saline (0.85% NaCl in distilled water), compounds **3b**, **8**, and **10** were administered in saline plus Tween 80, and compound **6** was administered in saline plus Tween 80 in most experiments (experiments 4–8, Table I) and, also, in suspension in saline.

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Registry No. **3b**, 4239-10-5; **4c**, 88343-71-9; **6**, 88343-72-0; **7**, 88343-73-1; **8**, 88343-74-2; **9**, 88343-75-3; **10**, 61801-29-4; **17**, 35329-86-3; **18**, 22317-89-1; 2-chloroethanol, 107-07-3; 2-fluoroethanol, 371-62-0; 2-bromoethanol, 540-51-2; methanesulfonyl chloride, 124-63-0.

Synthesis and Antiviral Evaluation of Carbocyclic Analogues of Ribofuranosides of 2-Amino-6-substituted-purines and of 2-Amino-6-substituted-8-azapurines

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Carbocyclic analogues of ribofuranosides of 2-amino-6-substituted-purines and of 2-amino-6-substituted-8-azapurines were prepared from the 2-amino-6-chloropurine ribofuranoside analogue (**2**) and the 2-amino-6-chloro-8-azapurine ribofuranoside analogue (**9**), respectively. Analogues of purine ribofuranosides with the chloro, amino, methylamino, or methylthio group at position 6, the thioguanosine analogue, and the previously reported guanosine analogue were evaluated in vitro against herpes simplex virus, type 1 (HSV-1). 8-Azapurine ribofuranoside analogues with the chloro, amino, or methylthio group at position 6 and the previously reported 8-azaguanosine analogue were also evaluated against HSV-1. The carbocyclic analogue (**6**) of 2,6-diaminopurine ribofuranoside is highly active against HSV-1 and, also, against vaccinia virus. The 2-amino-6-chloropurine, 2-amino-6-(methylamino)purine, and the 2,6-diamino-8-azapurine derivatives also demonstrated significant activity against HSV-1.

Carbocyclic analogues of 6-substituted-purine ribofuranosides, including the racemic analogue (C-Ado) of adenosine, constituted the first group of carbocyclic analogues of nucleosides.[1-3] The adenosine analogue was subsequently isolated as the antibiotic aristeromycin (1′*R*,2′*S*,3′*R*,4′*R* enantiomer, nucleoside numbering).[4,5] The identity of C-Ado and aristeromycin was reported[5] and was confirmed in more detail[6] after a later synthesis and resolution were claimed.[7] Other ribofuranoside analogues synthesized in the early stages of this work were the carbocyclic analogues of guanosine,[8] 8-azaguanosine,[8] and 8-azapurine ribofuranosides.[9] Initial biochemical studies showed that C-Ado may function either as a substrate for or as an inhibitor of enzymes involved in the biosynthesis de novo or in interconversions of purine nucleotides,[10,11] and tests of the 8-azaadenosine analogue in vivo showed that it is active against P388 leukemia in mice.[12] Bennett et al.[13] reported in 1975 that several members of the initial group of carbocyclic analogues of 6-substituted-purine ribofuranosides have antiviral activity. Subsequently, it was shown that carbocyclic analogues of cytidine and arabinofuranosylcytosine (*ara*-C),[14-16] arabinofuranosyladenine (*ara*-A),[17] 3-deazaadenosine,[18] and 5-substituted-2′-deoxyuridines[19] also have antiviral activity. In addition to the guanosine (**3**) and 8-azaguanosine (**4**) analogues,[8] we had also prepared carbocyclic analogues of ribofuranosides of other 2-aminopurines and 2-amino-8-azapurines (1,2,3-triazolo[4,5-*d*]pyrimidines); we now describe the preparation, antiviral evaluation, and antineoplastic testing of these carbocyclic analogues.

