Registry No.—1-Ethoxycyclopropanol, 13837-45-1; *p*-(dimethylamino)bromobenzene, 586-77-6; 5-bromocoumarin, 66826-78-6; *p*-(methoxy)bromobenzene, 104-92-7; *p*-(methyl)bromobenzene, 106-38-7; bromobenzene, 108-86-1.

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Preparation of Optically Pure *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine and Its Antipode

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O-Benzyl-L-serine derivatives are useful in peptide synthesis. The currently available methods for preparing these compounds are laborious and not convenient for large-scale preparation. Okawa[1] prepared *O*-benzyl-L-serine via bromination of methyl acrylate and resolved the racemate of the *N*-acetyl derivative by acylase. The other method is benzylation of N-*tert*-butyloxycarbonyl-L-serine in sodium–liquid ammonia[2] or in sodium hydride–dimethylformamide.[3] The acylase method can obtain optically pure *O*-benzyl-L-serine but the amino-protecting group should be introduced again for peptide synthesis. The enzyme, however, is not cheap and is hard to obtain. The second method, benzylation of *N-tert*-butyloxycarbonyl-L-serine, is only around 50% in yield and racemization might occur in the benzylation process.

The direct resolution of *N-tert*-butyloxycarbonyl derivatives of racemic amino acids would be a better way of preparing optically pure protected amino acids rather than incorporating the protecting group onto optically active amino acids or derivatives.

We present here a new method for the preparation of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode. Both enantiomers appeared optically pure and the yields are higher than the published values.

Starting from methyl acrylate, *O*-benzyl-DL-serine obtained[1] was converted to *N-tert*-butyloxycarbonyl derivative[4] and then methylated by diazomethane.[5] The butyloxycarbonyl group might be introduced to the amino acid methyl ester prepared by thionyl chloride in methanol. The racemic acyl amino acid methyl ester was then hydrolyzed under papain catalysis to afford the L acid in 72% yield; its antipode was recovered in 81% yield from the unreacted D ester by mild alkaline treatment.

The same approach to other amino acids including threonine derivative, which has two optical centers, is under investigation.

Experimental Section

***N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine Dicyclohexylammonium Salt.** *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine (mp 90–91 °C, from ether/*n*-hexane) (5.9 g, 20 mmol) prepared from *O*-benzyl-DL-serine was dissolved in ether (100 mL). The ethereal solution of diazomethane[7] was dropped in until the solution remained pale yellow. The mixture was then washed twice with 20-mL portions of 1 N $NaHCO_3$, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to dryness. The oily ester (6.0 g, 98%) obtained was dissolved in 10 mL of dimethylformamide and then added to a phosphate buffer solution (0.05 M, pH 6.0) containing 5 mmol of β-mercaptoethanol, 5 mmol of EDTA and 500 mg of crude papain. The mixture was kept at 35 °C with stirring and the pH was maintained at 6.0 by addition of 1 N NaOH. After 4 h and with no decrease in pH, the mixture was extracted twice with 50-mL portions of ether to recover the unreacted ester. The aqueous solution was then acidified to pH 3.0 with 3 N HCl and extracted three times with 50-mL portions of ethyl acetate. The combined ethyl acetate was washed with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure to give a colorless oil. The oil was dissolved in 30 mL of ether/*n*-hexane (1:1 v/v) followed by addition of dicylcohexylamine (1.6 mL). The precipitates formed after cooling were collected by filtration to give the title compound (3.4 g, 72%): mp 135–136 °C; R_f 0.78 (system A), 0.20 (system B); $[\alpha]^{25}_D$ +25.0 (*c* 2, MeOH) [lit.[7] mp 135.5–136 °C, $[\alpha]^{25}_D$ +24.3 (*c* 2.94, MeOH)].

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 8.92; N, 6.03.

***N-tert*-Butyloxycarbonyl-*O*-benzyl-D-serine Dicyclohexylammonium Salt.** The unreacted ester obtained above in ether was washed with water, dried, and evaporated to give an oil (3.4 g, 11 mmol), which was further digested with papain (50 mg) in the same way as described above (in 100 mL of solution) for 4 h and the unreacted ester was isolated again (2.5 g, 8.1 mmol): R_f 0.88 (system B); $[\alpha]^{25}_D$ +2.5 (C 2, MeOH). It was hydrolyzed by stirring in a mixture of dioxane–1 N NaOH (1:1 v/v) (30 mL) with 1.5 equiv of alkali for 20 min. The solution was then acidified and followed by extraction to prepare the dicyclohexylammonium salt of *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine (3.8 g, 8 mmol): mp 133–134 °C; $[\alpha]^{25}_D$ −24.2 (*c* 2, MeOH) [lit.[7] mp 130–131 °C; $[\alpha]^{25}_D$ −23.6 (*c* 2.28, MeOH)]; TLC data were the same as for the L isomer.

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 9.11; N, 6.06.

The Steric Purity. An aliquot of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode obtained by the above procedure were dissolved in 5 mL of 2 N HCl–AcOH, respectively. After 1 h at room temperature, the reaction mixture was evaporated under reduced pressure at 25 °C to yield a residue which was then diluted to 5 mL with 1 N HCl for optical rotation determination. The samples showed the same optical rotation in absolute value, respectively, as a sample of *O*-benzyl-L-serine[1] similarly treated, $[\alpha]^{25}_D$ =7.4 (*c* 2, 1 N HCl).

Registry No.—*N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine dicyclohexylammonium salt, 30200-52-3; *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine, 53317-22-9; *O*-benzyl-DL-serine, 5445-44-3; dicyclohexylamine, 101-83-7; *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine dicyclohexylammonium salt, 10342-02-6.

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Synthesis of β-Dihydrothebaine

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The 6,14-*endo*-etheno and 6,14-*endo*-ethanotetrahydrooripavines are among the most potent analgesics known.[1]

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