spectrum showed a parent peak at *m/e* 532 (calcd mol wt 532) and a base peak at *m/e* 266, corresponding to the monomeric unit of the dimer. The NMR spectra of this compound in $DCCl_3$ is shown in Figure 3.

Heating the "primary ester" for 10 min at 180 °C followed by recrystallization of the resulting material resulted in a 40% yield of 3.

1,1',2,2',6,6'-Hexamethyl-3,3',5,5'-tetracarboethoxy-1,1',-2,4'-tetrahydro-2,4'-bipyridine (2,4' Dimer 8). A Solution of the "primary ester" in methanol was allowed to cool slowly to room temperature. After a few days at room temperature, small amounts of crystalline material were formed. More rapid cooling or at temperatures below room temperature resulted in precipitation of the "primary ester" as a powder. The crystalline material (mp 176.5–177 °C) showed the same parent and base peaks in its mass spectrum as observed for the 4,4 dimer **3**. The NMR spectrum in $DCCl_3$ is shown in Figure 4.

Kinetic Measurements. Solutions (0.01 M) of the "primary ester" mixture in chlorobenzene were placed in a three-neck flask equipped with a large coil condenser. The remaining necks were stoppered and the flask immersed in an oil temperature bath. At appropriate time intervals, a 25-ml portion of the solution was removed and evaporated to dryness on a rotatory evaporator. The resulting residue was dissolved in about 5 ml of 1,1,2,2-tetrachloroethane. Four or five NMR sample tubes from each sample were removed from the reaction mixture.

The NMR analyses were obtained as soon as possible after the tetrachloroethane solutions of the reaction mixtures were prepared to avoid any reaction of the reactants or products of the rearrangement with the solvent. The NMR integrations of the *N*-methyl signals of **3** and **8** in the region of 3.0 ppm were obtained using the field sweep mode with a sweep width of 250 Hz and sweep times of 100 s per sweep. The signals were integrated 14–16 times, and, employing the methodology of Kassler,[13] the best 10–12 integrations used to determine the ratios of the 2,4' dimer **8** and the 4,4' dimer **3**. The extent of reaction of the 2,4' dimer **8** at each time interval was determined from the ratio obtained and from the initial amount of the "primary ester". The first-order rate constants and their standard deviations in Table II were calculated from least-squares treatment of the data obtained in this manner.

Registry No.—**1**, 59348-50-4; 1 perchlorate, 59348-51-5; **3**, 61024-92-8; **4**, 14258-07-2; **6**, 1149-23-1; **8**, 61024-93-9; 2,6-dimethyl-3,5-dicarboethoxypyridine, 1149-24-2; methyl sulfate, 77-78-1.

References and Notes

(1) This work was supported by a grant (GM AM 18191) from the Department of Health, Education and Welfare.
(2) (a) O. Mumm and W. Beth, *Ber.*, **54**, 1591 (1921); (b) O. Mumm and H. Ludwig, *ibid.*, **59**, 1605 (1926); (c) O. Mumm and J. Diedricksen, *Justus Liebigs Ann. Chem.*, **538**, 195 (1939).
(3) E. S. Huyser, J. A. K. Harmony, and F. L. McMillian, *J. Am. Chem. Soc.*, **94**, 3176 (1972).
(4) Cf. W. J. Blaedel and R. G. Haas, *Anal. Chem.*, **42**, 918 (1970); W. J. Blaedel and R. A. Jenkins, *ibid.*, **47**, 1337 (1975); R. D. Braun, K. S. V. Santhanam, and P. J. Elring, *J. Am. Chem. Soc.*, **97**, 259 (1975); J. Kuthan, V. Simonek, V. Volkovi, and J. Volke, *Z. Chem.*, **11**, 111 (1971).
(5) For discussion and other examples of nonequivalence of methylene protons arising from chirality introduced by restricted rotation see J. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Vol. 5, 2d ed, Pergamon Press, Oxford, 1969, pp 378–379.
(6) See A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2d ed, Wiley, New York, N.Y., 1961, pp 109–115.
(7) A. T. Nielser, D. W. Moore, J. H. Mazur, and K. H. Berry, Jr., *J. Org. Chem.*, **29**, 2898 (1964); P. M. Atlani, J. F. Biellman, and J. Moron, *Tetrahedron*, **29**, 391 (1973); P. Atlani, J. F. Bielman, R. Briere, and A. Rassat, *ibid.*, **28**, 5805 (1972); P. Atlani, J. F. Biellman, R. Briere, H. Lemaire, and A. Rassat, *Ind. Chim. Belg.*, **36**, 1066 (1971); P. Atlani, J. F. Biellman, R. Briere, J. Lemaire, and A. Rassat, *Tetrahedron*, **28**, 2827 (1972).
(8) A. Singer and S. M. McElvain, "Organic Syntheses", Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N.Y., 1943, p 214.
(9) B. Loev and K. M. Snader, *J. Org. Chem.*, **30**, 1914 (1965).
(10) P. R. Brook and P. Karrer, *Justus Liebigs Ann. Chem.*, **605**, 1 (1957).
(11) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1969, p 30.
(12) R. N. McDonald and C. E. Reineke, *Org. Synth.*, **50**, 50 (1970).
(13) F. Kasler "Quantitative Analysis by NMR Spectroscopy", Academic Press, New York, N.Y., 1973, p 79.

