organic layer was extracted into ether. Workup provided 2.5 g of crude product with $[\alpha]^{25}_D$ +123.1°. Microdistillation at 62–63 °C (3.5 torr) [lit.[14] bp 90–93 °C (10 torr)] increased its rotation to $[\alpha]^{25}_D$ +130.7°. Spectral properties were identical with those of an authentic sample prepared by decarboxylation of β-methyl-β-phenylglycidic acid:[14] IR (neat) 3040, 2900, 2800 doubl (CHO), 1720 (C=O), 752, 695 cm^{-1}; NMR δ 1.42 (d, J = 7 Hz, 3 H, Me), 3.63 (m, J = 2 and 7 Hz, 1 H, PhCH), 7.30 (m, 5 H, Ph), 9.65 (d, J = 2 Hz, 1 H, CHO).

(*R*)-(−)-2-Phenylpropanal (5a). This substance was obtained in very low material and optical yield. A large quantity of ethanol was added to and allowed to stand for 2 days with the sodium bisulfite extract following oxidation of the (−)-diol mixture derived from **1a**, the purpose being to precipitate the bisulfite–aldehyde addition product. Workup of the precipitate led to a thick liquid, thought at first to be the aldehyde, but which had a very weak IR absorption at 1720 cm^{-1} and a very broad and strong absorption in the region 1100–1000 cm^{-1}, suggesting an acetal. Hydrolysis with dilute H_2SO_4 in H_2O–dioxane and workup led to approximately 400 mg of material with $[\alpha]^{25}_D$ −4.60° and an IR spectrum identical with authentic 2-phenylpropanal.

(*S*)-(+)-Hydratropic Acid (6b). To provide further proof of the structure of **5b** (and of **1b**), aldehyde **5b** was oxidized to (*S*)-(+)-hydratropic acid (**6b**). A solution of 1.5 g (9.4 mmol) of $KMnO_4$ and 1.13 g (9.4 mmol) of anhydrous $MgSO_4$[19] (to maintain neutrality) in 30 mL of H_2O was added dropwise to a vigorously stirred solution of 1.51 g (11.3 mmol) of **5b** in 20 mL of acetone, never allowing the temperature above 5 °C while the flask was immersed in an ice bath. The mixture then was warmed to room temperature and filtered, the ether was removed under reduced pressure, and 5 mL of 10% NaOH was added to the aqueous residue. After two ether extractions the aqueous residue was acidified with 6 N HCl and again extracted to remove the organic acid. Following drying and solvent removal, the residue was distilled to give 0.85 g (51%) of pure (*S*)-(+)-hydratropic acid: $[\alpha]^{25}_D$ +42.6°; bp 140 °C (10 torr) [lit.[20] bp 143 °C (12 torr)]; IR (neat) 2800–2400, 1710, 1215, 925, 755, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (d, J = 7 Hz, 3 H, Me), 3.67 (t, J = 7 Hz, 1 H, CH–), 7.25 (m, 5 H, Ph), 11.9 (broad, 1 H, COOH).

Registry No.—**1a,** 33530-46-0; (±)-**1a** acid, 68330-60-9; **1a** acid brucine salt, 68330-57-4; **1a** acid sodium salt, 59492-56-7; **1a** acid silver salt, 68330-58-5; **1b,** 59492-57-8; **1b** acid brucine salt, 68365-92-4; **1b** acid silver salt, 68365-93-5; **2a,** 770-88-7; **2b,** 68330-54-1; **3a,** 68258-23-1; **3b,** 68258-24-2; **4a,** 53777-08-5; **4b,** 1006-06-0; **5a,** 38235-74-4; **5b,** 33530-47-1; **6b,** 7782-24-3; (±)-**7,** 68330-59-6; **7a,** 68330-55-2; **7b,** 68330-56-3; 3-phenyl-1,2-butanediol, 68258-25-3.

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Pyridopyrimidines. 10. Nucleophilic Substitutions in the Pyrido[3,2-*d*]pyrimidine Series

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A new, simple approach to the synthesis of a wide variety of pyrido[3,2-*d*]pyrimidines is described. The approach involves Michael addition of 5-aminouracil to dimethyl acetylenedicarboxylate followed by thermal cyclization to give 6-(carbomethoxy)-2,4,8-trioxopyrido[3,2-*d*]pyrimidine. The latter compound is then converted to the trichloro derivative, which can undergo selective nucleophilic substitution in the order 4 > 2 > 8 to give the desired pattern of substituents.

Since an extensive review of the literature of pyridopyrimidines appeared in 1969,[1] little work has been reported describing synthetic approaches to the rather difficulty accessible pyrido[3,2-*d*]pyrimidines. Among the more important of these few studies from the point of view of biological activity was the extension of earlier work[2] by DeGraw et al.[3] to the synthesis of 8-deazafolic acid. This compound was found to be as potent as methotrexate in the inhibition of certain bacterial cell lines and was active against some methotrexate resistant strains.[3]

Two general approaches to the pyrido[3,2-*d*]pyrimidine ring system have been described. The first involved the cyclization of 3-aminopicolinic acid with various isocyanates or isothiocyanates to give 2,4-dioxo (or thio) derivatives.[4,5] This method suffers from the serious disadvantage that 3-aminopyridine-2-carboxylates bearing additional substituents in useful positions are very difficult to obtain. The alternative approach has been the cyclization of 5-aminouracils or 5-amino-2,4-dimethoxypyrimidine with β-dicarbonyl or α,β-unsaturated carbonyl compounds.[1,6] Of these cyclizations, the best from a synthetic point of view was the cyclization with diethyl ethoxymethylenemalonate to give 7-(carbethoxy)-8-oxopyrido[3,2-*d*]pyrimidines such as **1**.

In its quest for the synthesis of "multisubstrate analogue

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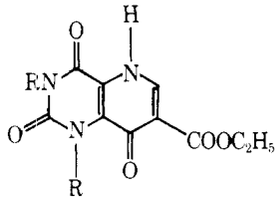

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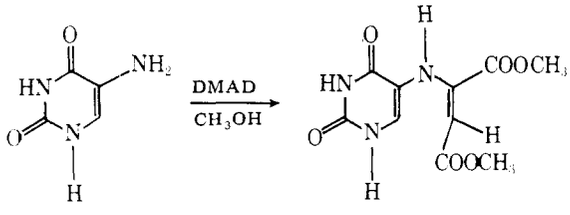
inhibitors" of the enzyme thymidylate synthetase, this laboratory has undertaken the preparation of a variety of pyrido[3,2-*d*]pyrimidines bearing a readily modifiable group at position 6 of the product. This present report describes a general approach to a wide variety of such pyrido[3,2-*d*]pyrimidines.

