Synthetic Strategies toward the Synthesis of 2,4-Dimethoxypyrrolo[3,2-*d*]pyrimidine[1]

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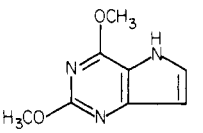
Two approaches to prepare 2,4-dimethoxypyrrolo[3,2-*d*]pyrimidine (1) are described. 2,4-Dimethoxy-6-methyl-5-nitropyrimidine (2) was converted to 6-(cyanomethyl)-2,4-dimethoxy-5-nitropyrimidine (6) in two steps. Subsequent catalytic hydrogenation of 6 produced 1. In a second approach, 2 was formylated, giving rise to 6-[2-(dimethylamino)vinyl]-2,4-dimethoxy-5-nitropyrimidine (7). Hydrogenation of 7 resulted in the formation of 1. Reduction of 2 provided 5-amino-2,4-dimethoxy-6-methylpyrimidine (10). Reaction of compound 10 with triethyl orthoformate produced 2,4-dimethoxy-5-[(ethoxymethylene)amino]-6-methylpyrimidine (11). Reaction of 11 with lithium diisopropylamide gave 2,4-dimethoxy-5-isocyano-6-methylpyrimidine (12).

The first synthetic pyrrolo[3,2-*d*]pyrimidine to demonstrate[2] biological activity was 4-aminopyrrolo[3,2-*d*]pyrimidine. More recently, 4-amino-7-*C*-(1-β-D-ribofuranosyl)pyrrolo[3,2-*d*]pyrimidine (9-deazaadenosine) has demonstrated[3] significant in vitro and in vivo antitumor activity[3,4] and has renewed interest in this ring system. Approaches toward the synthesis of compounds in this ring system have been made by (1) constructing a pyrimidine ring onto an appropriately substituted aminopyrrole[3,5,7] or pyrrole dicarboxylate,[6] (2) the chemical transformation of a bicyclic heterocycle to produce a pyrrolo[3,2-*d*]pyrimidine,[8,9] and (3) annulation of a pyrrole ring onto an appropriately substituted pyrimidine.[10,11] As part of a study in the area of *C*-nucleosides, we have been interested in the conversion of pyrimidines into model pyrrolo[3,2-*d*]-pyrimidines which are unsubstituted in the 6- and 7-positions. The synthesis[10,12] of such unsubstituted pyrrolo-[3,2-*d*]pyrimidines has only been accomplished by the pyrolytic (300 °C, copper powder) decarboxylation of the corresponding 6-carboxypyrrolo[3,2-*d*]pyrimidine. We now report[13] two procedures by which a readily available 5-nitropyrimidine is converted under mild conditions into a 6,7-unsubstituted pyrrolo[3,2-*d*]pyrimidine.

Results and Discussion

We elected to prepare 2,4-dimethoxypyrrolo[3,2-*d*]pyrimidine (1)as the target compound since subsequent hydrolysis of the methoxy groups should provide a compound amenable to elaboration into a variety of 2- and 4-substituted pyrrolo[3,2-*d*]pyrimidines.[12] To accomplish the



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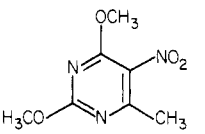

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synthesis of 1, we started with 2,4-dimethoxy-6-methyl-5-nitropyrimidine[14] (2). Compound 2 was particularly suited for our purposes because after the introduction of an additional carbon atom onto the 6-methyl group, the 5-nitro group was envisioned to be the source of the pyrrole nitrogen atom.

A brief look in the literature indicated that the Pschorr–Hoppe reaction[15] might be adapted to the formation of the pyrrolo[3,2-*d*]pyrimidine ring system, and this therefore formed the basis of the first approach. The Pschorr–Hoppe procedure involved the catalytic hydrogenation of a 2-(cyanomethyl)nitrobenzene to form an indole. In order to investigate a similar ring closure in our scheme, we proceeded to synthesize the requisite 6-(cyanomethyl)-2,4-dimethoxy-5-nitropyrimidine (6) from 2 (Scheme I). A variety of bromination procedures were attempted (see Table I) in order to prepare 6-(bromomethyl)-2,4-dimethoxy-5-nitropyrimidine (3), and a method involving the reaction of 2 with bromine and excess sodium acetate in glacial acetic acid was found to be the most satisfactory. This method furnished a mixture of 6-(bromomethyl)-2,4-dimethoxy-5-nitropyrimidine (3) in 43% yield and 6-(dibromomethyl)-2,4-dimethoxy-5-nitropyrimidine (4) in 31% yield plus a small amount of unreacted starting material. Compounds 3 and 4 were readily isolated by using silica gel chromatography. For preparation of the 6-cyanomethyl derivative 6, potassium cyanide was reacted with 3 under phase-transfer conditions using Aliquot 336.[16] However, rather than 6, 2,2-bis-

(1) This study was supported by funds from the National Institutes of Health (Training Grant No. 5-T32-GM 007767) and the American Cancer Society (Grant CH-133).

(2) Hartenstein, R. C.; Fridovitch, I. *J. Biol. Chem.* **1967**, *242*, 740.

(3) Lim, M.-I.; Klein, R. S. *Tetrahedron Lett.* **1981**, *22*, 25.

