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Yasuhiro Yamada[a] & Hirosuke Okada[a]
[a] Department of Fermentation Technology, Faculty of Engineering, Osaka University, Yamada-kami, Suita-shi, Osaka, Japan
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Synthesis of DL-4-Amino-2-hydroxybutyric Acid

Yasuhiro YAMADA and Hirosuke OKADA

Department of Fermentation Technology, Faculty of Engineering, Osaka University, Yamada-kami, Suita-shi, Osaka, Japan

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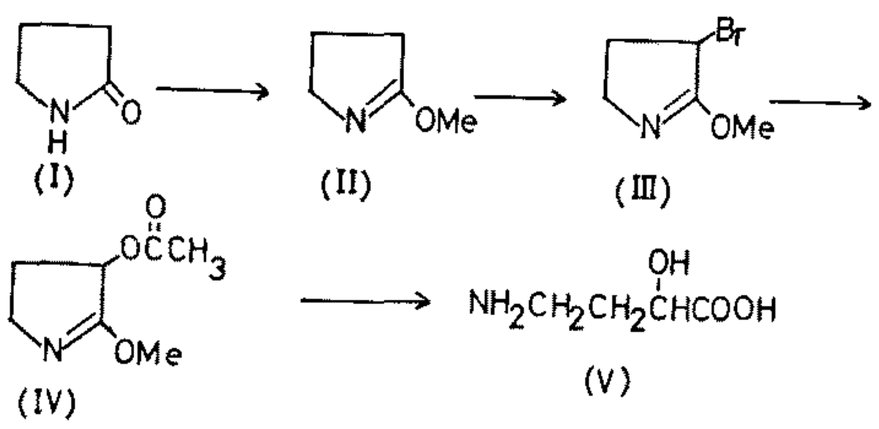
L-(−)-4-Amino-2-hydroxybutyric acid (V) is a component of butirosin A and B which are antibiotics produced by *Bacillus circulans*.[1] Butirosin A and B are aminoglycoside antibiotics to which L-4-amino-2-hydroxybutyric acid is attached to form an amide bonding with deoxystreptamine moiety of these molecules.[2] These antibiotics are active against many gram-positive and some gram-negative bacteria.[1,3] Additionally, acylation of an amino group in 2-deoxystreptamine moiety of some aminoglycosidic antibiotics with L-4-amino-2-hydroxybutyric acid afforded a group of new type semisynthetic antibiotics.[4] In this connection, it is of considerable current interest to devise a new method to synthesize 4-amino-2-hydroxybutyric acid.

P. W. K. Woo *et al.* synthesized L-(−)-4-amino-2-hydroxybutyric acid through partial deamination of L-(+)-2,4-diaminobutyric acid in their attempts at structural elucidation of butirosins.[2a] Recently S. Iriuchijima *et al.* reported effective synthesis of N-benzyloxycarbonyl-4-amino-2-hydroxybutyric acid from N-benzyloxycarbonyl-β-alanine methylester and dimethylsulfoxide by applying the Pummerer reaction.[5] H. Sato *et al.* also reported synthesis of DL-4-amino-2-hydroxybutyric acid starting from methyl acrylate and nitromethane ethyl ester.[6] In this report we wish to describe four-step transformation of 2-pyrrolidone (I) into DL-4-amino-2-hydroxybutyric acid (V).



2-Pyrrolidone (I) was converted into 2-methoxy-1-pyrroline (II) by treatment with dimethylsulfate.[7] Iminoether (II) was brominated in the C-3 position by refluxing with an equivalent amount of N-bromosuccinimide in CCl_4.[8] 3-Bromo-2-methoxy-1-pyrroline (III) was transformed into 3-acetoxy-2-methoxy-1-pyrroline (IV) by refluxing with 2 equivalents of potassium acetate in acetonitrile in the presence of a catalytic amount of 18-crown-6. In the absence of 18-crown-6, this substitution reaction did not take place in acetonitrile. In dimethylsulfoxide, without 18-crown-6, acetoxylation took place at 40°C with sodium acetate or silver acetate. However, under these conditions, the yield was low (40～55%) and the reaction was not completed after 24 hr, resulting in a product contaminated with (III).

3-Acetoxy-2-methoxy-1-pyrroline (IV) was smoothly hydrolysed into 4-amino-2-hydroxybutyric acid (V) by treatment with hydrochloric acid solution. Amino acid (V) thus obtained showed reasonable analytical values and spectra of NMR and IR.

EXPERIMENTAL

3-Acetoxy-2-methoxy-1-pyrroline (IV)

3-Bromo-2-methoxy-1-pyrroline* (1.78 g, 0.02 mole) was refluxed in 21 ml of acetonitrile for 3 hr with 0.2 g of 18-crown-6 acetonitrile complex. After cooling the reaction mixture, precipitated potassium bromide was removed by filtration and the filtrate was concentrated under reduced pressure. Dichloromethane (30 ml) was added to the residue and the precipitate was filtered. The filtrate was concentrated and distilled under reduced pressure. A slightly yellow oil was obtained. bp 65～72°C (5 mmHg), Yield 1 g (63.7%). IR ν_{max}^{film} cm^{-1}: 1740 (C=O), 1660 (C=N), 1240. NMR (in $CDCl_3$, TMS as reference) δ: 2.04 ($COCH_3$, singlet), 3.80 (OCH_3, singlet), 5.55 (C3–H, double doublet, J= 8 Hz, 7 Hz). 3.5～3.8 (two C5-H, multiplet), 1.8～2.1 (C3-H, multiplet), 2.3～2.6 (C3-H, multiplet). *Anal.* Found: C, 53.33; H, 7.19; N, 9.05. Calcd. for $C_7H_{11}O_3N$: C, 53.49; H, 7.05; N, 8.91%.

DL-4-Amino-2-hydroxybutyric acid (V)

3-Acetoxy-2-methoxy-1-pyrroline (IV) (1.0 g) was refluxed in 10 ml of 6 N HCl solution for 5 hr. Water and hydrochloric acid were evaporated under reduced pressure and the residue was dissolved in a small amount of water. This solution was placed on a column of Dowex 50W–X8 and washed with water. 4-Amino-2-hydroxybutyric acid was eluted with 2% ammonia solution. After evaporation of water and ammonia from this fraction, curde crystals of the amino acid were obtained. The crude product thus obtained was recrystallized from methanol-water (1:1) yield, 0.73 g (96.3%). Mp 189°C. IR ν_{max}^{Nujol} cm^{-1}: 3420, 1640 (C=O), 1560, 1290, 1090. NMR (in D_2O DSS as reference) δ: 1.8～2.3 (two C3-H, multiplet), 3.11 (two C4-H, triplet, 7.5 hz), 4.12 (C_2–H, double doublet, J=

* As 3-bromo-2-methoxy-1-pyrroline (III) is thermally labile, it is better to use the crude product for the next acetoxylation reaction without distillation.

7.5 Hz, 5 Hz). *Anal.* Found: C, 40.02; H, 7.94; N, 11.69. Calcd. for $C_4H_9O_8N$: C, 40.33; H, 7.62; N, 11.76%.

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