Results and Discussion

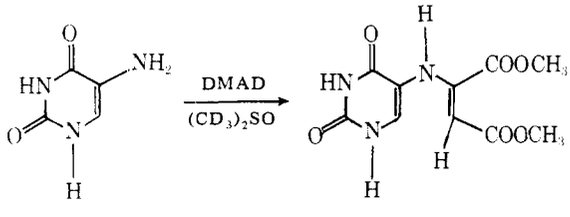
The electrophilic cylizations to give compounds of type 1 cited above and earlier reports from this laboratory describing the synthesis of pyrido[2,3-*d*]pyrimidines by the reaction of 6-aminouracils with dimethyl acetylenedicarboxylate (DMAD)[7,8] suggested that the reaction of DMAD with 5-aminopyrimidines might provide access to 6-(carbomethoxy)pyrido[3,2-*d*]pyrimidines. The initial product of the reaction of 5-aminouracil (**2**) with DMAD in methanol was the fumarate derivative **3** resulting from Michael addition to the



2 3

triple bond. That the reaction has occurred at the amino group rather than C-6 was established by the demonstration of two singlets at δ 5.13 and 7.33 in the ^{1}H NMR spectrum of **3**, corresponding to the vinyl proton and the pyrimidine C-6 H, respectively.

Based upon earlier studies in the 6-aminouracil series,[7] it was anticipated that the reaction of **2** with DMAD in protic media would give rise to the fumarate adduct **3**, as indeed was found to be the case. In aprotic media 6-aminouracil reacted with DMAD to give predominantly the maleate derivative, presumably by intramolecular proton transfer via a six-membered intermediate.[7] Although such an intermediate is not possible in the reaction of **2** with DMAD, the reaction in dimethyl sulfoxide (followed by ^{1}H NMR) rapidly gave the maleate derivative **4** as the sole initial product. The maleate



2 4

4 underwent a facile isomerization within 1 h at room temperature to give predominantly the thermodynamically more stable *Z* isomer. The equilibrium mixture consisted of **3** and **4** in an approximate ratio of 3:1. A similar finding was reported by Huisgen in the reaction of various anilines with DMAD.[9] Apparently, intramolecular proton transfer to give the thermodynamically less stable *E* isomer occurs even if the transfer must involve a four-membered rather than a six-membered ring. In keeping with previous observations,[7,9] the vinyl proton ^{1}H NMR signal for the maleate derivative **4** appeared at δ 4.60, about 0.5 ppm upfield from that of **3**.

Upon heating a solution of **3** in Dowtherm A at reflux for 45 min, cyclization occurred to give 6-(carbomethoxy)-2,4,8-trioxypyrido[3,2-*d*]pyrimidine (**5**) in good yield. The structure was confirmed by the absence of the pyrimidine C-6 H, the appearance a new singlet at δ 7.50 (C-7 H), and the presence of only one *O*-methyl group in the ^{1}H NMR spectrum. A molecular ion of 237 in the mass spectrum and the elemental analysis were also consistent with the assigned structure.

In order to assess the scope of this new approach, a variety of 2,4-disubstituted-5-aminopyrimidines were studied. Only the adduct with 5-amino-2,4-dimethoxypyrimidine was found to give reasonable yields of the desired pyridopyrimidine. Although this product, 6-(carbomethoxy)-2,4-dimethoxy-8-oxopyrido[3,2,-*d*]pyrimidine (**6**), proved to be of more synthetic value than originally anticipated (vide infra), it did not afford the desired flexibility for the preparation of a wide variety of substituted pyridopyrimidines. An alternative approach involving synthesis of the trichloropyridopyrimidine and selective nucleophilic displacement was undertaken.

Trioxo derivative **5** was smoothly converted to 6-(carbomethoxy)-2,4,8-trichloropyrido[3,2-*d*]pyrimidine (**7**) by treatment with phosphoryl chloride/diethyl aniline at reflux. The presence of three chlorine atoms in **7** was confirmed by the presence of molecular ion peaks at *m/e* 291, 293, and 295 in a ratio of 3:3:1 in the mass spectrum. This pattern arises from the isotope distribution of chlorine and is highly characteristic. The ^{1}H NMR spectrum contained only two signals, a three-proton singlet at δ 4.03 corresponding to the *O*-methyl group and a one-proton singlet at δ 8.03 attributable to C-7 H.

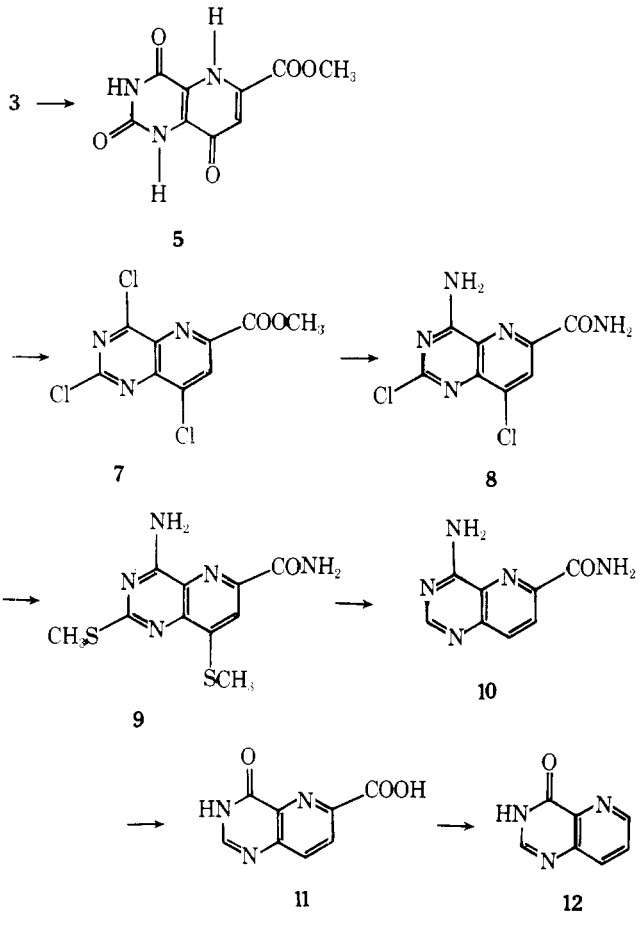
In order for a compound such as **7** to be of general utility as an intermediate in the synthesis of many different derivatives, three conditions must be met. First, selective nucleophilic displacement must be possible. Second, each of the chlorines must be susceptible to nucleophilic displacement even in the presence of electron-releasing groups in other positions. Finally, it must be possible to unambiguously determine the order of nucleophilic substitution.

The reaction of **7** with methanolic ammonia at room temperature gave a new single compound **8**. The ^{1}H NMR spectrum showed loss of the *O*-methyl group present in **7** and the presence of two pairs of D_2O exchangeable two-proton doublets at δ 8.79 and 7.76 and at δ 9.06 and 8.79. The mass spectrum revealed the presence of two chlorine atoms, a molecular ion peak of 257 and a loss of 17 mass units from the molecular ion corresponding to the loss of ammonia. Based on the above information and the known lability of 4-chloro groups in pyrido[3,2-*d*]pyrimidines,[2,10] structure **8** was tentatively assigned to the compound (Scheme I). However, it was not possible to unequivocally eliminate positional isomers.

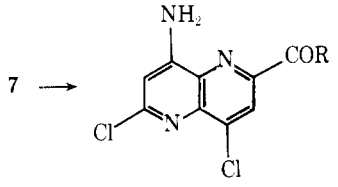
In order to confirm the assumption that the initial amination indeed occurred at position 4 of the pyrimidine ring, compound **8** was converted to 4-oxopyrido[3,2-*d*]pyrimidine (**12**). Reaction of **8** with sodium methyl mercaptide in $(CH_3)_2SO$ gave 4-amino-6-(carboxamido)-2,8-bis(methylmercapto)pyrido[3,2-*d*]pyrimidine (**9**). Raney nickel dethiation of **9** in refluxing DMF gave **10**; alkaline hydrolysis yielded 4-oxopyrido[3,2-*d*]pyrimidine-6-carboxylic acid (**11**). Thermal decarboxylation of **11** gave 4-oxopyrido[3,2-*d*]pyrimidine (**12**), which was identical in all respects with an authentic sample of the same compound prepared by an unambiguous procedure[10] from 3-aminopicolinic acid and formamide. The above reactions are outlined in Scheme I.