Chemistry. The synthesis of the pyrimidine precursor (**1**) of both the 2-aminopurine and 2-amino-8-azapurine analogues was described earlier.[8] Previously, the acid-catalyzed reaction of triethyl orthoformate with pyrimidine **1** in dimethylformamide and the use of the total crude product of this reaction to produce the guanosine analogue (**3**) were reported.[8] In addition to forming the purine ring, interaction of **1** and triethyl orthoformate should produce

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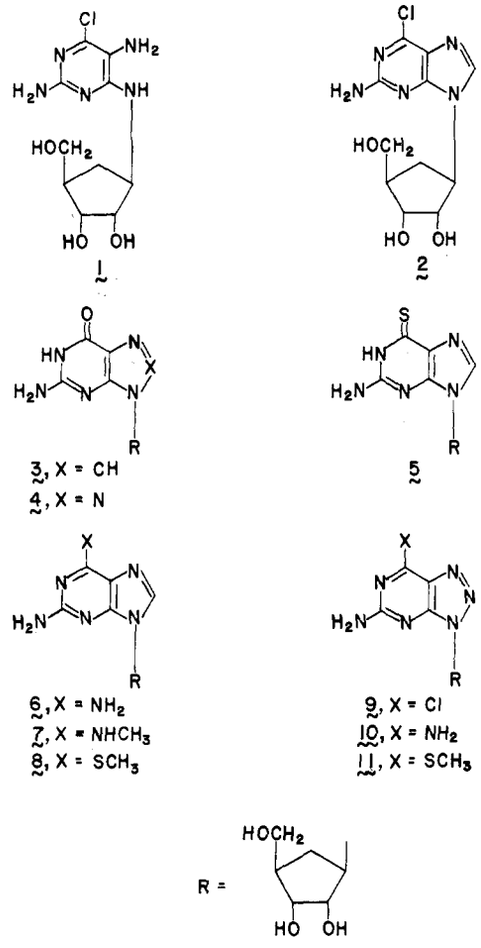

derivatives of the hydroxyl and the 2-amino groups. Isolation of pure specimens of the 2-amino-6-chloropurine (**2**) was not attempted at that time. Subsequently, pure specimens of **2** were isolated by treating the crude product, obtained from the reaction of **1** and triethyl orthoformate in dimethylacetamide, with 50% acetic acid and then with methanolic ammonia to liberate the hydroxyl and amino groups. The thioguanosine analogue (**5**) was prepared by treating the 2-amino-6-chloropurine (**2**) with thiourea in refluxing propanol and isolating the product as the sulfate. Similarly, the 2,6-diaminopurine ribofuranoside analogue (**6**) and the 6-(methylamino) derivative (**7**) were isolated as sulfate salts after reactions of **2** with ammonia and methylamine, respectively, at 80 °C. The 2-amino-6-(methylthio)purine (**8**) was prepared by treating **2** with sodium methyl mercaptide in a mixture of methanol and methanethiol at temperatures in excess of 100 °C.

The preparation of the 2-amino-6-chloro-8-azapurine (**9**) from pyrimidine **1** was described earlier.[8] The carbocyclic analogues (**10** and **11**) of 2,6-diamino-8-azapurine ribofuranoside and 2-amino-6-(methylthio)purine ribofuranoside were prepared from **9** by methods similar to, but less strenuous than, those used to obtain the corresponding purines.

Biological Evaluation. A standard method, which has been described previously,[16,20] for determining the inhibition of virus-induced cytopathogenic effects (CPE) by antiviral compounds was used to evaluate the ribofuranoside analogues against herpes simplex virus, type 1 (HSV-1), and against influenza virus in vitro. A few of these compounds were also tested against vaccinia virus.

The antiviral activity of each compound was expressed in terms of a virus rating (VR), and the potency was measured as a minimum inhibitory concentration (MIC_{50}). The VR, determined by a modification of the method of Ehrlich et al.,[21] is a weighted measurement of antiviral activity which takes into account the degree of inhibition of virus-specific CPE and the degree of cytotoxicity produced by the test compound. A VR greater than or equal to 1.0 indicates definite antiviral activity, a VR of 0.5 to 0.9 indicates marginal to moderate antiviral activity, and a VR less than 0.5 usually indicates no significant antiviral activity. The MIC_{50} is the concentration of the tested compound required to inhibit virus-induced CPE by 50%.