Pyridopyrimidines. 6. Nucleophilic Substitutions in the Pyrido[2,3-*d*]pyrimidine Series[1]

Gary L. Anderson, Jaewon L. Shim, and Arthur D. Broom*

Department of Biopharmaceutical Sciences, College of Pharmacy, University of Utah, Salt Lake City, Utah 84112

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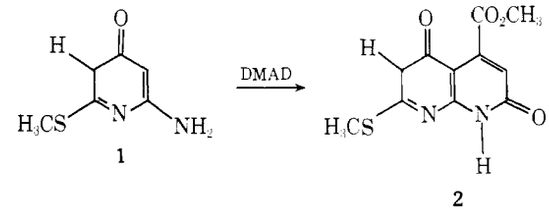
The scope of the reaction between 6-aminopyrimidines and dimethyl acetylenedicarboxylate to give 5-carbomethoxy-7-oxopyrido[2,3-*d*]pyrimidines was found to be limited primarily to 6-aminouracil derivatives. The preparation of a key synthetic intermediate, 2,4,7-trichloropyrido[2,3-*d*]pyrimidine, is reported. A study of nucleophilic displacement on this intermediate revealed that the reactivity was in the order 4 > 7 > 2 except in the case of aqueous sodium hydroxide, which gave 5-carboxy-7-chloro-2,4-dioxopyrido[2,3-*d*]pyrimidine. The observed selectivity enabled the preparation of a number of otherwise inaccessible pyridopyrimidines.

Unsubstituted 6-aminouracil and a variety of its *N*-alkyl derivatives have recently been found to react with dimethyl acetylenedicarboxylate (DMAD) in protic media (water or methanol) to give 5-carboxamido-7-oxopyrido[2,3-*d*]pyrimidines.[2,3] Our interest in pyrido[2,3-*d*]pyrimidines and nucleosides derived from them prompted us to continue the study of the utility of this reaction in providing candidate antitumor pyridopyrimidines. The present paper describes the synthesis of such heterocycles and their characterization; a companion paper[4] will describe the synthesis of ribonucleoside analogues from these bases.

It has been firmly established[2,3] that the reaction of DMAD with 6-aminouracils gave the 7-oxo rather than the 5-oxopyridopyrimidine isomer and the probable mechanism of this reaction has been described.[2] Since the procedure is a very



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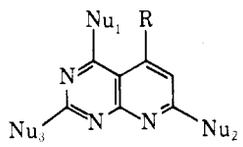
simple one, it was of interest to assess the scope of the reaction with a variety of pyrimidines. It was found that 6-amino-2-methylthio-4-oxopyrimidine (**1**) could be converted to 5-carbomethoxy-4,7-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (**2**) in low yield. Of a number of other 6-aminopyrimidines studied, including 4,6-diamino-2-methylthio-, 4,6-diamino-2-oxo-, 4-amino-6-methylthio-2-oxo-, and 2,4-diamino-6-

oxopyrimidines, none gave isolable amounts of pyrido[2,3-*d*]pyrimidine products in the complex reaction mixtures. Thus the reaction of 6-aminouracils appears to be rather unique in forming pyrido[2,3-*d*]pyrimidines with DMAD in significant yield, probably because the relative isolation of the C-5, C-6 double bond enhances the reactivity of C-5 toward electrophilic attack.