The reaction of **7** with ammonia in dioxane gave a new single

Scheme I



compound (**13**). The ^{1}H NMR spectrum revealed the presence of an $-OCH_3$ group at δ 4.00 and a broad two-proton doublet at δ 8.56 and 8.99. The mass spectrum revealed the presence of two chlorine atoms and a molecular ion peak at *m/e* 272. Compound **13** was quantitatively converted to **8** when treated with methanolic ammonia. The above reaction confirmed that amination had occurred in position 4 of the pyrimidine ring. Therefore, compound **13** was assigned the structure, 4-

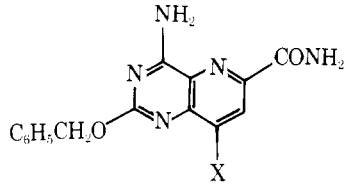


13, R = OCH_3
8, R = NH_2

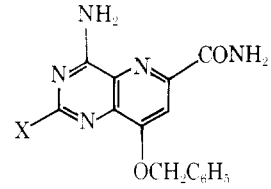
amino-6-(carbomethoxy)-2,8-dichloropyrido[3,2-*d*]pyrimidine.

In the pyrido[2,3-*d*]pyrimidine series, a chlorine at position 6 (pyridine ring) was found to be intermediate in reactivity between the 4 and the 2 chlorines (pyrimidine ring).[8] Examination of structure **8**, however, reveals that the presence of an electron-releasing group at C-4 should, by a mesomeric effect, stabilize the 8-chloro function toward nucleophilic displacement. It was not possible, therefore, to predict the relative ease of displacement of 8 vs. 2 substituents. Treatment of **8** with sodium benzylate in benzyl alcohol gave a new compound (**14** or **15**). ^{1}H NMR spectroscopy confirmed the presence of a benzyl group and mass spectra revealed the presence of only one chlorine atom.

The final chlorine in **14** (or **15**) was displaced with sodium methyl mercaptide in $(CH_3)_2SO$ to give compound **16** (from **14**) or **17** (from **15**). Raney nickel dethiation of **16** to **18** would give rise to a pair of doublets in the ^{1}H NMR for the 7 and 8 protons, whereas dethiation of **17** to **19** would give rise to a new singlet for the 2 protons in addition to the singlet for C-7 H. The ^{1}H NMR spectrum of the product **18** (or **19**) consisted of



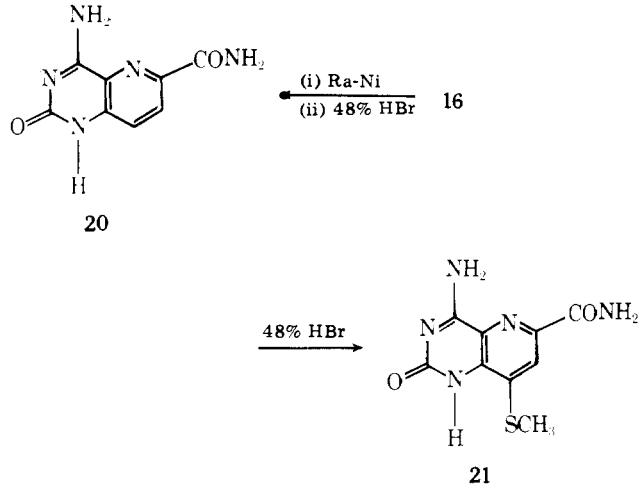
14, X = Cl
16, X = SCH_3
18, X = H



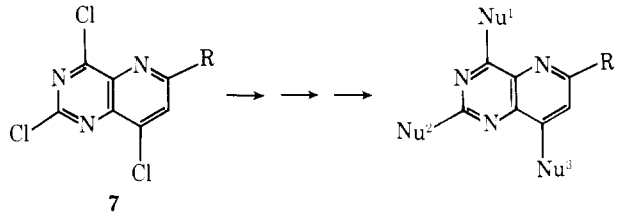
15, X = Cl
17, X = SCH_3
19, X = H

a pair of doublets at δ 7.95 and 8.29 with $J_{7,8}$ = 9.0 Hz. The above results conclusively proved that the methylthio group was present in position 8 of the pyridopyrimidine **16**. The Raney nickel dethiation of **16** gave **18** and a very small amount of **20**, 4-amino-6-(carboxamido)-2-oxopyrido[3,2-*d*]pyrimidine. Treatment of the mixture with 48% HBr gave only **20**.

Compound **16** was debenzylated using 48% HBr to give **21**, 4-amino-6-(carboxamido)-8-(methylthio)-2-oxopyrido[3,2-*d*]pyrimidine.

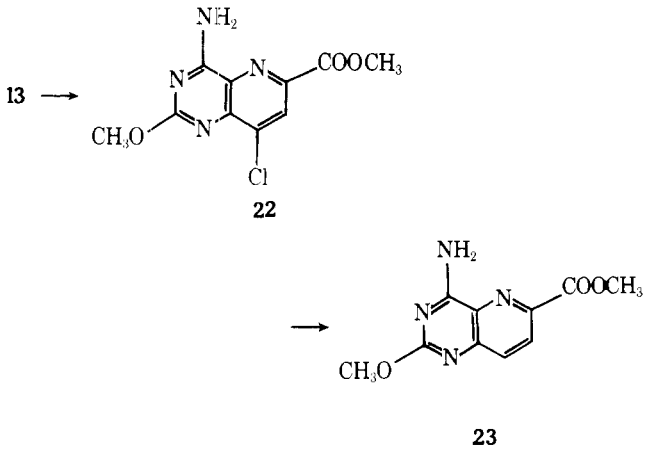


These results unequivocally established that the order of substitution with ammonia, sodium benzylate, and sodium methyl mercaptide occurred at 4, 2 and 8 positions, respectively, of the 2,4,8-trichloropyrido[3,2-*d*]pyrimidine **7**.



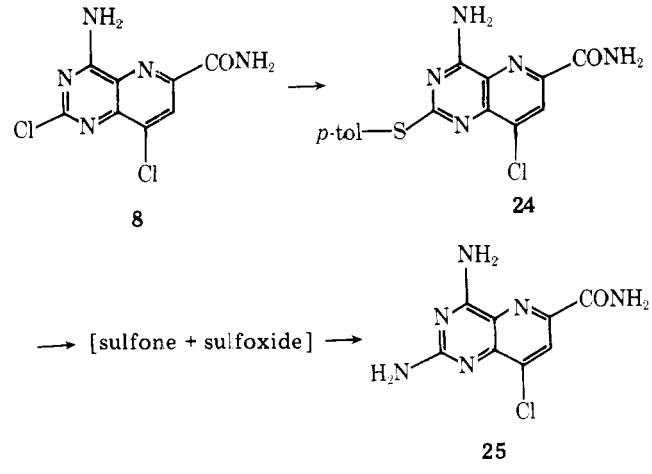
The order of nucleophilic displacement was confirmed for a different nucleophile by the following set of reactions. Compound **13** was reacted with sodium methoxide in methanol at room temperature to give 4-amino-6-(carbomethoxy)-8-chloro-2-methoxypyrido[3,2-*d*]pyrimidine (**22**). Catalytic hydrogenolysis of **22** gave 4-amino-6-(carbomethoxy)-2-methoxypyrido[3,2-*d*]pyrimidine (**23**), which was identified by the presence of a pair of doublets ($J_{7,8}$ = 9.0 Hz) in the ^{1}H NMR spectrum.

