A New Synthesis of L-4-Amino-2-hydroxybutyric Acid. Carboxyl-Assisted Nitrile Synthesis from Primary Amides

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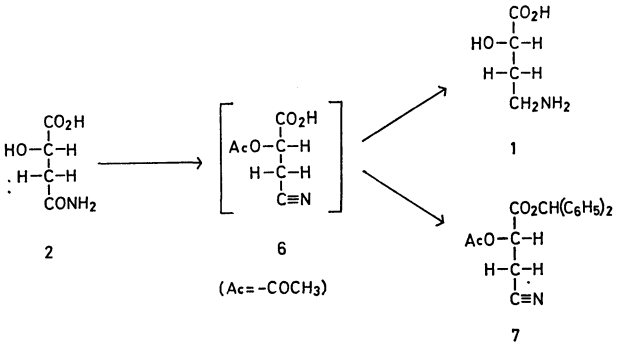
L-2-Hydroxysuccinamic acid prepared from L-asparagine was dehydrated with acetic anhydride in pyridine, affording the respective ω-cyano acid, which, on catalytic hydrogenation, gave the title compound. Similarly, the amide groups of some other β- and γ-amic acids were dehydrated to give the respective cyano acids in good yields.

Butirosin B,[1,2] an antibiotic produced by *Bacillus circulans*, is a derivative of ribostamycin acylated with the title acid (**1**) at the C-1 amino group of the 2-deoxystreptamine moiety, and it is active against ribostamycin- and kanamycin-resistant organisms, including *Pseudomonas* strains. Kawaguchi *et al.*[3] synthesized amikacin (BB-K8) by the condensation of kanamycin A with **1** at the C-1 amino group of the deoxystreptamine moiety. Amikacin is also active against kanamycin-resistant organisms. On the basis of these facts, **1** is presumed to be a valuable amino acid in chemical-modification studies of amino-sugar antibiotics.

Although **1** had previously been synthesized by the partial deamination of L-2,4-diaminobutyric acid[2,4] or by the Hofmann degradation of L-2-hydroxyglutaramic acid[5] prepared from L-glutamine, we have searched for other potential methods which might be more convenient and adequate for large-scale perparation. We wish now to describe a three-step synthesis of **1** using L-asparagine as the starting material.

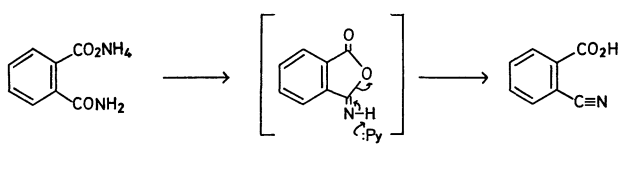
L-Asparagine was first converted to L-2-hydroxysuccinamic acid (**2**) by treatment with sodium nitrite.[6] Then we attempted to transform the amide group of **2** into the nitrile group without the protection of the other functional groups. Among several known dehydration methods of primary amides into nitriles, *p*-toluenesulfonyl chloride–pyridine[7] or trifluoroacetic abhydride–pyridine[8] methods were assumed to be adequate. However, the treatment of **2** with these reagents according to the described procedures afforded no cyano derivatives, but only a tarry product. Pyriadi *et al.*[9] reported that *N*-alkylmaleamic acids were easily converted to 4-(alkylimino)-2-butenolides with an acetic anhydride–triethylamine or acetyl chloride–triethylamine mixture. This fact prompted us to consider that the 3-iminophthalide produced from primary amide and carboxylate by the above methods might be convertible to nitrile and carboxyl groups as is shown in Scheme 1. As expected, the treatment of ammonium phthalamate (**3**) with two equivalents of acetic anhydride in pyridine afforded the *o*-cyanobenzoic acid (**5**) as a single product. Under similar conditions, benzamide was not converted to benzonitrile, but was recovered unchanged. Judging from these experimental results, the reaction is likely to proceed through the intermediary 3-iminophthalide (**4**), as is shown in Scheme 1. Indeed, the treatment of **2** with acetic anhydride in pyridine at room temperature afforded L-2-acetoxy-3-cyanopropionic acid (**6**). The hydrogenation of **6** with platinum oxide in aqueous ethanol under acidic conditions afforded **1** in a 30% yield form L-asparagine. As **6** was unstable,[10,11] the structure was confirmed as that of the corresponding benzhydryl ester (**7**).



