radiation chemical yield measured in mol J^{-1}).

γ-Radiolysis. Quinone solutions were first saturated with N_2O gas in syringes as above, before being irradiated by a ^{60}Co source. Dose rates of 36 Gy min^{-1} were used, as measured by Fricke dosimetry.[30] Ion-selective electrodes for bromide (Russell pH Ltd.) and chloride (E.I.L.) were then used to monitor the release of leaving groups from quinones 1 and 2. Upon completion of irradiation, 20-mL aliquots of quinone solution were mixed with an ionic strength adjuster (20 mL of 0.2 M KNO_3 in the case of bromide ion detection, and 2 mL of 0.5 M ammonium acetate with 0.5 M acetic acid for chloride ions), and electrode measurements were carried out with continuous N_2 gassing to minimize reoxygenation. Results were compared with predetermined calibration measurements.

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Acknowledgment. This work was supported by the Cancer Research Campaign and by Grant CH-211 from the American Cancer Society. We thank Dr. G. M. Cohen (School of Pharmacy, University of London) for helpful discussions and for providing a sample of thiodione.

Synthesis and Anti-Herpes-Virus Activity of Acyclic 2′-Deoxyguanosine Analogues Related to 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine[1,2]

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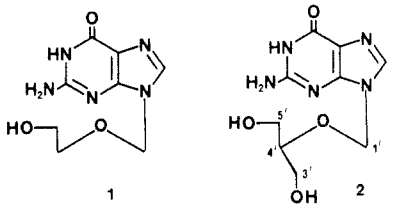
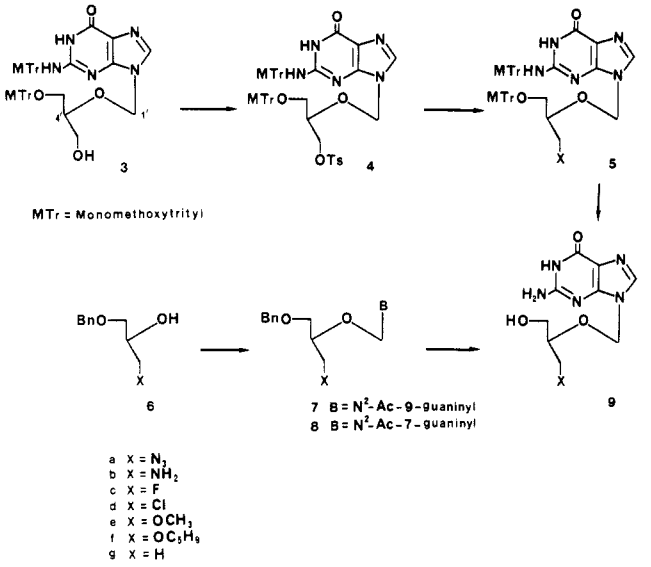
Several "sugar" modified acyclic nucleoside analogues related to 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **2**) were synthesized and evaluated for antiviral activity. The preparation generally involved the condensation of the acetoxymethyl ether of alcohols **6c–g** and **10–12a** with diacetylguanine to give adducts **7c–g** and **14–16**, which were then deprotected to afford analogues **9c–g** and **17–19**. Alternatively, alcohols **12a** and **13a** were converted to iodides via their tosylates **12b** and **13b** and then reacted with the sodium salt of guanine to afford, after deprotection, analogues **22** and **23**. A crossed aldol–Cannizzaro reaction on aldehyde **27** readily afforded **28**, which was deprotected to give analogue **29**. An in vitro assay against HSV-1 showed that all compounds tested were less active than DHPG, though several were good substrates for the viral thymidine kinase. The more promising acyclic nucleosides **9c**, **19**, and **29** were evaluated in a mouse encephalitis model and proved ineffective at preventing death at a dose of 20 mg/kg.

The report of the anti-herpes-virus activity of acyclovir (**1**)[4] followed more recently by the discovery of the substantially greater in vivo potency of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **2**)[5,6] has stimulated a



substantial research effort in the synthesis of acyclic guanosine analogues.[7]

Scheme I



Both acyclovir and DHPG are unusually selective as compared to other nucleoside antiviral agents.[8] The se-

(1) Contribution 206 from the Institute of Bio-Organic Chemistry, Syntex Research.

(2) Presented in part at the 185th National Meeting of the American Chemical Society, Seattle, WA; March 24, 1983; CARB 43.

(3) Current address: Pharmaceutical Research and Development, Bristol-Myers Co., Wallingford, CT 06492-7660.