In view of the limited scope of the reaction of DMAD with 6-aminopyrimidines, an alternative procedure for obtaining pyrido[2,3-*d*]pyrimidines of potential biological interest was sought. The selective displacement of the 4-chloro group in 2,4-dichloropyrido[2,3-*d*]pyrimidine as demonstrated by Robins and Hitchings[5] suggested that conversion of 5-carbomethoxy 2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**3**) to the trichloropyrido[2,3-*d*]pyrimidine (**4**) would give a compound which might be expected to undergo nucleophilic displacement of the chloro groups in the order of reactivity of 4 > 7 > 2.[6] If indeed this reactivity order were observed, the synthesis of the desired pyrido[2,3-*d*]pyrimidines would be as outlined in Scheme I. If selective displacement of the chloro groups of **4** were possible, the synthesis of pyrido[2,3-*d*]pyrimidines of general structure **5** can be envisioned by reaction with different nucleophiles in the order of Nu_1, Nu_2, and Nu_3.



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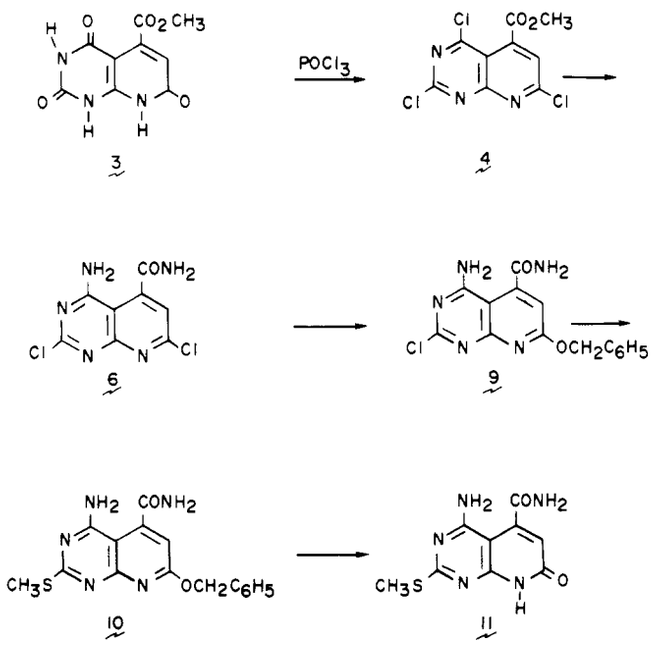
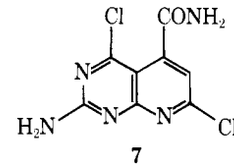
When **3** was refluxed in phosphorus oxychloride no reaction occurred, which contrasts with the ease of chlorodehydroxylation of 2,4-dioxopyrido[2,3-*d*]pyrimidine to give 2,4-dichloropyrido[2,3-*d*]pyrimidine.[5] When *N,N*-diethylaniline was added to the reaction mixture, an excellent yield was obtained of a single compound. This was determined to be structure **4** on the basis of elemental analysis, ^{1}H NMR, and mass spectrometry. The presence of three chlorine atoms was

Scheme I



confirmed by the appearance of peaks at *m/e* 291, 293, and 295 in the ratio of 3:3:1 for M^+, due to the isotope abundance of chlorine. Peaks were also present for the loss of $-OCH_3$ (M − 31) and $-CO_2CH_3$ (M − 59) which confirmed that the ester was present. ^{1}H NMR spectroscopy confirmed the presence of an *O*-methyl group and a single aromatic proton resonating at δ 4.05 and 7.58, respectively.

The reaction of **4** with methanolic ammonia at room temperature for 24 h gave a single new compound, which was tentatively assigned structure **6**. The ^{1}H NMR spectrum of **6** showed the loss of the signal due to the *O*-methyl of **4**, which was replaced by a broad two-proton doublet at δ 8.53 and 8.73 corresponding to one proton each for the amide protons. These signals disappeared on addition of D_2O. The mass spectrum revealed the presence of two chlorines as well as a loss of 17 mass units from the molecular ion of 257 corresponding to loss of NH_3. However, it was not possible to unequivocally eliminate the alternate structures, **7** and **8**.



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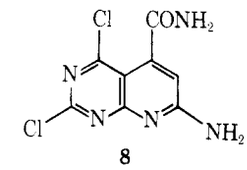

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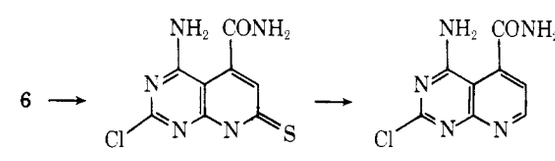
Nucleophilic displacement of the 7-chloro group of **6** was achieved by reaction with sodium benzylate in dimethyl sulfoxide. A signal centered at δ 7.45 which represents the phenyl ring and a singlet at δ 5.50 for the methylene group appeared in the ^{1}H NMR spectrum of **9**. Mass spectral data confirmed that one chlorine remained on the product. The final chlorine was displaced with sodium methylmercaptide in dimethyl sulfoxide to give compound **10**. The benzyloxy group of **10** was easily converted to the oxo group by reaction with 48% HBr to give compound **11**.

