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Pyrazolo[4,3-*d*]pyrimidines. Regioselectivity of N-Alkylation. Formation, Rearrangement, and Aldehyde Coupling Reactions of 3-Lithio Derivatives

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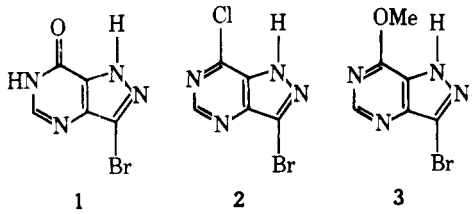
N-Alkylation reactions of 3-bromopyrazolo[4,3-*d*]pyrimidin-7-one and 3-bromo-7-chloro- and 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidines were studied. Alkylations in aqueous base yielded predominately N-1 alkyl products, as did trimethysilylation using hexamethyldisilazane. In contrast, alkylation with 2-chlorotetrahydropyran and sodium hydride in dimethylformamide or with dihydropyran and an acid catalyst in ethyl acetate yielded predominantly N-2 alkyl products. Formation of 3-lithio derivatives of N-1 and N-2 alkylated 7-alkoxypyrazolo[4,3-*d*]pyrimidines from the corresponding 3-bromo compounds was accomplished by treatment with *n*-butyllithium at low temperatures. N-1 alkyl compounds yield complex mixtures of products, including those of N-dealkylation and rearrangement with rupture of the pyrazole ring. The N-2 alkylated compound, 3-lithio-7-methoxy-2-tetrahydropyran-2′-ylpyrazolo[4,3-*d*]pyrimidine, was stable and reacted with benzaldehyde in high yield.

In connection with research in our laboratory directed toward the development of methods for *C*-nucleoside syntheses[1] via coupling of metallo heterocyclic compounds with appropriately derivatized sugars,[2] we have investigated the utility of derivatives of 3-bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (**1**) as precursors to the corresponding 3-lithio species. Such heterocyclic organometallic compounds might serve as convenient intermediates for synthesis of the potent antibiotic formycin[1,4] and related compounds. An important aspect of the present work was a detailed study of the regioselectivity of N-alkylation of 3-bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (**1**), 3-bromo-7-chloropyrazolo[4,3-*d*]pyrimidine (**2**), and 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**3**).



1 **2** **3**

Regioselectivity of N-Alkylation. The factors which influence N-1 vs. N-2 alkylation of pyrazoles, while carefully studied,[5] are not clear. Similar studies of indazoles[6] have led to the following general rules: (1) in alkaline solutions both isomers result, generally in about equal amounts, and (2) heating with alkyl halides under neutral conditions results in exclusive or predominate N-2 substitution. Several exceptions to the first rule have been found as isopropyl, allyl, and benzyl bromides yield only the N-1 derivatives. Alkylation reactions of pyrazolo[4,3-*d*]pyrimidines are practically unknown. The reaction of formycin[1,4] with methyl iodide in ethanol containing sodium ethoxide led to isolated yields of 24% 2-methylformycin and 4% 1-methylformycin.[7]

Synthesis and Alkylation Reactions. 3-Bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (**1**) was synthesized, with modifications which led to substantial improvements in overall yield,[8] by the nine-step procedure of Robins et al.[9] The conversion of **1** to 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**3**) was effected in two steps by chlorination (phosphorus oxychloride) to yield 3-bromo-7-chloropyrazolo[4,3-*d*]pyrimidine (**2**), followed by treatment of **2** with sodium methoxide.

In Scheme I are shown the studied alkylation reactions of **1**, **2**, and **3** and interconversions which aided in proof of structures. The regioselectivities of the various alkylation reactions are listed in Table I. To obtain the data in Table I, crude product mixtures were analyzed by ^{1}H nuclear magnetic resonance (^{1}H NMR) since crystallization often led to isolation of a single product. Following the determination of N-1/N-2 alkyl isomer ratios by analysis of their ^{1}H NMR spectra, definitive structure assignments of the N-1 and N-2 alkyl isomers were made relying primarily on analysis of ^{13}C nuclear magnetic resonance spectra (^{13}C NMR). These data indicate that while N-1 alkylation is predominate in general, use of the highly reactive 2-chlorotetrahydropyran (or dihydropyran with acid catalysis) yields predominately N-2 alkylation.

Structure Assignments for N-1 and N-2 Alkylated Derivatives. Recently, Pugmire and Grant[10] and others[5b-e] have shown that ^{13}C NMR spectroscopy can be used effectively to distinguish between sites of alkylation of nitrogen heterocycles. The basic principle guiding interpretation of the ^{13}C NMR spectra of isomeric N-alkyl heterocycles is that a carbon adjacent (α) to an alkylated or protonated (i.e., trisubstituted) nitrogen resonates upfield of the signal of that same carbon in other isomers. For an N-1 alkylated pyrazolo[4,3-*d*]pyrimidine, therefore, the ^{13}C NMR absorption of C-7a will be upfield and that of C-3 will be downfield of the corresponding signals in the spectrum of the N-2 alkylated isomer.