(4) Chu, M. Y.; Landry, L. B.; Klein, R. S.; Lim, M.-I.; Bogden, A. E.; Crabtree, G. W. *Proc. Am. Assoc. Cancer Res.* **1982**, *23*, 220.

(5) Lim, M.-I.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 3826.

(6) Garcia-Lopez, M. T.; de las Heras, F. G.; Stud, M. *J. Chem Soc., Perkin Trans. 1* **1978**, 483.

(7) Lim, M.-I.; Klein, R. S.; Fox, J. J. *Tetrahedron Lett.* **1980**, *21*, 1013.

(8) Klein, R. S.; Lim, M.-I.; Tam, S. Y-K.; Fox, J. J. *J. Org. Chem.* **1978**, *43*, 2536.

(9) Crane, L. E.; Beardsley, G. P.; Maki, Y. *J. Org. Chem.* **1980**, *45*, 3827.

(10) Amarnath, V.; Madhav, R. *Synthesis* **1974**, *6*, 837.

(11) (a) Senda, S.; Hirota, K. *Chem. Pharm. Bull.* **1974**, *22*, 2593. (b) Sokolova, V. N.; Modnikova, G. A.; Novitsky, K. V.; Kravchenko, A. I.; Chernov, V. A.; Shcherbakova, L. I.; Pershin, G. N. *Khim.-Farm. Zh.* **1979**, *13*, 17. (c) Sizova, O. S.; Britikova, N. E.; Novitskiik, Y.; Shcherbakova, L. I.; Pershin, G. N. *Khim. Farm. Zh.* **1980**, *14*, 63.

(12) Imai, K. I. *Chem. Pharm. Bull.* **1964**, *12*, 1030.

(13) Cupps, T. L.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1982**, *23*, 4759.

(14) Compound 2 was prepared from 2,4-dichloro-6-methyl-5-nitropyrimidine by using a slightly improved procedure over the one reported by: Backer, H. J.; Brevenstuk, A. B. *Recl. Trav. Chim. Pays-Bas* **1945**, *64*, 115. While carrying out the preparation of 2, it was discovered that 2,4-dichloro-6-methyl-5-nitropyrimidine reacted with 1 equiv of methoxide ion to produce two compounds which were isolated by using chromatography. The major product was 2-chloro-4-methoxy-6-methyl-5-nitropyrimidine (i), mp 65–67 °C (lit. mp 62–63 °C: Hirata, M.; Nagasaki, S.; Isoda, S.; Nakazawa, N.; Kobayashi, T.; Oshima, Y.; Naito, T. *Yakaguku Zasshi* **1967**, *87*, 410)], while the minor product was the other positional isomer, 4-chloro-2-methoxy-6-methyl-5-nitropyrimidine (ii), mp 49–50 °C. The experimental details for these three compounds have been included in the Experimental Section.

(15) (a) Pshorr, R.; Hoppe, G. *Chem. Ber.* **1910**, *43*, 2543. (b) recent references: Walker, G. N. *J. Am. Chem. Soc.* **1955**, *77*, 3844. Bourdais, J.; Germain, C. *Tetrahedron Lett.* **1970**, 195.

(16) Aliquot 336 was obtained commercially from Aldrich Chemical Co., Milwaukee, WI.

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Scheme I

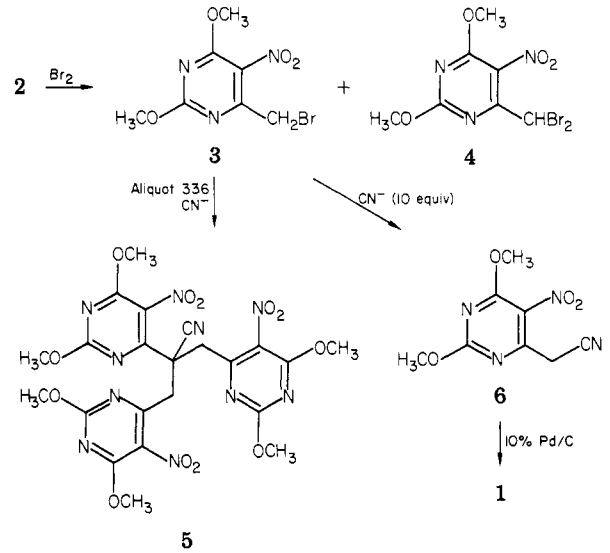


Table I. Halogenation Reactions Attempted on Compound 2

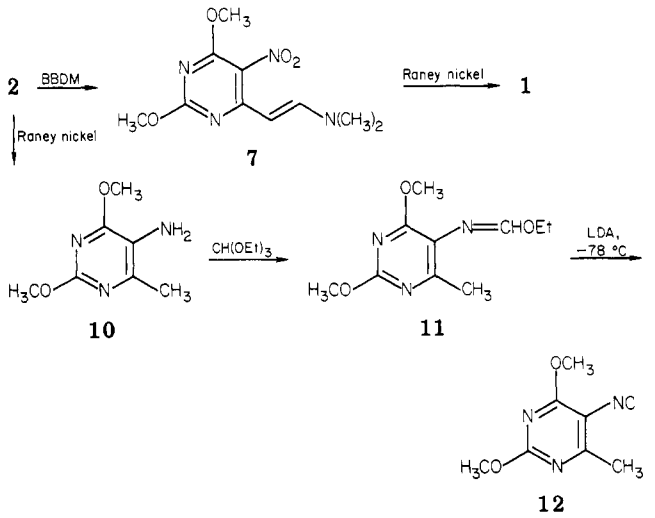
halogenation reagent	conditions	results
NBS[a]	CCl_4, N_2, Δ[b]	*c*
NBS	CCl_4, $h\nu$, Δ	*c*
NBS	AcOH, Bper,[d] $h\nu$, Δ	*e*
Br_2	C_6H_6, NaH, 20 °C	*c*
Br_2	DMF, NaH, 20 °C	complex
Br_2	$CHCl_3$, pyr,[f] 60 °C	*c*
Br_2 (2)[g]	AcOH, NaOAc, Δ	6 (80%)
Br_2 (0.9)[g]	AcOH, NaOAc, Δ	5 (43%), 6 (31%)
dioxane-Br_2	MeOH-$CHCl_3$, Δ	5, 6, hydr[h]
I_2	AcOH, NaOAc, Δ	*c*
PBP[i]	AcOH, NaOAc, Δ	5, 6, hydr[h]

