Synthesis of 4-Amino-1*H*-pyrrolo[2,3-*b*]pyridine (1,7-Dideazaadenine) and 1*H*-Pyrrolo[2,3-*b*]pyridin-4-ol (1,7-Dideazahypoxanthine)[1]

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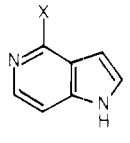
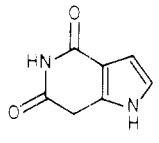
4-Amino-1*H*-pyrrolo[2,3-*b*]pyridine (1,7-dideazaadenine) (**5**) has been synthesized by the iron and acetic acid reduction of 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**13**), obtained by nitration of 1*H*-pyrrolo[2,3-*b*]-pyridine-3-carboxamide 7-oxide (**17**). Other nitration reactions in the 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide series are disclosed. The preparation of 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (1,7-dideazahypoxanthine) (**6**) began with the hydrolysis of ethyl 1-benzyl-3-cyano-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**21**) to the 3,5-dicarboxylic acid derivative of 1-benzyl-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (**22**). Decarboxylation of **22** with subsequent debenzylation formed **6**.

Much effort has been expended on the synthesis and biological evaluation of deazapurines as potential chemotherapeutic agents and biomechanistic probes.[2] Aside from recent disclosures of the synthesis of 3,7-dideazaadenine (**1**),[3] -hypoxanthine (**2**),[3] -xanthine (**3**),[4] and -isoguanine (**4**),[5] little attention has focused on the dideazapurine derivatives in which one —N= in the imidazole ring and one in the pyrimidine ring of purine are each replaced by a —CH=. This report expands the availability of such dideazapurines by describing the synthesis of 4-amino-1*H*-pyrrolo[2,3-*b*]pyridine (**5**) and 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (**6**) as the first 1,7-dideazapurines which are analogues of the naturally occurring purines (i.e., 1,7-dideazaadenine (**5**) and 1,7-dideazahypoxanthine (**6**)).



1, X = NH_2
2, X = OH



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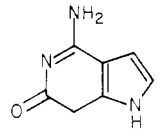

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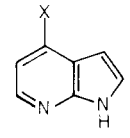


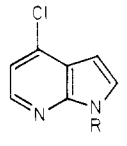
5, X = NH_2
6, X = OH

Initially, a simple nucleophilic displacement reaction by ammonia and hydroxide ion at the 4-chloro center of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (**7**)[6] seemed to offer the most straightforward approach to **5** and **6**, respectively. However, both **7**[7,8] and its N-7 oxide (**8**)[9] were unreactive toward both of these nucleophiles. A similar problem[3] in the attempted synthesis of **1** from **9** with ammonia was overcome by alkylation of the N-1 position of **9** with a benzyl group (which was later removed). However, the two alkylated derivatives **10** and **11**[10,11] were also unreactive.

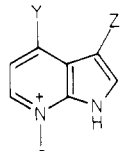
Table I

	chemical shift, δ[a]					coupling constant, (Hz)	
	other	H-2	H-3	H-5	H-6	$J_{2,3}$	$J_{5,6}$
7		7.58	6.48	7.15	8.15	3.0	6.0
10	5.43 (CH_2)	7.20	6.50	7.05	8.17	3.6	6.0
11	3.82 (CH_3)	7.10	6.45	7.00	8.13	3.6	6.0

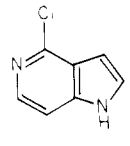
[a] Using $CDCl_3$ as solvent and a Varian EM-360 60-MHz spectrometer.



7, R = H
10, R = $CH_2C_6H_5$
11, R = CH_3



8, Y = Cl; Z = H
12, Y = Z = H
13, Y = NO_2; Z = H
14, Y = H; Z = NO_2
15, Y = H; Z = Br
16, Y = H; Z = CN
17, Y = H; Z = $CONH_2$
18, Y = NO_2; Z = $CONH_2$
19, Y = H; Z = CO_2H



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(1) Presented in part at: (i) the 29th Southeast Regional Meeting of the American Chemical Society, Tampa, FL, November 9–11, 1977, Heterocycles 221; (ii) the 175th National Meeting of the American Chemical Society, Anaheim, CA, March 12–17, 1978, ORGN 67; and (iii) the 7th International Congress of Heterocyclic Chemistry, Tampa, FL, August 12–17, 1979, R1530B.