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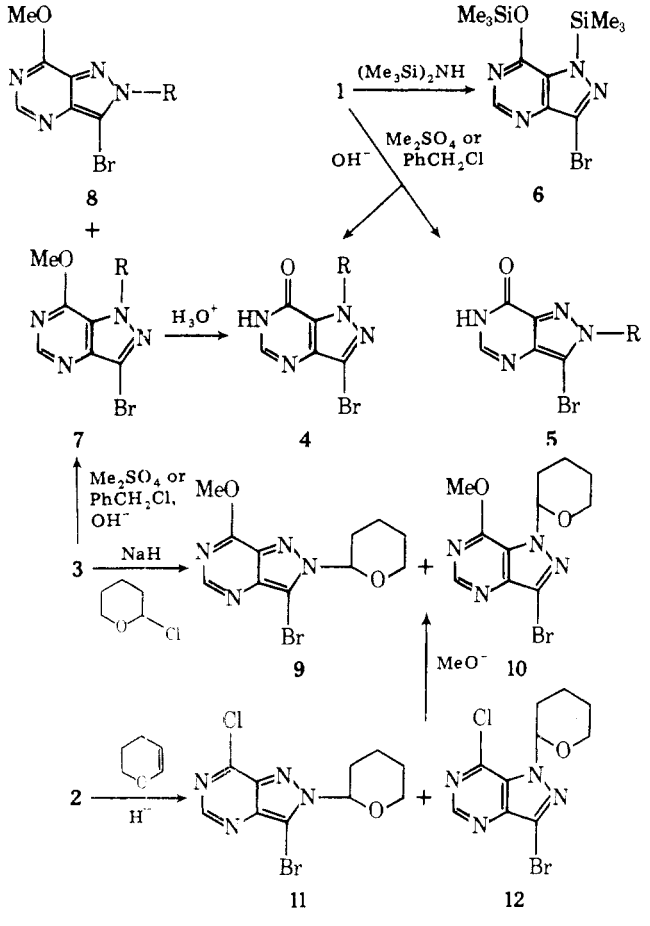
Table I. Regioselectivity in N-Alkylation Reactions of Pyrazolo[4,3-*d*]pyrimidines

starting material	alkylating agent	registry no.	reaction conditions	product distribution,[a] % N-1	% N-2
1	dimethyl sulfate	77-78-1	0.3 N NaOH	70	30
	benzyl chloride	100-44-7	0.3 N NaOH	100	
	hexamethyldisilazane	999-97-3	neat, reflux	100	
3	dimethyl sulfate		0.3 N NaOH	100	
	benzyl chloride		1.1 equiv *t*-BuOK, DMF[b]	88	12
	2-chlorotetrahydropyran	3136-02-5	1.1 equiv NaH, DMF[b]	20	80
2	dihydropyran	110-87-2	ethyl acetate, H_2SO_4[c]	11	89

[a] Determined by integration of ^{1}H NMR signals assignable to corresponding features of the respective isomers; see discussion in the text and Experimental Section. [b] Dimethylformamide. [c] Catalytic quantity.

Scheme I. N-Alkylation and Structure Correlation Reactions



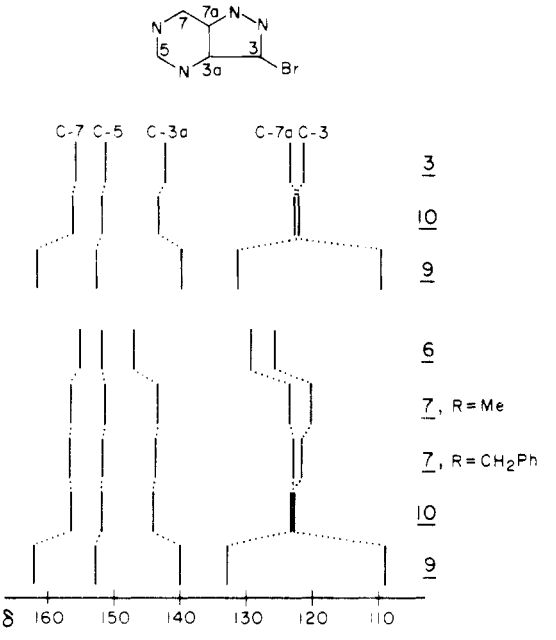


Figure 1. Comparison of ^{13}C chemical shifts for pyrazolo[4,3-*d*]pyrimidine ring carbons of N-1 and N-2 alkylated derivatives. See Table II for complete chemical shift data for all carbons.