[a] *N*-Bromosuccinimide. [b] Reflux; [c] No reaction. [d] Benzoyl peroxide. [e] Minimal reaction. [f] Pyridine. [g] Number of equivalents. [h] Hydrolysis of methoxy groups. [i] Pyridinium bromide-perbromide.

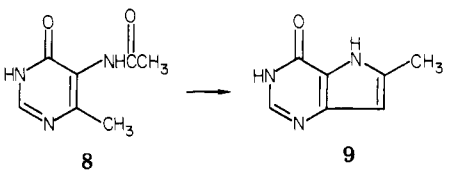
[(2,4-dimethoxy-5-nitropyrimidin-6-yl)methyl]-2-(2,4-dimethoxy-5-nitro-6-pyrimidin-6-yl)acetonitrile (**5**) was produced in 54% yield. For circumvention of dialkylation, an alternate approach was developed in which the cyanide displacement was carried out in cold aqueous methanol. A tenfold excess of potassium cyanide was used to assure that bromo displacement occurred before alkylation became a competing reaction. Under these conditions, 6-(cyanomethyl)-2,4-dimethoxy-5-nitropyrimidine (**6**) was obtained in 55% yield. The conversion of **6** into **1** was accomplished in a 47% yield by a catalytic reduction employing the Pshorr–Hoppe conditions, i.e., 10% palladium on carbon at 70 °C and 80 psig. Raney nickel was also found to effect the reductive annulation to compound **1** although somewhat lower yields were realized.

To explore a second method for the introduction of a formyl equivalent onto the 6-methyl group of pyrimidine **2**, we reacted the mild formylating agent *tert*-butoxybis(dimethylamino)methane[17] (BBDM) with **2** to obtain 2,4-dimethoxy-6-[2-(dimethylamino)vinyl]-5-nitropyrimidine (**17**) in a 77% yield (Scheme II). For production of the desired pyrrolo[3,2-*d*]pyrimidine, **7** was catalytically hydrogenated with Raney nickel. This reaction led to the one-step formation of **1** in 27% yield from **7**. This reductive annulation evidently involved an initial nitro group reduction followed by cyclization with loss of dimethylamine. The spectral data for **1** obtained by this method were identical with those of **1** obtained by the first method.

Scheme II



The conversion of 5-acetamido-6-methylpyrimidin-4-one (**8**) to 6-methylpyrrolo[3,2-*d*]pyrimidin-4-one (**9**) has been



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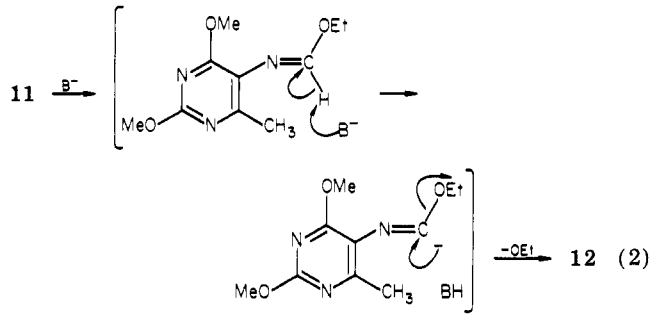
reported by treatment of **8** with base in an inert atmosphere and at elevated temperature.[18] This prompted us to investigate whether the same type of ring closure could be effected on an appropriately substituted (ethoxyimino)pyrimidine. 2,4-Dimethoxy-5-[(ethoxymethylene)amino]-6-methylpyrimidine (**11**) was prepared by catalytically reducing **2** to produce 5-amino-2,4-dimethoxy-6-methylpyrimidine (**10**) in a quantitative yield. Compound **10** was subsequently reacted with triethyl orthoformate to afford a good yield of **11**. In light of the reaction of **8** to form **9**, it was felt that **11** might also undergo a base-controlled ring closure to produce the pyrrolo[3,2-*d*]pyrimidine ring system. In order to form the intermediate carbanion more readily and thereby lead to pyrrole ring closure under less severe conditions, the use of a stronger base than sodium ethoxide was explored. Thus, compound **11** was treated with the base 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dry DMF. However, no reaction was noted at room temperature, and at elevated temperature substantial decomposition was observed. Reaction of **11** with lithium diisopropylamide (LDA) at −78 °C afforded a new product. However, instead of the desired pyrrolo[3,2-*d*]pyrimidine, 2,4-dimethoxy-5-isocyano-6-methylpyrimidine (**12**) was produced in 39% yield. The structure of **12** was determined spectrally by an observation of the characteristic isocyanide band at 2120 cm^{-1} in the IR spectrum and three characteristic singlets in the ^1H NMR spectrum and by elemental analysis. A possible mechanism for the formation of **12** is depicted in eq 2 and involves the abstraction of a proton from the imino carbon followed by

(17) (a) Bredereck, H.; Simchen, G.; Rebsdat, S.; Katlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41. (b) For a recent example of the use of BBDM in the formylation of an active methylene compound see: DeBernardo, S.; Weigele, M. *J. Org. Chem.* **1977**, *42*, 109.