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(6) The structural formulas of DHPG (**2**) and the related acyclic nucleoside analogues have been depicted in a "ribose-like" conformation only to draw attention to the similarity in structure between these compounds and 2′-deoxynucleosides. In accordance with this representation, the two terminal carbons of the glycerol are referred to as the 3′ and 5′ positions.

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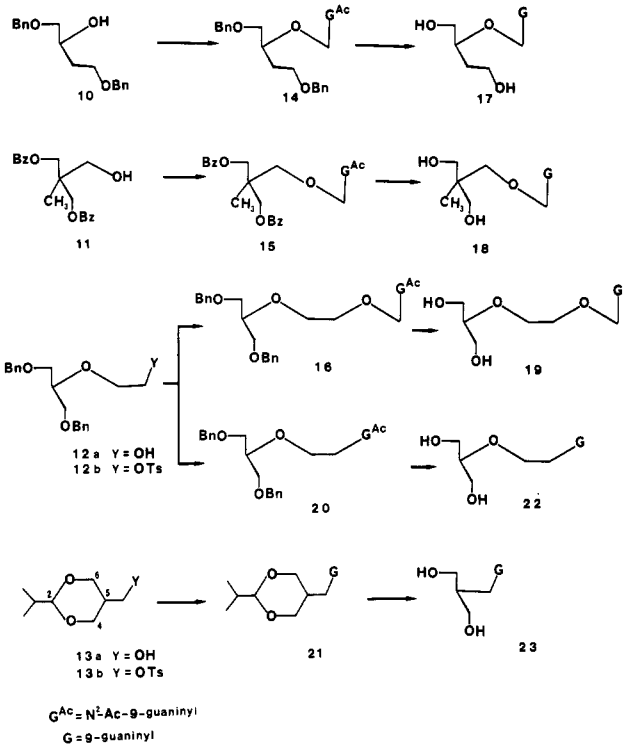
Scheme II



lectivity of these analogues is due in part to the fact that they are appreciably phosphorylated only in virus-infected cells, where a virus-specified thymidine kinase of low substrate specificity converts the nucleoside analogues to monophosphates.[9] The monophosphates are next converted to diphosphates and then to the corresponding nucleoside triphosphates by cellular enzymes. The triphosphates prevent virus replication by inhibition of the viral DNA polymerase. Additional selectivity is realized at this stage because the host polymerase is less sensitive than the viral polymerase to the nucleoside triphosphate analogue.

We have been synthesizing a number of analogues of DHPG in order to further study the effects of structural modifications on antiviral activity and toxicity and now report the preparation and antiviral activity of a number of "sugar" modified DHPG analogues.

Chemistry. The synthesis of the DHPG analogues with one of the alcohol functionalities on the side chain replaced by another functionality is depicted in Scheme I. DHPG was converted to N^2,*O*-bis(monomethoxytrityl) derivative **3** in 43% yield. Tosylation of **3** gave **4**, which was converted to azide **5a** in 96% overall yield. Deprotection of **5a** with aqueous acetic acid gave azide **9a** (88%). Alternatively, reduction of **5a** with Raney nickel afforded **5b**, which was deprotected to furnish amine **9b** (78% overall).

Substituted glycerol derivatives **6c–g** were used for the synthesis of other analogues. Halohydrins **6c,d** were prepd. by the BF_3 etherate catalyzed opening of epifluorohydrin and epichlorohydrin with benzyl alcohol.[10] Ethers **6e,f** were synthesized by the treatment of **6d** with the appropriate sodium alcoxide. Propylene glycol derivative **6g** was prepared by the reaction of propylene oxide with sodium benzoxide. Alcohols **6c–g** were chloromethylated, treated with sodium acetate, and then reacted with N^2,9-diacetylguanine to give **7c–g** and **8c–g** (Table I). The isomers were separated by chromatography. The structures of the N^9-isomers **7** and **9** and the N^7-isomer **8** were con-