In Figure 1 are graphic comparisons of the chemical shifts of pyrazolo[4,3-*d*]pyrimidine ring carbon resonances of 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**3**) and the related nitrogen-alkylated derivatives **7** and **8** (R = Me, $PhCH_2$) and **9** and **10**; more extensive ^{13}C NMR data are contained in Table II. The assignments of the resonances to individual carbons were made using the following criteria: (a) the C-5 and C-7 resonances are assigned by their downfield chemical shifts (two adjacent heteroatoms) and are distinguished by the nuclear Overhauser effect (NOE) of C-5; (b) the C-3 absorption is assigned by its short (relative to C-3a and C-7a) relaxation time due to the scalar relaxation contributed to ^{79}Br;[11] and (c) the resonance of C-3a is expected to be approximately 15 ppm downfield of C-7a by analogy to formycin[12,13] for N-1 alkylated or protonated derivatives, with this difference being less for N-2 alkylated compounds.

The ^{13}C NMR spectra of **3**, **9**, and **10** were obtained using dimethyl-d_6 sulfoxide solutions owing to the limited solubility of **3** in chloroform. Analysis of these spectra (Figure 1, Table II) using the criteria of Pugmire and Grant[10] allows definitive assignments of the sites of alkylation of **9** (N-2) and **10** (N-1) and indicates that **3** is protonated on N-1. It is interesting that, at room temperature, **3** does not exhibit the broad spectral lines for C-3 and C-7a due to tautomerism of the N–H between N-1 and N-2 which are observed for formycin.[12,13]

The ^{13}C NMR chemical shifts of the pyrazolo[4,3-*d*]pyrimidine ring carbons of **6**, **7** (R = CH_3 and $PhCH_2$), **9**, and **10** in $CDCl_3$ solution are also represented graphically in Figure 1, with chemical shift data listed in Table II. Again, interpretation of the spectra of **9** and **10** as isomeric N-2 and N-1 alkyl compounds, respectively, is straightforward. Since pure samples of isomers were not available, assignment of **6** and **7** (R = CH_3 and $PhCH_2$) to the N-1 alkylated series was made by comparison of their ^{13}C NMR spectra (see Figure 1, Table II) with spectra of **9** and **10**; in each instance a striking correspondence to the spectra of the authentic N-1 alkylated isomer **10** was apparent.

Additional support for the assignments was furnished by consideration of the ^{1}H NMR spectra of the N-1 and N-2 methylated 3-bromopyrazolo[4,3-*d*]pyrimidin-7-ones [**4** and **5** (R = CH_3), respectively]. The ^{1}H NMR spectrum (Me_2SO-d_6) of the crude reaction mixture resulting from treatment of **1** with dimethyl sulfate in aqueous base exhibits two sharp singlets at δ 4.19 and 4.10 assignable as *N*-methyl resonances. The resonance at δ 4.19 was assigned to the 3-bromo-1-methylpyrazolo[4,3-*d*]pyrimidin-7-one (**4**, R = CH_3) on the basis of the expected deshielding of the methyl hydrogens due

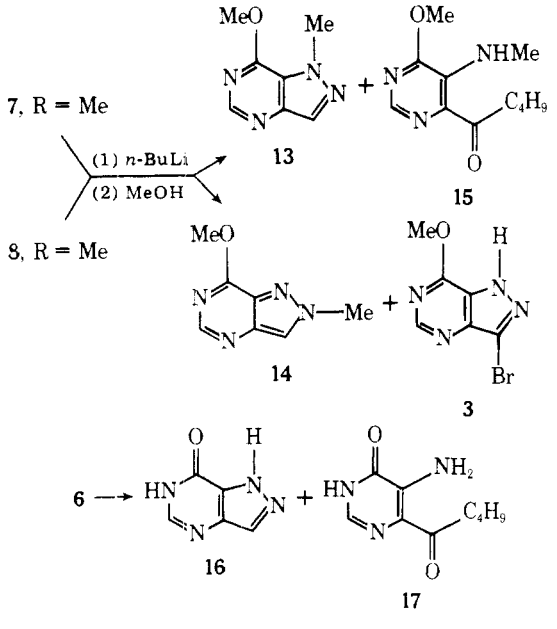
Table II. Carbon-13 Chemical Shifts[a] for N-Alkyl Derivatives of 3-Bromopyrazolo[4,3-*d*]pyrimidines