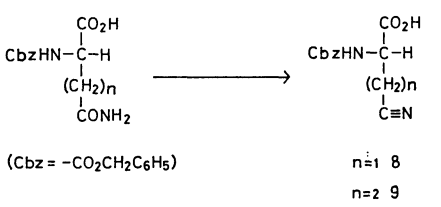
Scheme 2.

In order to extend this dehydration reaction further, we treated N^2-benzyloxycarbonyl-L-asparagine with acetic anhydride in pyridine. The product isolated in an 83% yield was identical with authentic *N*-benzyloxycarbonyl-3-cyano-L-alanine (**8**).[13] Similary, N^2-benzyloxycarbonyl-L-glutamine gave L-2-(benzyloxycarbonylamino)-4-cyanobutyric acid (**9**) in a good yield as a thick syrup. The hydrogenation of **9** gave ornithine and a trace amount of proline, both of which were identified by paper chromatography.[13]

The mild conditions, easy dehydration, and reasonable yields of **5**, **6**, **8**, and **9** indicate that this dehydration method would be useful for the synthesis of various β- and γ-cyano carboxylic acids.



Scheme 1.



Scheme 3.

Experimental

The melting points are uncorrected. The optical rotation were measured with a Perkin-Elmer Model 241 polarimeter. The NMR spectra were recorded at 60 MHz with a Varian S-60T spectrometer.

o-Cyanobenzoic Acid (5). A solution of ammonium phthalamate (**3**) (165 mg) and acetic anhydride (0.2 ml) in pyridine (4 ml) was kept at room temperature for 1 h. Almost all of the solvent was then removed by evaporation under reduced pressure, and the residue was diluted with ethyl acetate (15 ml). The resulting solution was washed with 1M-hydrochloric acid and a saturated aqueous sodium chloride solution, and dried over sodium sulfate. The solution was subsequently concentrated to give a white powder (105 mg). Recrystallization from ethyl acetate afforded a white granule of **5** (72 mg); mp 227—228 °C (lit,[10] mp 226—230 °C); IR (KBr): 1690 (COOH) and 2240 cm^{-1} (CN).

Found: C, 65.19; H, 3.50; N, 9.78%. Calcd for $C_8H_5NO_2$: C, 65.30; H, 3.43; N, 9.52%.

L-4-Amino-2-hydroxybutyric Acid (1). A solution of L-2-hydroxysuccinamic acid (**2**)[6] (532 mg) and acetic anhydride (1.5 ml) in pyridine (15 ml) was kept at room temperature for 1 h. The solution was then concentrated to thick syrup under reduced pressure. The resulting crude L-2-acetoxy-3-cyanopropionic acid (**6**) was dissolved in a mixture of ethanol (20 ml), water (5 ml), and concd hydrochloric acid (1 ml), and hydrgenated with platinum oxide (50 mg) for 6 h under a pressure of 3 atm. After the removal of the catalyst, the filtrate was concentrated to a thick syrup, which was dissolved in water (10 ml) and chromatographed on Dowex 50W-X4 resine (H^+ form). After being washed with water, the column was developed with 0.5M-ammonium hydroxide. The eluted fraction was concentrated to give a crude compound, **1** (291 mg). This was dissolved in a mixture of methanol (9.6 ml) and water (2.3 ml) and then stored at 5 °C overnight. The crystals thus precipitated were collected and dried. 177 mg (37.2%); mp 197—198.5 °C, $[\alpha]_D^{25}$ −28.2° (*c* 1.2, water) (lit, mp 203—206 °C,[2] 200—200.5 °C,[4] $[\alpha]_D^{25}$ −28.2° (*c* 1.22, water),[2] −29.1° (*c* 1.0, water)[4]); NMR (D_2O): δ 1.97 (2H, m, CH_2), 3.16 (2H, t, N-CH_2), 4.16 (1H, q, C<u>H</u>(OH)COOH).

Found: C, 40.27; H, 7.65; N, 12.01%. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76%.

