Tetrahedron Letters Vol. 21, pp 3135 - 3138 0040-4039/80/0809-3135$02.00/0

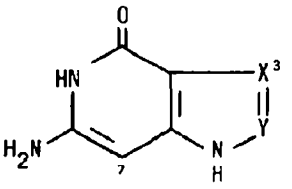
6-AMINO-1*H*-PYRROLO[3,2-*c*]PYRIDIN-4(5*H*)-ONE (3,7-DIDEAZAGUANINE)

Stewart W. Schneller,* Jiann-Kuan Luo, and Ramachandra S. Hosmane

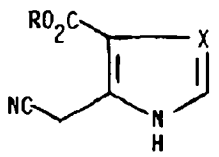
Department of Chemistry, University of South Florida, Tampa, Florida 33620 USA

The synthesis of 6-amino-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (3,7-dideazaguanine) from the ammonium chloride promoted reaction of 3-(ethoxycarbonyl)pyrrole-2-acetonitrile and ammonia is reported. Several preliminary reactions which led to this synthetic route are also described.

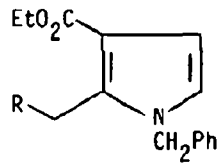
6-Amino-1*H*-imidazo[4,5-*c*]pyridin-4(5*H*)-one (1; 3-deazaguanine) has demonstrated very interesting antitumor and antiviral properties[1] whereas an isomer of 1 (2; 6-amino-1*H*-pyrazolo-[4,3-*c*]pyridin-4(5*H*)-one, or 3,7-dideaza-8-azaguanine) is void[2] of any such characteristics. In a structure-activity analysis of 1 the latter result suggests that the N-3 atom of 1 (N-7 by purine numbering) is critical to its biological properties. However, in view of the remarkable biological data for other 7-deazapurines,[3] this result is surprising. Thus, in order to ascertain the bio-significance of the N-3 atom of 1, the synthesis of 6-amino-1*H*-pyrrolo[3,2-*c*]-pyridin-4(5*H*)-one (3; 3,7-dideazaguanine) was sought as a better means of addressing this question than was possible with 2 whose biological analysis may be misleading since it retains two nitrogen atoms in its five-membered ring. The successful pursuit of 3 is described herein.



1; X=N, Y=CH
2; X=CH, Y=N
3, X=Y=CH



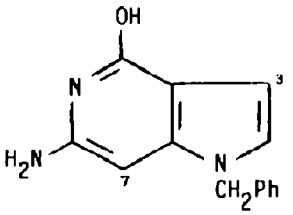
4; R=Me, X=N
5; R=Et, X=CH



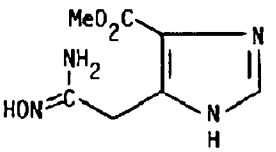
6, R=CN
7, R=CO_2Et
8, R=$CONH_2$

The most logical approach to 3 was foreseen as paralleling that for the synthesis of 1[1a] which involved the reaction of 4(5)-(methoxycarbonyl)imidazole-5(4)-acetonitrile (4) with ammonia. However, no reaction occurred when 5 was treated with liquid ammonia in a sealed reaction vessel at a number of temperatures and for varying durations.[4] Evaluation of the pos-