A closer scrutiny of the ^{1}H NMR spectra of **8**, **14**, and **16** also indicated that the second and final displacements occurred at positions 2 and 8, respectively. The C-7 protons in both **8**



and 14 appear at δ 8.29, indicating that the pyridine moiety was unperturbed. Replacement of the 8-chloro group in 14 by methylthio shifted the 7-proton signal upfield by 0.33 ppm.

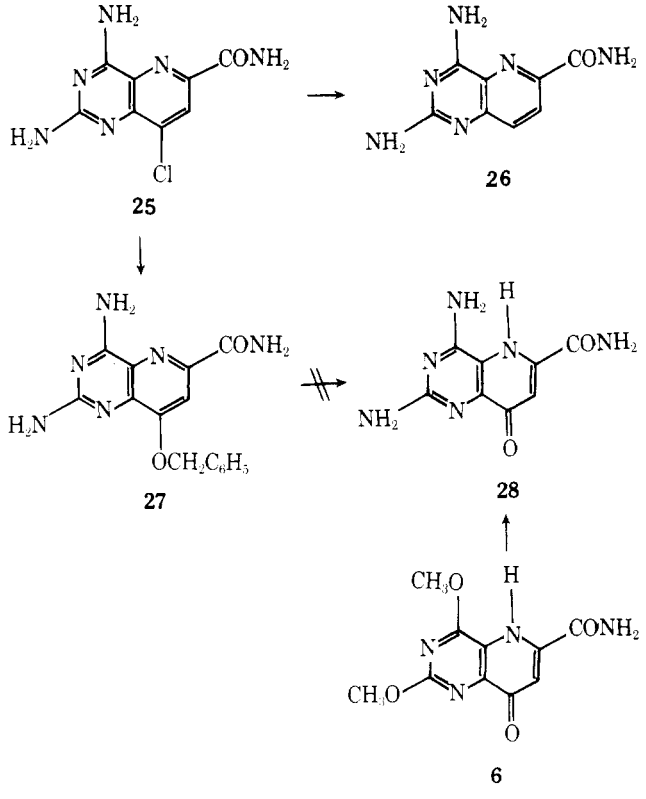
In order to prepare 8-oxopyrido[3,2-*d*]pyrimidines substituted at the 2 and 4 positions, it was necessary to introduce a sulfur function at the 2 position which could be converted to an amino group and a benzyloxy function at the 8 position. Reaction of 8 with excess *p*-thiocresol in refluxing 2-propanol gave **24** in good yield. The presence of the C-7 H signal at δ 8.29 indicated that the displacement occurred at the 2 position. Oxidation of **24** with *m*-chloroperbenzoic acid followed by displacement with NH_3 gave 6-(carboxamido)-8-chloro-2,4-diaminopyrido[3,2-*d*]pyrimidine (**25**). The presence of



peaks at *m/e* 238 and 240 in a ratio of 3:1 in the mass spectrum and a singlet at δ 8.30 in the ^1H NMR spectrum support the assigned structure.

Catalytic hydrogenolysis of **25** gave 6-(carboxamido)-2,4-diaminopyrido[3,2-*d*]pyrimidine (**26**). The presence of a pair of doublets ($J_{7,8}$ = 9.0 Hz) in the ^1H NMR spectrum confirmed the structural assignments of compounds **24, 25,** and **26**. Treatment of **25** with sodium benzylate at 80–90 °C in $(CH_3)_2SO$ gave **27**, 8-(benzyloxy)-6-(carboxamido)-2,4-diaminopyrido[3,2-*d*]pyrimidine. Compound **27** was resistant to debenzylation (48% HBr, Pd/C (10%) hydrogenolysis). An alternative route to **28** was sought; it was found that ammonolysis of **6** with liquid ammonia in a sealed bomb at 170 °C gave compound **28**.

This study has provided a general approach to a wide variety of pyrido[3,2-*d*]pyrimidines (8-deazapteridines) bearing a readily modifiable carbomethoxy group at position 6. Studies dealing with the conversion of these compounds to multisubstrate analogue inhibitors of thymidylate synthetase are in progress.



Experimental Section

The ^1H NMR spectra were recorded on a JEOL C-60H or a Varian EM-360 spectrometer in dimethyl-d_6 sulfoxide with DSS as an internal standard, unless otherwise stated. UV spectra were obtained on a Cary Model 15 spectrophotometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Mass spectra were recorded on a LKB-GCMS Model 9000S or a Varian 112S spectrometer. Only molecular ion and first major fragments are reported. All compounds were shown to be homogeneous in one or more of the following systems: $CHCl_3/CH_3OH$, 85:15; $EtOAc/CH_3OH$, 90:10; and CH_3CN/H_2O, 80:20. Elemental analyses were performed by Het-Chem-Co., Harrisonville, Mo., and Galbraith Laboratories, Knoxville, Tenn.

Dimethyl 2-(2,4-Dioxopyrimidin-5-yl)aminofumarate (3). To a suspension of 12.7 g (0.1 mol) of 5-aminouracil[11] (**2**) in 300 mL of absolute methanol was added 15.6 g (0.11 mol, 13.5 mL) of dimethyl acetylenedicarboxylate.[12] The suspension was stirred for 10 h at room temperature and filtered to give 22.3 g (83%) of **3**. A small amount was crystallized from methanol to give a white solid: mp 245–246 °C; MS *m/e* 269 (M^+), 237 ($M^+ - CH_3OH$); UV λ_{max} (ϵ_{max}) (pH 1) 260 nm (8300); (pH 7) 320 nm (12 350); (pH 11) 292 nm (13 450); ^1H NMR δ 3.63 (s, 3, $COOCH_3$), 3.66 (s, 3, $COOCH_3$), 5.13 (s, 1, CH), 7.33 (s, 1, C-6 H), 8.93 (br, 1, NH), 10.66 (br, 1, NH), 11.16 (br, 1, NH).

Anal. Calcd for $C_{10}H_{11}N_3O_6$: C, 44.57; H, 4.11; N, 15.68. Found: C, 44.43; H, 4.35; N, 15.73.

6-(Carbomethoxy)-2,4,8-trioxopyrido[3,2-*d*]pyrimidine (5). A suspension of 13.45 g (0.05 mol) of **3** in 350 mL of "Downtherm A" was refluxed for 45 min. The solution was cooled to room temperature, and the addition of 600 mL of petroleum ether (30–60 °C) gave a yellow solid. Crystallization from DMF gave 8.4 g of pure **5**: mp >300 °C; MS *m/e* 237 (M^+), 205 ($M^+ - CH_3OH$); UV λ_{max} (ϵ_{max}) (pH 1) 240 nm (21 150), 248 (19 600), 257 (15 250), 326 (7250); (pH 7) 248 nm (27 500), 256 (22 000), 325 (8600); (pH 11) 248 nm (27 500), 315 (6800); ^1H NMR δ 3.89 (s, 3, $COOCH_3$), 7.5 (s, 1, C-7 H), 10.68 (br, 1, NH), 11.40 (br, 2, NH).

