Synthetic Study in the Pyrrolo[2,3-*d*]imidazole System

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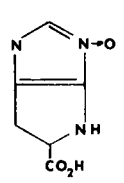
As part of our program directed toward the synthesis of potential cofactors for biotin-dependent enzymes we have synthesized several compounds possessing the pyrrolo[2,3-*d*]imidazole ring system. These compounds should serve as useful intermediates for the synthesis of nitrogen analogs of biotin (1,2). No general route has been reported thus far for the convenient preparation of the pyrrolo[2,3-*d*] imidazole system. Von Euler and Hasselquist reported on *N*-oxide **1** as one of two possible products arising from the hydrogen peroxide treatment of L-histidine in glacial acetic acid (3,4) whereas **2** was isolated in 3% yield by Tomita and co-workers from the sensitized photooxidation of *N*-benzoylhistidine (5).

Our synthesis, as outlined in Chart I, began with 1,2-dicarbethoxy-3-pyrrolidin-3-one (**3**) prepared by base-catalyzed Dieckmann condensation according to the method of Blake (6). Ketoester **3** was converted quantitatively to 1,2-dicarbethoxy-3-oximinopyrrolidine (**4**) by the usual method. The catalytic hydrogenation of **4** over platinum in acetic anhydride gave 1,2-dicarbethoxy-3-acetamidopyrrolidine (**5**) in good yield. All attempts to crystallize the product failed. The reduced **5** was then converted to hydrazide **6** in 90% yield by stirring the ester in an excess of hydrazine hydrate at room temperature. By treatment with nitrous acid, the hydrazide **6** was converted to an intermediate acyl azide which decomposed when heated, giving a 47% yield of bicyclic product **7**. Base hydrolysis of **7** gave carbamate **8**, whereas acidic conditions (glacial acetic saturated with hydrogen bromide) gave amine **9** as the hydrobromide salt.



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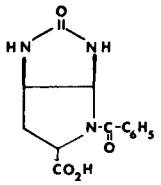

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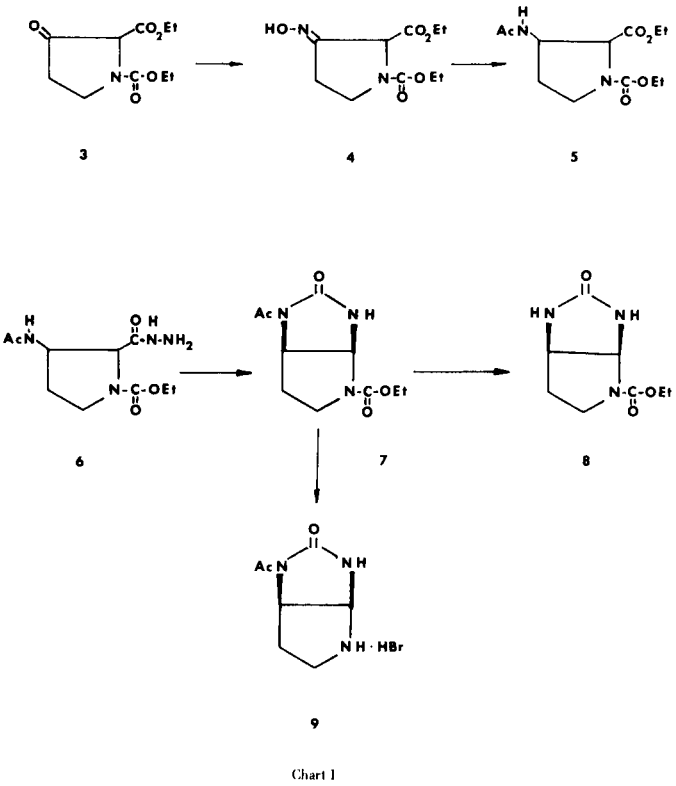

Chart I

EXPERIMENTAL (7)

1,2-Dicarbethoxy-3-oximinopyrrolidine (**4**).

To **3** (1.6 g., 7 mmoles) was added the filtrate from a mixture of sodium acetate trihydrate (1.43 g., 10.5 mmoles) and hydroxylamine hydrochloride (0.73 g., 10.5 mmoles) in 90% aqueous methanol (6 ml.). The reaction mixture was stirred at room temperature for 3 hours, evaporated to dryness, then washed with water. The residue was extracted with several portions of chloroform. The combined chloroform extracts were dried and evaporated, leaving a colorless oil (1.7 g., 100%) which crystallized upon standing. Several recrystallization from a mixture of ether and petroleum ether (b.p. 30-60°) afforded an analytical sample, m.p. 77-78°; ir (chloroform): 3584, 3333 (OH), 1733 (ester CO), 1694 cm^{-1} (carbamate CO); pmr (deuteriochloroform): δ 1.28 (t, 6H, J = 7 Hz, CH_3 of ester and carbamate), 2.90 (t, 2H, J = 7 Hz, C_4-CH_2), 3.82 (t, 2H, J = 7 Hz, C_5-CH_2), 4.26 (q, 4H, J = 7 Hz, CH_2 of ester and carbamate), 4.93 (s, 1H, C_2-CH), 9.50 (s, 1H, NOH).

Anal. Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.17; H, 6.60; N, 11.48. Found: C, 49.15; H, 6.48; N, 11.40.

1,2-Dicarbethoxy-3-acetamidopyrrolidine (**5**).