(18) Tanaka, K.; Sugawa, T.; Nakamori, R.; Sanno, Y.; Ando, Y.; Imai, K.-I. *Chem. Pharm. Bull.* **1964**, *12*, 1024.



ethoxide extrusion. The treatment of several arylimino ethers with any of a number of organometallics has been shown[19] to produce aryl isocyanides. This, however, is the first report of the use of this reaction to form a heterocyclic isonitrile. The synthetic potential of **12** is currently under investigation in our laboratory.

In summary, two methods have been developed for the synthesis of 2,4-dimethoxypyrrolo[3,2-*d*]pyrimidine (**1**), a compound of particular interest as a model for the future synthesis of certain *C*-nucleosides. Both methods involved ring closure of the pyrrole ring onto a functionalized pyrimidine. In the first, the *o*-nitro(cyanomethyl)pyrimidine **6** was hydrogenated to afford **1**, and in the second, the *o*-nitro[(dimethylamino)vinyl]pyrimidine **7** was catalytically reduced to the target compound **1**. Both procedures involved mild reaction sequences which contained a maximum of three steps. It should also be noted that existing methodology[12] should allow for the chemical conversion of **1** into a number of variously substituted pyrrolo[3,2-*d*]pyrimidines. Finally, a particularly facile reaction to form a heterocyclic isonitrile was observed when the 5-[(ethoxymethylene)amino]pyrimidine **11** was treated with LDA.

Experimental Section

General Methods. Low-pressure column chromatography was performed by using Merck Lobar (silica gel 60) prepacked columns (size A, B, or C), with typical flow rates of 5–10 mL/min being delivered by a Fluid Metering Instruments metering pump. Fractions (15 mL) were collected by using an ISCO Retriever III automatic fraction collector. For compounds which were UV absorbing, the fractions containing the compound were detected by using an Altex Model 152 dual wavelength UV detector (254 nm) with a preparative flow cell. Gravity column chromatography was accomplished by using 70–230-mesh Merck silica gel. Thin-layer chromatography (TLC) was accomplished by using SilicAR 7GF (250-μm layer) on prescored glass plates (2.5 × 8 cm) purchased from Analtech, Inc., Newark, DE. The solvent systems used were as follows: (a) hexanes[20]/ethyl acetate (2:4 v/v), (b) hexanes/ethyl acetate (3:1 v/v), (c) methylene chloride, (d) methylene chloride/methyl ethyl ketone (10:1, v/v). In vacuo evaporations were carried out with a Buchler flash evaporator, a water aspirator, and room temperature water bath unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained by using a Varian EM-360 spectrometer with tetramethylsilane (Me_4Si) as the internal standard. The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ex = D_2O exchangeable. Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. UV spectra were recorded by using a Hewlet-Packard UV 8450 spectrometer. IR spectra were recorded on a Perkin-Elmer 281 spectrophotometer. Mass spectral data were obtained on Finnigan Model 4023 GC/MS by using electron ionization (EI) or chemical impact (CI). Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ.

(19) Pornet, S.; Miginiac, L. *Tetrahedron Lett.* **1971**, 967.
(20) Obtained commercially as such from Mallinkrodt, Inc.

Preparation[14] of 2-Chloro-4-methoxy-6-methyl-5-nitropyrimidine (i) and 4-Chloro-2-methoxy-6-methyl-5-nitropyrimidine (ii). A solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (2.08 g, 0.01 mol) in methanol (10 mL) was cooled to 0 °C and treated dropwise with a solution of sodium methoxide (0.80 g, 0.015 mol) in methanol (10 mL). After 15 min the reaction was quenched by the addition of acetic acid (1 mL) and evaporated to afford a residue which was suspended in methylene chloride (50 mL), washed with saturated sodium bicarbonate solution (3 × 20 mL), washed with saturated sodium chloride solution (1 × 20 mL), and then dried over magnesium sulfate. Filtration and evaporation of the filtrate afforded a residue which was chromatographed on a Lobar column (size B) by eluting with hexanes/ethyl acetate (25:1 v/v). After the proper fractions (TLC, solvent system b) were pooled and evaporated, compounds i (0.98 g, 48%) and ii (0.38 g, 19%) were obtained.

Compound i: mp 65–67 °C (crystallized from hexanes); R_f 0.60 (solvent system b); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.57 (3, s, 6-CH_3), 4.23 (3, s, 4-OCH_3). Anal. Calcd for $C_6H_6N_3O_3Cl$: C, 35.40; H, 2.97; N, 20.64. Found: C, 35.25; H, 3.14; N, 20.69.