The results of antiviral evaluations of the carbocyclic analogues of 2-aminopurine ribofuranosides are summarized in Table I. In tests against strain HF of HSV-1 replicating in human epidermoid carcinoma cells (H.Ep.-2), the carbocyclic analogue (**6**) of 2,6-diaminopurine ribofuranoside displayed high activity (VR = 4.6) and potency (MIC_{50} = 0.32 mcg/mL). 1-β-D-Arabinofuranosyladenine (*ara*-A), a known antiviral agent, was the positive control and was less active (VR = 2.0–2.2; MIC_{50} = 2.5-10 mcg/mL). The 2-amino-6-(methylamino)purine (**7**), 2,6-diamino-8-azapurine (**10**), and 2-amino-6-chloropurine (**2**) derivatives also displayed significant activity (VR = 1.3–1.7, Table I) against strain HF of HSV-1, and the 2-amino-6-chloro-8-azapurine (**9**) was modestly active (VR = 0.9). Four of the analogues were tested against vaccinia virus replicating in H.Ep.-2 cells (Table I). In this test, the 2,6-diaminopurine ribofuranoside analogue (**6**) was highly active, the 2-amino-6-chloropurine (**2**) was significantly active, and the 2-amino-6-chloro-8-azapurine (**9**) was marginally active. Compounds **2–4** and **6–11** were also tested against influenza virus Ao/PR-8/34 replicating in Madin–Darby canine kidney cells; none showed activity. After these ribofuranoside analogues (**2–11**) had been synthesized, the synthesis of several arabinofuranoside analogues by the same route[8] was reported.[22] Only the carbocyclic analogue of 2,6-diaminopurine arabinofuranoside showed significant activity (VR = 1.5) against strain HF of HSV-1.[22] Thus, compounds **6** and **10** (ribofuranoside analogues) appear to be considerably more active in this test than are the corresponding arabinofuranoside analogues, and compound **6** also appears to be more active in vitro than is the carbocyclic analogue of arabinofuranosyladenine.[17] All of these carbocyclic analogues were evaluated in the same way in these laboratories.[17,22,23]

The results of tests of compounds **2–11** for cytotoxicity to cancer cells in culture and against leukemia L1210 in mice are summarized in Table II. Compounds **5–7** and **9** were cytotoxic at relatively high concentrations to KB or H.Ep.-2 cells. The guanosine analogue (**3**) was tested on three dosage schedules against leukemia L1210 in vivo and was found to be without activity in prolonging life span. The toxicity of **3** in vivo appears to be greater than its cytotoxicity indicated. Compounds **2** and **6** were not active when tested q.d. 1–9 against L1210 leukemia. Except for compound **7**, the remaining analogues received at least one test in vivo: compounds **4**, **5**, **9**, and **10** were not active or toxic when administered on day 1 (only) at 400

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Table I. Evaluation of Carbocyclic Analogues of Ribofuranosides of 2-Aminopurines and 2-Amino-8-azapurines for Antiviral Activity in Vitro[a]

compd	substituent at position 6[b]	HSV-1, strain HF		vaccinia	
		VR[c]	MIC_{50}, mcg/mL	VR	MIC_{50}, mcg/mL
		Purines			
2	Cl	1.7	10	1.2	20
3	O	0		0	
5	S	0[d]		NT	
6	NH_2	4.6	0.3	3.8	2.3
7	$NHCH_3$	1.3	320	NT	
8	SCH_3	0.1		NT	
		8-Azapurines			
4	O	0		NT	
9	Cl	0.9	81	0.6	
10	NH_2	1.4	100		
11	SCH_3	0		NT	
ara-A (positive control)		2.0-2.2	2.5-10		

[a] Antiviral assays of these compounds were performed by using the HF strain of HSV-1 and the Lederle Chorioallantoic strain of vaccinia virus, both replicating in human epidermoid carcinoma no. 2 (H.Ep.-2) cells. The compounds tested against HSV-1 (HF) were also tested against influenza virus; none showed activity. [b] Purine numbering system for 8-azapurines. [c] VR = virus rating; see the discussion. [d] Strain 377 was used in evaluating compound 5.