(2) See, for example: Townsend, L. B.; Cline, B. L.; Panzica, R. P.; Fagerness, P. E.; Roti Roti, L. W.; Stoeckler, J. D.; Crabtree, G. W.; Parks, R. E., Jr. *Lect. Heterocycl. Chem.* **1978**, *4*, S-79.

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

(4) Schneller, S. W.; Hosmane, R. S.; MacCartney, L. B.; Hessinger, D. A. *J. Med. Chem.* **1978**, *21*, 990.

(5) Schneller, S. W.; Hosmane, R. S. *J. Heterocycl. Chem.* **1978**, *15*, 1505.

(6) Clark, B. A. J.; Parrick, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2270.

(7) The authors of ref 6 have also found that **7** fails to undergo nucleophilic substitution when treated with refluxing aqueous sodium hydroxide solution or sodium methoxide in methanol.

(8) Analogous problems have been encountered in attempting nucleophilic displacement reactions on similar chloro derivatives of other deazapurines (for example: Markees, D. G.; Kidder, G. W. *J. Am. Chem. Soc.* **1956**, *78*, 4130; Rousseau, R. J.; Townsend, L. B.; Robins, R. K. *Biochemistry* **1966**, *5*, 756; de Roos, K. B.; Salemink, C. A. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1263; Schelling, J. E.; Salemink, C. A. *Ibid.* **1972**, *91*, 650) and in 4-chloroquinolines (Smalley, R. K. "Quinolines"; Jones, G., Ed.; Wiley: New York, 1977; Part I, pp 543–547, 569).

(9) Both Katritzky and Lagowski ("Chemistry of the Heterocyclic N-Oxides"; Academic Press: New York, 1971; pp 397, 398, 402, 403) and Abramovitch and Smith ("Pyridine and Its Derivatives," Abramovitch, R. A., Ed.; Wiley: New York, 1974; Supplement, Part II, pp 204–218) discuss the effects of *N*-oxides on the nucleophilic substitution reactions in chloro-substituted heterocyclic compounds.

(10) Since benzylation of **7** was initially foreseen as possibly giving the N-1 as well as the undesired N-7 benzylated products, **10** was prepared unambiguously via chlorination of **23**. Then it was possible to confirm that benzylation of **7** led exclusively to **10** in a higher yield than that from **23**. The assignment of **11** as the only methylation product of **7** was, in turn, accomplished by comparing the ^1H NMR spectrum of **10** with that for **11** (see Table I). It can be seen that methylation of **7** produced a high-field shift for the H-2 proton with no significant chemical shift change for H-6 and an increase in the $J_{2,3}$ value with no change in $J_{5,6}$, both trends similar to that observed for the benzylation of **7**.

(11) (a) Compound **11** was brought into this plan as a model compound for the synthesis of 3-deazatubercidin[11b] from **7**. (b) For a review of pyrrolopyrimidine nucleosides (including tubercidin, sangivamycin, and toyocamycin), see: Suhadolnik, R. J. "Nucleoside Antibiotics"; Wiley-Interscience: New York, 1970; Chapter 8.

0022-3263/80/1945-4045$01.00/0

Table II. 1*H*-Pyrrolo[2,3-*b*]pyridine 7-Oxides[a]

compd	crystalline color	yield, %	mp, °C	crystallization solvent	formula[b]
8	white	83.4	221-222 dec	benzene	$C_7H_5ClN_2O$
13	yellow	84.4	229-230.5 dec	95% ethanol	$C_7H_5N_3O_3$
14	yellow	53.3,[c] 47.5,[d] 21,[e] 74[f]	276-277.5 dec	95% ethanol	$C_7H_5N_3O_3$
15	white	61.6	231-231.5 dec	95% ethanol	$C_7H_5BrN_2O$
16	white	94.5	312-313 dec	water	$C_8H_5N_3O$
17	white	98	292.5-293 dec	water	$C_8H_7N_3O_2$[g]
18	yellow	55	307 dec	ethanol-water	$C_8H_6N_4O_4$

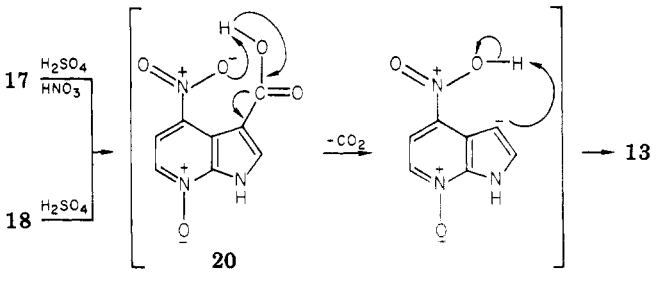
[a] See the paragraph at the end of this paper for information on supplementary material. [b] Satisfactory analytical data (+0.4% for C, H, N) were reported for all new compounds listed in the table. [c] From 7-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridinium *m*-chlorobenzoate. [d] From **12**. [e] From **15**. [f] From **12** and nitronium tetrafluoroborate. [g] Possesses 1.0 mol of hydration.