Compound ii: mp 49–50 °C (crystallized from hexanes); R_f 0.45 (solvent system b); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.62 (3, s, 6-CH_3), 4.23 (3, s, 2-OCH_3). Anal. Calcd for $C_6H_6N_3O_3Cl$: C, 35.40; H, 2.97; N, 20.64. Found: C, 35.49; H, 3.04; H, 20.70.

2,4-Dimethoxy-6-methyl-5-nitropyrimidine (2). A cloudy solution of reagent grade sodium methoxide (13.5 g, 0.25 mol) in absolute methanol (200 mL) was added dropwise over a period of 10 min to a well-stirred solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (20.8 g, 0.1 mol) in anhydrous methanol (100 mL). The solution became dark orange, and a white precipitate formed. This mixture was heated at reflux for 2 h, cooled to room temperature, and filtered. The collected precipitate was washed with methanol (2 × 50 mL). The combined filtrate and washings were evaporated to an orange residue which was suspended in ethyl acetate (500 mL) and washed with water (4 × 100 mL). The combined aqueous layers were extracted with chloroform (3 × 50 mL). The ethyl acetate and chloroform layers were then combined and dried over magnesium sulfate. After filtration of the mixture and evaporation of the solvents, the residue was recrystallized from hexanes to yield compound **2**: 10.87 g (55%); mp 81–81 °C; R_f 0.34 (solvent system c); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.50 (3, s, 6-CH_3), 4.08 and 4.05 (6, 2 s, 2-OCH_3 and 4-OCH_3). Anal. Calcd for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; H, 21.10. Found: C, 42.15; H, 4.67; N, 21.03.

6-(Bromomethyl)-2,4-dimethoxy-5-nitropyrimidine (3) and 6-(Dibromomethyl)-2,4-dimethoxy-5-nitropyrimidine (4). A well-stirred solution of **2** (3.00 g, 0.015 mol), bromine (1.2 g, 0.39 mL, 0.01 mol), and anhydrous sodium acetate (2.15 g, 0.03 mol) in glacial acetic acid (150 mL) was heated at reflux for 1 h, after which time the bromine color was gone. An additional portion of bromine (0.2 mL, 0.004 mol) was then added, and the reflux conditions were continued. After 15 min a final portion of bromine (0.2 mL) was added, and the reflux conditions were continued until the color had again disappeared. The solution was cooled to 20 °C and then evaporated to dryness to remove the acetic acid. A suspension of the remaining residue in ethyl acetate (100 mL) was filtered and evaporated to give a pale yellow solid (3.7 g) which was chromatographed on a Lobar column (size C) by eluting with methylene chloride. Three compounds were isolated by evaporation of the proper fractions (TLC, solvent system c), compound **3** (1.53 g, 43%), compound **4** (1.41 g, 31%), and starting material **2** (0.45 g).

Compound 3: yellow oil; R_f 0.57 (solvent system c); ^{1}H NMR ($CDCl_3$) δ 4.08 and 4.12 (6, 2 s, 2-OCH_3 and 4-OCH_3), 4.48 (2, s, 6-CH_2Br); mass spectrum, m/z 279, 277 (M*^{81}Br, M*^{79}Br), 247, 249 (M* – CH_2O), 198 (M* – Br, parent), 138, 123; 111. Anal. Calcd for $C_7H_8N_3O_4Br$: C, 30.24; H, 2.90; N, 15.11. Found: C, 30.27; H, 3.07; N, 15.06.

Compound 4: mp 90–91 °C; R_f 0.80 (solvent system c); ^{1}H NMR ($CDCl_3$ δ 4.15 (6, s, 2-OCH_3 and 4-OCH_3), 6.83 (1, s, 6-$CHBr_2$); mass spectrum (EI), m/z 355, 357, 359 (M*$^{79}Br_2$ M*^{79}Br^{81}Br, M*$^{81}Br_2$), 325, 327, 329 (M* – CH_2O), 276, 278 (M* – ^{79}Br, M* – ^{81}Br), 248, 250, 138, 111. Anal. Calcd for $C_7H_7N_3O_4Br_2$: C, 23.55; H, 1.98; N, 11.77. Found; C, 23.84; H, 2.22; N, 11.90.

2,2-Bis[(2,4-dimethoxy-5-nitropyrimidin-6-yl)methyl]-2-(2,4-dimethoxy-5-nitropyrimidin-6-yl)acetonitrile (5). Compound **3** (1.65 g, 0.0059 mol), sodium cyanide (0.87 g, 0.018 mol), chloroform (30 mL), and water (30 mL) were combined, cooled to 0 °C, and then treated with Aliquot 336 (0.24 g, 0.0006 mol). After being stirred at 0 °C for 4 h, the biphasic solution was allowed to warm to 25 °C and then stirred for 24 h. The layers were separated, and the aqueous layer was washed with chloroform (2 × 10 mL). The combined organic layers were washed with 1 N hydrochloric acid (2 × 10 mL) and saturated sodium chloride solution (1 × 10 mL) and then dried over sodium sulfate. The mixture was filtered, and the filtrate was evaporated to a dark syrup which was chromatographed on a silica gel column (30 × 2.5 cm i.d.) by eluting with solvent system a. Fractions were collected, and those containing compound (TLC, solvent system b) were combined and evaporated to a yellow foam which was crystallized from methanol to yield compound **5**: 0.72 g (54%); mp 139–141 °C; R_f 0.10 (solvent system b); ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 4 protons), 3.98, 4.07, 4.10 (3 s, 18 protons); mass spectrum (CI), m/z 619 (M^*H^+); mass spectrum (EI) m/z 619, 572, 436, 420, 373, 304, 214, 199, 182; IR (film) 2250 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_{10}O_{12}\cdot 0.5H_2O$: C, 42.11; H, 3.69; H, 22.32. Found: C, 42.14; H, 3.67; H, 22.29.