Table I. Physical Data

compd	% yield	mp, °C/solvent	formula
3	43	159–161/ethanol	$C_{49}H_{45}N_5O_6 \cdot 0.5H_2O$
4	99	126–128/ethanol	$C_{56}H_{51}N_5O_8S$
5a	96	190–192/ethyl acetate–hexane	$C_{49}H_{44}N_8O_5 \cdot H_2O$
5b	80	206–210 dec/methanol-dichloromethane	$C_{49}H_{46}N_6O_5 \cdot 2H_2O$
6c	33	oil	$C_{10}H_{13}O_2F$
6e	75	oil	$C_{11}H_{16}O_3$
6f	64	oil	$C_{15}H_{22}O_3$
6g	46	oil	$C_{10}H_{14}O_2$
7c	18	167–170/methanol–ethyl acetate	$C_{18}H_{20}N_5O_4F$
7d	20	174–175/methanol–ethyl acetate	$C_{18}H_{20}N_5O_4Cl$
7e	16	140–141/ethyl acetate–hexane	$C_{19}H_{23}N_5O_5$
7f	19	146–148/ethyl acetate–hexane	$C_{23}H_{29}N_5O_5$
7g	15	173–175/ethanol	$C_{18}H_{21}N_5O_4$
8c	11	127–133/ethanol	$C_{18}H_{20}N_5O_4F$
8d	6	151–153/ethyl acetate–hexane	$C_{18}H_{20}N_5O_4Cl$
8e	3	94–95/ethyl acetate–hexane	$C_{19}H_{23}N_5O_5 \cdot 0.5H_2O$
8f	5	102–103/ethyl acetate–hexane	$C_{23}H_{29}N_5O_5$
9a	88	207–208/water–methanol	$C_9H_{12}N_8O_3$
9b[a]	78	157–158/water–ethanol	$C_9H_{14}N_6O_3 \cdot HCl \cdot 0.25H_2O$
9c	32	255–256/water–methanol	$C_9H_{12}N_5O_3F \cdot 0.5H_2O$
9d	50	206–208/water–methanol	$C_9H_{12}N_5O_3Cl$
9e	67	208–210/water–methanol	$C_{10}H_{15}N_5O_4 \cdot 0.5H_2O$
9f	78	224–226/water–methanol	$C_{14}H_{21}N_5O_4$
9g[b]	91	275 dec/water/ethanol	$C_9H_{13}N_5O_3 \cdot H_2O$
10	87	oil	$C_{18}H_{22}O_3$
11	50	oil	$C_{19}H_{20}N_5$
12a	50	oil	$C_{19}H_{24}O_4$
12b	92	oil	$C_{26}H_{30}O_6S$
13b	66	89–90/diethyl ether–petroleum ether	$C_{15}H_{22}O_5S$
14	11	122–124/ethyl acetate–hexane	$C_{26}H_{29}N_5O_5$
15	30	184–186/ethyl acetate–hexane	$C_{27}H_{27}N_5O_7$
16	25	133–135/ethyl acetate–ether	$C_{27}H_{31}N_5O_6$
17	55	222–223/water–methanol	$C_{10}H_{15}N_5O_4 \cdot 0.5H_2O$
18	81	230–232/methanol	$C_{11}H_{17}N_5O_4 \cdot H_2O$
19	67	167–169/ethanol	$C_{11}H_{17}N_5O_5$
20	4	144–146/ethyl acetate–hexane	$C_{26}H_{29}N_5O_5$
21	29	293–295/methanol	$C_{13}H_{19}N_5O_3$
22	50	220–222/methanol	$C_{10}H_{15}N_5O_4$
23	77	297–298/water–methanol	$C_9H_{13}N_5O_3$
24	98	243–244/methanol	$C_{10}H_{13}N_5O_4$
26	78	179–181/ethanol	$C_{28}H_{27}N_5O_4 \cdot 0.5H_2O$
28	53	159–161/ethanol	$C_{30}H_{31}N_5O_6 \cdot 1.5H_2O$
29[c]	85	>300/water	$C_{10}H_{15}N_5O_5$

[a] Mp reported 158–160 °C.[7g] [b] Previously disclosed without physical data.[9b] [c] Mp reported >300 °C.[15]

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Scheme III

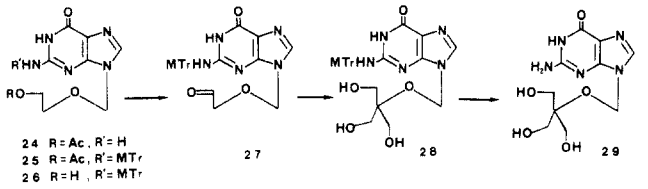

Table II. Phosphorylation of Nucleoside Analogues by Purified HSV-1 (F Strain) Thymidine Kinase and Antiviral Activities against HSV-1 (F Strain) in Cell Culture

compd	vel, % rel to thymidine	ID_{50}, μM	compd	vel, % rel to thymidine	ID_{50}, μM
1	23	0.5	**9g**	(28)[b]	(2.3)[b]
2	98	0.2 (0.5)[a]	17	111	95
9a	25	>100	18	100	>100
9b	<10	32 (100)[a]	19	23	7 (>100)[a]
9c	67	7 (>100)[a]	22	35	>100
9d	33	60	23		>100
9e	32	70	29	77	3.5[c] (55)[a]
9f	21	40			

[a] Antiviral activities against HSV-2 (G strain) in cell culture. [b] Biological data previously reported.[9b] [c] ID_{50} previously reported 54 μM.[15]

firmed by spectroscopic comparisons (^{13}C NMR,[11] UV) with the natural nucleosides. The N^9-isomers **7c–g** were deprotected by normal or transfer hydrogenation[12] and then ammonolysis to give **9c–g**.

