Syntheses of 3,3-Dimethyl-2-hydroxybutyric Acid and Tertiary Leucine and Their Optical Resolutions

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DL-3,3-Dimethyl-2-hydroxybutyric acid (I) was prepared by the reduction of trimethylpyruvic acid (II) with sodium amalgam[1] and by catalytic hydrogenation with palladium black.[2] The optical resolution of I has not yet been attempted, however.

DL-*t*-Leucine (III) was prepared by the reduction of trimethylpyruvic acid oxime[3] and resolved into its optical isomers by the treatment of the *N*-formyl derivative of III with brucine.[4] The absolute configuration of the (−) isomer (IIIa) was finally determined to be L by Izumiya *et al.*[5]

In the present work, I was prepared by the catalytic hydrogenation of II with a Raney nickel catalyst and was resolved into optically-active isomers with brucine and cinchonidine. The absolute configuration of the (+) isomer (Ia) was determined to be L_s by the deamination of L-(−)-*t*-leucine (IIIa) with nitrous acid to Ia.

III was prepared by the reductive amination of II with a Raney nickel catalyst and was converted into the *N*-acetyl derivative and the amide. The (−) isomer was obtained with cinchonidine from the former and with D-tartaric acid from the latter.

Experimental

Preparation of DL-3,3-Dimethyl-2-hydroxybutyric Acid (I). The ether extracts of the oxidized product of 120 g of pinacolone with pottasium permanganate[6] were concentrated, and then the residue was neutralized with 5 N sodium hydroxide. The resulting solution was hydrogenated at 50°C in the presence of a Raney nickel catalyst prepared from 5 g of alloy.[7] After the catalyst had been removed by filtration, the filtrate was passed through a column of sulfonic resin (H^+ form) and then concentrated to dryness *in vacuo* at below 50°C. Crude crystals were dissolved in a minimal volume of benzene, and then petroleum benzin was added. The crystals were collected to give 80 g of I. Mp 87—88°C.

Found: C, 54.36; H, 9.11%. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15%.

Optical Resolution of I into L-(+)-3,3-Dimethyl-2-hydroxybutyric Acid (Ia). Seventy-five grams of I and 224 g of brucine were dissolved in 1 *l* of water, and then the solution was concentrated to 500 m*l*. After the solution had been allowed to stand overnight in a refrigerator, the brucine salts were collected. Six recrystallizations of the salt from water yielded the pure brucine salt of Ia. Yield 22 g; mp 223—224°C (decomp.), $[\alpha]_D^{20}$ −31° (*c* 1, alcohol).

Found: N, 5.32 Calcd for $C_{29}H_{38}N_2O_7$: N, 5.33%.

Twenty grams of the salts were treated with 5 N sodium hydroxide, and the liberated brucine was removed by filtration. The filtrate was treated with sulfonic resin to remove a trace of brucine and sodium ions, and then concentrated to dryness under reduced pressure. The crystallization of the crude material from benzene-petroleum benzin gave optically-pure Ia. Yield 3.9 g; mp 51—52°C, $[\alpha]_D^{20}$ +4.5° (*c* 4, water). $[\alpha]_D^{20}$ −63° (*c* 1, water, 48.5 mg ammonium molybdate in 10 m*l*).

Found: C, 54.75; H, 9.30%.

Optical Resolution of I into D-(−)-3,3-Dimethyl-2-hydroxybutyric Acid (Ib). Thirty-five grams of cinchonidine and 15.8 g of I were dissolved in 100 m*l* of alcohol, and then the solution was allowed to stand overnight in a refrigerator to give 33 g of the cinchonidine salt. Five recrystallizations of the salt from alcohol gave pure cinchonidine salt of Ib. Yield 9 g; Mp 220—221°C, $[\alpha]_D^{20}$ −10.2° (*c* 1, alcohol).

Found: C, 69.46; H, 8.11; N, 6.24%. Calcd for $C_{25}H_{34}N_2O_4$: C, 70.09; H, 8.03; N, 6.57%.

Nine grams of the salt obtained were suspended in 100 m*l* of hot water, and then decomposed with 5 m*l* of 5 N sodium hydroxide under vigorous stirring for a day. After the removal of the cinchonidine by filtration, the filtrate yielded pure Ib when treated by the procedure described above. Yield 2.3 g; mp 50—51°C, $-[\alpha]_D^{20}$ −4.3° (*c* 4, water), $[\alpha]_D^{20}$ +65° (*c* 1, water, 51 mg of ammonium molybdate in 10 m*l*).

Found: C, 54.36; H, 9.38%.

Preparation of (+)-3,3-Dimethyl-2-hydroxybutyric Acid (Ia) from L-(−)-*t*-Leucine (IIIa). A solution of 0.77 g of sodium nitrite in 10 m*l* of water was added, drop by drop, to a solution of 1.4 g of L-(−)-*t*-leucine (IIIa) ($[\alpha]_D^{20}$ −8.5) in 10 m*l* of 2 N sulfuric acid. After the evolution of nitrogen had ceased, 5 m*l* of 2 N sulfuric acid was added and the product was extracted with ether. The ether extract was concentrated, and the residue was dissolved in 10 m*l* of water and decolorized with charcoal. After concentration *in vacuo*, the residual crude crystals were dissolved in a minimal volume of benzene, and then petroleum benzin was added. The resulting solution was cooled to give an acid (Ib). Yield, 70 mg; mp 43°C, $[\alpha]_D^{20}$ −58° (*c* 1, water, 50 mg of ammonium molybdate in 10 m*l*).