Another route to **5** was envisioned via the nitration of 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**12**) to the 4-nitro derivative **13** with subsequent reduction of **13** to **5**. This was based on the directive patterns for electrophilic substitution (e.g., nitration) in the pyridine *N*-oxides,[12] 3*H*-imidazo[4,5-*b*]pyridine 4-oxide[13] and thieno[2,3-*b*]pyridine 7-oxide,[14] and the reduction of the resultant 4-nitro derivatives of the latter two *N*-oxides to adenine analogues. Unexpectedly, however, nitration of **12** yielded 3-nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**14**)[15] rather than **13**. In an effort to block the 3-position and direct substitution to C-4, nitration of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**15**) was considered. This also produced **14** by an electrophilic substitution process similar to the nitration of various 1-bromoimidazo[1,5-*a*]pyridines to the corresponding 1-nitro derivatives.[16] Such results with **12** and **15**[17] indicate that the electrophilic substitution directive influence of the pyrrole ring nitrogen exceeds that of the *N*-oxide.

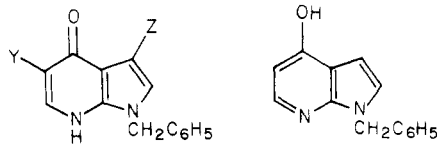
With the intention of blocking the 3-position of **12** with a functional group less vulnerable to replacement by the nitronium ion and which, subsequently, could be removed in the realization of **5**, 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile 7-oxide (**16**) and -3-carboxamide 7-oxide (**17**) were subjected to the nitrating conditions. It should be mentioned that **16** and **17** were also chosen as potential precursors to 3-deazatoyocamycin and 3-deazasangivamycin, respectively.[11b]

Nitration of **16** gave 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide 7-oxide (**18**), a product in which hydration[18] of the nitrile was accompanied by introduction of the nitro group at the desired position. On the other hand, nitration of **17** proceeded with nitration and hydrolysis/decarboxylation to give the required **13**[19] in 84.4% yield. Subsequent reduction of **13** with iron and acetic acid produced **5** as an unstable oily material which was characterized as its picrate.

The conversion of **17** into **13** is believed to involve initial nitration of **17** at C-4 prior to decarboxamidation (otherwise **14** would have been obtained). The evidence presented below indicates that the amide functionality is lost via hydrolysis to the corresponding carboxylic acid with subsequent decarboxylation but, at this time, it is not easy to decide whether hydrolysis occurs before or after nitration. However, the 4-nitro group must be present for decarboxylation to occur. This was evident from the acidic hydrolysis (as would be possible in the nitrating medium)[17] of **18** to give **13** and of **17** to yield **19** without accompanying decarboxylation. Therefore, at some stage in the **17** → **13** transformation, it seems reasonable to propose that 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid 7-oxide (**20**) forms and undergoes decarboxylation in the following manner:



The synthesis of **6** involved hydrolysis of the ester **21**[20] to the dicarboxylic acid **22**. Decarboxylation of **22** in diphenyl ether gave 1-benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (**23**) which, upon debenzylation with sodium in liquid ammonia,[21] was converted into the desired **6**.



21, Y = CO_2Et; Z = CN
22, Y = Z = CO_2H

23

It should be noted that **21** and **22** were assigned the 4-oxo tautomeric structures whereas **23** and **6** were placed in the 4-enolic arrangement. This was based on their solid-state infrared spectral data which indicated the presence of two and three carbonyl groups for **21** and **22**,