Alcohols **10–13a** were used as starting materials for the synthesis of chain-length-modified analogues of DHPG (Scheme II). Alcohol **10** was synthesized by the treatment of 4-benzyloxy-1-butene oxide[13] with sodium benzoxide. Dibenzoate **11** was synthesized by the reaction of the corresponding triol with 2 equiv of benzoyl chloride. Hydroxyethyl derivative **12a** was prepared by reacting the sodium salt of 1,3-di-*O*-benzyl glycol with bromoacetaldehyde diethyl acetal followed by hydrolysis and reduction.

Alcohols **10–12a** were converted as described for the preparation of **7c** to their corresponding acetoxymethyl ethers and then condensed with diacetylguanine to give **14–16**. Standard deprotection afforded analogues **17–19**. Alternatively, alcohols **12a** and **13a**[14] were converted to their corresponding iodides via the tosylate intermediates **12b** and **13b** and then reacted with the sodium salt of guanine to give intermediates **20** (includes acetylation to aid purification) and **21**. Deprotection gave the free acyclic nucleosides **22** and **23**.

The trihydroxy analogue **29**, recently reported by Ogilvie and co-workers,[15] was synthesized by a method developed in this laboratory for the synthesis of 4'-hydroxymethylated nucleosides.[16] Acyclovir (1) was acetylated to give **24**, which in turn was monomethoxytritylated to **25** and then deacetylated to furnish **26**. Moffatt oxidation of **26** afforded intermediate aldehyde **27**, which was hydroxymethylated by treatment with paraformaldehyde and NaOH to give **28**. Deprotection of **28** with aqueous acetic acid afforded the desired analogue **29** (Scheme III).

Table III. Effects of Subcutaneous Treatment with **9c**, **19**, and **29** on an HSV-2 Encephalitis Infection in Mice

compd	dose, mg/kg	survivors/total	mean survival time, days
placebo		2/20 (10%)[a]	9.2 ± 1.9[b]
DHPG	20	10/16 (62%)[c]	13.5 ± 1.8[d]
9c	20	2/10 (20%)[e]	8.5 ± 1.1[e]
19	20	3/10 (30%)[e]	10.3 ± 1.5[d]
29	20	3/10 (30%)[e]	9.3 ± 0.75[e]

[a] Percent survival. [b] Standard deviation. [c] Statistical significance of $p < 0.05$ by two-tailed Fisher exact test. [d] Statistical significance of $p < 0.05$ by two-tailed Mann–Whitney test. [e] Not statistically significant.

Biological Results and Discussion

The antiviral activities of the "sugar" modified DHPG analogues were determined against herpes simplex virus type 1 (F strain) by plaque reduction in Vero cells. The ability of these analogues to function as substrates for a viral-specified thymidine kinase was also measured and compared with the above in vitro antiviral effect (Table II). The data in the table indicate that of the C-3′ (C-5′) substituted analogues, **9a–f**, the fluoro analogue **9c** is the more active member and is phosphorylated by the viral kinase at 67% the rate of thymidine. Although analogues **9a–f** are phosphorylated by the viral kinase at rates comparable to acyclovir, the attenuated antiviral activity exhibited by these compounds can possibly be attributed to the inefficient conversion of the substrate to the triphosphate or, once at that level, failure to inhibit the viral DNA polymerase. This is further evinced by the low antiviral activity of homologues **17** and **18** in spite of their phosphorylation by the viral kinase at a rate comparable to that of thymidine (100%). In addition, it has previously been demonstrated that certain analogues of DHPG[7e] and acyclovir[9b] were inactive as antivirals despite being substrates for the viral kinase.

Examination of the series of compounds **17–19**, **22**, **23**, and **29** clearly demonstrates that a change of one or two carbons or branching at various points on the DHPG "sugar" portion generally leads to decreased antiviral activity, although some affinity for the viral kinase is retained. Prominent among these are compounds **19** and **29**, which retained moderate in vitro antiviral activities with ID_{50} of 7 and 3.5 μM, respectively, against HSV-1.

