was not possible since only data of poor precision were obtained at 0.003 M.

The solutions were prepared from pure 1,1-pentamethylene (A) and 1,1-diethyl-3-hydroxyazetidinium chlorides (B), 1-di-*n*-butylamino-3-chloro-2-propanol (C), and 3-chloro-1-piperidyl- (D), 3-chloro-1-diethylamino- (E), and 3-chloro-1-di-*n*-butylamino-2-propyl acetates (F) for final measurements. Typical parallel runs are described to illustrate the procedure.

1,1-Pentamethylene-3-hydroxyazetidinium chloride (**1c**, at least two independently purified samples) was weighed into calibrated volumetric flasks (50 or 250 ml). Reagent acetonitrile (Fisher Sci. Co.) which had been distilled from phosphorus pentoxide was added. The tightly stoppered flasks were placed in the 40.00 ± 0.01° bath. At the elapsed times listed, aliquots (5 or 25 ml) were analyzed by titration with 0.104 M silver perchlorate in acetonitrile by potentiometric titration using the silver–glass electrodes. The reagent was standardized against reagent lithium chloride with addition of a drop of triethylamine; the LiCl dissolved slowly. (Pure azetidinium chlorides were convenient soluble standards.) From the chloride remaining in solution the corrected molarities of each component and the cyclization constants were calculated. The times for establishment of equilibrium at each temperature were found by one or more checks at each temperature. In the following runs only the 40° point was confirmed initially because earlier runs had shown that this system equilibrated within the allowed times.

TABLE V

TYPICAL EQUILIBRATION RUNS

Time, days	Temp, °C	K_{cyc} Run 1[a]	K_{cyc} Run 2[b]	K_{cyc} Av	K_{cyc} Av dev
0.8	40.00	0.1272	0.1308	0.1303	0.0019
			0.1335		
1.0	40.00 (to 35)		0.1322		
2.1	35.00 (to 30)	0.1578	0.1529	0.1554	0.0025
3.8	30.00 (to 40)	0.1819	0.1756	0.1788	0.0032
4.8	40.00	0.1298	0.1282	(above)	

[a] Conditions were 0.2406 g of **1c** and c_i = 0.02709 M. [b] Reaction conditions were 0.2373 g of **1c** and c_i = 0.02672.

In other cases, notably systems E and F, equilibration at 30° required up to 3 days. A number of runs at low concentrations gave erratically higher values of K_{cyc}'s and, in these cases, the final 40° value was always higher than the initial 40° value and usually drifted even higher. Apparently traces of moisture caused hydrolysis or catalyzed minor (bimolecular?) side reactions, resulting in high chloride concentrations. This effect was finally controlled by suspending the flasks by the necks in rubber stoppers fitted in holes drilled in a rigid, plastic bath cover. Confirmation of the 40° values after several days at 30 and 35° established the reversibility of the actual reaction mixtures for which values are reported.

Registry No.—1C, 15314-02-0; 1D, 15285-53-7; 1F, 15285-55-9; **1a**, 15314-03-1; **1a** acetate, 15285-56-0; **1b**, 15285-57-1; **1c**, 15285-58-2; **2a**, 15285-59-3; **2a** acetate, 15285-60-6; **2** (R = *n*-Bu), 15285-61-7; **2** (R = *n*-Bu), acetate, 15285-62-8; **2c**, 15285-63-9; **2c** acetate, 15285-64-0; 1,3-bis(diethylamino)-2-propanol, 3492-47-5; (3-diethylamino-2-hydroxy-1-propyl)trimethylammonium chloride, 15285-65-1; N-(3-diethylamino-2-hydroxy-1-propyl)-N-methylaniline, 15288-04-7; N-(3-diethylamino-2-hydroxy-1-propyl)-N-methylaniline acetate, 15288-05-8; 3-*t*-butylmercapto-1-diethylamino-2-propanol, 15288-06-9; 4-diethylamino-3-hydroxybutyronitrile, 15288-07-0; 1-diethylamino-3-phenoxy-2-propanol, 15288-08-1; 1-diethylamino-3-methoxy-2-propanol, 3141-80-8; **3** (R = Et), 15288-10-5; 1-*t*-butylmercapto-3-piperidyl-2-propanol, 15288-11-6.