Anal. Calcd for $C_9H_7N_3O_5$: C, 45.53; H, 2.97; N, 17.80. Found: C, 45.39; H, 3.11; N, 18.06.

6-(Carbomethoxy)-2,4-dimethoxy-8-oxopyrido[3,2-*d*]pyrimidine (6). (a) Dimethyl 2-(2,4-Dimethoxypyrimidin-5-yl)aminofumarate. To a solution of 1.55 g (10 mmol) of 5-amino-2,4-dimethoxypyrimidine[13] in 30 mL of absolute methanol was added 1.56 g (11 mmol, 1.4 mL) of dimethyl acetylenedicarboxylate, and the bright yellow solution was stirred for 2–3 h. The solidified mass was filtered and washed with small amounts of methanol. Crystallization from methanol gave 2.1 g (72%) of the fumarate: mp 112–113 °C; MS *m/e* 297 (M^+), 265 ($M^+ - CH_3OH$); UV λ_{max} (ϵ_{max}) (pH 1) 245 nm

(7250), 315 (9400); (pH 7) 235 nm (7900), 321 (11 900); (pH 11) 240 nm (6200), 299 (11 400); ^{1}H NMR ($CDCl_3$) δ 3.7 (s, 6, $2OCH_3$), 3.90 (s, 3, $COOCH_3$), 3.93 (s, 3, $COOCH_3$), 5.43 (s, 1, vinyl), 7.80 (s, 1, C-6 H).

Anal. Calcd for $C_{12}H_{15}N_3O_6$: C, 48.48; H, 5.08; N, 14.13. Found: C, 48.22; H, 4.99; N, 14.42.

(b) A solution of 0.59 g (2 mmol) of fumarate from a above in 12 mL of "Dowtherm A" was refluxed for 5 min and cooled to room temperature. The crystallized solid was filtered and washed with petroleum ether (30–60 °C). Recrystallization from ethyl acetate gave 0.28 g (53%) of **6:** mp 214–215 °C; MS *m/e* 265 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 246 nm (24 200), 261 (13 850), 312 (6300), 341 (6000); (pH 7) 255 nm (27 850), 258 (27 800), 325 (7260), 335 (7950); (pH 11) 257 nm (28 500), 333 (8950); ^{1}H NMR ($CDCl_3$) δ 4.13 (s, 3, $COOCH_3$), 4.2 (s, 3, OCH_3), 4.31 (s, 3, OCH_3), 8.0 (s, 1, C-7 H).

Anal. Calcd for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 49.84; H, 4.24; N, 15.70.

6-(Carbomethoxy)-2,4,8-trichloropyrido[3,2-*d*]pyrimidine (7). Compound **5** (5 g, 21.1 mmol) was refluxed with 125 mL of $POCl_3$ containing 5 mL of *N,N'*-diethylaniline for 10–12 h. The volume was reduced to approximately 25 mL by distillation under reduced pressure. The dark brown syrup was poured into excess ice and stirred vigorously for 10 min. The ice-cold suspension was extracted with CH_2Cl_2 (~600 mL). The organic layer was washed with water until the washings were neutral. The solution was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to give 3.8 g (63%) of a red powder. Crystallization from petroleum ether (90–120 °C) gave pure **7:** mp 195–196 °C; MS *m/e* 291 (M^+), 260 ($M^+ - CH_3OH$), 232 ($M^+ - COOCH_3$); UV λ_{max} (ϵ_{max}) (pH 1) 231 nm (30 800), 295 (8900), 308 (7200), 320 (5500); (pH 7) 223 nm (30 600), 295 (8500), 307 (7100), 320 (5500); (pH 11) 247 nm (15 000), 332 (9300), 345 (7600); ^{1}H NMR ($CDCl_3$) δ 4.03 (s, 3, $COOCH_3$), 8.03 (s, 1, C-7 H).

Anal. Calcd for $C_9H_4N_3O_2Cl_3$: C, 36.92; H, 1.37; N, 14.36. Found: C, 36.82; H, 1.66; N, 14.22.

4-Amino-6-(carboxamido)-2,8-dichloropyrido[3,2-*d*]pyrimidine (8). Compound **7** (600 mg, 2 mmol) was stirred for 12 h with 40 mL of methanolic ammonia, saturated at 0 °C, and for 12 h at room temperature. The precipitated solid was filtered, washed with methanol and crystallized from a DMF/H_2O mixture to give 0.35 g (68%) of **8:** mp >300 °C; MS *m/e* 257 (M^+), 214 ($M^+ - HCNO$), 179 ($M^+ - HCNO - Cl$); UV λ_{max} (ϵ_{max}) (pH 1) 238 nm (23 300), 317 (10 000), 330 s (8400); (pH 7) 238 nm (23 700), 317 (10 000), 330 (8400); (pH 11) 238 nm (23 600), 317 (9300), 330 s (8000); ^{1}H NMR δ 7.76 and 9.06 (br s, 2, NH_2), 8.79 (br s, 2, $CONH_2$), 8.29 (s, 1, C-7 H).

Anal. Calcd for $C_8H_5N_5Cl_2O{\cdot}0.5H_2O$: C, 35.97; H, 2.26; N, 26.22. Found: C, 35.79; H, 2.17; N, 26.04.

For large scale preparation of **8** the following procedure was used. Compound **5** (11.85 g, 0.05 mol) was refluxed with 300 mL of $POCl_3$ and 12 mL of *N,N'*-diethylaniline for 12 h. Workup was carried out as described earlier. The crude trichloro compound was stirred with 300 mL of methanolic ammonia overnight and filtered to give 10.8 g (81%) of **8**, identical with that prepared from **7** in all respects.

4-Amino-2,8-bis(methylthio)-6-(carboxamido)pyrido[3,2-*d*]pyrimidine (9). Compound **8** (2.67 g, 10 mmol) was stirred with a solution of CH_3SNa in Me_2SO (prepared by adding CH_3SH to 50 mL of Me_2SO containing 0.69 g (30 mmol) of sodium) for 1 h. The light yellow solution was slowly poured into 500 mL of water. The yellow solid was filtered, dried, and crystallized from DMF/H_2O to give 2.31 g (77%) of **9:** mp 317–318.5 °C; MS *m/e* 281 (M^+), 238 ($M^+ - HCNO$), 236 ($M^+ - SCH_3$), 190 $M^+ - 2SCH_3$); UV λ_{max} (ϵ_{max}) (pH 1) 290 nm (29 990), 346 (13 800); (pH 7) 277 nm (27 500), 350 (15 000); (pH 11) 277 nm (26 100), 350 (12 250); ^{1}H NMR δ 2.60 (s, 3, SCH_3), 2.63 (s, 3, SCH_3), 7.78, 8.26 (br s, 2, NH_2), 8.10 (s, 1, C-7 H), 8.70, 8.95 (br s, 2, $CONH_2$).