(12) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 3rd ed.; Wiley-Interscience: New York, 1976; pp 249-254.
(13) Jain, P. C.; Chatterjee, S. K.; Anand, N. *Indian J. Chem.* **1966**, *4*, 403.
(14) Klemm, L. H.; Barnish, I. T.; Zell, R. *J. Heterocycl. Chem.* **1970**, *7*, 81.
(15) The use of nitronium tetrafluoroborate (as in, for example: Huang, G.-F.; Torrence, P. F. *J. Org. Chem.* **1977**, *42*, 3821) with **12** also resulted in **14**.
(16) Glover, E. E.; Peck, L. W.; Doughty, D. G. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1833.
(17) The only conditions which produced any nitrated product involved a mixture of 70% nitric acid and 98% sulfuric acid.
(18) In view of the reaction conditions employed,[17] this result is not surprising.
(19) It should also be noted that compound **13** is an isostere of 4-nitroquinoline 1-oxide which is carcinogenic and mutagenic (see, for example: Varnes, M. E.; Biaglow, J. E. *Cancer Res.* **1979**, *39*, 2960, and the introductory paragraph of Abramovitch, R. A.; Smith, E. A. *J. Heterocycl. Chem.* **1975**, *12*, 969).
(20) Brodrick, A.; Wibberley, D. G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1910.
(21) The debenzylation of pyrroles has been reported by others to be a difficult task (see, for example: Anderson, H. J.; Groves, J. K. *Tetrahedron Lett.* **1971**, 3165; Lim, M.-I.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 3826).

respectively, and only a hydroxyl group for **23** and **6**.

Experimental Section

General. All 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 ^1H NMR spectra were determined at 60 MHz with a Varian EM-360 spectrometer and are reported in parts per million downfield from Me_4Si as an internal standard. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), m (multiplet), and br (broad). Elemental analyses were performed by Het-Chem-Co., Harrisonville, MO, Galbraith Laboratories, Knoxville, TN, and M-H-W Laboratories, Phoenix, AZ.

General Procedure for Preparation of 1*H*-pyrrolo[2,3-*b*]pyridine 7-Oxides 8, 15, 16, and 17. To 0.38 g (2.5 mmol) of **7**[22] and 0.3 g (1.5 mmol) of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine,[23] 0.4 g (2.79 mmol) of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile,[23,24] or 0.4 g (2.48 mmol) of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide (whose preparation is described below) in absolute Et_2O (40 mL for **7** and 18 mL for 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine) or THF (35 mL for 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile and 40 mL for 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide) was added 1.5–1.6 mol equiv of 85% *m*-chloroperoxybenzoic acid. The resulting mixture was stirred at room temperature for 2 h and the precipitate which formed during this time was isolated by aspirator filtration, washed with cold Et_2O or THF, purified, and characterized as **8**, **15**, **16**, and **17**, as described in Table II.

1*H*-Pyrrolo[2,3-*b*]pyridine-3-carboxamide. To a mixture of 0.19 g (1.32 mmol) of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile[23,24] and 0.08 g of KOH in 4 mL of absolute EtOH contained in a two-necked flask with an efficient stirrer was slowly added 4 mL of 30% H_2O_2 solution. The reaction mixture was then heated at 55–60 °C, with stirring, for 30 min at which time an additional 1 mL of 30% H_2O_2 solution was added and the heating and stirring were continued for 40 min. After the transferral of the reaction mixture to an Erlenmeyer flask, combining this with the EtOH (3 mL) used to rinse the reaction vessel and chilling this solution, 0.19 g (89%) of 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide precipitated and was obtained by filtration and recrystallized from EtOH as white crystals: mp 275–276 °C dec; IR (KBr) 3450 (asymmetric NH stretching), 3330 (symmetric NH stretching), 3150 (pyrrole NH), 1690 (C=O), 1615 cm^{-1} (NH_2 bending); ^1H NMR (Me_2SO-d_6) δ 7.17 (s, 2 H exchangeable with D_2O, NH_2), 7.15 (d of d, 1 H, $J_{4,5}$ = 6, $J_{5,6}$ = 8 Hz, H-5), 8.20 (s, 1 H, H-2), 8.25 (d of d, 1 H, $J_{4,5}$ = 6, $J_{4,6}$ = 2 Hz, H-4), 8.47 (d of d, 1 H, $J_{4,6}$ = 2, $J_{5,6}$ = 8 Hz, H-6).

Anal. Calcd for $C_8H_7N_3O$: C, 59.61; H, 4.38; N, 26.07. Found: C, 59.56; H, 4.41; N, 26.16.