It was necessary to eliminate the other five isomers which would be obtained if the order of nucleophilic displacement were not in the sequence 4, 7, and 2. The unequivocal determination that the isomer was indeed **11** was made by performing two sets of reactions. The first set showed that, after amination, the second reaction occurred in the 7 position. This indicated that initial amination was in the pyrimidine ring, either the 2 or 4 position. The second set of reactions confirmed that the final nucleophilic displacement with methylmercaptide occurred at the 2 position. Thus the initial amination had occurred only at the 4 position, followed by substitution at the 7 position with sodium benzylate and finally at the 2 position to give ultimately **10**.

The replacement of the 7 substituent in these pyrido[2,3-*d*]pyrimidines with a hydrogen would give rise to a pair of doublets in the ^{1}H NMR spectrum for the 6 and 7 protons. The same displacement at the 2 or 4 position would give rise to a new singlet in addition to the singlet for C-6 H. The conversion of **6** into the pyrido[2,3-*d*]pyrimidine-7-thione **12** was

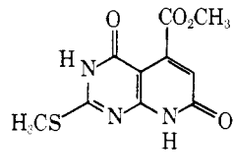


12 **13**

accomplished with sodium hydrosulfide in DMF. The use of 1 equiv of sodium hydrosulfide, when added slowly, allowed selective displacement of only the 7-chloro group. Confirmation was achieved by mass spectrometry which again showed the isotope effect of the single chloride present; peaks at *m/e* 255 and 257 in ratio of 3:1 were in complete accord with the proposed empirical formula. The shift in the long wavelength absorption band in the ultraviolet spectrum of **12** to 385 nm as compared with 314 nm of **6** was supportive of a 7-thione substitution.[7] Unequivocal evidence for the position of the thione group was provided by the conversion of **12** to

13 with Raney nickel. That the product of this reaction was 13 was determined by ^{1}H NMR and mass spectrometry as well as elemental analysis. The ^{1}H NMR spectrum of 13 showed two doublets at δ 7.53 and 9.03 with a $J_{6,7}$ = 4.8 Hz, as well as D_2O exchangeable signals at δ 8.45 (two protons), 8.48 (one proton), and 8.70 (one proton) for the amino group and amide group. The mass spectrum again contained the isotope effect of the chlorine on the molecular ion. These results clearly demonstrated that the initial nucleophilic attack with ammonia occurred in the pyrimidine ring. However, it was not possible to determine from these results if this displacement was at the 4 or 2 position of the pyrido[2,3-*d*]pyrimidine ring.

The final displacement was shown to be at the 2 position by conversion of 11 to 14. When 11 was treated with sodium



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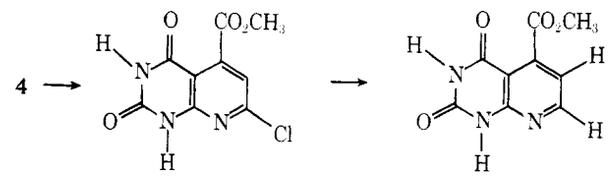
nitrite in dilute sulfuric acid, diazotization and subsequent hydrolysis of the 4-amino group occurred to give a mixture of two compounds as judged by thin layer chromatography. This mixture was hydrolyzed in aqueous sodium hydroxide to give 4,7-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine-6-carboxylic acid (14). The mass spectrum of 14 supported the structural assignment with the molecular ion at 253. A peak at M − 44 (209 amu) corresponding to loss of CO_2 further supported the presence of the carboxylic acid group. The ^{1}H NMR spectrum contained signal for C_6H and the methylthio at δ 6.95 and 2.47, respectively. Confirmation of the structure lay in the preparation of 14 by the basic hydrolysis of the ester 2. The product of this hydrolysis proved to be identical by TLC, UV, ^{1}H NMR, and mass spectrometry with 14 obtained from compound 11. Since the reaction of 1 with DMAD could only yield a pyrido[2,3-*d*]pyrimidine (2) with the methylthio group at position 2, compound 11 must have the methylthio group also at position 2. In addition, these reactions also confirmed that the product (2) of DMAD and 1 was the 7-oxo- and not the alternate 5-oxopyrido[2,3-*d*]pyrimidine. These results unequivocally established that the order of substitution with ammonia, sodium benzylate, and sodium mercaptide occurred at the 4, 7, and 2 positions, respectively, of the trichloropyrido[2,3-*d*]pyrimidine (4).