compd	solvent	C-3	C-3a	C-5	C-7	C-7a	OCH_3	other
formycin[b]	Me_2SO-d_6	143.7	138.7	151.6	151.6	123.0		
3	Me_2SO-d_6	121.1	142.1	151.1	155.9	122.7	54.3	
9	Me_2SO-d_6	109.6	139.4	152.2	161.5	131.1	54.2	86.0, 66.9, 28.2, 24.4, 21.3 (THP)[c]
10	Me_2SO-d_6	121.7	143.2	151.8	156.1	122.3	54.9	86.2, 67.1, 28.5, 24.5, 22.1 (THP)[c]
6	$CDCl_3$	125.3	146.8	151.8	155.1	129.0		0.48, 0.38 (OMe_3Si, NMe_3Si)
7 (R = CH_3)	$CDCl_3$	120.0	143.0	151.3	156.3	123.0	54.5	39.5 (NCH_3)
7 (R = CH_2Ph)	$CDCl_3$	121.4	143.8	151.7	156.3	122.7	54.5	136.2, 128.8, 128.3, 127.8 (Ph); 56.2 (NCH_2)
9	$CDCl_3$	109.0	139.8	152.7	162.1	132.4	54.4	86.8, 68.1, 29.1, 24.7, 22.1 (THP)[c]
10	$CDCl_3$	122.9	144.2	151.9	156.4	122.8	54.8	86.9, 67.9, 29.4, 25.0, 22.7 (THP)[c]

[a] Spectra were obtained using solution concentrations of 200 mg/3 mL. The resonances of the solvents served as internal references; chemical shifts are given in parts per million and were corrected to tetramethylsilane (Me_4Si) using $\delta(Me_4Si - Me_2SO\text{-}d_6) = 39.6$ ppm and $\delta(Me_4Si - CDCl_3) = 77.2$ ppm. For numbering of ring carbons, see Figure 1. [b] Data taken from ref 13. [c] Tetrahydropyran-2'-yl.

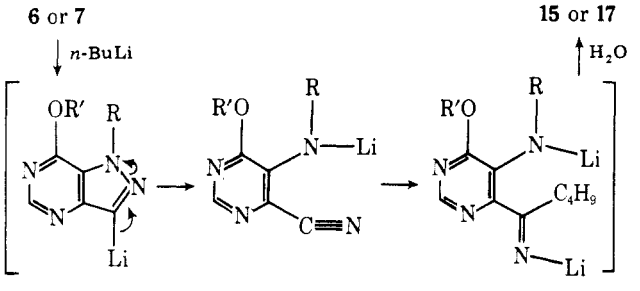
to the adjacent C-7 carbonyl. Further, acidic hydrolysis of 3-bromo-7-methoxy-1-methylpyrazolo[4,3-*d*]pyrimidine (**7**, R = CH_3), for which the structure was assigned on the basis of its ^{13}C NMR spectrum, yielded 3-bromo-1-methylpyrazolo[4,3-*d*]pyrimidin-7-one (**4**, R = CH_3), identical with that obtained by alkylation of **1**. Similarly, acidic hydrolysis of 1-benzyl-3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**7**, R = $PhCH_2$) yielded 1-benzyl-3-bromopyrazolo[4,3-*d*]pyrimidin-7-one (**4**, R = $PhCH_2$), which exhibited spectral properties identical with those of the corresponding product formed upon alkylation of **1** with benzyl chloride in aqueous base.

Formation and Reactions of 3-Lithiopyrazolo[4,3-*d*]-pyrimidines. To assess the utility of 3-bromopyrazolo[4,3-*d*]pyrimidine derivatives as intermediates for generation of the corresponding 3-lithio compounds, 1 equiv of *n*-butyllithium was added to a solution of a derivative in an aprotic solvent at −78 °C followed, after a time, by the addition of a proton source (methanol). When a mixture of 3-bromo-7-methoxy-1-methyl- and 3-bromo-7-methoxy-2-methylpyrazolo[4,3-*d*]pyrimidines (**7** and **8**, respectively) was treated in this way, a mixture of products was produced. Chromatographic separation yielded the expected debromination products 7-methoxy-1-methyl- and 7-methoxy-2-methylpyrazolo[4,3-*d*]pyrimidines (**13** and **14**) in 37% yield plus a



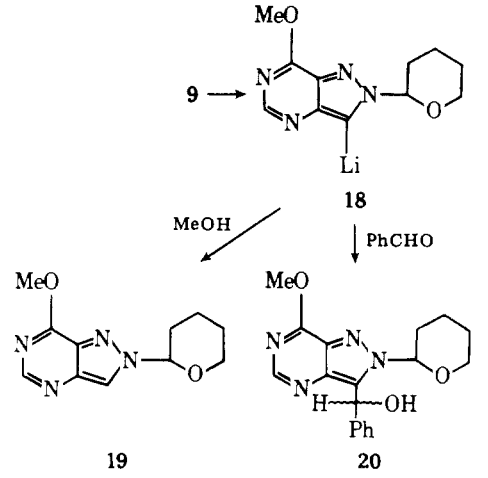
comparable amount of the *N*-demethyl derivative **3**[14] and 6% of a butylated, ring-opened compound **15**. Similarly, treatment of 3-bromo-7-(trimethylsiloxy)-1-(trimethylsilyl)pyrazolo[4,3-*d*]pyrimidine (**6**) with *n*-butyllithium led to an

Scheme II. Possible Mechanism for Formation of Butylated, Ring-Opened Products



instantaneous precipitation, and after addition of methanol a mixture of **1**, the debrominated compound **16**, and a butylated, ring-opened derivative **17** was isolated.