6-(Cyanomethyl)-2,4-dimethoxy-5-nitropyrimidine (6). A solution of sodium cyanide (7.8 g, 0.16 mole) in water (10 mL) was added in one portion to a chilled (5 °C) and stirred solution of compound **3** (3.09 g, 0.011 mol) in ethanol (50 mL). After 2 h the red slurry was poured into a vigorously stirred mixture of ethyl acetate (200 mL) and 1 N hydrochloric acid (200 mL). The yellow organic layer was separated, washed with water (2 × 50 mL) and then with saturated sodium chloride solution (2 × 25 mL), and then dried over magnesium sulfate. Filtration and evaporation of the filtrate provided a brownish residue. The residue was partially dissolved in boiling 5% ethyl acetate in hexanes (25 mL), and the supernatant was decanted. The remaining brown residue was treated a second time with boiling 5% ethyl acetate in hexanes (25 mL), again the supernatant was decanted and combined with the first supernatant, and the resulting mixture was allowed to crystallize at 20 °C. The remaining brownish pot residue was dissolved in methylene chloride (2 mL) and chromatographed on a Lobar column (size B) by eluting with solvent system a. Compound-containing fractions (TLC, solvent system a) were combined and evaporated to a crystalline mass which was combined with the material crystallized from the original combined supernatants to yield compound **6**: 1.36 g (55%); mp 75–77 °C; R_f 0.16 (solvent system b); ^{1}H NMR ($CDCl_3$) δ 4.07 (2, s, CH_2CN), 4.12 (6, 2 s, 2-OCH_3 and 4-OCH_3); mass spectrum (EI), m/z 224 (M*), 2.7, 194 (parent), 169, 148. Anal. Calcd for $C_8H_8N_4O_4$: C, 42.86; H, 3.60; N, 24.99. Found: C, 43.04; H, 3.80; N, 24.93.

2,4-Dimethoxypyrrolo[3,2-*d*]pyrimidine (1). Method 1. A solution of compound **6** (0.032 g, 0.14 mmol) in ethyl acetate was treated with palladium on carbon (10%, 0.040 g) and then hydrogenated in a Parr shaker apparatus for 90 min at 70 °C and at 80 psig. After cooling to 20 °C, the mixture was filtered, and the collected catalyst was washed with hot ethyl acetate (3 × 5 mL). The combined filtrate and washings were evaporated in vacuo to yield crystalline compound **2**: 0.012 g (47%); mp 174–176 °C. The mp was raised to 183–185 °C with one crystallization from ethyl acetate; however, the original material was used for the analytical sample: R_f 0.09 (solvent system b); UV (MeOH) λ_{max} 262 nm (ϵ 3450), 277 (sh, 2400), λ_{max} (pH 1) 280 (5440); λ_{max} (pH 11) 263 (3660), 280 (sh, 2500). ^{1}H NMR (acetone-d_6) δ 3.87 and 4.03 (6, 2 s, 2-OCH_3 and 4-OCH_3), 6.37 (1, t, C_7H, $J_{6,7}$ = 3.0 Hz, $J_{7,NH}$ = 3.0 Hz), 7.52 (1, t, C_6H, $J_{6,7}$ = 3.0 Hz, $J_{6,NH}$ = 3.0 Hz), 11.73 (1, ex, br s, NH); mass spectrum (EI), m/z 179 (M*), 164 (M* – CH_3), 149 (M* – CH_2O), 134, 108. Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.06; N, 23.45. Found: C, 53.67; H, 5.19; N, 23.51.

Method 2. A solution of **7** (0.27 g, 0.0011 mol) in ethanol (25 mL) was treated with T_1-Raney nickel[21] (0.15 g, wet weight in ethanol) and hydrogenated at ambient temperature for 16 h. The solution was purged with a stream of nitrogen for 30 min and then filtered through a thin Celite pad. The collected Raney nickel was washed immediately with ethanol (3 × 10 mL). The combined filtrate and ethanol washes were evaporated to a dark syrup which was chromatographed on a silica gel column (25 g, 4 cm i.d.) by eluting with solvent system d. The appropriate fractions (TLC, solvent system d) were collected and evaporated, yielding an orange residue. This residue was crystallized from ethanol, affording compound **1**: 0.051 g (27%); mp 183–184 °C; R_f 0.29 (solvent system d), 0.09 (solvent system b); ^{1}H NMR ($CDCl_3$/Me_2SO-d_6) δ 4.00 and 4.08 (6, 2 s, 2-OCH_3 and 4-OCH_3), 6.43 (1, t, H-7, $J_{7,6}$ = $J_{7,NH}$ = 3 Hz), 7.35 (1, t, H-6, $J_{6,7}$ = $J_{6,NH}$ = 3 Hz), 10.90 (1, ex, br s, NH).