Table II. Tests of Compounds 2-11 for Antineoplastic Activity

compd	cytotoxicity		L1210 in vivo[a]		
	cells	ED_{50}, mcg/mL	schedule	dose, mg/kg	T/C,[b] %
2	KB	>100	day 1	400	104
			q.d. 1-9	200	67t
			q.d. 1-9	100	85t
			q.d. 1-9	50	101
3	H.Ep.-2	>100	day 1	300	t[c]
			day 1	150	75t[d]
			day 1	75	88[d]
			days 1, 5, 9	75	70t
			days 1, 5, 9	38	92
			days 1, 5, 9	19	94
			q.d. 1-9	38	71t
			q.d. 1-9	19	83t
			q.d. 1-9	9	101
4	H.Ep.-2	>100	day 1	400	109
5	KB	50	day 1	400	99
6	KB	19	day 1	400	t
			q.d. 1-9	200	67t
			q.d. 1-9	100	70t
			q.d. 1-9	50	89
			q.d. 1-9	25	102
7	KB	18			
8	KB	>100	q.d. 1-9	100	108
9	H.Ep.-2	8	day 1	400	111
10	KB	>100	day 1	400	97
11	KB	>100	q.d. 1-9	100	94

[a] Tested in accordance with the protocols of the National Cancer Institute.[24] Mice were inoculated intraperitoneally with 10^5 leukemia L1210 cells on day 0. Solutions or suspensions of the compounds were administered intraperitoneally. T = treated mice; C = untreated, leukemic control mice. [b] A dose is considered[24] to be toxic (t) if mortality by day 5 is greater than or equal to three of six mice, if T/C is <85%, or if the weight-change difference (T - C) is greater in magnitude than -4 g. [c] Mortality = 5/6 by day 5. [d] The difference in weight change (T - C) by day 5 was -5.6 g at 150 mg/kg and -3.9 g at 75 mg/kg.

mg/kg, and compounds 8 and 11 were not toxic or active at 100 mg/kg per day when administered daily (q.d. 1-9).

Experimental Section[25]

General Methods. Decomposition and melting temperatures (mp) were determined in capillary tubes heated in a Mel-Temp apparatus. Ultraviolet spectra (UV) were recorded with a Cary Model 17 spectrophotometer, and absorption maxima are reported in nanometers; sh = shoulder. Solutions for ultraviolet spectral determinations were prepared by diluting a 5-mL aliquot of a water solution to 50 mL with 0.1 N hydrochloric acid, phosphate buffer (pH 7), or 0.1 N sodium hydroxide. Absorption maxima of these solutions are reported as being determined at pH 1, 7, or 13, respectively. Infrared spectra (IR) were recorded with a Perkin-Elmer Model 521 or 621 spectrophotometer from samples in pressed potassium bromide disks: s = strong; sh = shoulder; w = weak. Mass spectral data (MS) were taken from low-resolution, electron-impact spectra determined at 70 eV with a Varian/MAT 311A spectrometer (except for the data for 5, which came from a spectrum determined with a Hitachi Perkin-Elmer RMU-6D mass spectrometer). The peaks listed are those arising from the molecular ion (M), those attributable to the loss of certain fragments (M minus a fragment), and some other prominent peaks. Fragments containing the complete purine moiety may

(25) In accordance with *Chemical Abstracts* nomenclature, compounds 2 and 6-11 are named as 1,2-cyclopentanediols, and substituents on the cyclopentane ring are designated 1α,2α,3β,5β. Compounds 3-5 are named as cyclopentylpurines or 1,2,3-triazolo[4,5-*d*]pyrimidines; therefore, substituents on the cyclopentane ring are designated 1α,2β,3β,4α.

be designated P plus an atom or group. Nuclear magnetic resonance spectra were determined with a Varian Model XL-100-15 spectrometer operating at 100.1 MHz for proton (^{1}H NMR) spectra. The internal standard was tetramethylsilane: s = singlet; t = triplet; m = multiplet. Thin-layer chromatography (TLC) was performed on plates of silica gel H.