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The Preparation of 9-Amino-9H-purines. II. 9-Amino-6-chloro-9H-purin-8(7H)-one[1,2]

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Reaction of benzyl 3-(5-amino-4-chloro-6-pyrimidinyl)carbazate (**11**) and 5-amino-4-chloro-6-[2-(diphenylmethyl)hydrazino]pyrimidine (**12**), respectively, with the phosgene–pyridine complex gave benzyl 6-chloro-7,8-dihydro-8-oxo-9H-purine-9-carbamate (**7**) and 6-chloro-9-(diphenylmethyl)amino-9H-purin-8(7H)-one (**8**). The blocking groups of **7** and **8** were removed with HBr in AcOH to give 9-acetamido-6-bromo-9H-purin-8(7H)-one (**1**) rather than 9-amino-6-chloro-9H-purin-8(7H)-one (**6**). Treatment of **8** with concentrated HCl, however, gave **6**. Previously, **6** was reported to result from the interaction of 5-amino-4-chloro-6-hydrazinopyrimidine (**9**) with phosgene. The product of this reaction is now identified as 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidin-3(2H)-one (**13**), which is rearranged in ethanolic HCl to 8-amino-7-chloro-*s*-triazolo[1,5-*c*]pyrimidin-2(3H)-one (**15**).

The cyclization of 5-amino-4-chloro-6-hydrazinopyrimidine (**9**) has been shown to give 9-aminohypoxanthine with HCO_2H,[2] 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine with ethyl orthoformate–concentrated HCl,[3] and 8-amino-7-chloro-*s*-triazolo[4,3-*c*]-pyrimidine with diethoxymethyl acetate.[4] The interaction of **9** with phosgene was reported to give 9-amino-6-chloro-9H-purin-8(7H)-one (**6**), which was rearranged in ethanolic HCl to give an isomeric compound tentatively identified as 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazin-3(4H)-one (**3**).[5] In this paper we wish to report the unambiguous synthesis of **6** and to identify the product from the reaction of **9** and phosgene as 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidin-3(2H)-one (**13**), which under acidic conditions was rearranged to the isomeric 8-amino-7-chloro-*s*-triazolo[1,5-*c*]pyrimidin-2(3H)-one (**15**). The physical properties and chemical reactions of **13** and **15** are consistent with the assigned structures.

(1) This investigation was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

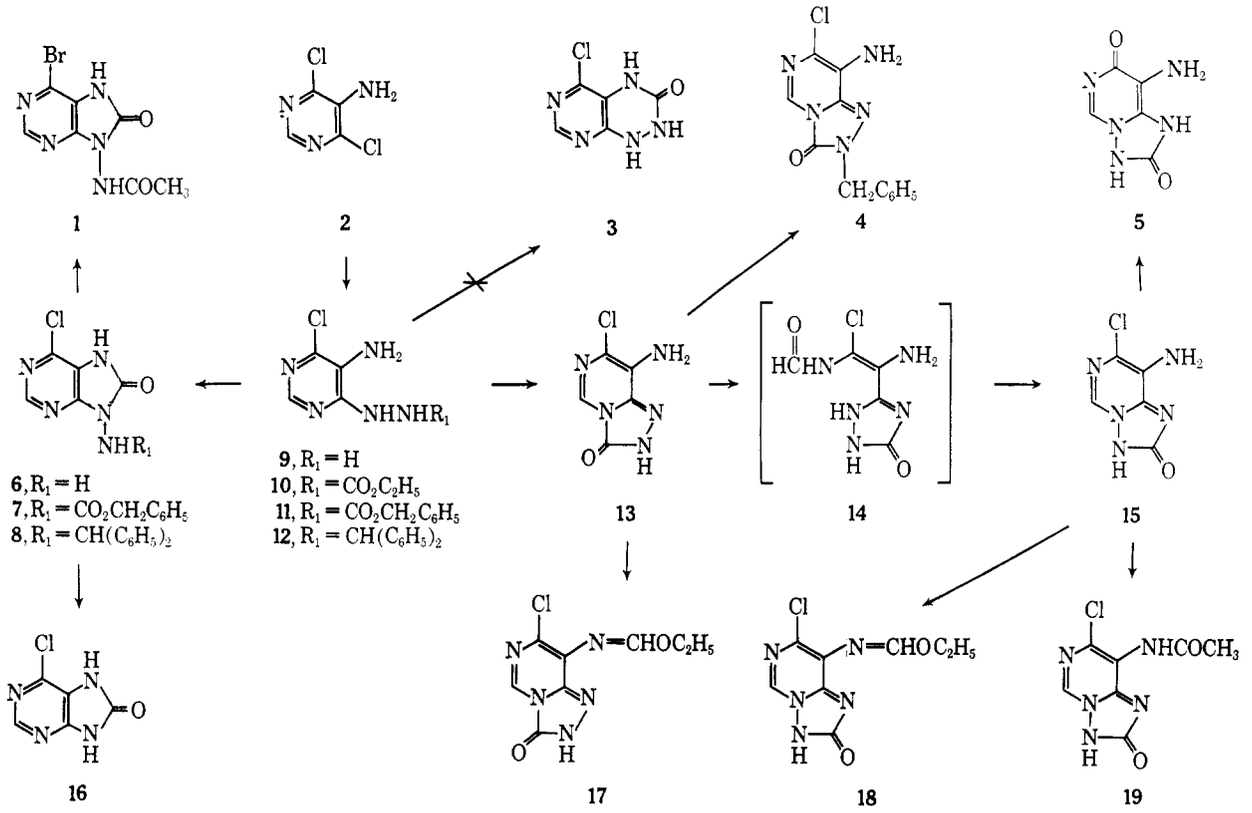
(2) For the first paper in this series, see J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **82**, 4592 (1960).