2,4-Dimethoxy-6-[2-(dimethylamino)vinyl]-5-nitropyrimidine (7). A solution of compound **2** (0.20 g, 0.001 mol) in dry DMF (0.75 mL, dried over 4-Å sieves) was treated with *tert*-butoxybis(dimethylamino)methane (BBDM, 10 mL) and stirred at 20 °C. The solution, which turned orange immediately upon the addition of the BBDM, was stirred for 1 h, and then the yellow-orange precipitate was collected by filtration, washed with diethyl ether (4 × 10 mL), and air-dried to yield **13**: 0.075 g; mp 160–162 °C. Additional product was obtained by adding water (25 mL) to the filtrate, causing an orange solid to precipitate. This precipitate was collected by filtration, washed with diethyl ether (4 × 10 mL), and air-dried to yield crude **7** (0.12 g). The crude **7** appeared to be only slightly contaminated when compared by TLC (solvent system b) with the initial product. The total crude yield of **7** was about 77%: R_f 0.15 (solvent system b); ^{1}H NMR ($CDCl_3$) δ 3.03 (6, s, $N(CH_3)_2$), 3.98 and 4.02 (6, 2 s, 2-OCH_3 and 4-OCH_3), 5.35 (1, d, $J_{1,2}$ = 12, $CH{=}CHN(CH_3)_2$), 8.13 (1, d, $J_{2,1}$ = 12 Hz, $CH{=}CHN(CH_3)_2$). Anal. Calcd. for $C_{10}H_{14}N_4O_4$: C, 47.24; H, 5.55; N, 22.04. Found: C, 47.09; H, 5.54; N, 21.96.

5-Amino-2,4-dimethoxy-6-methylpyrimidine (10). A solution of **2** (5.19 g, 0.026 mol) in methanol (100 mL) was treated with T_1-Raney nickel[21] (2.5 g, wet weight in ethanol) and then hydrogenated at 20 °C and ambient pressure for 24 h. The catalyst was collected by filtration and washed with hot methanol (3 × 30 mL). The filtrate was then evaporated to afford a yellow residue which slowly darkened on standing. Chromatography of this material was conducted on a silica gel column (125 g, 3 cm i.d.) by eluting with chloroform/methanol (40:1 v/v). Fractions were collected, and those containing product (TLC, solvent system b) were combined and evaporated to a white crystalline material, compound **10**: 4.13 g (91%); mp 74–75 °C (crystallized from hexanes); R_f 0.12 (solvent system a); ^{1}H NMR ($CDCl_3$) δ 2.27 (3, s, 6-CH_3), 3.30 (2, br s, NH_2), 3.90 and 4.00 (6, 2 s, 2-OCH_3 and 4-OCH_3). Anal. Calcd for $C_7H_{11}N_3O_2\cdot{}^1/_6H_2O$: C, 48.82; H, 6.63; N, 24.40. Found: C, 48.77; H, 6.52; H, 24.29.

2,4-Dimethoxy-5-[(ethoxymethylene)amino]-6-methylpyrimidine (11). A solution of compound **10** (1.69 g, 0.010 mol) in triethyl orthoformate (15 mL) was heated under reflux for 16 h and then evaporated, affording a dark solid. The solid was dissolved in boiling ligroin (bp 60–90 °C), treated with decolorizing charcoal, filtered, and allowed to crystallize at about 5 °C. The off-white solid was collected by filtration, washed with cold ligroin (20–30 mL), and then air-dried, yielding compound **11**: 1.52 g (68%); mp 63–64.5 °C; R_f 0.47 (solvent system a); ^{1}H NMR ($CDCl_3$) δ 1.37 (3, t, CH_2CH_3), 2.33 (3, s, 6-CH_3), 3.93 (6, s, 2-OCH_3 and 4-OCH_3), 4.33 (2, q, CH_2CH_3), 7.90 (1, s, N=CH). Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.68. Found: 53.62; H, 6.87; N, 18.87.

2,4-Dimethoxy-5-isocyano-6-methylpyrimidine (12). A solution of diisopropylamine (0.14 mL, distilled from potassium hydroxide and stored under nitrogen) in dry THF (3 mL) was chilled at 0 °C and treated with a 1.55 M solution of *n*-butyllithium in *n*-hexane (0.65 mL) under nitrogen. After 20 min, the stirred solution was cooled to −78 °C and then treated dropwise with a solution of compound **11** (0.225 g, 0.001 mol) in THF (3 mL) over a period of 8 min. Stirring was continued for an additional 20 min, and then the solution was allowed to warm gradually to room temperature. The orange, cloudy solution was poured into a well-stirred mixture of diethyl ether (50 mL) and 1 N hydrochloric acid (10 mL). The organic layer was separated, washed with saturated sodium bicarbonate solution (2 × 10 mL) and with saturated sodium chloride solution (1 × 10 mL), and then dried over magnesium sulfate. Filtration and evaporation yielded an

(21) Dominguez, X. A.; Lopez, I. C.; Franco, R. *J. Org. Chem.* **1961**, *26*, 1625.

orange residue (mp 90–95 °C) which was chromatographed on a silica gel column (30 × 1 cm i.d.) by eluting with methylene chloride/ethyl acetate (15:1 v/v). Compound-containing fractions (TLC, solvent system a) were evaporated, yielding white, crystalline **12**: 0.070 g (39%); mp 98–100 °C; R_f 0.53 (solvent system a); IR (KBr) 2120 cm^{-1} (NC); ^1H NMR ($CDCl_3$) δ 2.50 (3, s, 6-CH_3), 4.00 and 4.07 (6, 2 s, 4-OCH_3 and 2-OCH_3). Anal. Calcd for $C_8H_8N_3O_2$: C, 53.93; H, 4.53; N, 23.58. Found: C, 53.74; H, 4.73; N, 23.58.

