# The Preparation of Four Optically Active Isomers of 3-Methylmalic Acid

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3-Methylmalic acid contains two asymmetric centers and, hence, exists in two racemic forms — four optically active forms. Although there have been several reports[1-3] on the preparation of this hydroxy acid, these procedures all yield a mixture of the two isomeric racemates. Therefore, neither the two racemic forms nor their four optically active forms have yet been identified.

In the present work, the two racemic forms and four optically active forms were prepared. A mixture of isomeric racemates was synthesized from ethyl ethoxalyl propionate by Scherp's procedure,[2] and then it was separated into two racemic forms by means of the differential solubility of their barium salts in water. The less soluble salt yielded the racemic form with a m. p. of 115°C (I), while the more soluble one yielded the racemic form with a m. p. of 129°C (II). Then, their optical resolutions were performed by the usual method, using brucine as a resolving reagent. The values of the optical rotation of the optically active isomers were as follows:

(A) From the racemic form with the lower melting point (I):

(+)-isomer $[\alpha]^{20}_{\mathrm{D}}$ +9.1° (*c* 3.7, water)

(−)-isomer $[\alpha]^{20}_{\mathrm{D}}$ −8.9° (*c* 3.7, water)

(B) From the racemic form with the higher melting point (II):

(+)-isomer $[\alpha]^{20}_{\mathrm{D}}$ +5.2° (*c* 3.2, water)

(−)-isomer $[\alpha]^{20}_{\mathrm{D}}$ −5.3° (*c* 3.2, water)

The racemic form with the m. p. of 129°C (II) was assigned the threo form by the method of the nitrous acid deamination of DL-*threo*-3-methylaspartic acid, whose configuration had previously been proved by Baker et al.[4]

## Experimental*

**The Preparation of the Mixture of Isomeric Racemates.**—The mixture of isomeric racemates was prepared from ethyl ethoxalylpropionate by the method of Scherp,[2] but using a Raney nickel catalyst in place of platinum oxide catalyst.

**The Separation of the Mixture into Two Racemic Forms.**—A very viscous colorless syrup of the mixture, weighing 148 g., was dissolved in 1000 ml. of water; the mixture was then adjusted to pH 8 with a 10% barium hydroxide solution. The resulting solution was stored overnight in a refrigerator. Then the salt which had precipitated was collected by filtration, washed several times with cold water, and dried in air at 80°C. Yield, 155 g. The salt was dissolved in 300 ml. of 6 N hydrochloric acid, and the resulting solution was then concentrated under reduced pressure. The residue was treated with a small amount of water, and the solution was again evaporated in vacuo to remove as much free hydrochloric acid as possible. This treatment was repeated several times to ensure the complete removal of the hydrochloric acid, and then the residue was extracted with six 30 ml. portions of acetone. The acetone extracts were combined and evaporated to a very viscous syrup. This was then dissolved in 100 ml. of ethyl acetate, and to the solution there was added 50 ml. of petroleum ether. This solution was stored in a refrigerator, and the precipitated crystalline product was collected by filtration. Yield, 65 g. The recrystallization of this product from ethyl acetate - petroleum ether (2 : 1) gave white crystals of I. Yield, 46 g. M. p. 113—115°C.

Found: C, 39.26; H, 5.51. Calcd. for $C_5H_8O_5$: C, 40.54; H, 5.44%.

The mother liquor of the barium salt of I was stored for a week, and a small amount of crystalline precipitate was filtered off. The clear solution was concentrated and decomposed with 120 ml. of concentrated hydrochloric acid, and then treated as has been described above. In this way, 28 g. of white crystals of II were obtained. M. p. 128—129°C.

Found: C, 39.81; H, 5.73. Calcd. for $C_5H_8O_5$: C, 40.54; H, 5.44%.

