Chlorination of 1*H*-Pyrrolo[3,2-*c*]pyridin-4,6(5*H*,7*H*)dione (3,7-Dideazaxanthine) and its 5-Methyl Derivative

S. W. Schneller and R. S. Hosmane*

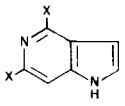
Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received August 16, 1977

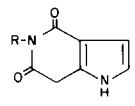
The chlorination of 1*H*-pyrrolo[3,2-*c*]pyridin-4,6(5*H*,7*H*)dione (3,7-dideazaxanthine) (**2**) and 5-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-4,6(5*H*,7*H*)dione (1-methyl-3,7-dideazaxanthine) (**3**) with phenylphosphonic dichloride has yielded 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine (2,6-dichloro-3,7-dideazapurine) (**1**). A mechanism for the demethylation of the 5-methyl derivative under these conditions is proposed. Ammonolysis of 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine was unsuccessful while catalytic reduction of this dichloro derivative produced 1*H*-pyrrolo[3,2-*c*]-pyridine (**4**).

J. Heterocyclic Chem., 15, 325 (1978)

As part of our investigation into the preparation of 3,7-dideaza analogs of biologically functional purines (1), 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine (*i.e.*, 2,6-dichloro-3,7-dideazapurine) (**1**) was viewed as a potentially fruitful precursor to such molecules *via* judiciously chosen nucleophilic displacement sequences. Even though treatment of

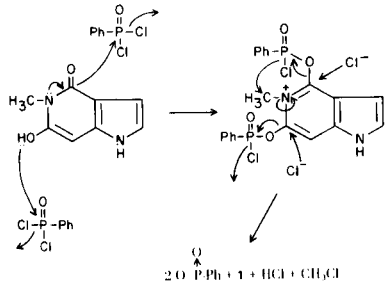


1, X = Cl
4, X = H



2, R = H
3, R = CH_3

1*H*-pyrrolo[3,2-*c*]pyridin-4,6(5*H*,7*H*)dione (**2**) with phosphorus oxychloride failed to yield **1**, the use of phenylphosphonic dichloride as the chlorinating agent did produce **1** from **2**. Surprisingly, however, the 5-methyl analog of **2** (*i.e.*, **3**) under the identical reaction conditions also produced **1**. This latter result is similar to the preparation of 7-methyl-2,6-dichloropurine from theobromine (2a) and 7-methyl-2,6,8-trichloropurine from 8-chlorotheobromine (2b) with phosphorus oxychloride and of a 4-chloromethylquinazoline derivative from 2,3-dimethyl-4(3*H*)-quinazoline with phosphorus oxychloride/phosphorus pentachloride (3). A reasonable explanation for this occurrence with **3** is outlined below.



In order to test the nucleophilic displacement potential of the chloro substituents of **1** it was treated with ammonia but found to lead to recovery of unreacted **1** in quantitative amount even under the most rigorous conditions. A similar reactivity problem has been reported (4) for 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine and is apparently due to removal of the pyrrolo NH by the ammonia to result in an anion whose delocalization throughout the ring system renders C-4 and C-6 electron rich and unattractive to the ammonia nucleophile.

The dichloro derivative **1** was, however, readily dehalogenated upon catalytic hydrogenation to afford 1*H*-pyrrolo[3,2-*c*]pyridine (**4**).

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), d (doublet), t (triplet), and m (multiplet). The elemental analysis was performed by Het-Chem-Co., Harrisonville, Missouri.

4,6-Dichloro-1*H*-pyrrolo[3,2-*c*]pyridine (**1**).

A mixture of either **2** or **3** (1) (3 mmoles) and phenylphosphonic dichloride (1.3 ml., 9 mmoles) was heated in an oil bath at 160° for 2 hours. After cooling to room temperature, the contents of the reaction flask were poured onto 30 ml. of ice water. The semi-solid which separated was isolated by decantation and triturated with 15 ml. of 1 *N* sodium hydroxide. The resultant insoluble solid was obtained by filtration, washed with water, dried, and recrystallized from ethyl acetate as white needles of **1** (0.524 g., 2.8 mmoles, 95%), m.p. 258°; ir (potassium bromide): 3190 and 3150 (N-H), 1605 (C=C) cm^{-1}; pmr (DMSO-d_6): δ 6.5 (m, 1 H, H-3), 7.5 (m, 2 H, H-7 and H-2), 12.0 (broad, 1 H, pyrrole N-H).

Anal. Calcd. for $C_7H_4Cl_2N_2$: C, 44.95; H, 2.16; N, 14.98. Found: C, 44.77; H, 2.00; N, 15.06.

1*H*-Pyrrolo[3,2-*c*]pyridine (**4**).

A mixture of **1** (400 mg., 2.12 mmoles), potassium hydroxide (224 mg., 4 mmoles) and 5% palladium on carbon (240 mg.) in 95% ethanol (40 ml.) was hydrogenated for 24 hours at 15 p.s.i. The suspension was filtered with the assistance of an aspirator and the filtrate evaporated on a rotary evaporator to yield an oil to which 10 ml. of petroleum ether was added. After cooling this solution in a refrigerator for 3 days, crystals of **4** separated (189 mg., 1.6 mmoles, 40%), m.p. 109-110° (lit. (4) 111°); ir (potassium bromide): 3390 (N-H), 3080 (C-H), 1605 (C=C) cm^{-1}; pmr (DMSO-d_6): δ 6.52 (d, J = 3 Hz, 1 H, H-3), 7.35 (t, J = 3 and 5 Hz, 2 H, H-2 and H-7), 8.15 (d, J = 5 Hz, 1 H, H-6), 8.8 (s, 1 H, H-4), 11.5 (broad, 1 H, pyrrole N-H).

Acknowledgment.

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

(1a) S. W. Schneller and R. S. Hosmane, *J. Heterocyclic Chem.*, **14**, 1291 (1977); (b) S. W. Schneller, R. S. Hosmane, L. B. MacCartney, and D. A. Hessinger, *J. Med. Chem.*, in press.

(2a) E. Fischer, *Ber.*, **30**, 2400 (1897); (b) E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, **28**, 1662 (1963).

(3) M. T. Bogert and C. E. May, *J. Am. Chem. Soc.*, **31**, 507 (1909).

(4) C. Ducrocq, E. Bisagni, J.-M. Lhoste, J. Mispelter, and J. Defaye, *Tetrahedron*, **32**, 773 (1976).