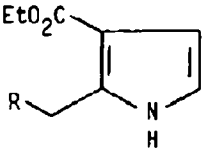
sible role played by the pyrrole NH of 5 in its failure to cyclize with ammonia led to the synthesis of 1-benzyl-3-(ethoxycarbonyl)pyrrole-2-acetonitrile (6) which began with the reaction of N-benzylaminoacetaldehyde hydrochloride[5] with diethyl acetonedicarboxylate in 20% NaOH solution to give ethyl 1-benzyl-3-(ethoxycarbonyl)pyrrole-2-acetate (7; 28%; mp 44-45°C; $\delta^{(CD_3)_2SO}_{ppm}$ 1.15 (m, 6 H, 2 CH_3 of esters), 3.95 (m, 6 H, 2 CH_2 of esters and CH_2 of acetate), 5.12 (s, 2 H, CH_2 of benzyl), 6.42 (d, 1 H, J=3 Hz, H-4), 6.75 (d, 1 H, J=3 Hz, H-5), 7.20 (m, 5 H, phenyl)). Treatment of 7 with liquid ammonia in a sealed reaction vessel at 120°C for 24 h yielded 1-benzyl-3-(ethoxycarbonyl)pyrrole-2-acetamide (8; 66%; mp 118-119°C; $\delta^{(CD_3)_2SO}_{ppm}$ 1.2 (t, 3 H, J=7 Hz, CH_3), 3.72 (s, 2 H, CH_2 of acetamide), 4.1 (q, 2 H, J=7 Hz, CH_2 of ester), 5.1 (s, 2 H, CH_2 of benzyl), 6.35 (d, 1 H, J=3 Hz, H-4), 6.72 (d, 1 H, J=3 Hz, H-5), 7.2 (m, 7 H, phenyl and amide NH_2)). Dehydration of 8 with phosphorus oxychloride gave 6 (81%; mp 84-86°C; $\delta^{(CD_3)_2SO}_{ppm}$ 1.28 (t, 3 H, J=7 Hz, CH_3), 4.23 (q, 2 H, J=7 Hz, CH_2 of ester), 4.25 (s, 2 H, CH_2 of acetonitrile), 5.3 (s, 2 H, CH_2 of benzyl), 6.5 (d, 1 H, J=3 Hz, H-4), 6.93 (d, 1 H, J=3 Hz, H-5), 7.25 (m, 5 H, phenyl)). When 6 was heated with liquid ammonia in a sealed reaction vessel at 160°C for 90 h cyclization occurred to give the guanine derivative, 6-amino-1-benzyl-1*H*-pyrrolo[3,2-*c*]pyridin-4-ol (9), in 42% yield (mp 263-264°C dec), whose spectral data indicated



9



10



11, R=C(=NOH)NH_2
12, R=$CONH_2$
13, R=C(=NH)NH_2

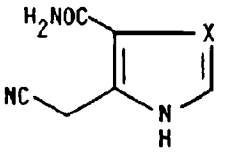
it to be in the enol tautomer as shown ($\nu^{KBr}_{cm^{-1}}$ 3200-2800 broad OH; $\delta^{(CD_3)_2SO}_{ppm}$ 5.11 (s, 2 H, CH_2 of benzyl), 5.37 (s, 3 H, H-7 and NH_2), 6.32 (d, 1 H, J=3 Hz, H-3), 6.85 (d, 1 H, J=3 Hz, H-2), 7.25 (m, 5 H, phenyl), 10.0 (s, 1 H, OH)). Unfortunately, numerous attempts at debenzylation of 9 (either chemically or catalytically) led to recovery of starting material or to total destruction of the heterocyclic unit.[6] The success achieved in cyclizing 6 in contrast to 5 is not presently understood.

Recently,[7] an improved procedure to 1 was reported to involve the reaction of 4 with hydroxylamine to afford the carboxamidoximyl derivative 10 which, upon hydrogenation over Raney nickel, produced 1. Similarly, treatment of 5 with hydroxylamine yielded ethyl 2-(carboxamidoximylmethyl) pyrrole-3-carboxylate (11; 66.6%; mp 159-161°C; $\delta^{(CD_3)_2SO}_{ppm}$ 1.24 (t, 3 H, J=7 Hz CH_3), 3.63 (s, 2 H, CH_2 of side chain), 4.16 (q, 2 H, J=7 Hz, CH_2 of ester), 5.36 (s, 2 H, NH_2)

6.33 (d, 1 H, J=2 Hz, H-4), 6.6 (d, 1 H, J=2 Hz, H-5), 8.9 (s, 1 H, OH), 11.23 (broad s, 1 H, NH)). However, hydrogenation of 11 under the reported[7] aqueous conditions led to the hydrolysis product 3-(ethoxycarbonyl)pyrrole-2-acetamide (12).[8] Variations in the hydrogenation conditions and attempts to isolate the amidine precursor to 3 (13) from 11 all met with failure.