Anal. Calcd for $C_{10}H_{11}N_5OS_2{\cdot}1.0H_2O$: C, 40.12; H, 4.04; N, 23.39. Found: C, 40.41; H, 3.99; N, 23.36.

4-Amino-6-(carboxamido)pyrido[3,2-*d*]pyrimidine (10). A solution of 2.8 g (9.3 mmol) of **9** in 250 mL of DMF was refluxed with 25 g (wet weight) of Ra-Ni[14] for 3 h. The mixture was filtered through Celite, and the filter cake was washed with hot DMF (15–20 mL). The combined filtrate was evaporated to give 1.1 g of yellow solid. Crystallization from DMF/H_2O gave 0.92 g (49%) of **10:** mp >330 °C; MS *m/e* 189 (M^+), 146 ($M^+ - HCNO$); UV λ_{max} (ϵ_{max}) (pH 1) 239 nm (23 800), 312 (11 900), 329 (11 500); (pH 7) 248 nm (22 720), 322 (8150); (pH 11) 247 nm (23 600), 322 (8200); ^{1}H NMR δ 7.81 and 8.21 (br s, NH_2), 8.70 (s, 1, C-2 H), 8.23 (d, $J_{7,8}$ = 9.0 Hz, 1, C-7 H), 8.55 (d, $J_{7,8}$ = 9.0 Hz, 1, C-8 H), 8.56 and 9.01 (br, 2, $CONH_2$).

Anal. Calcd for $C_8H_7N_5O{\cdot}0.5H_2O$: C, 48.48; H, 4.07; N, 35.33. Found: C, 48.22; H, 4.22; N, 35.26.

4-Oxopyrido[3,2-*d*]pyrimidine-6-carboxylic Acid (11). Compound **10** (0.95 g, 4.79 mmol) was refluxed with 15 mL of 1 N NaOH for 2 h. The dark brown solution was acidified with 6 N HCl. The dark solid was filtered, washed with water, dissolved in 10 mL of 1 N NaOH, and acidified with 6 N HCl. The solid was collected by filtration, and recrystallization from glacial acetic acid gave 0.41 g (38%) of **11:** mp >300 °C; MS *m/e* 191 (M^+), 147 ($M^+ - CO_2$), 120 ($M^+ - HCNO - CO_2$); UV λ_{max} (ϵ_{max}) (pH 1) 282 nm (1800), 283 (13 000), 285 (9850), 305 (8250), 313 (5400); (pH 7) 229 nm (15 700), 274 (9100), 304 (6150), 315 (4460); (pH 11) 243 nm (22 200), 314 (8100); ^{1}H NMR (CF_3COOH) δ 8.23 (s, 2, C-7 H, and C-8 H), 8.3 (s, 1, C-2 H).

Anal. Calcd for $C_8H_5N_3O_3{\cdot}2.0H_2O$: C, 42.29; H, 3.99; N, 18.49. Found: C, 42.61; H, 3.72; N, 18.22.

4-Oxopyrido[3,2-*d*]pyrimidine (12). The above acid **11** (0.38 g, 2 mmol) was heated in a vacuum sublimator at 300–320 °C for 2 h. The sublimate was washed with alcohol and crystallized from water to give 50 mg (17%) of **12,** mp >300 °C. This compound is identical in all respects [^{1}H NMR, MS, and TLC ($CHCl_3/CH_3OH$, 90:10; CH_3CN/H_2O, 80:20)] with that prepared from 3-aminopicolinic acid and formamide according to the procedure of Oakes, Rydon, and Pascoe.[10]

4-Amino-6-(carbomethoxy-2,8-dichloropyrido[3,2-*d*]pyrimidine (13). To a solution of 2.92 g (0.01 mol) of **7** in 100 mL of anhydrous dioxane was passed ammonia for 2 h. The mixture was stirred for 3 h at room temperature. Dioxane was removed in vacuo, and the residue was stirred with 30–50 mL of water, filtered, and dried. Crystallization from DMF/H_2O gave 2.1 g (76%) of **13:** mp >300 °C; MS *m/e* 272 (M^+), 241 ($M^+ - OCH_3$); UV λ_{max} (ϵ_{max}) (pH 1) 250 nm (21 000), 327 (10 500); (pH 7) 250 nm (20 750), 327 (9900), 340 s (8900); (pH 11) 247 nm (19 750), 301 (7250), 324 (8600), 337 (6900); ^{1}H NMR δ 4.00 (s, 3, $COOCH_3$), 8.43 (s, 1, C-7 H), 8.56 and 8.99 (br, 2, NH_2).

Anal. Calcd for $C_9H_6N_4O_2Cl_2{\cdot}0.5H_2O$: C, 38.32; H, 2.50; N, 19.86. Found: C, 38.23; H, 2.47; N, 19.57.

4-Amino-6-(carbomethoxy)-8-chloro-2-methoxypyrido[3,2-*d*]pyrimidine (22). Compound **13** (1.4 g, 5 mmol) was stirred with 50 mL of methanol in which 0.17 g (7.5 mmol) of sodium was already dissolved. After 15 h at room temperature, methanol was removed in vacuo and the residue was stirred with water. The precipitated solid was filtered, dried, and crystallized from methanol to give 0.9 g (68%) of **22:** mp 257–258 °C; MS *m/e* 268 (M^+), 237 ($M^+ - OCH_3$), 209 ($M^+ - COOCH_3$); UV λ_{max} (ϵ_{max}) (pH 1) 220 nm (35 850), 239 (28 450), 308 (8400), 318 (11 150); (pH 7) 224 nm (27 300), 248 (27 860), 308 (7800), 336 (9900); (pH 11) 244 nm (25 250), 295 (6830), 336 (8100); ^{1}H NMR δ 3.93 (s, 3, $COOCH_3$), 3.98 (s, 3, OCH_3), 8.25 (br, 2, NH_2), 8.33 (s, 1, C-7 H).

Anal. Calcd for $C_{10}H_9N_4O_3Cl$: C, 44.70; H, 3.37; N, 20.85. Found: C, 44.39; H, 3.29; N, 21.17.

4-Amino-6-(carbomethoxy)-2-methoxypyrido[3,2-*d*]pyrimidine (23). Compound **22** (0.67 g, 2.5 mmol) in 30 mL of DMF containing 200 mg of 10% Pd/C and 200 mg of sodium acetate was hydrogenated at 42 psi in a Parr hydrogenator for 10 h. The mixture was filtered through Celite, and the filter cake was washed with 5–10 mL of hot DMF. The combined filtrate was evaporated to dryness, and the residue was triturated with water. Filtration and crystallization from methanol gave 0.33 g (55%) of **23:** mp 254–255 °C; MS *m/e* 234 (M^+), 203 ($M^+ - OCH_3$), 175 ($M^+ - CO - OCH_3$); UV λ_{max} (ϵ_{max}) (pH 1) 219 nm (28 200), 240 (24 550), 316 (11 200), 330 (9700); (pH 7) 249 nm (30 700), 296 s (9000), 327 (11 700); (pH 11) 246 nm (31 200), 295 (8750), 325 (9200); ^{1}H NMR δ 3.95 (s, 3, $COOCH_3$), 3.95 (s, 3, OCH_3), 7.86 (br, 2, NH_2), 7.97 (d, $J_{7,8}$ = 9.0 Hz, 1, C-7 H), 8.27 (d, $J_{7,8}$ = 9.0 Hz, 1, C-8 H).

Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.60; H, 4.12; N, 23.76.

4-Amino-2-(benzyloxy-6-(carboxamido)-8-chloropyrido[3,2-*d*]pyrimidine (14). Compound **8** (2.58 g, 10 mmol) was stirred with 80 mL of benzyl alcohol in which 0.46 g (20 mmol) of sodium was already dissolved. After 3 days at room temperature, the mixture was diluted with 300–350 mL of ether. The precipitated solid was filtered and stirred with 100 mL of water. Filtration and recrystallization from DMF/H_2O gave 2.4 g (72%) of **14:** mp 267–269 °C; MS *m/e* 329 (M^+), 223 ($M^+ - C_6H_5CHO$); UV λ_{max} (ϵ_{max}) (pH 1) 225 nm (35 600), 237 (31 200), 307 (7300), 320 (10 700), 333 (9650); (pH 7) 247 nm (15 700), 304 (5600), 337 (5600); (pH 11) 247 nm (25 850), 304 (6350), 337 (6450); ^{1}H NMR δ 5.58 (s, 2 $OCH_2C_6H_5$), 7.41 (m, 5, C_6H_5), 8.29 (s, 1, C-7 H).

Anal. Calcd for $C_{15}H_{12}N_5O_2Cl{\cdot}0.5H_2O$: C, 53.18; H, 3.66; N, 20.67. Found: C, 53.25; H, 3.86; N, 20.87.

4-Amino-2-(benzyloxy)-6-(carboxamido)-8-(methylthio)pyrido[3,2-*d*]pyrimidine (16). To a solution of CH_3SNa in Me_2SO (prepared by adding CH_3SH to Me_2SO (30 mL) containing 0.35 g (15 mmol) of Na) was added 3.29 g (10 mmol) of **14.** After stirring for 2 h at room temperature, the light yellow solution was poured with stirring into 100–150 mL of water. The yellow precipitate was filtered and crystallized from DMF/H_2O to give 2.3 g (67%) of **16:** mp 285–286

°C; MS *m/e* 341 (M^+), 235 ($M^+ - C_6H_5CHO$); UV λ_{max} (ϵ_{max}) (pH 1) 243 nm (8100), 274 (4700), 335 (3600); (pH 7) 247 nm (8400), 287 (3100), 340 (3100), 352 s (2800); (pH 11) 248 nm (3850), 340 (3270), 352 (2950); ^1H NMR δ 2.58 (s, 3, SCH_3), 5.73 (s, 2, OCH_2), 7.40 (m, 6, C_6H_5, NH), 7.96 (s, 1, C-7 H), 7.96 (br, 1, NH), 8.86 (br, 2, $CONH_2$).

Anal. Calcd for $C_{16}H_{15}N_5O_2S \cdot 1.0H_2O$: C, 53.40; H, 4.76; N, 19.48. Found: C, 53.77; H, 4.68; N, 19.22.

4-Amino-6-(carboxamido)-8-(methylthio)-2-oxopyrido-[3,2-*d*]pyrimidine (21). Compound **16** (1.7 g, 4.7 mmol) was stirred with 20 mL of 48% HBr for 6 h at room temperature. The solution was diluted to 50 mL with water and neutralized with saturated bicarbonate solution. The precipitated solid was filtered and washed with water and dried to give 0.73 g (62%) of **21**, mp >300 °C. An analytical sample was prepared by dissolving 0.21 g of **21** in 150 mL of hot ammonium hydroxide and concentrating the solution to cloud point to give 0.12 g (60%): MS *m/e* 251 (M^+); UV λ_{max} (ϵ_{max}) (pH 1) 262 nm (17 000), 348 (6400); (pH 7) 251 nm (23 250), 348 (7900), 360 (5250); (pH 11) 258 nm (23 300), 357 (7900); ^1H NMR (CF_3COOH) δ 2.90 (s, 3, SCH_3), 8.56 (s, 1, C-7 H).

Anal. Calcd for $C_9H_9N_5O_2S$: C, 43.02; H, 3.61; N, 27.57. Found: C, 43.11; H, 3.84; N, 28.06.

4-Amino-6-(carboxamido)-2-oxopyrido[3,2-*d*]pyrimidine (20). A solution of 3.29 g (10 mmol) of **16** in 200 mL of DMF was refluxed with stirring with 30 g (wet weight) of Raney nickel[14] for 24 h. Thin-layer chromatography ($CHCl_3/CH_3OH$, 85:15) showed the complete disappearance of **16** and the presence of two components (**18** and **20**) approximately in a ratio of 95:5. The mixture was filtered through Celite, and the filter cake was washed with 50 mL of hot DMF. The combined filtrate was evaporated to a small volume, and trituration with water gave 1.4 g of white solid. The ^1H NMR spectrum in $(CD_3)_2SO$ consisted of a pair of doublets at δ 7.95 and 8.29 ($J_{7,8}$ = 9.0 Hz). The above compound was stirred with 20 mL of 48% HBr at room temperature for 1 h. The mixture was diluted to 50 mL with water and neutralized with dilute ammonium hydroxide to pH ~8. The precipitated solid was filtered. The solid was dissolved in 600 mL of hot ammonium hydroxide. The solution was concentrated to ~200 mL and allowed to cool to room temperature. The crystallized solid was filtered and dried to give 0.63 g (31% based on **16**) of **20**: mp >300 °C; MS *m/e* 205 (M^+), 162 ($M^+ - HCNO$); UV λ_{max} (ϵ_{max}) (pH 1) 265 nm (14 450), 315 (6700), 326 (6800); (pH 7) 258 nm (15 400), 315 (7600), 325 (6900); (pH 11) 241 nm (17 700), 301 (10 000), 329 s (7250); ^1H NMR (CF_3COOH) δ 8.24 (d, $J_{7,8}$ = 9.0 Hz, 1, C-7 H), 8.90 (d, $J_{7,8}$ = 9.0 Hz, 1, C-8 H).

Anal. Calcd for $C_8H_7N_5O_2 \cdot 2.5H_2O$: C, 38.40; H, 4.73; N, 27.90. Found: C, 38.20; H, 4.35; N, 27.48.

4-Amino-6-(carboxamido)-8-chloro-2-(*p*-toluoylthio)-pyrido[3,2-*d*]pyrimidine (24). A suspension of 2.58 g (10 mmol) of **8** in 300 mL of 2-propanol was stirred and refluxed with 6.2 g (50 mmol) of *p*-toluenethiol for 10–12 h. The mixture was cooled to room temperature. The precipitated solid was filtered and washed with ether. Crystallization from methanol gave 2.4 g (71%) of **24**: mp 292–293 °C; MS *m/e* 345 (M^+), 302 ($M^+ - HCNO$); UV λ_{max} (ϵ_{max}) (pH 1) 238 nm (26 500), 265 (16 300), 328 (13 900), 342 (12 900); (pH 7) 242 nm (8350), 292 (5100); (pH 11) 242 nm (7000); ^1H NMR δ 2.41 (s, 3, CH_3), 7.46 (q, 4, $-C_6H_4$), 7.98 and 8.31 (br, 2, NH_2), 8.29 (s, 1, C-7 H), 8.8 (br, 2, $CONH_2$).