(3) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **28**, 923 (1963).

(4) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *ibid.*, **28**, 2257 (1963).

(5) M. H. Krackov and B. E. Christensen, *ibid.*, **28**, 2677 (1963).

SCHEME I



The ultraviolet spectrum[5] of the product obtained by the action of phosgene on **9** was practically identical with that previously reported for **13**, prepared by treatment of **10** with aqueous $NaHCO_3$.[4] In the latter reaction the structure assignment was based in part on the similarity of the ultraviolet spectrum with that of 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidine[4] and the dissimilarity with that of 6-chloropurin-8(7H)-one (**16**).[5,6] The solid-state (KBr disk) infrared spectrum of this product, depending upon the method of isolation, exhibited one, two, or three carbonyl bands in the 1750–1700-cm^{-1} region of the spectrum (see Experimental Section). The infrared spectrum of a DMSO solution, however, showed only one band in this region, suggesting that the multiple bands in the solid-state spectra were due to crystal orientation effects[7] rather than to a combination of amide absorption and ring-stretching vibrations as previously proposed.[5] The proton magnetic resonance (pmr) spectrum of this product in DMSO-d_6 showed three bands, which could be assigned to the NH_2, CH, and NH, respectively, of either **6** or **13**. Unequivocal proof that this product is **13** and not **6** was provided by the synthesis of **6**.

The route used for the preparation of **6** involved the substitution of a suitable blocking group on the 2-nitrogen of the hydrazino group of **9**, cyclization of this pyrimidine with phosgene to give a 9-substituted amino-9H-purin-8(7H)-one, and removal of the blocking group with acid. Previously the use of the *p*-nitrobenzylidene moiety as a blocking group in a similar sequence of reactions was unsuccessful.[8] Initially, we investigated the use of the carbobenzoxy group. Reaction of **9** with benzyl chloroformate gave **11**, which was cyclized with the phosgene–pyridine complex in dioxane to give **7**. Treatment of **7** with 30% HBr in AcOH at room temperature cleaved the carbamate group, but during the reaction the resulting amino group was acetylated and the chloro group was exchanged for a bromo group to give **1** (Scheme I). This structure was indicated by elemental analyses and by the ultraviolet, infrared, and pmr spectra. The successful preparation of **6** involved the reaction of **2** with diphenylmethylhydrazine (benzhydrylhydrazine)[9] to give **12**. That substitution had occurred on the primary rather than the secondary nitrogen of the hydrazine was confirmed by the pmr spectrum of **12** in DMSO-d_6, which showed spin–spin coupling in the –NH–NHCH part of the hydrazino moiety. Reaction of **12** with the phosgene–pyridine complex in dioxane gave **8**. As with **7**, reaction of **8** with 30% HBr in AcOH gave **1**. Treatment of **8** with concentrated HCl at room temperature, however, removed the diphenylmethyl group to give the desired 9-amino-9H-purine **6**. The structure of **6** was confirmed by (1) elemental analyses, (2) pmr spectrum, (3) deamination with HNO_2 to give **16**,[2] and (4) comparison of the ultraviolet spectra of **6** with that of **13** and **16**.[4,5]