The ease of formation of 11 from 5 did suggest that the cyano functionality of 5 was capable of reacting with nucleophiles and that the failure of the reaction of 5 with ammonia to produce 3 was merely the result of a decreased nucleophilicity of ammonia compared to hydroxylamine. Acid catalysis was foreseen as a means of alleviating this problem by enhancing the reactivity of the cyano functionality in 5 towards ammonia. Therefore, 5 was treated with liquid ammonia, containing ammonium chloride, in a sealed reaction vessel at 125°C for 24 h to give the desired 3 in the tautomer shown (67%; sinters at 223-225°C; ν_{cm}^{KBr}-1 3380 (NH_2), 3220 (NH_2), 1640 (C=O); $\delta_{ppm}^{(CD_3)_2SO}$ 5.22 (s, 2 H, NH_2), 5.4 (s, 1 H, H-7), 6.23 (d of d, 1 H, $J_{2,3}$=3 Hz, $J_{NH,3}$=2 Hz, H-3) 6.67 (d of d, 1 H, $J_{2,3}$=3 Hz, $J_{NH,2}$=2 Hz, H-2), 9.95 (s, 1 H, NH), 10.67 (s, 1 H, pyrrole NH).

Presently, it seems reasonable that the successful cyclization of 4, without the need for an added acid catalyst, lies in the ease of formation[1a] of the 4(5)-carboxamide derivative 14 which is the precursor to 1. On the other hand, from studies in our laboratory with a number of N-unsubstituted 3-ethoxycarbonylpyrroles (including 5), it is obvious that the 3-ester functional group in this series of compounds is inert towards nucleophilic substitution. Thus, the conversion of 5 into the pyrrole analog of 14 (*i.e.*, 15) will not occur and a nucleophilic reaction must take place at the less reactive nitrile site of 5, a process requiring acid catalysis. This latter pathway to 3 would, thereby, proceed via the intermediate amidine 13 rather than 15.



14, X=N
15, X=CH

Acknowledgement. This investigation was supported by U.S. Public Health Service Research Grant Number CA 17878 from the National Cancer Institute and such assistance is gratefully acknowledged.

REFERENCES AND NOTES

1. (a) P.D. Cook, R.J. Rousseau, A.M. Mian, P. Dea, R.B. Meyer, Jr., and R.K. Robins, *J. Am. Chem. Soc.*, 98, 1492 (1976); (b) T.A. Khwaja, L. Kigwana, R.B. Meyer, Jr., and R.K. Robins, *Proc. Am. Assoc. Cancer Res.*, 16, 162 (1975); (c) T.A. Khwaja and J. Varven,

ibid., 17, 200 (1976); (d) L.B. Allen, J.H. Huffman, P.D. Cook, R.B. Meyer, Jr., R.K. Robins and R.W. Sidwell, *Antimicrob. Agents Chemother.*, 12, 114 (1977).

2. K.W. Ehler, R.K. Robins, and R.B. Meyer, Jr., *J. Med. Chem.*, 20, 317 (1977).
3. R.J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N.Y., 1970, Chapter 8.
4. S.W. Schneller and R.S. Hosmane, *J. Org. Chem.*, 43, 4487 (1978).
5. Prepared from the hydrolysis of N-benzylaminoacetaldehyde diethyl acetal (E. Fischer, *Ber.*, 26, 464 (1893)) with hydrochloric acid at -5°C.
6. Other reports of the difficulty of debenzylating N-benzylpyrroles can be found in the literature (*e.g.*, H.J. Anderson and J.K. Groves, *Tetrahedron Lett.*, 3165 (1971) and M.-I. Lim, R.S. Klein, and J.J. Fox, *J. Org. Chem.*, 44, 3826 (1979)).
7. P.C. Srivastava and R.K. Robins, *J. Heterocycl. Chem.*, 16, 1063 (1979).
8. S.W. Schneller, R.S. Hosmane, L.B. MacCartney, and D.A. Hessinger, *J. Med. Chem.*, 21, 990 (1978).

(Received in USA 28 January 1980)