The ^{1}H NMR spectra of the above compounds which contain both the 4-amino and 5-carboxamido groups (6, 9, 10, 11, 12, 13) revealed an interesting pattern for the signals associated with these groups. In each case two broad singlets representing one proton each and one broad singlet representing two protons were present. These can be assigned tentatively to the carboxamide and amino group, respectively, by the following observations. The signals attributed to the carboxamido protons underwent collapse at ~85 °C to give a broad singlet. This observation was similar to that of acetamide and resulted from the slow rotation about the C–N bond in planar amides.[8] The signals of the amino group appeared as a broad singlet, because of rapid rotation on the ^{1}H NMR time scale. The signal attributed to the amino group varied considerably as substituents were changed at the 2 and 7 positions, whereas the signal attributed to the carboxamido group remained virtually constant. It would be expected that the group directly attached to the pyrido[2,3-*d*]pyrimidine ring system would be shifted by a change in the substituents on the ring.[8]

When 4 was reacted with hydroxide ion at room temperature a different pattern of displacement occurred. With 1.5 equiv of hydroxide ion, 4 gave a single compound in less than 50% yield. The mass spectrum of the product showed a molecular ion at 255 amu and the M + 2 peak indicated that only one chlorine remained, establishing that the product was a dioxopyrido[2,3-*d*]pyrimidine. This product was subjected to catalytic hydrogenolysis to give a compound which was established as 16 by virtue of the presence of a pair of doublets ($J_{6,7}$ = 4.8 Hz) in the ^{1}H NMR spectrum. Thus, dehalogenation had occurred from the 7 position of the ring, which confirms that the dioxopyrido[2,3-*d*]pyrimidine obtained from 4 was 15 and not 17.



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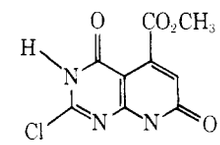

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This study has established the order of reactivity of nucleophilic attack for substituents in positions 2, 4, and 7 of the pyrido[2,3-*d*]pyrimidine ring system. Through the intermediacy of the key intermediate 4 a very wide variety of hitherto unavailable pyridopyrimidine derivatives may be readily prepared.

Experimental Section

The ^{1}H NMR spectra were recorded on a Jeol C-60H spectrometer with tetramethylsilane or DSS as an internal standard. Chemical shifts are expressed as δ, parts per million, from the standard. Ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer. Mass spectra were recorded on a LKB-GCMS Model 9000S, at 70 keV. Only the molecular ion and first major fragments are reported. Elemental analyses were performed by Het-Chem-Co, Harrisonville, Mo. Melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. All analytical samples were dried in the presence of P_2O_5 in vacuo.

Thin layer chromatography was performed on 5 × 20 cm plates of Mallinckrodt SilicAR TLC-7GF (250-nm thickness). Solvent systems employed were (1) $CHCl_3$–MeOH (19:1), (2) EtOAc–*n*-PrOH–H_2O (4:1:2, upper layer), and (3) 1,2-dimethoxyethane–MeOH–NH_4OH (12:1:1).

5-Carbomethoxy-4,7-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (2). To a solution of 4-amino-2-methylthio-6-oxopyrimidine (1, 0.80 g, 5.1 mmol) in water (25 ml) was added DMAD (0.90 g, 6.3 mmol). The solution was heated at reflux for 2 h, then cooled to room temperature. The precipitate was filtered and washed with methanol to give 50 mg of 2. An additional 84 mg was obtained after refrigeration of the filtrate: yield 134 mg (10%); mp 313 °C dec; UV (pH 1) 292 nm (ϵ 10 800), 325 (16 000); (pH 7) 256 (12 400), 330 (15 800); (pH 11) 331 (14 400); ^{1}H NMR δ 2.53 (s, 3 H, SCH_3), 3.73 (s, 3 H, OCH_3), 6.13 (s, 1 H, C-6 H), 12.57 (br s, 1 H, N-8 H).

Anal. Calcd for $C_{10}H_9N_3O_4S$: C, 44.9; H, 3.37; N, 15.7. Found: C, 44.6; H, 3.67; N, 15.4.