**The Optical Resolution of I.**—Thirty grams of I and 86 g. of brucine dihydrate were dissolved in 800 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 filtration; seven recrystallizations of this salt from ten parts of boiling water gave 25 g. of the pure brucine salt of I. This salt was suspended in 200 ml. of cold water and decomposed with 50 ml. of a N sodium hydroxide solution. The precipitated brucine was removed by filtration, and the alkaline filtrate was washed twice with 30 ml. portions 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 in order to remove the free hydrochloric acid. The residue was extracted several

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1) E. B. Abbot and A. McKenzie, *Ber.*, **71**, 1214 (1938).

2) H. W. Scherp, *J. Am. Chem. Soc.*, **68**, 912 (1946).

3) H. Gault and H. Gotliniaux, *Compt. rend.*, **231**, 287 (1950).

4) H. A. Baker, R. D. Smyth, E. J. Wawszkiewicz, M. N. Lee and R. M. Wilson, *Arch. Biochem. Biophys.*, **78**, 468, (1958).

* All the melting points given in this paper are uncorrected values.

times with 20 ml. 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, white crystals of (+)-I were obtained. Recrystallization from 10 ml. of ethyl acetate - petroleum ether (1 : 1) gave 3.6 g. of optically-pure (+)-I. m. p. 107°C, $[\alpha]^{20}_{\mathrm{D}}$ +9.1° (*c* 3.7, water).

Found: C, 40.36; H, 5.51. Calcd. for $C_5H_8O_5$: C, 40.54; H, 5.44%.

The mother liquor of the brucine salt of (+)-I was concentrated to a paste. After it had been stored for a week in an ice box, the brucine salt of (−)-I was collected. Optically-pure (−)-I was obtained from this salt by the procedure described above. Yield, 1.3 g. M. p. 106—107°C, $[\alpha]^{\mathrm{D}}_{20}$ −8.9° (*c* 3.7, water). Found: C, 40.40; H, 5.24%.

**The Optical Resolution of II.**—Twenty grams of II and 58 g. of brucine dihydrate were dissolved in 900 ml. of boiling water, and then the resulting solution was treated as described for the resolution of I. Thus, 2.7 g. of optically pure (−)-II crystallized out. M. p. 111°C; $[\alpha]^{\mathrm{D}}_{20}$ −5.3° (*c* 3.2, water).

Found: C, 40.32; H, 5.50. Calcd. for $C_5H_8O_5$: C, 40.54; H, 5.44%.

From the mother liquor of the brucine salt of (−)-II, 1.1 g. of optically pure (+)-II were obtained. M. p. 110—111°C, $[\alpha]^{20}_{\mathrm{D}}$ +5.2° (*c* 3.2 water). Found: C, 40.54; H, 5.39%.

**The Deamination of DL-*threo*-3-Methylaspartic Acid with Nitrous Acid.**—Five grams of DL-*threo*-3-methylaspartic acid4) were dissolved in 50 ml. of N hydrochloric acid, and the resulting solution was cooled to about 5°C in an ice bath. A solution of 3.5 g. of sodium nitrite in 30 ml. of water was then added slowly, with a continuous vigorous stirring and with cooling. (The addition required about 30 min.). After the addition, the reaction mixture was allowed to stand at 5°C for 1 hr., and then at room temperature overnight. To the reaction mixture, 50 ml. of concentrated hydrochloric acid were added, and the solution was evaporated to dryness in vacuo. Water was added, and the evaporation repeated. The yellowish residue was extracted several times with boiling acetone, and the white residue was discarded. The combined acetone extracts were evaporated under reduced pressure, and the resulting syrup was dissolved in a small amount of water. After decoloration with charcaol, the solution was again evaporated to a syrup; it was then allowed to stand in a refrigerator. The crystalline product was collected by suction, and two recrystallizations from ethyl acetate gave white crystals of II. Yield, 2.4 g.; m. p. 129°C. Found: C, 40.77; H, 5.59. Calcd. for $C_5H_8O_5$: C, 40.54; H, 5.44%.

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