The previously reported reaction of **13** with diethoxymethyl acetate was repeated to give **17**.[4] Treatment of the latter with 0.1 *N* hydrochloric acid again gave **13**, which indicated that rearrangement to **18** had not occurred (*vide infra*) during the formation of **17**. Alkylation of **13** with $C_6H_5CH_2Cl$ in DMF containing K_2CO_3 gave **4**, identified by elemental analyses and

(6) Structure **3** was eliminated from consideration as the product of these reactions by comparison of the ultraviolet spectrum with that of 5-chloro-1,2-dihydro-1-methylpyrimido[5,4-*e*]-*as*-triazin-3(4H)-one[5] and by reactions requiring the presence of an amino group.[4]

(7) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **28**, 3038 (1963).

(8) E. C. Taylor, J. W. Barton, and W. W. Paudler, *ibid.*, **26**, 4961 (1961).

(9) J. H. Biel, A. E. Drukker, T. F. Michtell, E. P. Sprengler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Am. Chem. Soc.*, **81**, 2805 (1959); S. G. Cohen and C. H. Wang, *ibid.*, **77**, 2457 (1955).

comparison of the ultraviolet and pmr spectra with those of **13**.

The acid-catalyzed rearrangement of **13**, previously described as the rearrangement of **6** to **3**,[5] was repeated and shown to give **15** presumably *via* **14** or a similar derivative. This type of rearrangement is now well known in both the pyrimidine and pyridine series.[10,11] The structure of **15** was also confirmed by the pmr spectrum and by the reaction with diethoxymethyl acetate to give **18**. The amino compound **15** was regenerated by treatment of **18** with 0.1 *N* HCl. Further treatment of **15** with ethanolic HCl caused hydrolysis of the chloro group. The product of this reaction is tentatively assigned structure **5** based on elemental analysis, the multiple bands in the ultraviolet spectrum, and the apparent acid stability of this ring system. Finally, reaction of **13** with Ac_2O in the presence of H_2SO_4 appeared to give the rearranged acetamide compound **19**, based on elemental analysis and comparison of the ultraviolet and pmr spectra with those of **15**.

Experimental Section

Melting points were determined either on a Kofler Heizbank apparatus or in capillary tubes in a stirred oil bath and are corrected. The ultraviolet absorption spectra were determined with a Cary Model 14 spectrophotometer on solutions containing 10% of the dissolving solvent and 90% of the appropriate aqueous solvent: A, MeOH; B, 8% ethanolic DMF; C, 0.1 *N* NaOH; D, EtOH. The infrared absorption spectra were determined in pressed potassium bromide disks (or in fixed-thickness cells equipped with windows of Irtran-2) with Perkin-Elmer Models 221-G and 521 spectrophotometers. Only the bands in the 1800–1500-cm^{-1} region of the spectrum are reported. The pmr spectra were determined on DMSO-d_6 solutions with a Varian A-60 or A-60A spectrometer at a probe temperature of about 40° using tetramethylsilane as the internal reference.

9-Acetamido-6-bromo-9H-purin-8(7H)-one (1). A.—A suspension of **7** (1.0 g) and 30% HBr in glacial AcOH (40 ml) was stirred at room temperature for 18 hr. The resulting solution was evaporated to dryness and the residue was dissolved in 2 *N* NH_4OH. Acidification of this solution with AcOH deposited a white solid (0.57 g), which was recrystallized from water: yield, 470 mg (55%); mp 153° with presoftening from 148°; λ^{A}_{max}, mμ (ε × 10^{-3}), pH 7, 266 (sh) (6.95), 291 (11.8); $\bar{\nu}$, cm^{-1}, 1755, 1700, 1620, 1590; pmr, τ 7.90 (CH_3), 1.57 (CH), −1.03 and −1.96 (NH).