It should be noted that compounds **9a–g** and **17**, due to the method of preparation, are in fact racemic mixtures. The two enantiomeric forms need not necessarily have the same antiviral activity.[17]

The in vivo efficacies of the more promising analogues **9c**, **19**, and **29** were compared with DHPG in a mouse encephalitis model (Table III). All three compounds tested showed no activity at a dose of 20 mg/kg in terms of survivor increase, but analogue **19** did statistically increase the mean survival time. In a related experiment in mice (HSV-2 encephalitis), compound **9b** showed a 31% increase in survivors at a dose of 500 mg/kg as compared to an equipotent dose of 200 mg/kg for acyclovir. Compound **9g** was inactive when tested at this high dose.

Experimental Section

Nuclear magnetic resonance spectra were recorded on samples dissolved in deuteriodimethyl sulfoxide unless otherwise stated.

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For convenience and where applicable, the peak assignments of the two terminal carbons of the glycerol side chain are numbered 3′ and 5′. All chromatographic purifications were carried out on silica gel. Melting points were determined on a hot-stage microscope and are corrected.

N^2-(*p*-Anisyldiphenylmethyl)-9-[[1-(*p*-anisyldiphenylmethoxy)-3-hydroxy-2-propoxy]methyl]guanine (3). A mixture of **2** (8.18 g, 32 mmol), *p*-anisylchlorodiphenylmethane (21.7 g, 70 mmol), triethylamine (13.3 mL, 95 mmol), and 4-(dimethylamino)pyridine (0.08 g, 0.7 mmol) in DMF (100 mL) was magnetically stirred under a drying tube at 40 °C for 2 h; then methanol (10 mL) was added, and the solvents were evaporated. The residue was dissolved in ethyl acetate, washed with aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated. The resulting oil was chromatographed (1:14 methanol/dichloromethane) and the product crystallized from ethanol to give 11.2 g (43%) of **3**: UV λ_{max} (methanol) 279 nm (ϵ 13 000), 260 (12 000); ^{1}H NMR δ 10.63 (br s, 1 H, NH), 7.75 (s, 1 H, H-8), 7.66 (s, 1 H, NH), 7.24, 7.13, 7.05, 6.85, 6.70 (m, 28 H, aromatic), 5.04, 4.96 (AB, J = 11 Hz, 2 H, H-1), 4.39 (t, 1 H, OH), 3.77, 3.59 (s, 6 H, OCH_3), 3.47 (m, 1 H, H-4′), 3.05, 2.95 (ABM, 2 H, J = 1, 3, 11 Hz, CH_2OH), 2.77, 2.60 (ABM, 2 H, J = 5, 11 Hz, CH_2OMTr).

N^2-(*p*-Anisyldiphenylmethyl)-9-[[1-(*p*-anisyldiphenylmethoxy)-3-(*p*-toluenesulfonyloxy)-2-propoxy]methyl]guanine (4). A solution of **3** (11.5 g, 14.1 mmol) and *p*-toluenesulfonyl chloride (10.5 g, 55 mmol) in pyridine (100 mL) was kept at room temperature for 2 days, and then water (10 mL) was added. The solution was evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to give 11.6 g (100%) of **4** as a foam. An analytical sample was obtained by crystallization from ethanol: UV λ_{max} (methanol) 273 nm (ϵ 15 100), 260 (16 400); ^{1}H NMR δ 10.69 (br s, 1 H, NH), 7.76 (s, 1 H, H-8), 7.74 (br s, 1 H, NH), 7.66–6.67 (m, 32 H, aromatic), 5.03 and 4.84 (AB, J = 12 Hz, 2 H, H-1′), 3.77 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.60–3.30 (m, 3 H, H-4′, CH_2OTs), 2.63 (m, 2 H, CH_2OMTr), 2.45 (s, 3 H, CH_3).

N^2-(*p*-Anisyldiphenylmethyl)-9-[[1-(*p*-anisyldiphenylmethoxy)-3-azido-2-propoxy]methyl]guanine (5a). A solution of **4** (11.6 g, 14.1 mmol) and NaN_3 (5.0 g, 77 mmol) in DMF (100 mL) was heated at 105 °C for 3 days. The solution was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to give 11.1 g (96%) of **5a** as a foam. An analytical sample was obtained by crystallization from ethyl acetate/hexane: UV λ_{max} (methanol) 276 nm (ϵ 13 900), 260 (14 900); IR 2100 (N_3) cm^{-1}; ^{1}H NMR δ 10.68 (br s, 1 H, NH), 7.78 (s, 1 H, H-8), 7.68–7.35 (m, 28 H, aromatic), 5.03 and 4.95 (AB, J = 12 Hz, 2 H, H-1′), 3.77 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3), 3.54 (m, 1 H, H-4′), 3.06–2.55 (m, 4 H, H-3′, H-5′).