The results obtained with 3-bromo-7-methoxy-2-(tetrahydropyran-2-yl)pyrazolo[4,3-*d*]pyrimidine (**9**) were quite different. Treatment of **9** with *n*-butyllithium followed by



methanol addition produced the debrominated compound, 7-methoxy-2-(tetrahydropyran-2-yl)pyrazolo[4,3-*d*]pyrimidine (**19**), in 88% yield with no evidence of butylated, ring-opened side products. Reaction of the stable intermediate, organolithium species **18**, with benzaldehyde produced 3-(hydroxyphenylmethyl)-7-methoxy-2-(tetrahydropyran-2-yl)pyrazolo[4,3-*d*]pyrimidine (**20**) in over 90% yield.

The formation of ring-opened, butylated products (i.e., **15** and **17**) upon reaction of 3-bromopyrazolo[4,3-*d*]pyrimidine derivatives with *n*-butyllithium can be rationalized as shown in Scheme II. The mechanism is possible only for N-1 alkylated derivatives and explains why **9**, which is N-2 alkylated, yielded no such decomposition products. Analogous examples have been reported in the indazole series. While N-2 alkylated

indazoles yield stable 3-lithio derivatives at −20 °C,[15] the 3-sodio derivatives of N-1 alkylated indazoles under similar conditions undergo a ring opening to yield *o*-cyanoanilines.[16] The 3-lithio derivatives of 1-methyl- and 1-(methoxymethyl)indazole formed under more drastic conditions (refluxing toluene) also yield the ring-opened 2-aminobenzophenones.[17]

Experimental Section

Melting points were determined on a microscope hot stage and are uncorrected. Ultraviolet spectra were obtained with a Perkin-Elmer 202 spectrophotometer. Mass spectra were obtained with CEC Dupont 21-110B or Dupont 21-491B mass spectrometers operated at 70 eV. ^{1}H NMR spectra were recorded on a Varian HA-100 spectrometer. ^{13}C NMR spectra were recorded at 15.158 mHz with a Varian XL-100 spectrometer operated in the FT mode using a Nicolet 12 mm Multi-Observable Nuclear Accessory (MONA) probe and a Nicolet TT-100 system. A 15° radio-frequency pulse excitation (varied between 5 and 60° for the progressive saturation experiments) with full proton decoupling was used.

Elemental analyses were by Heterocyclic Chemical Corp., Harrisonville, Mo., or by Dr. R. Wielesek, University of Oregon.

3-Bromo-7-chloropyrazolo[4,3-*d*]pyrimidine (2). To a slurry of 25.0 g (116 mmol) of finely ground 3-bromopyrazolo[4,3-*d*]pyrimidin-7-one[3,8] (**1**) in 250 mL of phosphorus oxychloride was added 26 mL of *N,N*-diethylaniline. After heating for 1.25 h under reflux, the excess phosphorus oxychloride was removed under reduced pressure. The residue was poured over ice and extracted with ethyl acetate (3 × 1 L). The ethyl acetate extract was washed with aqueous sodium bicarbonate, dried, decolorized with charcoal, and evaporated to dryness in the cold. The crude product was triturated with 250 mL of warm chloroform, cooled, and filtered to give 19.0 g (70%) of 3-bromo-7-chloropyrazolo[4,3-*d*]pyrimidine (**2**), mp 213–218 °C. An analytical sample, mp 215–218 °C dec, was obtained by several recrystallizations from ethyl acetate–hexane: ^{1}H NMR (Me_2SO-d_6) δ 8.78 (s, C-5 H); UV λ_{max} (pH 11) 229, 270, 344 nm; MS *m/e* 236, 234, 232, 199, 197.

Anal. Calcd for $C_5H_2N_4BrCl$: C, 26.9; H, 0.9; N, 23.7. Found: C, 26.9; H, 0.94; N, 23.9.

3-Bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (3). To an ice-cold solution of 2.3 g (100 mmol) of sodium in 300 mL of methanol was added 19.0 g (81.4 mmol) of 3-bromo-7-chloropyrazolo[4,3-*d*]-pyrimidine (**2**). After stirring at room temperature for 24 h, the solution was neutralized with acetic acid and concentrated in vacuo to 50 mL and 300 mL of water was added. The precipitate was collected by filtration, and recrystallization from methanol yielded 16.2 g (87%) of **3**: mp 243–245 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.57 (s, 1, C-5 H), 4.16 (s, 3, OCH_3); ^{13}C NMR (see Table II); UV λ_{max} (pH 11) 225, 253, 307 nm.

Anal. Calcd for $C_6H_5N_4OBr$: C, 31.4; H, 2.8; N, 24.5. Found: C, 31.6; H, 2.9; N, 24.7.