(1α,2α,3β,5β)-(±)-3-(2-Amino-6-chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (2). To a mixture of 1.45 g of pyrimidine **1**, 15 mL of dimethylacetamide, and 10 mL of triethyl orthoformate at 0–5 °C was added 0.5 mL of 12 N hydrochloric acid. The mixture was stirred at room temperature for 20 h, during which time it became homogeneous. The solution was concentrated under reduced pressure (oil pump) to a red syrup, which was concentrated further by adding and evaporating toluene in vacuo. A solution of the syrup in 60 mL of 50% acetic acid was stirred at room temperature for 4 h and then concentrated in vacuo to a dark red syrup. A solution of this syrup in 50 mL of ammonia–methanol (8% NH_3) was stirred at room temperature for 4 h and concentrated in vacuo. Several portions of methanol were added to and evaporated from the residue. A methanol solution of the crude product was diluted with water (15 mL) and concentrated in vacuo to remove most of the methanol. The aqueous solution was diluted with acetonitrile (5 mL), seeded with previously obtained crystals of **2**, and stored in a refrigerator. The red crystalline precipitate was collected by filtration, washed with acetonitrile–water (1:1), and dried in vacuo over P_2O_5: yield 770 mg (52%); mp 206–210 °C dec. A second crop (100 mg, 7%) of crude **2** was obtained by diluting the filtrate with acetonitrile and chilling the mixture to −20 °C. The two crops were combined, and the crude product was recrystallized from water (10 mL): yield 633 mg (43%); mp 216–218 °C dec. This material was suitable for the preparation of other 2-amino-6-substituted-purines. A specimen was recrystallized from water: mp 222–224 °C dec (inserted at 210 °C, 2 °C/min); UV max (pH 1) 313 nm (ε 7000), 242 (5500), 221 (25 100); UV max (pH 7) 307 nm (ε 7600), 245 (5100), 223 (27 000); MS (direct-probe temperature 20 °C), *m/e* 299 (M), 282 (M − OH), 268 (M − CH_2OH), 252 (M − OH − CH_2OH + H), 250 (M − H_2O − CH_2OH), 225, 224 (M − 75), 196 (P + C_2H_4), 170 (P + 2H), 169 (P + H); ^{1}H NMR (Me_2SO-d_6) δ 1.4–2.4 (m, CH_2 and $CHCH_2OH$), 3.49 (m, CH_2OH), 3.84 (m, $CHOHCHCH_2OH$), 4.28 (m, $NCHCHOH$), 4.62 (m, NCH), ca. 3.4–5.2 (3 OH), 6.82 (s, NH_2), 8.25 (s, purine CH). Anal. ($C_{11}H_{14}ClN_5O_3$) C, H, N.

(±)-2-Amino-1,9-dihydro-9-[(1α,2β,3β,4α)-2,3-dihydroxy-4-(hydroxymethyl)cyclopentyl]-6*H*-purine-6-thione (5) Sulfate. A mixture of 150 mg of **2**, 39 mg of thiourea, and 5 mL of 1-propanol was boiled under reflux for 2 h, and the reaction mixture was chilled (−20 °C) and filtered to collect a yellow solid. A solution of the solid (104 mg) in hot water (1 mL) was diluted with 6 M sulfuric acid (0.26 mL) and then with ethanol (ca. 1 mL). After the solution had been chilled (−20 °C), yellow crystals were collected by filtration, washed with ethanol, and dried in vacuo over P_2O_5 at 78 °C for 1.5 h: yield 66 mg (33%); mp, gradual decomposition; TLC, 1 spot [silica gel, butanol–water–acetic acid (5:3:2), detection by UV and by potassium permanganate spray]; IR (1700–1500-cm^{-1} region) 1640 (sh), 1605 (s), 1530 (w) cm^{-1}; UV max (pH 1) 348 nm (ε22 100), 264 (7600), 225 (sh), 207 (24 700); UV max (pH 7) 341 nm (ε25 900), 264 (7900), 231 (ε 17 800), 207 (22 100); UV max (pH 13) 318 nm (ε20 700), 269 (7500), 251 (12 000), 222 (16 700); MS (free base, direct-probe temperature 390 °C), *m/e* 297 (M), 280 (M − OH), 266 (M − CH_2OH), 250 (M − OH − CH_2OH + H), 248 (M − H_2O − CH_2OH), 222 (M − 75), 194 (P + C_2H_4), 168 (P + 2H), 167 (P + H); ^{1}H NMR (Me_2SO-d_6) δ 1.4–2.4 (m, CH_2 and $CHCH_2OH$), 3.4 (m, CH_2OH), 3.82 (m, $CHOHCHCH_2OH$), 4.23 (m, $NCHCHOH$), 4.5 (broad m, NCH, OH, H_2O, acidic H), 6.95 (NH_2), 8.53 (s, purine CH), 12.21 (m, NH). Anal. ($C_{11}H_{15}N_5O_3S{\cdot}H_2SO_4$) C, H, N.