5-Carbomethoxy-2,4,7-trichloropyrido[2,3-*d*]pyrimidine (4). Compound 3[2] (8.0 g, 33.8 mmol) was refluxed in $POCl_3$ (125 ml) containing *N*,*N*-diethylaniline (8.0 ml) for 10 h. The volume was reduced to approximately 25 ml by distillation at reduced pressure. The black syrup was poured onto excess ice and stirred vigorously by hand for 15 min. The iced water suspension was extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were extracted four times with cold 1 N HCl (250 ml), then dried over Na_2SO_4 and filtered through charcoal. Evaporation gave 6.7 g (68%) of red powder, which was dissolved in hot CH_2Cl_2 (50 ml). Petroleum ether (bp 90–120 °C) was added slowly to cloud point. Cooling gave white needles of pure 4 (4.96 g, 53%): mp 109–110 °C; MS *m/e* 291 (M^+), 260 (M − OCH_3), 256 (M − Cl), 232

(M − CO_2CH_3); UV (MeOH) 313 nm (ε 10 500); ^{1}H NMR δ 4.05 (s, 3 H, OCH_3), 7.58 (s, 1 H, C-6 H).

Anal. Calcd for $C_9H_4N_3O_2Cl_3$: C, 36.95; H, 1.38; N, 14.37. Found: C, 36.65; H, 1.32; N, 14.17.

4-Amino-5-carboxamido-2,7-dichloropyrido[2,3-*d*]pyrimidine (6). Compound **4** (300 mg, 1.0 mmol) was treated with methanolic ammonia (25 ml), saturated at 0 °C, for 24 h at room temperature. The white solid was filtered and washed with MeOH to give 219 mg (83%) of **6:** mp >310 °C; MS *m/e* 257 (M^+), 240 (M − NH_3), 205 (M − NH_3 − Cl); UV (pH 1) 314 nm (ε 8200); (pH 7) 314 (8700); (pH 11) 333 (8200); ^{1}H NMR δ 8.53 (br s, 2 H, 4-NH_2), 8.53, 8.73 (br s, 2 H, $CONH_2$), 7.58 (s, 1 H, C-6 H).

Anal. Calcd for $C_8H_5N_5OCl_2$: C, 37.32; H, 1.95; N, 27.14. Found: C, 37.11; H, 1.91; N, 26.94.

For large-scale reactions, it was found that the following procedure gave high yields. Compound **3** (12 g) was refluxed for 12 h in $POCl_3$ (125 ml) containing *N,N*-diethylaniline (12 ml). Excess $POCl_3$ was removed and the syrup poured into ice (1 kg). Extraction with CH_2Cl_2 followed by extraction with 1 N HCl was as before. Drying the CH_2Cl_2 extract with Na_2SO_4 followed by evaporation afforded crude **4.** Treatment of this solid with methanolic ammonia for 12 h and filtration of the solid gave 9.9 g (76% overall yield) of **6,** identical by TLC, UV, and ^{1}H NMR with **6** obtained directly from **4.**

4-Amino-7-benzyloxy-5-carboxamido-2-chloropyrido[2,3-*d*]pyrimidine (9). Compound **6** (7.74 g, 30 mmol) was suspended in Me_2SO (60 ml). Benzyl alcohol (35 ml), in which Na (1.04 g, 45 mmol) was previously dissolved, was added dropwise over 2 h. After another 2 h, the yellow solution was poured into H_2O (300 ml) and the solid filtered. Recrystallization from DMF–H_2O gave 7.9 g (76%) of **9:** mp 225 °C dec; MS *m/e* 329 (M^+), 223 (M − C_6H_5CHO); UV (pH 1) 320 nm (ε 15 300); (pH 7) 318 (8700); (pH 11) 318 (9200); ^{1}H NMR δ 8.20 (br s, 2 H, NH_2), 8.43, 8.70 (br s, 2 H, $CONH_2$), 7.05 (s, 6 H, C-7 H + C_6H_5).

Anal. Calcd for $C_{15}H_{12}N_5O_2Cl·H_2O$: C, 51.76; H, 4.02; N, 20.14. Found: C, 51.97; H, 4.19; N, 19.83.

4-Amino-7-benzyloxy-5-carboxamido-2-methylthiopyrido-[2,3-*d*]pyrimidine (10). To a solution of CH_3SNa in Me_2SO, prepared by adding CH_3SH to Me_2SO (15 ml) containing Na (140 mg, 6.1 mmol), was added **9** (1.0 g, 2.9 mmol). After stirring at room temperature for 90 min, the yellow solution was cautiously poured into H_2O (100 ml). The yellow precipitate was filtered to give 820 mg (79%) of **10.** Recrystallization from DMF–H_2O afforded 709 mg (68%): mp 264–266 °C dec; MS *m/e* 341 (M^+), 323 (M − NH_3), 235 (M − $OCHC_6H_5$); UV (pH 1) 261 nm (ε 25 400), 332 (19 200); (pH 7) 262 (30 300), 330 (13 600); (pH 11) 260 (31 500), 330 (13 000); ^{1}H NMR δ 2.53 (s, 3 H, SCH_3), 7.70 (br s, 2 H, NH_2), 8.33, 8.62 (br s, 2 H, $CONH_2$), 6.87 (s, 1 H, C-6H), 7.43 (s, 5 H, C_6H_5), 5.47 (s, 2 H, $-CH_2-$).

