Synthesis of 1,2,3,4-Tetrahydro-1-oxo-pyrido[1,2-*a*]benzimidazole

Kazuyuki MAEKAWA and Jiro OHTANI*

Department of Engineering, Kyushu-Kyoritsu University, Kita-Kyushu

*Mitsui-Toatsu Chemicals Co., Ohmuta Branch

Received August 29, 1977

In the previous paper, we reported that treatment of N-protected amino acids with *O*-phenylenediamine in the presence of DCC gave monoacyl derivative of *O*-phenylenediamine and this intermediate underwent cyclization by refluxing or gentle heating in acetic acid to give benzimidazole derivatives.¹⁾ By this procedure, however, glutamine derivative at above 75°C afforded a different compound. The compound was proved to be 5-benzoyloxycarbonylamino-1,2,3,4-tetrahydro-1-oxo-pyrido[1,2-*a*]benzimidazole (III).

This ring system has been prepared by various methods,²⁻¹⁴⁾ especially reductive cyclization of *O*-nitro-ter.-aniline derivatives.^{3,5,7,12)} To our knowledge, however, the present paper is the first report on the preparation of pyrido-benzimidazole from glutamine.

The structural determination of III was performed in terms of the results of elemental analyses and the spectroscopic properties of III. In the NMR spectrum (Fig. 1), the signal around δ 5.1 (1H, multiplet) was assigned to the methine proton at C₄-position. The resonance signal for the non-equivalent geminal protons (C₃-position) appeared around δ 2.1 (1H, multiplet) and 2.8 (1H, multiplet). The signal around δ 3.0 (2H, multiplet) was assigned to the methylene protons at C₂-position. The signals ascribable to the carbobenzoxy group were observed at δ 5.32 (2H, singlet) and 7.3~7.7 (5H, multiplet). The signal of amine proton was recognized at δ 6.10 (1H, exchangeable) and that of benzene ring of benzimidazole at δ 7.3~8.6 (4H, multiplet).

These results coincided with the structure suggested by elemental analyses, mass spectrum and chemical reactions.

The compound III was directly obtained from I by heating above 75°C in the presence of acetic acid. However, Z-Glu was not found to afford III, probably because this reaction proceeded only by removal of ammonia in an acid medium.

An attempt to prepare 3-benzoyloxycarbonylamino-1-oxo-2,3-dihydropyrrolo[1,2-*a*]benzimidazole from Z-Asn by the similar method was also unsuccessful. In this case, much more rigorous condition may be required for the formation of 5-membered moiety, pyr-

FIG. 1. 100 MHz NMR Spectrum of 4-Benzoyloxycarbonylamino-1-oxo-1,2,3,4-tetrahydro-pyrido[1,2-*a*]benzimidazole (in CDCl_3).

rolidone ring.

EXPERIMENTALS

4-(2-Benzimidazolyl)-4-(benzyloxycarbonylamino)-butanamide (II). To a solution of 2.8 g of benzyloxycarbonyl-Gln and 1.2 g of *O*-phenylenediamine in 30 ml of dimethylformamide (DMF) was added 2.2 g of DCC at 0°C with stirring. After stirring overnight, the filtrate freed from dicyclohexylurea was poured into water. The resulting crude product (I) was collected by filtration and recrystallized from ethyl acetate. Yield 3.4 g (92%).

A solution of the monoacyl-derivative of *O*-phenylenediamine (I) in 15 ml of acetic acid was heated with stirring for 30 min at 55°C. Then, the solution was cooled and neutralized with conc. aqueous ammonia. The precipitate was recrystallized from ethyl acetate. Yield 2.2 g (65% from Z-Gln). Mp 144~145°C.¹⁾

4-Benzoyloxycarbonylamino-1-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (III). A solution of 0.4 g of I in 10 ml of acetic acid was heated with stirring for 2 hr at 75°C, and the solution was neutralized with conc. aqueous ammonia. The resulting precipitate was collected by filtration and extracted with ethyl acetate. The extract was washed with 5% NaHCO₃, then water, and dried over Na₂SO₄. The purification of the crude product was achieved by applying silica gel column chromatography. Recrystallization from ethyl acetate-petroleum ether gave 0.3 g (79%) of III. Mp 165°C, mass spectrum *m/e* (rel. intensity), 335 (14.7, M⁺), 223 (10.5), 201 (15.2), 200 (100.0, M⁺ - C₆H₅-CH₂-O-CO-), 172 (25.3), 157 (13.3), 155 (12.0), 91 (74.6). NMR (CDCl₃) δ: 2.1 (1H, m), 2.8 (1H, m), 3.0 (2H, m), 5.1 (1H, m), 5.32 (2H, s), 6.10 (1H, exchangeable), 7.3~8.6 (9H, m).

Anal. Calcd. for C₁₉H₁₇O₅N₃: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.00; H, 5.09; N, 12.45.

4-Amino-1-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]benz-

imidazole (IV). One tenth gram of III was mixed with 5 ml of 25% HBr in acetic acid and the mixture was allowed to stand at room temperature overnight. Ether (50 ml) was added to the mixture and the solvent was removed by decantation. The resulting precipitate was washed with ether 3 times. The product was recrystallized from methanol-ether. Yield, 0.1 g (83%). Mp 147°C.

Anal. Calcd. for C₁₁H₁₃O₂N₄Br₂: C, 31.58; H, 4.31; N, 13.40. Found: C, 31.28; H, 4.62; N, 12.96.

REFERENCES

- 1) K. Maekawa and J. Ohtani, *Agric. Biol. Chem.*, **40**, 791 (1976); **41**, 811 (1977).
- 2) R. Garner and H. Suschitzky, *J. Chem. Soc. (C)*, **1967**, 74.
- 3) H. Suschitzky and M. E. Sutton, *Tetrahedron Lett.*, **40**, 3933 (1967).
- 4) H. Suschitzky and M. E. Sutton, *Tetrahedron*, **24**, 4581 (1968).
- 5) W. H. Wagner and E. Winkelmann, *Arzneim.-Forsch.*, **19**, 719 (1969).
- 6) R. K. Grantham and O. Meth-Cohn, *J. Chem. Soc. (C)*, **1969**, 70.
- 7) R. Fielden, O. Meth-Cohn and H. Suschitzky, *Tetrahedron Lett.*, **15**, 1229 (1970).
- 8) R. Garner, G. V. Garner and H. Suschitzky, *J. Chem. Soc. (C)*, **1970**, 825.
- 9) H. Ogura and K. Kikuchi, *J. Org. Chem.*, **37**, 2679 (1972).
- 10) R. M. Acheson and M. S. Verlander, *J. Chem. Soc. Perkin Trans. I*, **1972**, 1577.
- 11) S. Linke and C. Wünsche, *J. Heterocyclic Chem.*, **10**, 333 (1973).
- 12) I. Zugravescu, J. Herdan and I. Druta, *Rev. Roumaine de Chim.*, **19**, 649 (1974).
- 13) H. Takahashi, S. Sato and H. Ohtamasu, *Chem. Pharm. Bull.*, **22**, 1921 (1974).
- 14) O. Meth-Cohn, *Tetrahedron Lett.*, **6**, 413 (1975).