Anal. Calcd for $C_7H_6BrN_5O_2$: C, 30.90; H, 2.22; Br, 29.37; N, 25.74. Found: C, 31.49; H, 2.50; Br, 27.36; N, 26.16.

B.—Treatment of **8** (1.0 g) as described in A gave 0.44 g (57%) of **1**.

8-Amino-2-benzyl-7-chloro-*s*-triazolo[4,3-*c*]pyrimidin-3(2H)-one (4).—A suspension of **13** (1.0 g) in DMF (15 ml) containing K_2CO_3 (0.75 g) and $C_6H_5CH_2Cl$ (0.8 ml) was stirred at room temperature for 20 hr, then diluted with H_2O (30 ml). The solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield, 1.4 g (94%); mp 244–245°; λ^{B}_{max} mμ (ε × 10^{-3}), pH 7, 277 (13.0), 321 (6.98); $\bar{\nu}$, cm^{-1}, 1720, 1620, 1600, 1545, 1520; pmr, τ 4.90 (CH_2), 4.00 (NH_2), 2.68 (C_6H_5), 1.88 (CH).

Anal. Calcd for $C_{12}H_{10}ClN_5O$: C, 52.27; H, 3.65; Cl, 12.86; N, 25.40. Found: C, 52.18; H, 3.69; Cl, 12.90; N, 25.35.

8-Amino-*s*-triazolo[1,5-*c*]pyrimidin-2(1H),7(3H)-dione (5).—A suspension of **15** (1.0 g) in 0.6 *N* ethanolic HCl (50 ml) was refluxed for 20 hr. The solid was collected by filtration, partially dissolved in hot H_2O (70 ml) containing 10 drops of concentrated NH_4OH, and the resulting suspension was filtered. The filtrate was concentrated to remove excess NH_3 and the solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5: yield, 0.22 g (24%); mp >260°; λ^{C}_{max}, mμ (ε × 10^{-3}), 0.1 *N* NaOH, 268 (8.24), 370 (2.73); $\bar{\nu}$, cm^{-1}, 1680, 1640, 1500.

Anal. Calcd for $C_5H_5N_5O_2$: C, 35.93; H, 3.01; N, 41.90. Found: C, 35.78; H, 3.11; N, 41.65.

(10) J. A. Bee and F. L. Rose, *J. Chem. Soc.*, 2031 (1966).

(11) K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.*, **31**, 265 (1966).

9-Amino-6-chloro-9H-purin-8(7H)-one (6).—A suspension of **8** (1.0 g) in concentrated HCl (40 ml) was stirred at room temperature for 5 hr and the resulting solution was evaporated to dryness at 60° under reduced pressure. The residue was washed with ether, then recrystallized from EtOH to give **6** in two crops: yield, 330 mg (63%); mp 191–192° dec; λ^{A}_{max}, mμ (ε × 10^{-3}), 0.1 *N* HCl, 241 (2.95), 279 (12.6); pH 7, 282 (11.2); 0.1 *N* NaOH, 266 (sh) (5.47), 292 (12.1); $\bar{\nu}$, cm^{-1}, 1740 (sh), 1715, 1620, 1575; pmr, τ 4.87 (NH_2), 1.56 (CH), −1.94 (NH).

Anal. Calcd for $C_5H_4ClN_5O$: C, 32.36; H, 2.17; Cl, 19.1; N, 37.73. Found: C, 32.42; H, 2.33; Cl, 18.9; N, 37.49.

From the EtOH filtrate 130 mg of a mixture of **6** and **8** was obtained.

Benzyl 6-Chloro-7,8-dihydro-8-oxo-9H-purine-9-carbamate (7).—Phosgene was bubbled through a solution of pyridine (0.67 ml) in dioxane (30 ml) for 20 min and the resulting mixture was refluxed for 15 min to remove excess phosgene. After the addition of **11** (1.0 g) the mixture was refluxed for 2 hr and evaporated to a small volume under reduced pressure. The resulting gummy residue was dissolved in 2 *N* NH_4OH and acidified with AcOH to deposit a tan oil, which solidified on trituration with ether: yield, 0.73 g (67%); mp 197–203° dec. A sample (0.20 g) was recrystallized from a mixture of C_6H_6–EtOH and dried at 78° *in vacuo* over P_2O_5 to give **7** (0.14 g): mp 220–221°; λ^{A}_{max}, mμ (ε × 10^{-3}), pH 7, 265 (sh) (7.14), 288 (11.0); $\bar{\nu}$, cm^{-1}, 1770, 1700, 1635, 1590, 1560.