Anal. Calcd for $C_{16}H_{15}N_5O_2S·H_2O$: C, 53.47; H, 4.79; N, 19.49. Found: C, 53.22; H, 5.00; N, 19.89.

4-Amino-5-carboxamido-2-methylthio-7-oxopyrido[2,3-*d*]-pyrimidine (11). Compound **10** (1.7 g, 4.7 mmol) was stirred with 48% HBr (15 ml) for 3 min. The solution was adjusted to pH 3 with 1 N NaOH and the solid filtered. The solid was dissolved in hot DMF followed by addition of H_2O to cloud point. Filtration afforded 620 mg (52%) of **11:** mp >320 °C; MS *m/e* 251 (M^+), 234 (M − NH_3); UV (pH 1) 325 nm (ε 16 200); (pH 7) 263 (20 900), 330 (15 900); (pH 11) 335 (13 700); ^{1}H NMR δ 2.50 (s, 3 H, SCH_3), 7.45 (br s, 2 H, NH_2), 8.27, 8.57 (br s, 2 H, $CONH_2$), 6.27 (s, 1 H, C-6 H), 12.03 (br s, 1 H, N-8 H).

Anal. Calcd for $C_9H_9N_5O_2S$: C, 43.02; H, 3.61; N, 27.87. Found: C, 43.08; H, 3.93; N, 28.00.

4-Amino-5-carboxamido-2-chloro-7-thioxopyrido[2,3-*d*]pyrimidine (12). Compound **6** (1.59 g, 6.1 mmol) was dissolved in DMF (50 ml) by warming. To this solution was added NaSH (450 mg) in portions until all starting material had reacted (TLC). The solvent was removed in vacuo, and the solid triturated with MeOH (200 ml)–H_2O (50 ml). Filtration afforded 1.21 g (77%) of **12.** Recrystallization was carried out by dissolving in warm DMF and adding H_2O to cloud point. Cooling to room temperature gave 875 mg (56%) of **12** as yellow crystals: mp >220 °C (dec slowly); MS *m/e* 255 (M^+), 238 (M − NH_3); UV (pH 1) 266 nm (ε 12 500), 294 (9300), 385 (15 900); (pH 7) 270 (16 000), 373 (14 000); (pH 11) 272 (19 300), 368 (14 700); ^{1}H NMR δ 8.16 (br s, 2 H, NH_2), 8.33, 8.73 (br s, 2 H, $CONH_2$), 7.08 (s, 1 H, C-6H), 13.75 (br s, 1 H, N-8 H).

Anal. Calcd for $C_8H_6N_5OSCl$: C, 37.58; H, 2.37; N, 27.39. Found: C, 37.81; H, 2.47; N, 27.43.

4-Amino-5-carboxamido-2-chloropyrido[2,3-*d*]pyrimidine (13). Compound **12** (400 mg, 1.57 mmol) was dissolved in DMF (50 ml) and EtOH (10 ml). Raney nickel (2.5 g) was added, the mixture refluxed for 1 h and filtered through Celite, and the filtrate evaporated in vacuo. The solid was dissolved in hot DMF, water added to cloud point, and cooled. Filtration gave 196 mg (57%) of **13** as yellow crystals: mp >210 °C (dec slowly); MS *m/e* 223 (M^+), 206 (M − NH_3), 171 (M − NH_3 − Cl); UV (pH 1) 326 nm (ε 6 500); (pH 7) 326 (6400); (pH 11) 326 (6300); ^{1}H NMR δ 8.45 (br s, 2 H, NH_2), 8.48, 8.70 (br s, 2 H, $CONH_2$), 7.53 (d, 1 H, C-6 H), 9.03 (d, 1 H, C-7 H, $J_{6,7}$ = 4.8 Hz).

Anal. Calcd for $C_8H_6N_5OCl$: C, 42.97; H, 2.70; N, 31.32. Found: C, 43.09; H, 2.98; N, 31.12.