(1α,2α,3β,5β)-(±)-3-(2,6-Diamino-9*H*-purin-9-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (6) Sulfate. A solution of 500 mg of the 2-amino-6-chloropurine (**2**) in 50 mL of liquid ammonia was heated for 20 h at 80 °C in a stainless-steel bomb containing a glass liner. After the bomb had been chilled and opened, the ammonia was evaporated with a current of nitrogen, and water was twice added to and evaporated from the residue. A water (ca. 3 mL) solution of the residue was diluted with 1.8 M sulfuric acid (2.3 mL) and then with ethanol (6 mL). A precipitate was collected by filtration, washed with 50% ethanol, and dried in vacuo at 78 °C; yield 516 mg. The crude sulfate was recrystallized from 50% ethanol (30 mL) containing two drops of 1.8 M sulfuric acid and dried at 78 °C over P_2O_5: yield 487 mg (84% as $4{\cdot}0.5H_2SO_4{\cdot}H_2O$); mp 245–248 °C dec (inserted at 195 °C); IR (1700–1500 cm^{-1} region) 1695 (s), 1655 (s), 1625, 1570, 1530 cm^{-1}; MS (direct-probe temperature 130 °C), *m/e* 280 (M), 263 (M − OH), 249 (M − CH_2OH), 233 (M − OH − CH_2OH + H), 231 (M − H_2O − CH_2OH), 205 (M − 75), 177 (P + C_2H_4), 151 (P + 2H), 150 (P + H); UV max (pH 1) 291 nm (ε 10 400), 253 (10 200), 218 (22 400); UV max (pH 7) 280 nm (ε 10 700), 256 (8700), 250 (sh), 216 (29 200); UV max (pH 13) 281 nm (ε 10 900), 256 (8700), 250 (sh); ^{1}H NMR (Me_2SO-d_6) δ 1.4–2.4 (m, CH_2 and $CHCH_2OH$), 3.48 (m, CH_2OH), 3.84 (m, $CHOHCHCH_2OH$), 4.24 (m, $NCHCHOH$), 4.60 (m, NCH), 5.14 (broad m, OH, H_2O, NH_3), 7.8 (NH_2), 8.04 (s, purine CH). Anal. ($C_{11}H_{16}N_6O_3{\cdot}0.5H_2SO_4{\cdot}H_2O$) C, H, N.

(1α,2α,3β,5β)-(±)-3-[2-Amino-6-(methylamino)-9*H*-purin-9-yl]-5-(hydroxymethyl)-1,2-cyclopentane (7) Sulfate. The 2-amino-6-chloropurine (**2**; 200 mg) was treated with methylamine (25 mL) by the method described for the preparation of compound **6**. The reaction mixture from the bomb was concentrated to dryness, and the residue was dissolved in a mixture of water (3 mL), ethanol (3 mL), and 1.8 M sulfuric acid (1 mL). The solution was filtered, and the filtrate was concentrated under reduced pressure by the addition of several portions of ethanol during the concentration. A hot solution of the residual thin syrup in ethanol (10 mL) was filtered, and the filtrate was rewarmed in order to dissolve a slight precipitate, allowed to stand at room temperature, and then stored in a refrigerator overnight. The white crystalline sulfate was collected by filtration, dried in vacuo at room temperature over P_2O_5, and recrystallized from 80% ethanol (5 mL). The white solid was dried in vacuo over P_2O_5 at 78 °C for 4 h: yield 172 mg (69% as the sulfate 1.5-hydrate); mp 166–168 °C dec; MS (direct-probe temperature 150 °C), *m/e* 294 (M), 277 (M − OH), 263 (M − CH_2OH), 247 (M − OH − CH_2OH + H), 245 (M − H_2O − CH_2OH), 219 (M − 75), 191 (P + C_2H_4), 165 (P + 2H), 164 (P + H); UV max (pH 1) 291 nm (ε 11 500), 255 (10 400), 216 (sh), 208 (19 200); UV max (pH 7) 281 nm (13 600), 262 (sh), 215 (23 800); UV max (pH 13) 281 nm (ε 13 600), 262 (sh). Anal. ($C_{12}H_{18}N_6O_3{\cdot}0.5H_2SO_4{\cdot}1.5H_2O$) C, H, N.