A solution of **4** (1.48 g., 6 mmoles) in acetic anhydride (50 ml.) was hydrogenated over platinum oxide (300 mg.) under a hydrogen pressure of approximately 60 psi at room temperature for 21 hours. After filtration of the catalyst, the solvent was removed by vacuum distillation. A colorless oil (1.27 g., 77%) was obtained. Tlc on silica gel G (20% methanol in ethyl acetate) showed one spot with rf 0.40; ir (chloroform): 3448, 3333 (NH), 1727 (ester CO), 1680 cm^{-1} (acetamide and carbamate CO); pmr (deuteriochloroform); δ 1.28 (t, 6H, J = 7 Hz, CH_3 of ester and carbamate), 2.00 (s, 3H, CH_3-CON), 4.20 (q, 4H, J = 7 Hz, CH_2 of ester and carbamate), 6.56 (s, 1H, NH). All attempts to crystallize the product failed.

1-Acetyl-4-carbethoxy-perhydropyrrolo[2,3-*d*]imidazol-2-one (**7**).

A mixture of **5** (1.26 g., 4.6 mmoles) and hydrazine hydrate (5 ml.) was stirred at room temperature for 2 hours. The excess hydrazine hydrate was removed by distillation *in vacuo*, leaving a white solid of **6** (1.08 g., 90%), m.p. 186-191°. Tlc on silica gel G (20% methanol in ethyl acetate) showed one spot. The crude product was used without further purification in the following step. Sodium nitrite (0.22 g.) in water (1 ml.) was added dropwise to an ice-cooled solution of **6** (0.435 g., 1.68 mmoles) in 2 *N* hydrochloric acid (3 ml.) with stirring. After an additional 10 minutes of stirring, the resultant azide was extracted with cold ethyl acetate and the extract dried over anhydrous sodium sulfate. The ethyl acetate solution was then refluxed for 3 hours on a steam bath to decompose the azide. After the removal of the solvent, the residue (0.360 g.) was crystallized from ethyl acetate, giving product **7** as colorless needles (0.148 g., 47%), m.p. 185-186°; ir (chloroform): 3448, 3311 (NH), 1795, 1686 (imide CO), 1686 cm^{-1} (carbamate CO).

Anal. Calcd. for $C_{10}H_{15}N_3O_5$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.66; H, 6.22; N, 17.61.

4-Carbethoxy-perhydropyrrolo[2,3-*d*]imidazol-2-one (**8**).

A solution of **7** (0.48 g., 2.0 mmoles) in a 50% methanol-water mixture (5 ml.) was mixed with a 5% sodium carbonate solution (10 ml.). The reaction mixture was maintained at 60° on a water bath for 2 hours. The solvents were evaporated under reduced pressure and the product extracted with hot absolute ethanol. Upon cooling, a crystalline product was obtained (0.34 g., 86%), m.p. 207-209° dec. Recrystallization from ethanol gave colorless prisms, m.p. 208-209° dec.; ir (Nujol): 3300, 3205 (NH), 1698 (ureide CO) 1666 cm^{-1} (carbamate CO).

Anal. Calcd. for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58; N, 21.09. Found: C, 48.17; H, 6.57; N, 20.97.

1-Acetyl-perhydropyrrolo[2,3-*d*]imidazol-2-one Hydrobromide (**9**).

Compound **7** (1.0 g., 4.14 mmoles) was added to a saturated solution of hydrogen bromide in glacial acetic acid. After 24 hours of stirring at room temperature, the solvent and excess hydrogen bromide were removed under reduced pressure yielding a dark brown crystalline residue. Recrystallization from ethanol-ether mixture gave an off-white crystalline product (0.83 g., 80%) m.p. 205-206° dec. Treatment with decolorizing charcoal and two subsequent recrystallizations from 95% ethanol gave the analytical sample, m.p. 205-207° dec.; ir (Nujol): 3322 (NH), 1739, 1680 cm^{-1} (imide CO); pmr (deuterium oxide): δ 2.48 (s, 3H, CH_3-CON), 3.20-3.77 (m, 2H, C_6-CH_2), 4.83-5.24 (m, 2H, C_5-CH_2), 5.80 (d, 1H, J = 7 Hz, C_{3a}-CH).

Anal. Calcd. for $C_7H_{11}N_3O_2$·HBr: C, 33.61; H, 4.84; N, 16.80. Found: C, 33.69; H, 4.84; N, 16.73.

A picrate salt was also prepared in the usual manner and recrystallized from aqueous ethanol, m.p. 179-181°.

Anal. Calcd. for $C_{13}H_{14}N_6O_9$: C, 39.20; H, 3.54; N, 21.10. Found: C, 38.98; H, 3.72; N, 20.78.

REFERENCES

(1) H. C. Wormser, *J. Pharm. Sci.*, **59**, 1732 (1970).

(2) H. C. Wormser, S. Israsena, M. S. Meiling, C. Williams, and D. Perlman, *J. Pharm. Sci.*, **61**, 1168 (1972).

(3) H. von Euler and H. Hasselquist, *Arkiv Kimi*, **13**, 185 (1958).

(4) Several attempts were made by the authors of this note to reproduce the work cited in reference 3, namely, to oxidize L-histidine with 30% hydrogen peroxide in glacial acetic acid to obtain compound **1**. The reaction invariably led to the known imidazole-4-acetic as the sole product.

(5) M. Tomita, M. Irie, and T. Ukita, *Tetrahedron Letters*, 4933 (1968).

(6) J. Blake, C. D. Willson, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 5293 (1964).

(7) Melting-points were determined on a Fisher-Johns melting-point stage and a Thomas-Hoover melting-point apparatus and are uncorrected. Ir absorption spectra were recorded on Beckman (models 8 and 33) recording spectrophotometers. Pmr spectra were determined in deuteriochloroform using TMS as reference standard and in deuterium oxide using sodium 2,2-dimethyl-2-silapentane sulfonate on a Varian EM 360 spectrometer. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Michigan.