Anal. Calcd for $C_{13}H_{10}ClN_5O_3$: C, 48.83; H, 3.15; N, 21.91. Found: C, 48.92; H, 3.33; N, 21.81.

6-Chloro-9-(diphenylmethyl)amino-9H-purin-8(7H)-one (8).—Phosgene was bubbled through a solution of pyridine (1.86 ml) in dioxane (90 ml) for 20 min and the resulting mixture was refluxed for 20 min to remove excess phosgene. After the addition of **12** (6.0 g), the mixture was refluxed for 2 hr and evaporated to dryness *in vacuo*. The resulting solid was triturated with 2 *N* NH_4OH and after filtration the filtrate was acidified with glacial AcOH to give crude **8**: yield, 3.4 g. Recrystallization from EtOH gave the analytical sample: yield, 1.7 g (27%); mp 216–217°; λ^{A}_{max}, mμ (ε × 10^{-3}), pH 7, 283 (8.37); $\bar{\nu}$, cm^{-1}, 1720, 1620, 1585, 1505.

Anal. Calcd for $C_{18}H_{14}ClN_5O$: C, 61.44; H, 4.01; N, 19.91. Found: C, 61.45; H, 4.23; N, 19.68.

Benzyl 3-(5-Amino-6-chloro-4-pyrimidinyl)carbazate (11).—A mixture of **9** (5.0 g), benzyl chloroformate (5.6 g), and NaOAc (3.3 g) in dioxane (100 ml) was stirred at room temperature for 18 hr. The mixture was filtered and the filtrate was evaporated *in vacuo* to give a glass, which was recrystallized from ethyl acetate: yield, 5.4 g (59%); mp 134–136°; λ^{A}_{max}, mμ (ε × 10^{-3}), pH 7, 256 (7.14), 290 (8.28); $\bar{\nu}$, cm^{-1}, 1705, 1625, 1575, 1520.

Anal. Calcd for $C_{12}H_{12}ClN_5O_2$: C, 49.07; H, 4.12; Cl, 12.1; N, 23.84. Found: C, 48.89; H, 4.30; Cl, 12.5; N, 23.98.

5-Amino-4-chloro-6-[2-(diphenylmethyl)hydrazino]pyrimidine (12).—A solution of 5-amino-4,6-dichloropyrimidine **2** (10.0 g) and diphenylmethyl hydrazine (25.0 g) in propanol (200 ml) was refluxed for 4 hr. The resulting mixture was evaporated to dryness *in vacuo* and the residue was washed, then recrystallized from EtOH: yield, 11.5 g (58%); mp 215–217° dec; λ^{B}_{max} mμ (ε 10^{-3}), pH 7, 261 (9.73), 293 (9.08), 345 (sh) (3.52); $\bar{\nu}$, cm^{-1}, 1650, 1575, 1490; pmr, τ 4.98 (NH_2), 4.67 (CHN), 4.53 (2-NH), 2.68 (C_6H_5), 2.13 (2-CH), 1.72 (1-NH).

Anal. Calcd for $C_{17}H_{16}ClN_5$: C, 62.67; H, 4.95; Cl, 10.9; N, 21.49. Found: C, 62.78; H, 5.05; Cl, 10.7; N, 21.52.

8-Amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidin-3(2H)-one (13) was prepared by the reported procedures:[4,5] (a) treatment of **10** with 5% $NaHCO_3$ solution and (b) treatment of **9** in HCl with phosgene. The product from (b) was dried at 70° *in vacuo* over P_2O_5 for 24 hr to give a 74% yield of **13**: mp 285–288° dec (reported[5] on sublimed **13**, 285–295° dec). The infrared spectrum showed a sharp carbonyl band at 1718 cm^{-1} in a KBr disk and at 1730 cm^{-1} in a 4% (w/v) solution in DMSO; pmr, τ 4.03 (NH_2), 1.92 (CH), −2.50 (NH).

