 5.94%.

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