(1α,2α,3β,5β)-(±)-3-[2-Amino-6-(methylthio)-9*H*-purin-9-yl]-5-(hydroxymethyl)-1,2-cyclopentanediol (8). A mixture of 300 mg of **2**, 10 mL of methanol (dried over molecular sieves), and 2 mL of 1.0 N sodium methoxide was cooled to 5 °C and saturated with methanethiol. The solution was heated at 104 °C for 18 h in a stainless-steel bomb containing a glass liner. After the bomb had been chilled and opened, the reaction mixture was concentrated to dryness in vacuo, methanol (50 mL) was added to and evaporated from the residue, and a solution of the residue in water (10 mL) was neutralized to pH 7 with 1 N hydrochloric acid. The neutral solution was concentrated to dryness in vacuo at 35 °C, several portions of ethanol were added to and evaporated from the residue, and the residue was then leached with several portions of acetonitrile–ethanol (4:1). The extracts were combined and filtered, and the filtrate was concentrated to dryness in vacuo. A solution of the residue in water–acetonitrile (1:5) was concentrated to a glass that was homogeneous by TLC: yield 248 mg; MS, *m/e* 311 (M). Anal. ($C_{12}H_{17}N_5O_3S{\cdot}H_2O$) C, H, N. A solution of the glass in hot ethyl acetate to which a small amount of ethanol had been added deposited a white solid; two additional crops of solid were obtained by diluting the filtrate with hexane. The solid (three portions combined) was crystallized from ethanol–ethyl acetate, washed with ethyl acetate, and dried in vacuo over P_2O_5 at 78 °C for 2 h: yield 137 mg (38% as an ethanolate); mp 105–109 °C dec; MS (direct-probe temperature 80 °C) *m/e* 311 (M), 293 (M − H_2O), 280 (M − CH_2OH), 264 (M − OH − CH_2OH + H), 262 (M − H_2O − CH_2OH), 236 (M − 75), 208 (P + C_2H_4), 182 (P + 2H), 181 (P + H), 46 (EtOH); IR (1700–1500-cm^{-1} region) 1620 (s), 1580 (s), 1565 (s), 1500 cm^{-1}; UV max (pH 1) 324 nm (ε 11 700), 261 (sh), 248 (9900), 227 (16 600); UV max (pH 7) 310 nm (ε 12 800), 245 (12 100), 224 (ε 21 500); UV max (pH 13) 310 nm (ε 12 900), 245 (12 000), 224 (20 900) (also, slight sh at 261 and 253 nm at pH 7 and 13); ^{1}H NMR (Me_2SO-d_6) δ 1.06 (t, CH_3 of EtOH), 1.4–2.4 (m, CH_2 and $CHCH_2OH$), 2.58 (s, SCH_3), 3.48 (m, CH_2OH), 3.4 (CH_2 of EtOH, overlapped by CH_2OH multiplet of

8), 3.84 (m, CHOHCHCH$_2$OH), 4.26 (m, NCHCHOH), 4.64 (m, NCH), ca. 4.4–5.0 (OH), 6.4 (NH_2), 8.04 (s, purine CH). Anal. ($C_{12}H_{17}N_5O_3S\cdot C_2H_5OH$), C, H, N.

(1α,2α,3β,5β)-(±)-3-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]-pyrimidin-3-yl)-5-(hydroxymethyl)-1,2-cyclopentanediol (10). The 2-amino-6-chloro-8-azapurine[8] (**9**, 875 mg) was treated with liquid ammonia (35 mL) at 60 °C for 18 h by the method described for the preparation of **6**. The solid remaining from the evaporation of volatile components from the reaction mixture was triturated with hot water (25 mL), and the mixture was cooled in an ice bath. The solid was collected by filtration and dried in vacuo over P_2O_5 at 78 °C during 2 h: yield 806 mg. The crude product was recrystallized from water and dried as before: recovery 91%; mp 224–226 °C; shrinking at 198 °C; MS (direct-probe temperature 160 °C), *m/e* 281 (M), 264 (M – OH), 250 (M – CH_2OH), 234 (M – OH – CH_2OH + H), 206 (M – 75), 194, 178 (P + C_2H_4), 176, 152 (P + 2H), 151 (P + H), 150 (P), 126, 110; IR (1700-1500-cm^{-1} region) 1670, 1635 (s), 1605 (s), 1505 (s) cm^{-1}; UV max (pH 1) 286 nm (ε 7700), 256 (9600), 214 (25 500); UV max (pH 7 and 13) 287 nm (ε 10 700), 258 (5800), 223 (26 000). Anal. ($C_{10}H_{15}N_7O_3\cdot H_2O$), C, H, N.