1-Benzyl-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (10). Method A. A cooled solution of 30 mL of phosphorus oxychloride in 10 mL of $CHCl_3$ was added dropwise to a mixture of 0.56 g (2.5 mmol) of **23** (whose preparation is described below) in 5 mL of $CHCl_3$. After the addition, the resultant mixture was heated at 85–90 °C in an oil bath for 3 h. The yellow solution was then cooled to room temperature and the phosphorus oxychloride and $CHCl_3$ were removed under reduced pressure to give a viscous residue to which ice water (50 mL) was added. Following neutralization of this aqueous mixture with 28% NH_4OH, it was extracted with Et_2O (3 × 30 mL). The combined Et_2O extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness to give 0.2 g (0.82 mmol, 33%) of **10** which was purified by distillation [bp 66.5–68.5 °C (0.2 mmHg)] as a colorless liquid: IR (neat) 3040 (aromatic CH), 2930 cm^{-1} (aliphatic CH); ^1H NMR ($CDCl_3$) δ 5.43 (s, 2 H, CH_2), 6.50 (d, 1 H, $J_{2,3}$ = 3.6 Hz, H-3), 7.05 (d, 1 H, $J_{5,6}$ = 6 Hz, H-5), 7.20 (d, 1 H, $J_{2,3}$ = 3.6 Hz, H-2), 7.23 (m, 5 H, phenyl H), 8.17 (d, 1 H, $J_{5,6}$ = 6 Hz, H-6).

Anal. Calcd for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.57; N, 11.54. Found: C, 69.02; H, 4.52; N, 11.42.

Method B. A solution of 0.4 g (2.62 mmol) of **7**[22] in 2 mL of hexamethylphosphoramide in a 25-mL three-necked flask was flushed with N_2 and chilled to 0 °C. Sodium hydride (0.07 g, 2.92 mmol) was added to this solution over a period of 2 min and the mixture was then stirred at room temperature for 5 h. At this point the solution was rechilled to 0 °C and 0.45 g (2.62 mmol) of benzyl bromide added rapidly. The resulting mixture was allowed to come to room temperature and stirred overnight after which time it was diluted with 3 mL of water and extracted with Et_2O (3 × 25 mL). The Et_2O extracts were combined, washed with water, dried over anhydrous $MgSO_4$, and evaporated to a residue which, following purification as described above, gave **10** (0.6 g, 2.47 mmol, 94.3%) which was identical with that obtained by method A.

1-Methyl-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (11). By the procedure described in method B above for the preparation of **10**, reaction of 1.0 g (6.55 mmol) of **7**[22] in 10 mL of hexamethylphosphoramide with 0.16 g (6.58 mmol) of NaH and then 0.93 g (6.55 mmol) of CH_3I gave, after purification, 0.5 g (3.0 mmol, 46%) of **11** as a colorless liquid: bp 56–57 °C (1 mmHg); IR (neat) 2940 (aliphatic CH), 1410 cm^{-1} (CH_3N); ^1H NMR ($CDCl_3$) δ 3.82 (s, 3 H, CH_3), 6.45 (d, 1 H, $J_{2,3}$ = 3.6 Hz, H-3), 7.00 (d, 1 H, $J_{5,6}$ = 6 Hz, H-5), 7.10 (d, 1 H, $J_{2,3}$ = 3.6 Hz, H-2), 8.13 (d, 1 H, $J_{5,6}$ = 6 Hz, H-6).

Anal. Calcd for $C_8H_7ClN_2$: C, 57.67; H, 4.23; N, 16.82. Found: C, 57.62; H, 4.40; N, 16.68.

7-Hydroxy-1*H*-pyrrolo[2,3-*b*]pyridinium *m*-Chlorobenzoate. To 0.5 g (4.23 mmol) of 1*H*-pyrrolo[2,3-*b*]pyridine[25] dissolved in 15 mL of redistilled 1,2-dimethoxyethane was added 1.2 g (5.9 mmol) of 85% *m*-chloroperoxybenzoic acid. The resulting yellow solution was stirred at room temperature for 1.5 h during which time the product precipitated. The mixture was cooled and the light yellow product isolated by filtration and washed with Et_2O to give 0.45 g (79%) of 7-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridinium *m*-chlorobenzoate: mp 145–145.5 °C; IR (KBr) 3100 (pyrrole NH), 2700–2200 (br OH), 1695 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 6.70 (d, 1 H, $J_{2,3}$ = 4 Hz, H-3), 7.35 (d of d, 1 H, $J_{5,6}$ = 6, $J_{4,5}$ = 8 Hz, H-5), 7.58 (br s, 4 H, benzene H), 7.90 (d, 1 H, $J_{4,5}$ = 8 Hz, H-4), 8.20 (d, 1 H, $J_{2,3}$ = 4 Hz, H-2), 8.45 (d, 1 H, $J_{5,6}$ = 6 Hz, H-6).