9-[[3-Amino-1-(*p*-anisyldiphenylmethoxy)-2-propoxy]methyl]-N^2-(*p*-anisyldiphenylmethyl)guanine (5b). A mixture of **5a** (11.1 g, 13.5 mmol) and Raney nickel[18] (60 g) in THF (150 mL) and ethanol (200 mL) was magnetically stirred under H_2 (1 atm) for 4 days. The mixture was filtered through Celite and the filtrate evaporated to dryness. The residue was chromatographed (1:9 methanol/dichloromethane) to give 8.63 g (80%) of **5b** as a foam: UV λ_{max} (methanol) 276 nm (ϵ 14 700), 260 (16 400), 232 (30 300); ^{1}H NMR δ 7.79 (br s, 1 H, NH), 7.76 (s, 1 H, H-8), 7.37–6.68 (m, 28 H, aromatic), 5.03 and 4.80 (AB, J = 12 Hz, 2 H, H-1′), 3.77 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3), 3.40 (m, 1 H, H-4′), 2.82 (m, 2 H, CH_2OMTr), 2.40 (m, 2 H, CH_2NH_2).

9-[(1-Azido-3-hydroxy-2-propoxy)methyl]guanine (9a). A solution of **5a** (1.24 g, 1.5 mmol) in 80% aqueous acetic acid (20 mL) was heated at 80 °C for 2 h and then evaporated to dryness. The residue was triturated with 1:3 ethyl acetate/hexane and then crystallized from water/methanol to give 0.37 g (88%) of **9a**: UV λ_{max} (0.1 N HCl) sh 275 nm (ϵ 8000), 256 (11 100), (0.1 N NaOH) 265 (10 400); IR 2110 (N_3) cm^{-1}; ^{1}H NMR δ 10.69 (br s, 1 H, NH), 7.83 (s, 1 H, H-8), 6.51 (br s, 2 H, NH_2), 5.47 (s, 2 H, H-1′), 4.87 (t, J = 5 Hz, 1 H, OH), 3.79 (m, 1 H, H-4′), 3.40 (m, 2 H, CH_2OH), 3.35, 3.27 (ABX, J = 6 and 12 Hz, 2 H, CH_2N_3); ^{13}C NMR (75.453 MHz) δ 156.77 (C-6), 153.76 (C-2), 151.30 (C-4), 137.53 (C-8), 116.38 (C-5), 78.04 (C-4′), 71.12 (C-1′), 60.59 (CH_2OH), 50.98 (CH_2N_3).

9-[(1-Amino-3-hydroxy-2-propoxy)methyl]guanine Hydrochloride (9b). A solution of **5b** (8.63 g, 10.3 mmol) in 0.1 N methanolic HCl (500 mL) was kept at room temperature for 15 h and then evaporated to dryness. The residue was crystallized from water/ethanol to give 2.34 g (78%) of **9b**: UV λ_{max} (0.1 N HCl) sh 276 nm (ϵ 8300), 257 (12 000), (0.1 N NaOH) 266 (10 800); ^{1}H NMR δ 10.85 (br s, 1 H, NH), 8.00 (br s, 3 H, NH_3Cl), 7.87 (s, 1 H, H-8), 6.69 (br s, 2 H, NH_2), 5.50 and 5.43 (AB, J = 11 Hz, 2 H, H-1′), 3.87 (m, 1 H, H-4′), 3.52 and 3.42 (after D_2O added, ABX, J = 5 and 11 Hz, 2 H, CH_2OH), 3.05 and 2.90 (after D_2O added, ABX, J_{AB} = 12 Hz, J_{AX} = 8 Hz, J_{BX} = 3 Hz, 2 H, CH_2NH_2).

1-Benzyloxy-3-fluoro-2-propanol (6c). A solution of epifluorohydrin (10 g, 0.13 mol), benzyl alcohol (35 mL, 0.34 mol), and BF_3 etherate (1.5 mL, 15 mmol) was kept at 0 °C for 2 h and then at room temperature for 17 h. The solution was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to an oil. The residual oil was chromatographed with 3:10 ethyl acetate/hexane to give 7.94 g (33%) of **6c**: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 7.35 (s, 5 H, aromatic), 4.75, 4.20 (dd, J = 55, 3 Hz, 2 H, H-3), 4.57 (s, 2 H, benzylic), 4.0 (m, 1 H, H-2), 3.58 (m, 2 H, H-1), 2.40 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 22.62 MHz) δ 137.74, 128.61, 127.86 (aromatic), 86.97 (d, J = 169 Hz, C-F), 73.67 (benzylic), 70.07 (d, J = 6.6 Hz, C-1), 69.43 (d, J = 22 Hz, C-2).