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6) R .Adams and E. W. Adams, "Organic Syntheses," Coll. Vol. II, p. 459 (1948).
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Preparation of DL-*t*-Leucine Hydrochloride (IV). Sodium trimethylpyruvate prepared from 62 g of II was subjected to reductive amination in 300 m*l* of concentrated aqueous ammonia (at 100 atm and 60°C) with a Raney nickel catalyst prepared from 3 g of alloy. The reaction mixture was then concentrated under reduced pressure. After the addition of sufficient 6 N hydrochloric acid to form the hydrochloride, the solution was evaporated to dryness and the IV was taken up with methanol. After the removal of the methanol, there remained 50 g of IV.

Preparation of *N*-Acetyl-DL-*t*-Leucine (V). III prepared from 50 g of IV by neutralization with 10 N sodium hydroxide was acetylated with a mixture of 90 m*l* of acetic anhydride and 20 m*l* of acetic acid at room temperature for 6 hr. The reaction mixture was then evaporated to dryness, and the product was taken up with alcohol. After the removal of the alcohol, the residual substance was recrystallized from alcohol. Yield 31.5 g; mp 229—231°C.

Found: C, 55.39; H, 8.59; N, 8.02%. Calcd for $C_6H_{14}NO_2Cl$: C, 55.47; H, 8.73; N, 8.39%.

Optical Resolution of V and Isolation of L-*t*-Leucine (IIIa). Sixty-five grams of V and 110 g of cinchonidine were dissolved in 200 m*l* of hot alcohol, after which the solution was allowed to stand overnight in a refrigerator. The crystalline precipitates were then collected. Six recrystallizations of the salt from alcohol gave 12 g of pure cinchonidine salt of IIIa. Twelve grams of the salt were decomposed with 1 N sodium hydroxide, and the liberated cinchonidine was filtered off. The filtrate was shaken with chloroform, acidified with 2 N hydrochloric acid, concentrated to 100 m*l* and extracted with ethyl acetate. The extract was evaporated to dryness, and the residue was recrystallized from a mixture of water and alcohol. 1.2 g of (−)-*N*-acetyl-*t*-leucine (VI) were obtained; mp 228—229°C, $[\alpha]_D^{20}$ −40° (*c* 1, water).

1.2 g of VI were hydrolyzed with hydrochloric acid, and then the hydrolysate was concentrated and the excess hydrochloric acid was removed by azeotropic distillation with water. The resulting crystals were dissolved in 20 m*l* of water and neutralized with diethylamine, and then 2 m*l* of alcohol were added. After the solution had stood overnight, IIIa was obtained. Yield 820 mg; mp 280°C (sublimed), $[\alpha]_D^{20}$ −9.5° (*c* 2, water).

Preparation of DL-*t*-Leucine Methylester Hydrochloride (VII). The product obtained from the reductive amination of 50 g of II was concentrated *in vacuo*, and the residue was extracted with 300 m*l* of methanol. Then to the extract there were added 100 m*l* of toluene, and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in 300 m*l* of methanol, and the solution was saturated with hydrogen chloride, refluxed for 6 hr, and concentrated to dryness *in vacuo* at below 60 °C. A trace of water remaining in the residue was removed by azeotropic distillation with toluene; the subsequent addition of 5 m*l* of ether to the residue gave 27 g of VII. Mp 180—181°C.

Preparation and Optical Resolution of DL-*t*-Leucine Amide and Isolation of (−)-*t*-Leucine (III). Twenty-seven grams of VII were dissolved in 1 *l* of chloroform, and then dry ammonia was bubbled into the solution at 0°C. The ammonium chloride formed was filtered off, and the chloroform was removed under reduced pressure. The residual syrup was shaken with 200 m*l* of liquid ammonia in a 1-*l* autoclave for 12 hr at 55—60°C. After the ammonia had been evaporated off, the residue and 33.5 g of D-tartaric acid were dissolved in 45 m*l* of water. Storage overnight in a refrigerator gave 24.4 g of the salt. The salt was twice recrystallized from water to give 13.6 g of the pure D-tartrate of IIIa. $[\alpha]_D$ +0.88 (*c* 5, water).

13.6 g of the salt was hydrolyzed with 230 m*l* of 4 N hydrochloric acid for 6 hr, and the hydrolysate was concentrated to dryness. The residue was dissolved in 200 m*l* of water, and the solution was passed through a column of a weakly basic resin (Amberlite GC-45, OH^- form) to remove the tartaric acid and hydrochloric acid. *t*-Leucine was eluted with 400 m*l* of 0.5% aqueous acetic acid, after which to the eluate there was added 10 m*l* of concentrated hydrochloric acid. The resulting solution was concentrated to dryness. The residue was dissolved in a mixture of 9 m*l* of methanol and 4 m*l* of water, and the pH of the resulting solution was adjusted to 6.5 with diethylamine to yield 3 g of crude IVa, which was then recrystallized from a mixture of water and alcohol. Yield 1.7 g, $[\alpha]_D^{20}$ −9.0° (*c* 4, water). Found: C, 54.78; H, 10.09; N, 10.74%.

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