Analytical data obtained from specimens dried for a longer period or at a higher temperature were in agreement with unhydrated **10** or with a one-fourth hydrate of **10**. Three melting temperatures were observed, the highest being 245–247 °C; for example, a specimen dried at 78 °C for 2 h and then at 100 °C for 4 h melted at 199–200 °C, resolidified, melted again at 224–226 °C, resolidified, and melted with decomposition at 245–247 °C.

(1α,2α,3β,5β)-(±)-3-[5-Amino-7-(methylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(hydroxymethyl)-1,2-cyclopentanediol (11). Methanethiol was passed from a cylinder containing the compressed gas into a flask that was immersed in a dry ice–acetone bath at –70 °C and that contained a mixture of anhydrous magnesium sulfate and anhydrous calcium sulfate. The cold mixture was shaken for 3 h to dry the liquid methanethiol (25–30 mL), and the thiol was then passed as a gas into a mixture, protected from atmospheric moisture, of 286 mg of **9** and 25 mL of anhydrous methanol (dried over molecular sieves). A solution of sodium methoxide in methanol (1.48 M, 1.35 mL) was then added, and the mixture was stirred at room temperature under a dry ice condenser for 12 h. The reaction mixture was concentrated to dryness, the residual solid was dissolved in a mixture of methanol (20 mL) and water (3 mL), the solution was neutralized (pH 6–7) with 2 N hydrochloric acid and then concentrated, and the concentrated mixture containing a crystalline precipitate was stored at 5 °C overnight. The white crystalline solid was collected by filtration and dried in vacuo over P_2O_5 at room temperature: yield 242 mg (82%); mp 143–146 °C; MS *m e* 312 (M). TLC revealed the presence of a small amount of an impurity, HPLC indicated that the ratio of **11** to the impurity was 95:5, and a ^{1}H NMR spectrum indicated that the impurity was the analogous 2-amino-6-methoxy-8-azapurine [δ 4.08 (s, OCH_3)]. A specimen was purified further by preparative TLC on silica gel (86:14 butanol–water) and then by recrystallization from water: mp 149–150 °C dec; MS (direct-probe temperature 20 °C), *m/e* 312 (M), 297 (M – CH_3), 295 (M – OH), 284 (M – N_2), 281 (M – OH), 265 (M – SCH_3, M – OH – CH_2OH + H), 237 (M – 75), 235, 225, 209 (P + C_2H_4), 207, 183 (P + 2H), 182 (P + H), 180 (P), 167, 165, 157, 155; IR (1700–1500-cm^{-1} region) 1625, 1590 (s), 1560 (s) 1495 (s) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.6–2.5 (m, CH_2 and CHCH$_2$OH), 2.67 (s, SCH_3), 3.32 (H_2O), 3.48 (m, CH$_2$OH), 3.88 (m, CHOHCHCH$_2$OH), 4.36 (m, NCHCHOH), 4.9 (m, NCH), 4.6–5.1 (m, 3 OH), 7.16 (NH_2); UV max (pH 1) 313 nm (ε 10 800), 278 (9400), 245 (sh), 223 (16 900); UV max (pH 7) 318 nm (ε 10 400), 277 (8500), 247 (sh), 225 (17 400); UV max (pH 13) 317 nm (ε 10 700), 275 (8600), 245 (sh), 223 (16 900). Anal. ($C_{11}H_{16}N_6O_3S\cdot 0.67H_2O$) C, H, N.

Antiviral Evaluations in Vitro. The methods and procedures used in the evaluations of compounds **2–11** for antiviral activity in vitro have been described previously.[16,20] The viruses and host cells, replicating in culture, used in these evaluations were the following: strain HF of HSV-1, H.Ep.-2 cells; the Lederle chorioallantoic strain of vaccinia virus, H.Ep.-2 cells; influenza virus, Madin-Darby canine kidney cells.

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