Benzhydryl L-2-Acetoxy-3-cyanopropionate (7). To a solution of crude **6**, obtained from **2**, (775 mg) as described for **1**, in acetone (16 ml), we added diazodiphenylmethane[12] (2 g) in acetone (6 ml). The solution was then allowed to stand at room temperature for 2 h. After working up with acetic acid, almost all of the solvent was removed under reduced pressure, and the residue was diluted with benzene (50 ml). The resulting solution was washed with water and dried over sodium sulfate. The solution was concentrated to *ca.* one-fifth in volume, and this residue was chromatographed on silica gel. Subsequent elution with benzene–ethyl acetate (50:1) afforded a thick syrup of **7** (1.5 g, 84%) on evaporation, $[\alpha]_D^{25}$ −36.3° (*c* 1.2, methanol); NMR ($CDCl_3$) : δ 2.13 (3H, s, $COCH_3$), 2.85 (2H, d, CH_2CN), 5.37 (1H, t, C<u>H</u>($OCOCH_3$)), 6.87 (1H, s, $CH(C_6H_5)_2$), 7.30 (10H, s, C_6H_5). IR (KBr): 2260 cm^{-1} (CN). Found: *m/e* 323.1163. Calcd for $C_{19}H_{17}NO_4$: M, 323.1157.

N-Benzyloxycarbonyl-3-cyano-L-alanine (8). A solution of N^2-benzyloxycarbonyl-L-asparagine (2.66 g). in acetic anhydride (1.2 ml) and pyridine (30 ml) was kept at room temperature for 1 h. The solution was then concentrated to a thick syrup under reduced pressure, and the residue was diluted with 1M-hydrochloric acid to give colorless needles of **8** (2.05 g, 83%). Recrystallization from 1,2-dichloroethane afforded pure **8**; mp 129—131.5 °C, $[\alpha]_D^{25}$ −18.7° (*c* 1.27, methanol) (lit,[13] mp 131—134 °C, $[\alpha]_D^{25}$ −19.0° (*c* 1.25, methanol)); IR (KBr): 1745 (COOH) and 2280 cm^{-1} (CN); NMR (C_5D_5N–D_2O): δ 3.43 (2H, d, CH_2CN), 5.11 (1H, t, C<u>H</u>(COOH)).

Found: C, 58.33; H, 4.91; N, 11.23%. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.05; H, 4.88; N, 11.29%.

L-2-(Benzyloxycarbonylamino)-4-cyanobutyric Acid (9). A solution of N^2-benzyloxycarbonyl-L-glutamine (1 g) in acetic anhydride (0.44 ml) and pyridine (15 ml) was kept at room temperature overnight. Most of the solvent was then removed under reduced pressure, and the residue was diluted with elthyl acetate (50 ml). The solution was washed with 1M-hydrochloric acid and a saturated aqueous sodium chloride solution, and then dried over sodium sulfate. The solution was concentrated to *ca.* 5 ml, which quantity was chromatographed over silica gel. Elution with chloroform–methanol (5 : 1) afforded a thick syrup of **9** (855 mg, 91%) on evaporation, $[\alpha]_D^{25}$ −12.5° (*c* 1.18, methanol); IR (film): 2245 cm^{-1} (CN). Found: *m/e* 262.0931. Calcd for $C_{13}H_{14}N_2O_4$: M, 262.0953.

The hydrogenation of this compound with palladium on charcoal in the presence of hydrochloric acid led to ornithine and proline, the structure of which were confirmed by paper chromatography.

References

1) P. W. K. Woo, H. W. Dion, G. L. Coffey, S. A. Fusari, and G. Senos, Ger. Offen., 1914527 (1969).
2) P. W. K. Woo, H. W. Dion, and O. R. Bartz, *Tetrahedron Lett.*, **1971**, 2617.
3) H. Kawaguchi, T. Naito, S. Nakagawa, and K. Fujisawa, *J. Antibiot.*, **25**, 695 (1972).
4) Y. Horiuchi, E. Akita, and T. Ito, *Agric. Biol. Chem.*, **40**, 1649 (1976).
5) T. Naitoh *et al.*, Japan Patent 504019 (1975).
6) T. Miyazawa, E. Akita, and T. Ito, *Agric. Biol. Chem.*, **40**, 1651 (1976).
7) M. Zaoral and J. Rudinger, *Collect. Czech. Chem. Commun.*, **24**, 1933 (1959).
8) F. Campagna, A. Carotti, and G. Gassini, *Tetrahrdron Lett.*, **1977**, 1813.
9) T. M. Pyriadi and H. J. Harwood, *J. Org. Chem.*, **36**, 821 (1971).
10) S. Wideqvist, *Arkiv. Kemi.*, **2**, 383 (1950).
11) S. Wideqvist, *Arkiv. Kemi.*, **3**, 281 (1951).
12) J. R. Adamson, R. Bywood, D. T. Eastlick, G. Gallagher, D. Walker, and E. M. Wilson, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 2030.
13) M. Wilcheck, S. Ariely, and A. Patchornik, *J. Org. Chem.*, **33**, 1258 (1968).