3-Bromo-1-(trimethylsilyl)-7-(trimethylsilyloxy)pyrazolo-[4,3-*d*]pyrimidine (6). A mixture of 2.15 g (10 mmol) of **1** and 0.1 g of ammonium sulfate in 15 mL of hexamethyldisilazane (HMDS) was heated under reflux until solution occurred (2 h). The excess HMDS was removed by distillation, the residue was dissolved in 20 mL of carbon tetrachloride, the solution was filtered, and the solvent was evaporated in vacuo to leave **6** as a crystalline residue in quantitative yield. Sublimation of the residue (150 °C/0.1 mm) yielded 3.4 g (95%) of **6**: mp 106–110 °C; MS *m/e* 360, 358, 279; ^{13}C NMR (see Table II); ^{1}H NMR (CCl_4) δ 0.50 (s, 9), 0.61 (s, 9), 8.49 (s, 1). This compound was extremely susceptible to hydrolysis; storage and transfer required strictly anhydrous environments.

Alkylation of 3-Bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (3) with Dimethyl Sulfate. To a solution of 1.14 g (5 mmol) of **3** in 50 mL of water containing 0.6 g (15 mmol) of sodium hydroxide was added 1.0 g (8 mmol) of dimethyl sulfate. After stirring for 1 h at room temperature, the solution was cooled to 5 °C for 1 h and the precipitate was collected by filtration and dried to yield 1.1 g (91%) of crude 3-bromo-7-methoxy-1-methylpyrazolo[4,3-*d*]pyrimidine (**7**, R = CH_3): ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1, C-5 H), 4.23 (s, 3, methyl), 4.19 (s, 3, methyl); ^{13}C NMR (see Table II); UV λ_{max} (MeOH) 223, 290, 298, 310 nm.

Anal. Calcd for $C_7H_7N_4OBr$: C, 34.6; H, 2.90; N, 23.0. Found: C, 34.5; H, 3.04; N, 22.8.

Alkylation of 3-Bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (3) with Benzyl Chloride. To a solution of 1.14 g (5 mmol) of **3** in 25 mL of dimethylformamide containing 1.2 g (10 mmol) of potassium *tert*-butoxide was added 0.76 g (6 mmol) of benzyl chloride. After stirring for 4 h, the solution was poured into 150 mL of water and extracted three times with 50-mL portions of dichloromethane. The combined dichloromethane extracts were washed twice with 150 mL of water and dried over sodium sulfate, and the solvent was removed in vacuo. The ^{1}H NMR spectrum of the crude residue revealed a 7:1 ratio of N-1/N-2 benzyl derivatives. Crystallization from ethanol yielded 1.1 g (69%) of the N-1 alkylated compound **7** (R = CH_2Ph): mp 108–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (s, 1, C-5 H), 7.25 (s, 5, aryl), 5.66 (s, 2, benzyl), 4.18 (s, 3, methoxyl); ^{13}C NMR (see Table II); UV λ_{max} (MeOH) 223, 292, 298, 310 nm.

Anal. Calcd for $C_{13}H_{11}N_4OBr$: C, 48.9; H, 3.47; N, 17.5. Found: C, 48.6; H, 3.41; N, 17.6.

Alkylation of 3-Bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (3) with 2-Chlorotetrahydropyran. To an ice-cold solution of 1.14 g (5 mmol) of **3** in 20 mL of dimethylformamide was added 0.72 g (6 mmol) of sodium hydride. After evolution of hydrogen ceased, 0.72 g (6 mmol) of 2-chlorotetrahydropyran[18] was added dropwise. After stirring for 20 min, the solution was poured into 100 mL of water and extracted three times with 25 mL of ethyl acetate, and the combined ethyl acetate portions were dried over sodium sulfate. The solvent was removed in vacuo, and the ^{1}H NMR spectrum of the residue, 1.4 g (90%), revealed N-1/N-2 alkylation products in a ratio of 1:4. An analytical sample of 3-bromo-7-methoxy-2-(tetrahydropyran-2-yl)-pyrazolo[4,3-*d*]pyrimidine (**9**) was obtained by crystallization of the crude residue from methanol: mp 156–158 °C; ^{1}H NMR ($CDCl_3$) δ 8.46 (s, 1, C-5 H), 5.81 (dd, 1, *J* = 9, 3 Hz, C-2′ H), 4.12 (s, 3, methoxyl), 4.03 (m, 1, C-6′ H_{eq}), 3.69 (m, 1, C-6′ H_{ax}), 1.4–2.8 (m, 4, C-4′ and C-5′ H); UV λ_{max} (MeOH) 215, 294, 304, 316 nm.

Anal. Calcd for $C_{11}H_{13}N_4O_2Br$: C, 42.2; H, 4.18; N, 17.9. Found: C, 42.4; H, 4.19; N, 17.9.

