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The preparation of 4-amino-6-hydroxy-1*H*-pyrrolo[3,2-*c*]pyridine (3,7-dideaza*iso*guanine) (**1**) in five steps from 1*H*-pyrrolo[3,2-*c*]pyridin-4,6(5*H*,7*H*)dione (3,7-dideazaxanthine) (**2**) is described. Furthermore, prolonged treatment of **1** with 10% aqueous sodium carbonate solution is reported to lead to ring opening of the pyridine of **1** resulting in 3-carboxamidopyrrole-2-acetic acid (**3**).

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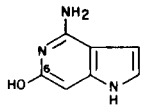
The atom exchange of a -CH= for a -N= in the purine ring system has been, and is, a fruitful means into understanding the biological roles of the nitrogen atoms in such molecules while developing substances of modified biological properties for potential use as therapeutic agents (1). Stimulated by these successes, we are pursuing deaza purine analogs in which one -N= in the imidazole ring and one in the pyrimidine ring are each replaced by a -CH= to result in 1,7- and 3,7-dideazapurines (2). In this direction the synthesis of 4-amino-6-hydroxy-1*H*-pyrrolo[3,2-*c*]-pyridine (3,7-dideaza*iso*guanine) (**1**), as an analog of the biologically active isoguanine system (3), was undertaken and is reported herein.

The preparation of **1** began with the observation (4) that 1*H*-pyrrolo[3,2-*c*]pyridin-4,6(5*H*,7*H*)dione (3,7-dideazaxanthine) (**2**) (2) undergoes facile nucleophilic ring opening at its C-6 carbonyl center to produce a number of 2,3-disubstituted pyrroles. Thus, reaction of **2** with 10%



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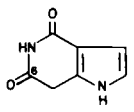

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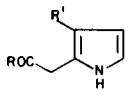

3, R = OH, R' = $CONH_2$
4, R = OMe, R' = $CONH_2$
5, R = OMe, R' = CN
6, R = NH_2, R' = CN
7, R = OH, R' = C(=NH)NH_2

sodium hydroxide solution followed by acidification provided 3-carboxamidopyrrole-2-acetic acid (**3**) (4,5) which, upon esterification with diazomethane (to **4**) and phosphorus oxychloride mediated dehydration, became methyl 3-cyanopyrrole-2-acetate (**5**). Ammonolysis of **5** with concentrated ammonium hydroxide formed 3-cyanopyrrole-2-acetamide (**6**) which cyclized to the desired **1** with a small amount of 10% aqueous sodium carbonate solution in ethanol.

It is interesting to note that prolonged (7 hours) treatment of **6** with refluxing 10% aqueous sodium carbonate solution produced **3**. By analogy to the aforementioned propensity of **2** to undergo nucleophilic ring opening at its C-6 center (4) this result is believed to arise from a similar opening of **1** (as its C-6 carbonyl tautomer) by water to yield **7** whose amidine functionality subsequently hydrolyzed to avail **3**.

EXPERIMENTAL

The melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman AccuLab 3 spectrophotometer and the proton magnetic resonance spectra were obtained on a Varian EM-360 spectrometer and are reported in parts per million downfield from tetramethylsilane as an internal standard. The pmr spin multiplicities are indicated by the symbols s (singlet), t (triplet), and m (multiplet). The uv spectrum was accomplished using a Perkin Elmer 200 spectrophotometer. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Methyl 3-Carboxamidopyrrole-2-acetate (**4**).

3-Carboxamidopyrrole-2-acetic acid (**3**) (4) (1 g., 5.95 mmoles) was placed in a mixture of 20 ml. of anhydrous ether and 15 ml. of anhydrous tetrahydrofuran. A cold ethereal solution of diazomethane (8 mmoles) was then added in small portions with stirring over a period of 5-6 minutes. The mixture was stirred for an additional 4 hours. After decomposing the excess diazomethane with a few drops of glacial acetic acid, the mixture was filtered and the filtrate was evaporated to dryness on a rotary evaporator to leave a liquid which solidified on standing. The solid was recrystallized from chloroform-benzene (1:2) into white crystals of **4** (0.8 g., 4.4 mmoles, 74%), m.p. 127-128°; pmr (hexadeuteriodimethylsulfoxide): δ 3.57 (s, 3 H, CH_3), 4.0 (s, 2 H, CH_2), 6.55 (m, 2 H, H-4 and H-5), 7.1 (broad, 2 H, amide NH_2), 10.9 (broad, 1 H, pyrrole NH); ir (potassium bromide): 3460 (NH), 3300 (NH), 1705 (C=O), 1655 (C=O) cm^{-1}.

Anal. Calcd. for $C_8H_{10}N_2O_3 \cdot 0.5\ H_2O$: C, 50.26; H, 5.75; N, 14.65. Found: C, 50.51; H, 5.83; N, 14.65.

Methyl 3-Cyanopyrrole-2-acetate (**5**).

Compound **4** (0.5 g., 2.7 mmoles) was refluxed with 3 ml. (30 mmoles) of phosphorus oxychloride in an oil bath equipped with a magnetic stirrer. The mixture formed a uniform red solution after refluxing for 15 minutes. The solution was cooled and 15 g. of ice was added followed by cautious addition of concentrated ammonium hydroxide solution drop by drop maintaining the temperature below 10° until the pH rose to approximately 6. The mixture was extracted with boiling ethyl acetate (3 x 25 ml.) and the combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated on a rotary evaporator to leave a reddish oil which was distilled (b.p. 68°/0.2 mm) to obtain **5** as a colorless liquid (0.35 g., 2.1 mmoles, 79%); pmr (deuteriochloroform): δ 3.72 (s, 3H, CH_3), 3.82 (s, 2 H, CH_2), 6.3 (t, J = 2.7 and 3.0 Hz, 1H, H-4), 6.66 (t, J = 2.7 and 3.0 Hz, 1H, H-5), 9.72 (broad, 1 H, pyrrole NH); ir (neat): 3330 (NH), 2225 (C≡N), 1735 (C=O) cm^{-1}.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.47; H, 5.06; N, 16.84.

