BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 286—287 (1971)

The Resolution of *t*-Butyloxycarbonyl-DL-*α*-phenylsarcosine

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(Received August 26, 1970)

α-Phenylsarcosine was first found in nature by Sheehan *et al.* from the hydrolysate of etamycin and was proved to belong to the L-series.1) Although Sheehan *et al.*1) reported that the amino acid isolated from etamycin showed $[\alpha]_D^{31}$ +118° (in N hydrochloric acid), this value seemed to show not the actual value, but that of partially racemized α-phenylsarcosine. Since the actual specific rotation values of this amino acid has not yet been established as far as we know, we attempted to obtain optically pure components. In this paper the resolution of DL-α-phenylsarcosine using ephedrines is described. The usefulness of these substances for the resolution of amino acids has reported in a previous paper.2)

t-Butyloxycarbonyl-DL-α-phenylsarcosine (I), which was prepared by the *t*-butyloxycarbonylation of DL-α-phenylsarcosine,3) following a procedure of Sakakibara *et al.*,4) was mixed with (—)-ephedrine (molar ratio 1:1.1) in benzene - hexane to give crystalline *t*-butyloxycarbonyl-L-α-phenylsarcosine·(—)-ephedrine salt (II).

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1) J. C. Sheehan, H. G. Zachau, and W. B. Lawson, *J. Amer. Chem. Soc.*, **80**, 3349 (1958).

2) K. Oki, K. Suzuki, S. Tuchida, T. Saito, and H. Kotake; This Bulletin **43**, 2554 (1970).

3) T. Araga, T. Saito, and H. Kotake, *Nippon Kagaku Zasshi*, **86**, 111 (1965).

4) S. Sakakibara, I. Honda, and K. Takada, This Bulletin, **42**, 809 (1969).

The filtrate from this salt was treated with (+)-ephedrine in benzene - hexane at room temperature to give *t*-butyloxycarbonyl-D-α-phenylsarcosine·(+)-ephedrine salt (III). The salt II was treated with hydrochloric acid to give *t*-butyloxycarbonyl-L-α-phenylsarcosine (IV) ($[\alpha]^{24}_{D}$ +134.8°), which was then treated with formic acid[5] to give L-α-phenylsarcosine (VI), $[\alpha]^{34}_{D}$ +169.3° (in N hydrochloric acid). By a similar procedure, III was converted to *t*-butyloxycarbonyl-D-α-phenylsarcosine (V)($[\alpha]^{29}_{D}$ −134.1°),which was then treated with formic acid to give D-α-phenylsarcosine (VII), $[\alpha]^{34}_{D}$ −170.7° (in N hydrochloric acid). These values of L- and D-phenylsarcosine were supported by the results of an alternative method of resolution. The resolution of benzyloxycarbonyl-DL-α-phenylsarcosine with brucine, followed by the removal of the benzyloxycarbonyl group by means of catalytic reduction, gave L-α-phenylsarcosine, $[\alpha]^{34}_{D}$+169.9° (in N hydrochloric acid).

Experimental

All the melting points are uncorrected. The optical rotation values were measured with a Jasco DIP-SL-type polarimeter.

t-*Butyloxycarbonyl*-DL-*α-phenylsarcosine (I).* A stock solution of *t*-butyl chloroformate was added to a solution of 7.59 g (0.03 mol) of DL-α-phenylsarcosine in ethanol containing 3.89 g of potassium hydroxide, and then 10 m*l* of dimethylformamide was added with stirring at 0—−3°C. The reaction mixture was agitated vigorously during the addition over a period of about half an hour. The stirring was continued for a further 2 hr at 0°C, and then for an additional hour at room temperature. The reaction mixture was subsequently adjusted to pH 2—3 with N hydrochloric acid, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated solution of sodium chloride and dried over anhydrous sodium sulfate. The ethyl acetate was evaporated to dryness to afford 4.4 g of *t*-butyloxycarbonyl-DL-α-phenylsarcosine (55.3%). Recrystallization from benzene - petroleum ether gave 4.0 g of I with a melting point of 122—123°C (50.2%).