1-Benzyloxy-3-methoxy-2-propanol (6e). A solution of **6d** (20 g, 100 mmol) in 0.2 N methanolic $NaOCH_3$ was stirred for 16 h at room temperature then refluxed for 9 h. The resulting suspension was left at room temperature 16 h and was then concentrated and the residue partitioned between ethyl acetate and 5% aqueous HCl. The organic phase was washed successively with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to an oil, which was distilled at 101–105 °C/1 torr to afford 14.7 g (75%) of **6e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.28 (m, 5 H, aromatic), 4.56 (s, 2 H, benzylic), 4.0 (m, 1 H, *CH*OH), 3.55 and 3.50 (ABX, 2 H, J_{AX} = 4.4 Hz, J_{BX} = 6.3 Hz, J_{AB} = 6.8 Hz, CH_2OR), 3.47 and 3.43 (ABX, 2 H, J_{AX} = J_{AB} = 4.4 Hz, J_{BX} = 6.2 Hz, CH_2OR), 3.38 (s, 3 H, OCH_3), 2.55 (d, 1 H, OH); ^{13}C NMR ($CDCl_3$, 75.453 MHz) δ 138.23, 128.59, 127.88 (aromatic), 73.98 (CH_2OCH_3), 73.54 (benzylic), 71.50 (CH_2OBn), 69.54 (CHOH), 59.20 (OCH_3).

N^2-Acetyl-9-[(1-benzyloxy-3-fluoro-2-propoxy)methyl]guanine (7c). Hydrogen chloride gas (dried through concentrated H_2SO_4) was bubbled into a stirred mixture of **6c** (6.0 g, 33 mmol) and paraformaldehyde (2.0 g, 67 mmol) in dichloroethane (100 mL) at 0 °C until all the solids dissolved (3 h). The resulting solution was stored at 0 °C for 16 h, dried over $MgSO_4$, and evaporated to a clear oil. A solution of the oil and sodium acetate (4.0 g, 49 mmol) in DMF (75 mL) was kept at room temperature for 16 h and then evaporated to dryness. The residual oil was dissolved in ethyl acetate, washed with water and brine, dried over Na_2SO_4, and evaporated to a clear oil. A mixture of the oil, diacetylguanine (13.0 g, 55 mmol), bis(*p*-nitrophenyl)phosphate (0.10 g, 0.3 mmol), and sulfolane (22 mL) was heated at 95 °C with stirring for 5 days. The mixture was diluted with methanol and filtered through Celite. The filtrate was evaporated to dryness and chromatographed (1:19 methanol/dichloromethane) to give after crystallization from ethyl acetate 2.30 g (18%) of **7c**: UV λ_{max} (methanol) 279 nm (ϵ 11 500), 258 (16 000); ^{1}H NMR (300 MHz) δ 8.14 (s, 1 H, H-8), 7.35–7.18 (m, 5 H, aromatic), 5.59 and 5.58 (AB, J = 3 Hz, 2 H, H-1′), 4.62–4.30 (m, 4 H, CH_2F, benzylic), 4.08 (m, 1 H, H-4′), 3.61–3.38 (m, 2 H, CH_2O), 2.18 (s, 3 H, CH_3); ^{13}C NMR (22.62 MHz) δ 173.60 ($COCH_3$), 154.91 (C-6), 148.80 (C-4), 148.08 (C-2), 139.99 (C-8), 137.97, 128.18, 127.70, 127.21 (aromatic), 120.22 (C-5), 82.76 (d, J = 168.4 Hz, CH_2F), 76.16 (d, J = 18.4 Hz, C-4′), 72.24 (benzylic) 72.04 (C-1′), 68.19 (d, J = 8.1 Hz, CH_2OBn), 23.67 ($COCH_3$).

N^2-Acetyl-7-[(1-(benzyloxy)-3-fluoro-2-propoxy)methyl]guanine (8c). From the above chromatographic purification of **7c**, 1.39 g (11%) of **8c** was isolated after crystallization from ethyl acetate: UV λ_{max} (methanol) 264 nm (ϵ 13 800); ^{1}H NMR (300 MHz) δ 8.38 (s, 1 H, H-8), 7.31–7.23 (m, 5 H, aromatic), 5.78 (s, 2 H, H-1′), 4.60–4.10 (m, 5 H, CH_2F, H-4′, benzylic), 3.45 (m, 2 H, CH_2O), 2.18 (s, 3 H, $COCH_3$); ^{13}C NMR (75.453 MHz) δ 173.32 ($COCH_3$), 157.44 (C-4), 152.44 (C-6), 147.13 (C-2), 144.96 (C-8), 137.94, 128.09, 127.54, 127.28 (aromatic), 110.90 (C-5), 82.70

(18) Raney nickel was prepared as described by Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 729.