3-Cyanopyrrole-2-acetamide (**6**).

Methyl 3-cyanopyrrole-2-acetate (**5**) (0.7 g., 4.2 mmoles) dissolved in 5 ml. of methanol was added to boiling concentrated ammonium hydroxide (20 ml.) and heated for 15 minutes. The mixture was cooled, filtered and left under vacuum (aspirator) for 5 minutes. The filtrate was concentrated to 5 ml. on a rotary evaporator and cooled in an ice bath to obtain a white solid which was recrystallized from ethyl acetate-ligroin into white needles of **6** (0.5 g., 3 mmoles, 79%), m.p. 138-140°; pmr (hexadeuteriodimethylsulfoxide): δ 3.52 (s, 2 H, CH_2), 6.3 (t, J = 2.7 and 3.0 Hz, 1 H, H-4), 6.71 (t, J = 2.7 and 3.0 Hz, 1 H, H-5), 7.02 (broad, 1 H, amide NH), 7.5 (broad, 1 H, amide NH), 11.48 (broad, 1 H, pyrrole NH); ir (potassium bromide): 3340 (NH), 2220 (C≡N), 1680 (C=O) cm^{-1}.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.46; H, 4.83; N, 28.01.

4-Amino-6-hydroxy-1*H*-pyrrolo[3,2-*c*]pyridine (3,7-Dideaza*iso*guanine) (**1**).

3-Cyanopyrrole-2-acetamide (**6**) (0.25 g., 1.68 mmoles) was mixed with 15 ml. of 95% ethanol and placed in a 100 ml. three-necked flask. The mixture was heated to boiling at which time a uniform clear solution resulted. Then, 5 ml. of 10% aqueous sodium carbonate solution was added all at once. The solution started turning pink within a few minutes and after 30 minutes white crystals of sodium carbonate began to separate from it. Following a 2 hour reflux period, the hot mixture was filtered using an aspirator and the filtrate evaporated to dryness using a rotary evaporator. The residue was washed with 5 ml. of cold water, triturated with 15 ml. of hot ethanol, and filtered to isolate a solid which recrystallized from water into tan crystals of **1** (0.16 g., 1.08 mmoles, 64%), m.p. >300°; pmr (hexadeuteriodimethylsulfoxide): δ 5.32 (s, 1 H, H-7), 6.3-6.9 (broad, 4 H, NH_2, H-2 and H-3), 10.35 (broad, 1 H, pyrrole NH); ir (potassium bromide): 3445 (NH_2), 3300 (NH), 3200-2800 (broad, OH) cm^{-1}; uv λ max (*p*H 1): 263 nm (ε, 6,977), 308 (ε, 7,060); λ max (*p*H 7.1): 271 (ε, 7,723), 327 (ε, 6,894); λ max (*p*H 11): 272 (ε, 6,729), 332 (ε, 5,217).

Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.22; H, 4.83; N, 28.18.

Acknowledgment.

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REFERENCES AND NOTES

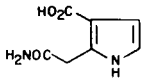
(1) For example, (a) General review: E. Bisagni, *Jerusalem Symp. Quantum Chem. Biochem.*, **4**, 439 (1972); (b) 1*H*-Imidazo-[4,5-*b*]pyridines (1-Deazapurines): T. Itoh, S. Kitano, and Y. Mizuno, *J. Heterocyclic Chem.*, **9**, 465 (1972); J. E. Schelling and C. A. Salemink, *Rec. Trav. Chim.*, **93**, 160 (1974); J. E. Schelling and C. A. Salemink, *ibid.*, **94**, 153 (1975); B. L. Cline, R. P. Panzica, and L. B. Townsend, *J. Heterocyclic Chem.*, **12**, 603 (1975); (c) 1*H*-Imidazo[4,5-*c*]pyridines (3-Deazapurines): R. J. Rousseau, L. B. Townsend, and R. K. Robins, *Biochemistry*, **5**, 756 (1966); R. T. Borchardt, J. A. Huber, and Y. S. Wu, *J. Med. Chem.*, **17**, 868 (1974); R. de Bode and C. A. Salemink, *Rec. Trav. Chim. Pays-Bas*, **93**, 3 (1974); P. Singh, J. May, L. B. Townsend, and D. J. Hodgson, *J. Am. Chem. Soc.*, **98**, 825 (1976); J. A. Montgomery, A. T. Shortnacy, and S. D. Clayton, *J. Heterocyclic Chem.*, **14**, 195 (1977); (d) 7*H*-Pyrrolo[2,3-*d*]-pyrimidines (7-Deazapurines): R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.*, **91**, 2102 (1969); R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N. Y., 1970, Chapter 8.

(2) S. W. Schneller and R. S. Hosmane, *J. Heterocyclic Chem.*, **14**, 1291 (1977).

(3) For example, R. D. Berlin, *Science*, **168**, 1539 (1970) and R. E. A. Gadd and J. F. Henderson, *Can. J. Biochem.*, **48**, 295 (1970).

(4) S. W. Schneller and R. S. Hosmane, *J. Org. Chem.*, in press.

(5) Reference 4 details the structure proof of **3** as the correct product (rather than the isomeric **i** which would have arisen from hydroxide ion attack at C-4 of **2**) from reaction of **2** with 10% aqueous sodium hydroxide solution.



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