Anal. Calcd for $C_{14}H_{11}ClN_2O_3$: C, 57.83; H, 3.79; N, 9.64. Found: C, 58.03; H, 3.99; N, 9.83.

1*H*-Pyrrolo[2,3-*b*]pyridine 7-Oxide (12).[26] A suspension of 2 g (6.8 mmol) of 7-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridinium *m*-chlorobenzoate in 20 mL of water was basified to pH 9 (pH paper) with saturated K_2CO_3 solution. Even though **12** began to precipitate at this point, the mixture was cooled in a refrigerator and the resultant precipitate isolated by filtration and recyrstallized from benzene to give 0.71 g (5.3 mmol, 77%) of **12**: mp 101–103 °C (lit.[6] mp 134–135 °C); IR (KBr) 3100 (NH), 1220 cm^{-1} (^+N–O^-), ^1H NMR (Me_2SO-d_6) δ 6.58 (d, 1 H, $J_{2,3}$ = 3 Hz, H-3), 7.10 (d of d, 1 H, $J_{4,5}$ = 8, $J_{5,6}$ = 6 Hz, H-5), 7.48 (d, 1 H, $J_{2,3}$ = 3 Hz, H-2), 7.67 (d, 1 H, $J_{4,5}$ = 8 Hz, H-4), 8.18 (d, 1 H, $J_{5,6}$ = 6 Hz, H-6).

3-Nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-Oxide (14). Method A. To a stirred mixture of 0.32 g (5 mmol) of 71% HNO_3 and 0.49 g (5 mmol) of 97% H_2SO_4 at 0 °C was added, portionwise, 2.4 mmol of either 7-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridinium *m*-chlorobenzoate or **12**. The mixture was then stirred in a water bath at room temperature for 2 h, added to 50 g of ice water, and stirred briefly, and the resulting yellow precipitate was collected by filtration. This product was characterized as **14** as described in Table II.

Compound **14** was also obtained from **15** (see Table II) by a similar procedure except that it was necessary to conduct the process at 55–60 °C for 2 h in order to achieve a reaction.

Method B. To a solution of 0.12 g (0.908 mmol) of nitronium tetrafluoroborate[27] in 2 mL of tetramethylene sulfone under a

(22) The use of phosphorus trichloride with 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**12**) to prepare **7** as reported in ref 6 led to 1*H*-pyrrolo[2,3-*b*]-pyridine in our laboratory. However, with phosphorus oxychloride as the chlorinating agent, it was possible to convert **12** into **7**.

(23) Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1956**, *78*, 1247.

(24) We have found that reaction of 3-bromo-1*H*-pyrrolo[2,3-*b*]-pyridine[23] with cuprous cyanide in DMF can also be used to prepare 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile but in a yield (13%) inferior to that reported[23] via dehydration of the corresponding 3-oxime.

(25) Commercially available from Aldrich Chemical Co. or via the procedure: Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1955**, *77*, 457.

(26) The synthesis of **12** by the literature method[6] could not be accomplished in our laboratory.

N_2 atmosphere was added, portionwise, 0.1 g (0.745 mmol) of **12**. After the addition of **12**, the reaction mixture was stirred at room temperature for 2 h and then poured into 20 mL of ice water. The resulting yellow precipitate was isolated by filtration, washed with cold water, and found to be identical (see Table II) with **14** obtained by method A.

4-Nitro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide 7-Oxide (18). To a stirred mixture of 1.1 g (12 mmol) of 71% HNO_3 and 2.4 g (24 mmol) of 98% H_2SO_4 at 0 °C was added, portionwise, 0.97 g (6.1 mmol) of **16**. This reaction mixture was heated at 63–68 °C for 2 h, cooled to room temperature, and then poured into ice water at which time precipitation occurred. After the mixture was chilled, the yellow solid was isolated by filtration, washed with water, and characterized as **18** (see Table II).

4-Nitro-1*H*-pyrrolo[2,3-*b*]pyridine 7-Oxide (13). To a stirred mixture of 1.6 g (17.4 mmol) of 71% nitric acid and 3.44 g (34.4 mmol) of 98% sulfuric acid at 0 °C was added, portionwise, 1.57 g (8.86 mmol) of **17**. The temperature was then increased slowly to 70 °C at which point a vigorous reaction took place with the evolution of heat and a gas (caution was exercised to avoid solution bumping at this point). The solution was kept at 70–75 °C for 1.5 h, cooled to room temperature, and then added to ice water. The resulting precipitate was collected to provide **13** which was purified and characterized as described in Table II.