Anal. Calcd for $C_5H_4ClN_5O$: C, 32.36; H, 2.17; N, 37.73. Found: C, 32.77; H, 2.39; N, 37.52.

The monohydrate was prepared by acidification of a solution of **13** in aqueous NaOH.[5] The infrared spectrum (KBr disk) of the hydrate exhibited a broad peak at 1705 cm^{-1}, whereas a sample of the hydrate that was triturated with boiling dioxane showed carbonyl bands at 1740 and 1720 cm^{-1}. The spectrum in DMSO-d_6 (10% w/v) was similar to that described above for anhydrous **13** with the exception that the NH and H_2O protons gave broad absorption near τ 5.5.

Anal. Calcd for $C_5H_4ClN_5O \cdot H_2O$: C, 29.49; H, 2.97; Cl, 17.41; N, 34.39. Found: C, 29.52; H, 3.03; Cl, 17.60; N, 34.48.

The hydrate was dried at 110° *in vacuo* over P_2O_5 for 30 hr to again give anhydrous **13**, which exhibited carbonyl bands at 1740, 1720, and 1715 cm^{-1} in a KBr disk and at 1735 cm^{-1} in a 5% (w/v) solution in DMSO.

8-Amino-7-chloro-s-triazolo[1,5-c]pyrimidin-2(3H)-one (15) was prepared in 70% yield as previously described:[5] λ_{max}, mμ ($\epsilon \times 10^{-3}$), pH 7, 243 (30.0), 272 (6.89); $\bar{\nu}$, cm^{-1}, 1700, 1625, 1585, 1550, 1510; pmr, τ 4.62 (NH_2), 1.27 (CH), *ca.* −1.0 (NH).

Anal. Calcd for $C_5H_4ClN_5O$: C, 32.36; H, 2.17; Cl, 19.1; N, 37.73. Found: C, 32.47; H, 2.32; Cl, 19.1; N, 37.87.

6-Chloropurin-8(7H)-one (16).—Sodium nitrite (25 mg) was added with stirring to a suspension of **6** (50 mg) in H_2O containing 1 *N* HCl (0.5 ml). After 1 hr the precipitate of **16** was collected by filtration and dried *in vacuo* over P_2O_5: yield, 22 mg (48%). This material was identified by thin layer chromatography and by comparison of its ultraviolet and infrared spectra with those of authentic **16**.[5] In addition, **16** was the only ultraviolet absorbing material detected in a chromatogram of the reaction filtrate.

7-Chloro-8-ethoxymethyleneamino-s-triazolo[1,5-c]pyrimidin-2(3H)-one (18).—A suspension of **15** (300 mg) in diethoxymethyl acetate (10 ml) was stirred at room temperature for 40 hr, heated for 10 min on a hot water bath, and the resulting solution was cooled to deposit 70 mg of crude **18**: mp 249–253° dec with sublimation from 230°. The filtrate was diluted with EtOH and evaporated to dryness *in vacuo*. Recrystallization of the resulting residue from THF–petroleum ether (bp 85–105°) gave 250 mg of **18** (64%): mp 258–260° dec with sublimation from 230°. The total yield of **18** was 320 mg (82%): λ^{D}_{max}, mμ ($\epsilon \times 10^{-3}$), EtOH, 240 (19.2), 250 (19.4), 283 (8.15); $\bar{\nu}$, cm^{-1}, 1625, 1570, 1515.

Anal. Calcd for $C_8H_8ClN_5O_2$: C, 39.76; H, 3.33; Cl, 14.67; N, 28.98. Found: C, 40.16; H, 3.54; Cl, 14.60; N, 28.82.

Treatment of **18** with 0.1 *N* HCl at room temperature gave **15**.

8-Acetamido-7-chloro-s-triazolo[1,5-c]pyrimidin-2(3H)-one (19).—A suspension of **13** (1.44 g) in Ac_2O containing 1 drop of concentrated H_2SO_4 was stirred at room temperature for 1.5 hr. The solid (1.1 g) was collected by filtration and recrystallized first from THF–petroleum ether (bp 85–105°), then from EtOH: yield, 0.17 g (10%); mp >264°; λ^{D}_{max}, mμ ($\epsilon \times 10^{-3}$), pH 7, 235 (39.4), 275 (sh) (3.72), 308 (3.65); $\bar{\nu}$, cm^{-1}, 1685 1650, 1575, 1540, 1500; pmr, τ 7.85 (CH_3), 0.62 (CH), −0.13 and −0.55 (NH).