Registry No. **1**, 84538-40-9; **2**, 30561-09-2; **3**, 84538-41-0; **4**, 84538-42-1; **5**, 84538-43-2; **6**, 84538-44-3; **7**, 83256-18-2; **10**, 84538-45-4; **11**, 84538-46-5; **12**, 84558-24-7; i, 1899-99-6; ii, 84538-47-6; 2,4-dichloro-6-methyl-5-nitropyrimidine, 13162-26-0.

Bromination of Some Pyridine and Diazine *N*-Oxides

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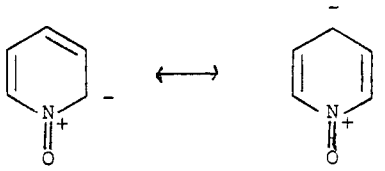
Selected monosubstituted pyridines, pyrazines, pyrimidines, and their *N*-oxides, having an electron-donating substituent, were successfully brominated under very mild conditions. The *N*-oxide function itself is not sufficient to cause these π-deficient systems to undergo electrophilic aromatic halogenation. Only strongly electron-donating substituents (amino groups) activate the heterocyclic nucleus toward bromination. These substituents direct the electrophilic substitution ortho/para to them with or without the *N*-oxide group present. Pyridine and diazines with moderately activating substituents such as alkoxy groups are brominated only when their ortho/para activation is augmented by the activation of the *N*-oxide function. Failure to brominate 5-methoxypyrimidine 1-oxide may well reflect the greater π deficiency of the pyrimidine ring.

It is a well-known axiom in heterocyclic chemistry that electrophilic substitution of the π-deficient azines and diazines occurs with great difficulty, if at all. If these compounds are converted to their *N*-oxides, electrophilic substitution occurs more readily. This increase in electrophilic reactivity has been attributed to resonance structures such as **1a** and **1b** contributing to the ground state of the *N*-oxides.[2a]



1a 1b

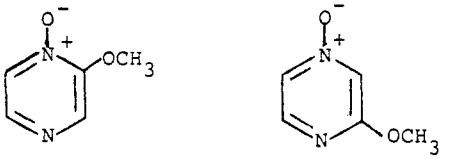
The presence of electron-donating groups on pyridine and the diazines, of course, also facilitates electrophilic substitution reactions.[2b]

We have recently described the bromination of a number of 1,2,4-triazine 1- and 2-oxides and have established that bromination occurs at the 6-position of these compounds. The 2-oxides also afford some of the corresponding deoxygenated compounds.[3,4]

In order to examine the relative activating influences of an *N*-oxide group and strongly electron-donating substituents and to gain some understanding of the bromination deoxygenation observed with 1,2,4-triazine 2-oxides, we studied the bromination of a number of substituted pyridines, diazines, and their *N*-oxides. The results of this bromination study, done under as identical conditions as possible, are the basis of this report.

Bromination of Pyrazines. The results of the bromination of a number of substituted pyrazines and their *N*-oxides are reported in Table I.

It is noteworthy that neither 2-methoxypyrazine (**2**) nor its 1-oxide (**6**) are brominated under these conditions, while



6 12

the isomeric 3-methoxy 1-oxide (**12**) affords the 6-bromo derivative (**26**). In this case, the methoxy group augments the ortho-activating behavior of the *N*-oxide. The other possible isomer (2-bromo-3-methoxypyrazine 1-oxide) is not obtained.

In the 2-amino and 2-(methylamino)pyrazine 1-oxides, the amino substitutents *activate* C-6 and *deactivate* C-3 and C-5 toward electrophilic bromination. Consequently, it is not surprising that, while the nonoxides yield the 3,5-dibromo derivatives (**16–18**), the 1-oxides react less readily and afford the 3,5-dibromo (**20–22**) as well as some of the 3-bromo compounds (**19–21**). The 2-(dimethylamino)pyrazine 1-oxide (**9**) affords the 3,5-dibromo derivative (**23**) exclusively. The selective formation of the 5-bromo 1-oxides in the 2-morpholino (**10**) and 2-piperidino (**11**) instances is most probably caused by the steric bulk of the substituents, preventing bromination at C-3.

Bromination of 3-aminopyrazine 1-oxides **13–15**, where the oxide group increases the reactivity of the same positions as do the substituents (C-2 and C-6), affords the

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(2) (a) Katritzky, A. R.; Lagowski, J. M "Chemistry of the Heterocyclic N-Oxides"; Academic Press: London, 1971. (b) Barton, Derek; Ollis, W. D. "Comprehensive Organic Chemistry"; Vol. IV, Sammes, P. A., Ed.; Pergamon Press: New York, 1979; Vol. IV, Parts 16.1 and 16.2 and references therein.

(3) Keen, B. T.; Radel, R. J.; Paudler, W. W. *J. Org. Chem.* **1977**, *42*, 3498.

(4) Radel, R. J; Atwood, J. L.; Paudler, W. W. *J. Org. Chem.* **1978**, *43*, 2514.

0022-3263/83/1948-1064$01.50/0