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Synthesis of (S)-Isoserine

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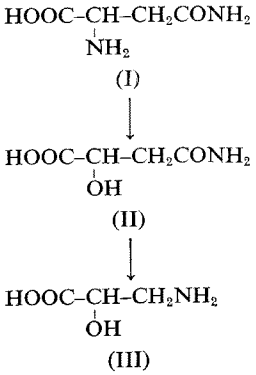
Butirosin,[1] a new aminoglycoside antibiotic, has an amino acid in its chemical structure. The amino acid was found to be (S)-(−)-4-amino-2-hydroxybutyric acid ((S)-HABA).[2] The chemical modification of butirosin in its amino acid side-chain was reported by Haskell *et al.*[3] The compound with (S)-(−)-4-amino-2-hydroxybutyryl side-chain had the highest activity against Gram-positive and Gram-negative bacteria and the compound with (S)-(−)-3-amino-2-hydroxypropionyl ((S)-isoseryl) side-chain was also found to be highly effective. All the attempts to prepare (S)-(−)-3-amino-2-hydroxypropionic acid from (S)-2, 3-diaminopropionic acid by the method described in the preceding paper[4] were failed.

A new synthetic route from L-asparagine (I) was devised and (S)-isoserine (III) was obtained in good yield by two steps. L-Asparagine has both a primary amino function and a primary amide function. Each function reacts with sodium nitrite to give an alcohol and a carboxylic acid respectively. But, generally, primary amino group is more sensitive to sodium nitrite than primary amide. We found the condition under which the amino group was converted to the hydroxy group while the amide group remained. Namely, 1 mole of L-asparagine reacted with 1～2 moles of sodium nitrite in aqueous acetic acid under cooling. The reaction mixture was purified by resin column chromatography and recrystallized from aqueous ethanol. (S)-3-Carbamoyl-2-hydroxypropionic acid (L-β-malamidic acid) (II) was obtained in good yield (83%).



The synthetic route from L-β-malamidic acid (II) to (S)-isoserine (III) was already reported by Freudenberg[5] using the Hofmann reaction; L-β-malamidic acid (II) was treated with sodium hypochlorite in an alkaline solution and purified by resin column chromatography and recrystallized from aqueous ethanol to give (S)-isoserine (III).

EXPERIMENTAL

L-β-Malamidic acid (II). To a solution of L-asparagine (I) (5.0 g) in aq. acetic acid (20%) was added a solution of sodium nitrite (3.45 g/100 ml H_2O) with vigorous stirring in an ice bath. The reaction mixture was stirred in an ice bath for one hour. After being stirred further overnight at room temperature, the solution was evaporated to a solid, which was dissolved in water and charged on a column of ion exchange resin IRA-400 (OH^-) (200 ml). After the column was washed with water (600 ml), it was developed with 5% acetic acid from 300 ml to 2300 ml to give a fraction containing L-β-malamidic acid, which was evaporated to a solid. This solid was recrystallized from 90% aqueous ethanol to give 3.13 g of L-β-malamidic acid in 83% yield. mp 143～144°C, $[\alpha]_D^{20}$ −10.5° (c=1.0, H_2O), IR ν_{max}^{KBr} cm^{-1}; 3400, 3250, 2890, 1735, 1720, 1670, 1650, 1575, 1414, 1260, 1180, 1103, 948. NMR (in Py d-5) δ: 10.33 (1H, s, COOH) 5.21 (1H, dd, J=5.2, 6.8 Hz, H-1) 3.41 (1H, dd, J=15.6, 6.8 Hz, H-2) 3.15 (1H, dd, J=15.6, 5.2 Hz, H-2′). *Anal.* Found: C, 36.13; H, 5.25; N, 10.54. Calcd. for $C_4H_7NO_4$: C, 36.09; H, 5.30; N, 10.53%.

(S)-Isoserine (III). To a solution of L-β-malamidic acid (500 mg) in 0.5 N sodium hypochlorite (8.4 ml), 2.5 N sodium hydroxide solution (8.4 ml) was added in an ice bath. The mixture was stirred for 1 hr in the ice bath and further for 30 min at 90°C. After the solution was neutralized with hydrochloric acid, the solution was charged on a column of Dowex 1×2 (OH^-) (70 ml) and the column was washed with water (350 ml). Elution with 5% aqueous acetic acid from 115 ml to 140 ml gave a fraction containing (S)-isoserine which was evaporated to a solid. This solid was recrystallized from 80% aqueous ethanol to give 112 mg of (S)-isoserine in 28% yield. mp 188～189°C $[\alpha]_D^{20}$ −31.7° (c=1.0, H_2O), IR ν_{max}^{KBr} cm^{-1}; 3270, 2870, 1620, 1535, 1403, 1380, 1082. NMR (in D_2O) δ: 4.28 (1H, dd, J=7.5, 4.8 Hz, H-1) 3.42 (1H, dd, J=13.0, 4.8 Hz, H-2) 3.10 (1H, dd, J=13.00, 7.5 Hz, H-2′). *Anal.* Found: C, 34.13; H, 6.63; N, 13.08. Calcd. for $C_3H_7NO_3$: C, 34.28; H, 6.72; N, 13.33%.

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