Picrate Derivative of 4-Amino-1*H*-pyrrolo[2,3-*b*]pyridine (1,7-Dideazaadenine) (5). A mixture of 0.2 g (1.11 mmol) of **13** and 0.8 g of Fe powder in 8 mL of glacial AcOH was heated with stirring at 100 °C for 2 h. The cooled (room temperature) mixture was diluted with 20 mL of water, adjusted to pH 10–11 (pH paper) with NaOH pellets, and then subjected to continuous extraction with 250 mL of Et_2O. The Et_2O extract was dried over anhydrous Na_2SO_4 and evaporated on a rotary evaporator to result in an unstable yellowish liquid. Attempts to distill this material led to extensive decomposition while several column chromatography runs (silica gel with $CHCl_3$–MeOH, 9:1, v/v) led to a liquid whose color darkened upon solvent removal and upon standing at room temperature.

Thus, the residue from the initial continuous ether extraction was dissolved in 2 mL of 95% EtOH and to this was added 2 mL of a cold saturated solution of picric acid in absolute EtOH. The resulting yellow precipitate was isolated by filtration, washed with a small amount of cold EtOH, and recrystallized from AcOH–water (1:9) to produce 0.12 g (0.33 mmol, 30%) of the picrate of **5** as yellow crystals: mp 300–300.5 °C dec; IR (KBr) 3470 (asymmetric NH stretching), 3370 (symmetric NH stretching), 3260 (OH), 3100 cm^{-1} (pyrrole NH); ^1H NMR (Me_2SO-d_6) δ 6.48 (d, 1 H, $J_{5,6}$ = 7 Hz, H-5), 6.82 (d, 1 H, $J_{2,3}$ = 3 Hz, H-3), 7.28 (d, 1 H, $J_{2,3}$ = 3 Hz, H-2), 7.87 (d, 1 H, $J_{5,6}$ = 7 Hz, H-6), 8.08 (s, 3 H, $^+NH_3$), 8.62 (s, 2 H, picrate H), 12.03 (s, 1 H, pyrrole NH).

Anal. Calcd for $C_{13}H_{10}N_6O_7$: C, 43.06; H, 2.78; N, 23.20. Found: C, 42.91; H, 2.82; N, 23.09.

1*H*-Pyrrolo[2,3-*b*]pyridine-3-carboxylic Acid 7-Oxide (19). A mixture of 0.12 g (0.68 mmol) of **18** in 2 mL of 25% H_2SO_4 was refluxed for 3 h. After the solution cooled, its pH was adjusted to 2–3 (pH paper) with concentrated NH_4OH solution. The white precipitate which resulted was collected by filtration, washed with water, and recrystallized from EtOH–water to provide 0.1 g (0.56 mmol, 82.5%) of **19**: mp 276 °C dec; IR (KBr) 3100 (NH), 2900–2500 (OH), 1700 (C=O), 1250 cm^{-1} (^+N–O^-); ^1H NMR (CF_3CO_2H) δ 7.73 (d of d, 1 H, $J_{4,5}$ = 7, $J_{5,6}$ = 8 Hz, H-5), 8.48 (s, 1 H, H-2), 8.65 (d, 1 H, $J_{4,5}$ = 7 Hz, H-4), 9.05 (d, 1 H, $J_{5,6}$ = 8 Hz, H-6).

Anal. Calcd for $C_8H_6N_2O_3$: C, 53.93; H, 3.40; N, 15.73. Found: C, 53.71; H, 3.55; N, 15.89.

(27) Commercially available from Aldrich Chemical Co. and used without further purification.

1-Benzyl-4-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-3,5-dicarboxylic Acid (22). A mixture of 1 g (3.11 mmol) of **21**[20] in 15 mL of 25% NaOH solution was refluxed until a clear solution resulted (1.5 h). The solution was cooled to room temperature and acidified with 18% HCl solution. The resulting precipitate was collected by filtration, washed with water, and dried to give 0.97 g (3.11 mmol, 100%) of **22** which was recrystallized from AcOH–water as white crystals: mp 237 °C dec; IR (KBr) 3120 (NH), 2900–2600 (OH), 1735 and 1670 (C=O of CO_2H), 1613 cm^{-1} (C=O of pyridine ring); ^1H NMR (Me_2SO-d_6) δ 5.53 (s, 2 H, CH_2), 7.32 (s, 5 H, phenyl H), 8.18 (s, 1 H, H-2), 8.64 (s, 1 H, H-6), 9.43 (br, 3 H, exchangeable with D_2O, NH and 2 CO_2H).