4,7-Dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine-5-carboxylic Acid (14). Method A. To a solution of $NaNO_2$ in H_2O (12 ml)–H_2SO_4 (4 ml) was added **11** (251 mg, 1.0 mmol). After stirring for 4 h, the yellow precipitate was filtered. TLC showed two products. The solid was refluxed in 1 N NaOH (10 ml) for 1 h. After cooling, the pH was adjusted to ~3 with HCl. The white precipitate was filtered to give 169 mg (58%) of **14:** mp >320 °C (slowly dec >275 °C); MS: *m/e* 253 (M^+), 209 (M − CO); UV (pH 1) 292 nm (ε 10 500), 326 (15 600); (pH 7) 291 (9 000), 324 (15 900); (pH 11) 255 (16 000), 327 (16 300); ^{1}H NMR δ 2.47 (s, 3 H, SCH_3), 6.95 (s, 1 H, C-6 H).

Anal. Calcd for $C_9H_7N_3O_4S·2H_2O$: C, 37.37; H, 3.87; N, 14.52. Found: C, 36.99; H, 3.69; N, 14.48.

Method B. Compound **2** (300 mg, 1.1 mmol) was refluxed in 1 N NaOH (10 ml) for 30 min. After cooling, the pH was adjusted to ~3 with HCl. The white precipitate was filtered to give 223 mg (69%) of **14.** One recrystallization from H_2O gave a sample which was identical by TLC, UV, mass spectrum, and ^{1}H NMR with **14** obtained by method A.

5-Carbomethoxy-7-chloro-2,4-dioxopyrido[2,3-*d*]pyrimidine (15). To **4** (585 mg, 2.0 mmol), dissolved in MeOH (50 ml), was added 1 N NaOH (3 ml, 3 mmol). The solution was stirred for 2 h at 30 °C. Evaporation to about 5 ml followed by addition of H_2O (20 ml) gave a white precipitate. This was filtered to give 248 mg (49%) of **15:** mp 310–313 °C dec; MS *m/e* 255 (M^+), 224 (M − OCH_3), 197 (M − OCH_3 − HCNO); uv (pH 1) 311 nm (ε 6700); (pH 7) 312 (6500); (pH 11) 268 (10 500), 323 (4700); ^{1}H NMR δ 3.87 (s, 3 H, OCH_3), 7.42 (s, 1 H, C-6 H).

Anal. Calcd for $C_9H_6N_3O_4Cl$: C, 42.29; H, 2.37; N, 16.44. Found: C, 41.98; H, 2.58; N, 16.34.

5-Carbomethoxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (16). Compound **15** (155 mg, 0.61 mmol), NaOAc (92 mg), and 10% Pd/C (100 mg) were placed in a hydrogenator in MeOH (100 ml) and shaken over H_2 (42 psi) for 60 h. The mixture was filtered through Celite and washed with MeOH. The filtrate was evaporated to dryness and triturated with H_2O. Filtration of the solid gave 89 mg (67%) of **16.** For analysis 50 mg was recrystallized from MeOH–H_2O to give 37 mg: mp 265 °C dec; UV (pH 1) 315 nm (9 600); (pH 7) 3.6 (8700); (pH 11) 273 (14 400), 340 (6300); ^{1}H NMR δ 3.88 (s, 3 H, OCH_3), 7.25 (d, 1 H, C-6H), 8.70 (d, 1 H, C-7H), 8.70 (d, 1 H, C-7 H, $J_{6,7}$ = 4.8 Hz).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.88; H, 3.19; N, 19.00. Found: C, 48.68; H, 3.38; N, 18.64.

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References and Notes

(1) Part 5 in this series: A. D. Broom and D. G. Bartholomew, *J. Org. Chem.*, **41,** 3027 (1976).
(2) A. D. Broom, J. L. Shim, and G. L. Anderson, *J. Org. Chem.*, **41,** 1095 (1976).
(3) H. Orgura and M. Sakaguchi, *Chem. Pharm. Bull.*, **21,** 2014 (1973).
(4) G. L. Anderson and A. D. Broom, *J. Org. Chem.*, following paper in this issue.
(5) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **77,** 2256 (1955).
(6) R. G. Shepherd and J. L. Fedrick, *Adv. Heterocycl. Chem.*, **4,** 146 (1964).
(7) B. S. Hurlbert, K. W. Ledig, P. Stenbuck, B. F. Valenti, and G. H. Hitchings, *J. Med. Chem.*, **11,** 703 (1968).
(8) L. M. Jackman and S. Sternhill, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p 361.
(9) T. Tsuji, S. Watanabe, Y. Nakadai, and S. Toyoshima, *Chem. Pharm. Bull.*, **10,** 9 (1962).