Anal. Calcd for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.65; Cl, 15.6; N, 30.76. Found: C, 36.91; H, 2.90; Cl, 15.8; N, 30.76.

Registry No.—**1**, 15152-49-5; **4**, 15128-97-9; **5**, 15128-96-8; **6**, 15128-98-0; **7**, 15206-32-3; **8**, 15128-99-1; **11**, 15180-19-5; **12**, 15129-00-7; **13**, 15206-33-4; **15**, 15129-01-8; **18**, 15129-02-9; **19**, 15129-03-0.

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Potential Folic Acid Antagonists. III. Deaza Analogs of Methotrexate. III. 1- and 3-Deaza Analogs of 2,4-Diamino-6-[(N-methylanilino)methyl]pteridine[1,2]

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The reaction of 1-amino-3-(N-methylanilino)-2-propanol with diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (**1**) and ethyl 4-amino-6-chloro-5-nitro-2-pyridinecarbamate (**8**), respectively, gave the corresponding 2-hydroxy-3-(N-methylanilino)propylaminopyridines **2** and **9**. Oxidation of these alcohols to the corresponding 3-(N-methylanilino)-2-oxopropylaminopyridines **4** and **12** was accomplished with dimethyl sulfoxide and N,N′-dicyclohexylcarbodiimide (Pfitzner–Moffatt procedure). Reductive cyclization of these 2-oxopropylaminopyridines followed by ring oxidation with potassium permanganate and basic hydrolysis of the urethan groups provided 5,7-diamino-3-[(N-methylanilino)methyl]pyrido[3,4-*b*]pyrazine (**14**) and 6,8-diamino-2-[(N-methylanilino)methyl]pyrido[2,3-*b*]pyrazine (**17**), the 1- and 3-deaza analogs of 2,4-diamino-6-[(N-methylanilino)methyl]pteridine.

Continuation of our studies on the structural requirements for binding to and, therefore, inhibiting the enzymes involved in folic acid metabolism prompted the synthesis of 5,7-diamino-3-[(N-methylanilino)-methyl]pyrido[3,4-*b*]pyrazine (**14**) and 6,8-diamino-2-[(N-methylanilino)methyl]pyrido[2,3-*b*]pyrazine (**17**), the 1- and 3-deaza analogs of 2,4-diamino-6-[(N-methylanilino)methyl]pteridine. In earlier papers the unambiguous synthesis of diamino 1- and 3-deazapteridines from pyridine intermediates containing adjacent chloro and nitro groups involved, respectively, the replacement of the chloro group with an α-amino ketone moiety, reductive cyclization, and oxidation.[2,3] Apparently this route is limited only by the availability of the α-amino ketone. Although procedures for the preparation of 1,3-diamino-2-propanols are well known,[4] a method for the oxidation of these alcohols to the corresponding 1,3-diaminoacetones has not been reported. The successful preparation of **14** and **17** involved as a key step the oxidation of a complex 2-hydroxy-3-(N-methylanilino)propylaminopyridine to the corresponding 3-(N-methylanilino)-2-oxopropylaminopyridine.

Reaction of the chloropyridine **1** with 1-amino-3-(N-methylanilino)-2-propanol[4] gave **2**, which was hydrogenated in the presence of Raney nickel to give the 3-aminopyridine **3**. The intramolecular cyclization of the latter to the tetrahydro derivative **5** under a variety of neutral and acidic conditions[5] was unsuccessful. When **3** was heated in refluxing propanol, ring closure occurred between the 3-amino and the 2-urethan groups to give **6**. The avoid this type of ring closure, oxidation of the secondary alcohol moiety of the propyl

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(2) For the second paper in this series, see R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1890 (1966).

(3) J. A. Montgomery and N. Wood, *ibid.*, **29**, 734 (1964).

(4) O. Eisleb, German Patent 473,219 (Aug 1926); *Chem. Zentr.*, **100** (II), 350 (1929).

(5) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 859 (1964); M. G. Reinecke and L. R. Kray, *ibid.*, **29**, 1736 (1964).