Anal. Calcd for $C_{16}H_{12}N_2O_5$: C, 61.54; H, 3.88; N, 8.97. Found: C, 61.37; H, 3.67; N, 8.85.

1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (23). Compound **22** (1.12 g, 3.59 mmol) was placed in 7 mL of diphenyl ether and refluxed until the effervescence ceased (2 h). After this solution was cooled to room temperature, petroleum ether was added and the precipitate which resulted after trituration was collected by filtration. This material was best purified by distillation [bp 105–108 °C (0.6 mmHg)] to give 0.6 g (2.68 mmol, 74.7%) of **23** as a glass: IR (KBr) 3100–2500 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 5.27 (s, 2 H, CH_2), 6.35 (d, 1 H, $J_{5,6}$ = 6 Hz, H-5), 6.60 (d, 1 H, $J_{2,3}$ = 3 Hz, H-3), 6.77 (d, 1 H, $J_{2,3}$ = 3 Hz, H-2), 7.08 (s, 5 H, phenyl H), 7.60 (d, 1 H, $J_{5,6}$ = 6 Hz, H-6), 8.80 (br, 1 H, OH).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.49. Found: C, 74.88; H, 5.55; N, 12.35.

1*H*-Pyrrolo[2,3-*b*]pyridin-4-ol (1,7-Dideazahypoxanthine) (6). To 300 mL of stirred, cooled, liquid ammonia was added 1.4 g (0.061 mol) of thinly cut Na. To this stirred blue solution was added, dropwise, 2.24 g (10 mmol) of **23** dissolved in 50 mL of anhydrous Et_2O, and the resulting solution was refluxed for 1 h. After this, 3.5 g of NH_4Cl was added slowly until the deep blue color of the solution disappeared, and then the mixture was allowed to stand at room temperature until the NH_3 and Et_2O evaporated. The residue was dissolved in 200 mL of water and then neutralized with AcOH. The resulting solution was continuously extracted with AcOEt (700 mL) for 2 days. The extract was then concentrated to 15 mL and purified by column chromatography (silica gel) using MeOH–CH_2Cl_2 (1:6, v/v) to afford, following recrystallization from acetone, 0.9 g (6.71 mmol, 67.1%) of **6** as colorless granular crystals: mp 238–239 °C dec; IR (KBr) 3390 (OH), 3130 cm^{-1} (NH); ^1H NMR (Me_2SO-d_6) δ 6.41 (d, 1 H, $J_{5,6}$ = 6 Hz, H-5), 6.50 (d, 1 H, $J_{2,3}$ = 3 Hz, H-3), 7.16 (d, 1 H, $J_{2,3}$ = 3 Hz, H-2), 7.90 (d, 1 H, $J_{5,6}$ = 6 Hz, H-6), 11.0 (br, NH, exchangeable with D_2O).

Anal. Calcd for $C_7H_6N_2O$: C, 62.67; H, 4.51; N, 20.89. Found: C, 62.62; H, 4.58; N, 20.61.

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Registry No. 5·picrate, 74420-01-2; **6**, 74420-02-3; **7**, 55052-28-3; **8**, 74420-03-4; **10**, 74420-04-5; **11**, 74420-05-6; **12**, 55052-24-9; **13**, 74420-06-7; **14**, 74420-07-8; **15**, 74420-08-9; **16**, 74420-09-0; **17**, 74420-10-3; **18**, 74420-11-4; **19**, 74420-12-5; **21**, 59661-65-3; **22**, 74420-13-6; **23**, 74420-14-7; 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine, 74420-15-8; 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide, 74420-16-9; 1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile, 4414-89-5; phosphorus oxychloride, 10025-87-3; benzyl bromide, 100-39-0; methyl iodide, 74-88-4; 7-hydroxy-1*H*-pyrrolo[2,3-*b*]pyridinium *m*-chlorobenzoate, 74420-18-1; 1*H*-pyrrolo[2,3-*b*]pyridine, 271-63-6.

Supplementary Material Available: Full NMR and IR data for compounds **8** and **13**–**18** (1 page). Ordering information is given on any current masthead page.