Dry column chromatography (silica gel/chloroform) of the mother liquors from the crystallization of **9**, followed by crystallization from methanol of the least polar fractions, yielded 3-bromo-7-methoxy-1-(tetrahydropyran-2-yl)pyrazolo[4,3-*d*]pyrimidine (**10**): mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (s, 1, C-5 H), 5.96 (dd, 1, *J* = 9, 3 Hz, C-2′ H), 4.21 (s, 3, methoxyl), 4.04 (m, 1, C-6′ H_{eq}), 3.71 (m, 1, C-6′ H_{ax}), 1.4–2.8 (m, 4, C-4′ and C-5′ H); UV λ_{max} (MeOH) 218, 287, 292, 304 nm.

3-Bromo-1-methylpyrazolo[4,3-*d*]pyrimidin-7-one (4, R = CH_3). To a solution of 0.6 g (2.5 mmol) of 3-bromo-7-methoxy-1-methylpyrazolo[4,3-*d*]pyrimidine (**7**, R = CH_3) in 30 mL of methanol was added 10 mL of concentrated hydrochloric acid. The solution was warmed for 15 min on a steam bath, 100 mL of water was added, and the solution was cooled to 5 °C and left to stand overnight. The precipitate was filtered and dried to yield 0.5 g (87%) of **4** (R = Me): mp >315 °C (sublimes); ^{1}H NMR (Me_2SO-d_6) δ 7.90 (s, 1, C-5 H), 4.17 (s, 3, methyl); UV λ_{max} (MeOH) 223, 228, 266, 283 nm.

Anal. Calcd for C_6H_5NOBr·0.5H_2O: C, 30.3; H, 2.54; N, 23.5. Found: C, 30.3; H, 2.39; N, 23.2.

Alkylation of 3-Bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (1) with Dimethyl Sulfate. To a solution of 1.07 g (5 mmol) of **1** in 50 mL of water containing 0.6 g (15 mmol) of sodium hydroxide was added 0.7 g (5.5 mmol) of dimethyl sulfate. After stirring for 24 h at room temperature, the solution was acidified to pH 5 with concentrated hydrochloric acid and cooled, and the resulting precipitate was filtered and dried to yield 0.93 g (82%) of a 7:3 mixture (as measured by the peak heights of the *N*-methyl peaks in the ^{1}H NMR spectrum) of N-1 (**4**, R = Me)/N-2 (**5**, R = Me) methylated compounds: ^{1}H NMR (Me_2SO-d_6) δ 7.96 (s, 0.7, C-5 H), 7.93 (s, 0.3, C-5 H), 4.19 (s, 0.7, methyl), 4.10 (s, 0.3, methyl).

1-Benzyl-3-bromopyrazolo[4,3-*d*]pyrimidin-7-one (4, R = CH_2Ph). To a solution of 0.80 g (2.5 mmol) of 1-benzyl-3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**7**, R = CH_2Ph) in 30 mL of methanol was added 10 mL of concentrated hydrochloric acid. The solution was warmed for 15 min on a steam bath, 100 mL of water was added, and the solution was cooled to 5 °C and left to stand overnight. The precipitate was then filtered and dried to yield 0.64 g (84%) of **4** (R = CH_2Ph). Crystallization from 95% ethanol yielded a sample with mp 285–287 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.98 (s, 1, C-5 H), 7.33 (s, 5, aryl), 5.76 (s, 2, benzyl); UV λ_{max} (MeOH) 223, 229, 285 nm.

Anal. Calcd for $C_{12}H_9BrN_4O$: C, 47.3; H, 2.95. Found: C, 47.7; H, 3.12.

Alkylation of 3-Bromopyrazolo[4,3-*d*]pyrimidin-7-one[3] (1) with Benzyl Chloride. To a solution of 1.07 g (5 mmol) of **1** in 100 mL of water containing 0.6 g (15 mmol) of sodium hydroxide was added 0.76 g (6 mmol) of benzyl chloride. The resulting mixture was stirred vigorously for 24 h at room temperature and then filtered through Celite. The filtrate was acidified with concentrated hydrochloric acid to pH 5 and cooled to 5 °C, and the precipitate was collected and dried to yield 1.1 g (64%) of **4** (R = CH_2Ph), which exhibited spectral characteristics and physical properties identical with those

described above.

Treatment of 7 and 8 (~1:1 Mixture) with *n*-Butyllithium. To a solution of 242 mg (1 mmol) of the mixture of **7** and **8** in 20 mL of dry tetrahydrofuran under nitrogen at −78 °C was added 0.5 mL of a 2 M solution of *n*-butyllithium in hexane. After 20 min, 2 mL of methanol was added, the solution was warmed to room temperature, and the solvent was removed. The resulting residue was partitioned between ethyl acetate and water. Acidification of the aqueous phase produced a precipitate which was collected to yield 100 mg (40%) of 3-bromo-7-methoxypyrazolo[4,3-*d*]pyrimidine (**3**).[3,14]

Evaporation of the ethyl acetate fraction yielded 85 mg of a gum, which upon silica gel chromatography using chloroform as eluent yielded 60 mg (37%) of 7-methoxy-1- and -2-methylpyrazolo[4,3-*d*]pyrimidines[3] **13** and **14** and 11 mg (6%) of a compound formulated as 5-(methylamino)-4-methoxy-6-valeroylpyrimidine (**15**) on the basis of its mass spectrum, which exhibited *m/e* 233 ($M^{+\cdot}$), 208 (M − Me), 194, 180, 166 (M − C_4H_9).