Anal. Calcd for $C_{15}H_{12}N_5SOCl$: C, 52.09; H, 3.49; N, 20.05. Found: C, 52.05; H, 3.29; N, 20.03.

6-(Carboxamido)-8-chloro-2,4-diaminopyrido[3,2-*d*]pyrimidine (25). To a suspension of 3.45 g (10 mmol) of **24** in 100 mL of chloroform was added 4.5 g of *m*-chloroperbenzoic acid. After stirring for 8 h at room temperature, the precipitated solid was filtered, washed with $CHCl_3$, and dried. The solid (mixture of sulfone and sulfoxide) was dissolved in 50 mL of anhydrous dimethylformamide. Gaseous ammonia was passed through the solution for 2 h. Dimethylformamide was removed in vacuo, and the residue was triturated with water. The solid was filtered, washed with water, and crystallized from DMF/H_2O to yield 1.53 g (53% based on **24**) of **25**: mp >300 °C; MS *m/e* 238 (M^+), 195 ($M^+ - HCNO$), 160 ($M^+ - HCNO - Cl$); UV λ_{max} (ϵ_{max}) (pH 1) 230 nm (37 000), 260 (30 000), 310 (7400), 323 (9600), 335 (8000); (pH 7) 228 nm (25 400), 248 (27 200), 265 (15 600), 307 (10 400), 350 (9000); (pH 11) 232 nm (20 800), 248 (24 800), 265 (15 200), 307 (10 400), 350 (9000); ^1H NMR δ 6.88 (br, 2, 2-NH_2), 7.70 (br, 2, 4-NH_2), 8.3 (s, 1, C-7 H), 8.53 and 8.83 (s, br, 2, $CONH_2$).

Anal. Calcd for $C_8H_7N_6OCl \cdot 2.0H_2O$: C, 35.06; H, 4.03; N, 30.59. Found: C, 35.39; H, 3.78; N, 30.29.

6-(Carboxamido)-2,4-diaminopyrido[3,2-*d*]pyrimidine (26). A solution of 0.27 g (1 mmol) of **25** in 20 mL of dimethylformamide and 10 mL of methanol containing 100 mg of sodium-acetate was hydrogenated in a Parr hydrogenator at 42 psi over 10% Pd/C (50 mg) for 24 h. The catalyst was removed by filtration, and the solvents were removed in vacuo. The residue was triturated with water and filtered. Crystallization from water gave 80 mg (39%) of **26**: mp >300 °C; MS *m/e* 204 (M^+), 160 ($M^+ - CONH_2$); UV λ_{max} (ϵ_{max}) (pH 1) 220 nm (30 600), 253 (22 550), 307 (7400), 319 (10 000), 331 (8050); (pH 7) 220 nm (22 400), 249 (23 000), 304 (8700), 336 (7900); (pH 11) 248 nm (21 600), 301 (8100), 346 (7350); ^1H NMR δ 6.96 (br, 2, 2-NH_2), 7.61 and 8.00 (br, 1 each, 4-NH_2), 7.76 (d, $J_{7,8}$ = 9.0 Hz, 1, C-7 H), 8.26 (d, $J_{7,8}$ = 9.0 Hz, 1, C-8 H), 8.61 and 8.83 (br, 2, $CONH_2$).

Anal. Calcd for $C_8H_8N_6O \cdot 1.5H_2O$: C, 41.55; H, 4.79; N, 36.34. Found: C, 41.85; H, 4.95; N, 36.36.

8-(Benzyloxy)-6-(carboxamido)-2,4-diaminopyrido[3,2-*d*]-pyrimidine (27). To a solution of sodium benzyl oxide in 25 mL of dry Me_2SO (prepared by adding 0.8 g (7.5 mmol) of distilled benzyl alcohol to Me_2SO containing 0.17 g (7.5 mmol) of metallic sodium) was added 1.35 g (5 mmol) of **25**, and the solution was stirred at 80–90 °C for 8 h. The solution was cooled to room temperature, and addition of water to the cloud point precipitated **27**. Crystallization from DMF gave 0.91 g (59%) of **27**: mp 271–272.5 °C; MS *m/e* 310 (M^+), 204 ($M^+ - C_6H_5CHO$); UV λ_{max} (ϵ_{max}) (pH 1) 240 nm (45 600), 290 (8660), 315 (8450), 328 (6150); (pH 7) 245 nm (33 600), 316 (12 000); (pH 11) 245 nm (32 100), 316 (12 300); ^1H NMR δ 5.33 (s, 2, $C_6H_5CH_2$), 6.55 (br, 2, 2-NH_2), 7.5 (m, 6, NH and C_6H_5), 7.73 (s, 1, C-7 H), 8.16 (br, 1, NH), 8.80 (br, 2, $CONH_2$).

Anal. Calcd for $C_{15}H_{14}N_6O_2 \cdot 0.5H_2O$: C, 56.42; H, 4.73; N, 26.31. Found: C, 56.37; H, 4.78; N, 26.17.

6-(Carboxamido)-2,4-diamino-8-oxopyrido[3,2-*d*]pyrimidine (28). Compound **6** (0.13 g, 0.5 mmol) was heated in a sealed bomb with 15–20 mL of liquid ammonia at 160–170 °C. The liquid ammonia was allowed to evaporate, and trituration of the solid with ethanol gave **28**. The solid was dissolved in hot ammonium hydroxide, decolorized with charcoal, filtered, and concentrated to the cloud point. The crystallized solid was filtered, washed with water, and dried over P_2O_5 at 100 °C to give 80 mg (72%) of **28**: mp >300 °C; MS *m/e* 220 (M^+), 177 ($M^+ - HCNO$); UV λ_{max} (ϵ_{max}) (pH 1) 245 nm (40 200), 290 (6700), 315 (5500), 326 (4200); (pH 7) 226 nm (24 500), 246 (24 000), 257 (24 100), 325 (6280); (pH 11) 245 nm (19 500), 340 (8900).

Anal. Calcd for $C_8H_8N_6O_2 \cdot 0.25H_2O$: C, 42.76; H, 3.81; N, 37.40. Found: C, 43.02; H, 3.85; N, 37.28.

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Registry No.—**2**, 932-52-5; **3**, 68409-23-4; **5**, 68409-24-5; **6**, 68409-25-6; **7**, 68409-26-7; **8**, 68409-27-8; **9**, 68409-28-9; **10**, 68409-29-0; **11**, 68409-30-3; **12**, 37538-67-3; **13**, 68409-31-4; **14**, 68409-32-5; **16**, 68409-33-6; **18**, 68409-34-7; **20**, 68409-35-8; **21**, 68409-36-9; **22**, 68409-37-0; **23**, 68409-38-1; **24**, 68409-39-2; **25**, 68409-40-5; **26**, 68409-41-6; **27**, 68409-42-7; **28**, 68409-43-8; dimethyl 2-(2,4-dimethoxypyrimidin-5-yl)aminofumarate, 68409-44-9; 5-amino-2,4-dimethoxypyrimidine, 14048-15-8; dimethyl acetylenedicarboxylate, 762-42-5; sodium methyl mercaptide, 5188-07-8; benzyl alcohol, 100-51-6; *p*-toluenethiol, 106-45-6; sodium benzyl oxide, 20194-18-7.

References and Notes

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