Found: C, 63.30; H, 7.35; N, 5.26%. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28%.

t-*Butyloxycarbonyl*-L-*α-phenylsarcosine*·(−)-*Ephedrine Salt (II) and* t-*Butyloxycarbonyl*-D-*α-phenylsarcosine*·(+)-*Ephedrine Salt (III).* 1.060 g (0.004 mol) of I and (−)-ephedrine hemihydrate (750 mg, 0.0043 mol) were dissolved in 2 m*l* of hot benzene, and then 7 m*l* of hexane were added. The mixture was then allowed to stand for 24 hr at room temperature. The deposited crystals were filtered off and washed with 4 m*l* of benzene - hexane (1 : 3) to afford 830 mg (92.6%) of II, mp 84—88°C. Two recrystallizations from ethyl acetate-petroleum ether gave 680 mg (75.9%) of the pure material with a melting point of 91—93°C. $[\alpha]^{27}_{D}$ +65.2° (*c* 0.951; absolute ethanol).

Found: C, 64.23; H, 8.10; N, 6.37%. Calcd for $C_{24}H_{34}O_5N_2\cdot H_2O$: C, 64.26; H, 8.09; N, 6.25%.

The mother liquor obtained after the removal of II was evaporated to dryness to give an oily material. This oily material was dissolved in 6 m*l* of ethyl acetate, and the ethyl acetate layer was washed with 3 m*l* of N hydrochloric acid and water. The organic layer was dried over anhydrous sodium sulfate and then evaporated to dryness to give 530 mg of an oily product. This product and (+)-ephedrine hemihydrate (375 mg, 0.0022 mol) were dissolved in 1.3 m*l* of hot benzene, and then 7 m*l* of hexane were added. The deposited crystals were filtered off to afford 560 mg (65.2%, mp 84—89°C) of III. Two recrystallizations from ethyl acetate-petroleum ether gave 500 mg (55.8%) of an optically pure material with a melting point of 91—93°C. $[\alpha]^{28}_{D}$ −65.2° (*c* 0.605; absolute ethanol).

Found: C, 63.85; H, 8.17; N, 5.93%. Calcd for $C_{24}H_{34}O_5N_2\cdot H_2O$: C, 64.26; H, 8.09; N, 6.25%. A mixed-melting-point determination of (−) and (+) salt was depressed to 80—85°C.

t-*Butyloxycarbonyl*-L-*α-phenylsarcosine (IV).* To a suspension of 600 mg (0.0014 mol) of II in 7 m*l* of ethyl acetate, there were added 2.3 m*l* of N hydrochloric acid; the mixture was then shaken effectively in a separatory funnel. After washing with water (three 1-m*l* portions), the ethyl acetate layer was dried over anhydrous sodium sulfate. The ethyl acetate was evaporated to dryness to give 370 mg of crude crystals (quantitative, mp 110—112°C). Recrystallization from benzene-petroleum ether gave 312 mg (84.3%) of pure crystals with a melting point of 111.5—112.5°C. $[\alpha]^{24}_{D}$ +134.8° (*c* 0.804, absolute ethanol).

Found: C, 63.73; H, 7.23; N, 5.60%. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28%.

t-*Butyloxycarbonyl*-D-*α-phenylsarcosine (V).* Following the method used for the preparation of IV, from 600 mg (0.0014 mol) of III, 340 mg of crude crystals were obtained (91.9%, mp 110—111°C). Recrystallization from benzene-petroleum ether gave 300 mg (80.1%) of pure crystals with a melting point of 112—112.5°C. $[\alpha]^{29}_{D}$ −134.1° (*c* 0.682, absolute ethanol).

Found: C, 63.25; H, 7.32; N, 5.18%. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28%.

L-*α-Phenylsarcosine (VI).* 150 mg (0.566 mmol) of IV were dissolved in 7.5 m*l* of formic acid, and the mixture was allowed to stand for 1.5 hr at 22°C. The formic acid was evaporated to dryness at 22°C to afford 87 mg of VI (93.7%). Recrystallization from water - acetone gave 80 mg of a pure material (86.2%). $[\alpha]^{34}_{D}$ +169.3° (*c* 0.655, N hydrochloric acid), mp 245° (sublime).

Found: C, 65.45; H, 6.72; N, 8.18%. Calcd for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.43%.

D-*α-Phenylsarcosine (VII).* Following the method used for the preparation of L-α-phenylsarcosine, 88 mg of VII was obtained from 150 mg of V (94.8%). Recrystallization from water - acetone gave 80 mg of a pure material (86.2%). $[\alpha]^{34}_{D}$ −170.7° (*c* 0.571, N hydrochloric acid), mp 244°C (sublime).

Found: C, 65.68; H, 6.84; N, 8.34%. Calcd for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.43%.

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[5] B. Halpern and D. E. Nitecki, *Tetrahedron Lett.*, **1967**, 3031.