Treatment of 3-Bromo-7-(trimethylsiloxy)-1-(trimethylsilyl)pyrazolo[4,3-*d*]pyrimidine (6) with *n*-Butyllithium. To a solution of 146 mg (0.405 mmol) of **6** in 10 mL of hexane at 78 °C under nitrogen was added 0.2 mL of an *n*-butyllithium solution (2 M in hexane). A yellow precipitate formed immediately. After 5 min 0.5 mL of methanol was added, causing the precipitate to redissolve. The solvent was removed, and the residue was partitioned between methylene chloride and water. From the aqueous layer, after acidification, was obtained a mixture of **1** and **16**[3,9] as determined by the observation of ions in the mass spectrum at *m/e* 216, 214 (**1**) and at *m/e* 136 (**16**). Evaporation of the methylene chloride solution yielded a gum which was crystallized from benzene–methylene chloride to yield 12 mg of 5-amino-6-valeroyl-4-pyrimidinone (**17**) as fine yellow plates: mp 197–198 °C; MS *m/e* 195 ($M^{+\cdot}$), 166, 153, 138 (M − C_4H_9), 125.

Treatment of 3-Bromo-7-methoxy-2-(tetrahydropyran-2-yl)pyrazolo[4,3-*d*]pyrimidine (9) with *n*-Butyllithium. To a solution of 233 mg (1 mmol) of **9** in 20 mL of dry tetrahydrofuran, under nitrogen, at −78 °C was added 0.5 mL of a 2 M solution of *n*-butyllithium in hexane. After stirring for 30 min at −78 °C, 0.5 mL of methanol was added and the solution was allowed to warm to room temperature. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was partitioned between ethyl acetate and water. The ethyl acetate extract was washed with water, dried, and evaporated to an oil. Trituration of the oil with hexane gave 205 mg (88%) of 7-methoxy-2-(tetrahydropyran-2-yl)pyrazolo[4,3-*d*]pyrimidine (**19**), mp 94–98 °C. A sample recrystallized from methanol–hexane: mp 98–100 °C; NMR ($CDCl_3$) δ 8.42 (s, C-5 H), 8.24 (s, C-3 H), 5.61 (inverse d of d, 1, J_{AX} = 7 Hz, J_{BX} = 3 Hz, C-2′ H), 4.09 (s, OCH_3), 4.01–3.50 (m, 2, C-6′ H_2), 2.45–1.42 (m, 6); UV λ_{max} (MeOH) 251, 282, 291, 303 nm; MS *m/e* 234, 151, 150, 85, 84.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.4; H, 5.98; N, 23.9. Found: C, 56.4; H, 5.74; N, 24.1.

3-(Hydroxyphenylmethyl)-7-methoxy-2-(tetrahydropyran-2-yl)pyrazolo[4,3-*d*]pyrimidine (20). To a solution of 1 mmol of lithio derivative **18**, prepared as previously described at −78 °C, was added 106 mg (1 mmol) of benzaldehyde, and the reaction mixture was stirred at −78 °C for 1 h, allowed to warm to room temperature, and stirred for an additional 30 min. The solution was evaporated to dryness in vacuo and partitioned between ethyl acetate and water. The ethyl acetate solution was washed with water, dried, and evaporated to yield 279 mg of a solid. NMR examination showed a mixture of ~5% of **19** and ~95% of the two anomers of **20**. A sample of **20** recrystallized from methanol exhibited the following: mp 184–192 °C; NMR ($CDCl_3$) δ 8.46, 8.44 (2s, C-5 H), 7.31 (phenyl), 6.62 (m, CHOH), 5.52, 5.50 (2 apparent t's, C-2′ H), 5.10 (br m, 1, OH), 4.18 (s, OCH_3), 3.8–2.7 (br m, C-6 H_2), 2.5–1.4 (m, 6); after treatment with D_2O, the multiplet at δ 6.62 simplified to two singlets at δ 6.63 and 6.60 and the broad multiplet of δ 5.10 disappeared; UV λ_{max} (MeOH) 255, 288, 297, 310 nm; MS *m/e* 340, 256, 255, 239.

Anal. Calcd for $C_{18}H_{20}N_4O_3$: C, 63.5; H, 5.88; N, 16.5. Found: C, 63.7; H, 5.71; N, 16.2.

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