(d, J = 168.5 Hz, CH_2F), 75.87 (d, J = 17.8 Hz, C-4'), 74.53 (C-1'), 72.18 (benzylic), 68.18 (d, J = 8.4 Hz, CH_2OBn), 23.63 ($COCH_3$).

9-[(3-Fluoro-1-hydroxy-2-propoxy)methyl]guanine (9c). A mixture of **7c** (1.05 g, 2.7 mmol), 2 drops of concentrated HCl, and 10% Pd/C in methanol (200 mL) and water (50 mL) was treated on a Parr hydrogenator with H_2 (50 psi) for 4 days. The mixture was filtered and the filtrate evaporated to dryness. A solution of the residue in concentrated NH_4OH (5 mL) and methanol (25 mL) was kept at room temperature for 18 h and then evaporated to dryness. The residue was crystallized from water/methanol to give 0.22 g (32%) of **9c**: UV λ_{max} (methanol) sh 273 nm (ϵ 9030), 253 (13 600); ^{1}H NMR (300 MHz) δ 7.83 (s, 1 H, H-8), 6.53 (br s, 2 H, NH_2), 5.45 (s, 2 H, H-1'), 4.88 (t, J = 5 Hz, 1 H, OH), 4.60–4.25 (m, 2 H, CH_2F), 3.91–3.76 (m, 1 H, H-4'), 3.40 (m, 2 H, CH_2OH); ^{13}C NMR (22.62 MHz) δ 156.79 (C-6), 153.77 (C-2), 151.36 (C-4), 137.68 (C-8), 116.38 (C-5), 82.68 (d, J = 167.7 Hz, CH_2F), 77.49 (d, J = 18.4 Hz, C-4'), 71.23 (C-1'), 59.15 (d, J = 8.1 Hz, CH_2OH).

1,3-Di-*O*-benzyl-2-*O*-(2-hydroxyethyl)glycerol (12a). A mixture of NaH (2.0 g, 50%, 42 mmol, prewashed with hexanes) and 1,3-di-*O*-benzylglycerol[10] (10.0 g, 37 mmol) in DMF (25 mL) was heated at 50 °C for 0.5 h then cooled to 0 °C. Bromoacetaldehyde diethyl acetal (6.3 mL, 42 mmol) was added and the resulting solution heated at 50 °C for 17 h then evaporated. The residue was dissolved in ether, washed with water and brine, dried over Na_2SO_4, and evaporated. The resulting clear oil was chromatographed (2:8 ethyl acetate/hexane) to give 8.9 g (62%) of 1,3-di-*O*-benzyl-2-*O*-(2,2-diethoxyethyl)glycerol as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 10 H, phenyl), 4.64 (t, J = 5 Hz, 1 H, acetal-H), 4.54 (s, 4 H, benzylic), 3.77 (m, 1 H, CHO), 3.71–3.51 (m, 10 H, CH_2O), 1.18 (t, J = 7 Hz, 6 H, CH_3).

To the above adduct (25 g, 64.3 mmol) in THF (60 mL) and H_2O (5 mL) was added *p*-toluenesulfonic acid (300 mg), and the solution was refluxed 7 h then evaporated. The residual oil was partitioned between toluene and dilute $KHCO_3$, and the organic phase was dried with Na_2SO_4 and evaporated to a yellow oil. The crude aldehyde was redissolved in MeOH (60 mL) at 0 °C to which was added $NaBH_4$ (2.0 g, 52.8 mmol). The reaction was stirred for 30 min then evaporated. The residue was partitioned between toluene and dilute HCl (1×), dilute $KHCO_3$ (1×), and H_2O (1×); the organic phase was dried with Na_2SO_4 and evaporated to a golden oil. Fractional distillation afforded 9.93 g (48%) of pure **12a**: bp 195–200 °C/0.5 torr; ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 10 H, phenyl), 4.60 (s, 4 H, benzylic), 3.75 (m, 5 H, H-4' and ethoxy), 3.55 (d, 4 H, H-3', H-5'), 3.05 (br, 1 H, OH).

5-[(*p*-Toluenesulfonyloxy)methyl]-2-isopropyl-1,3-dioxane (13b). A solution of alcohol **13a** (1 g, 6.17 mmol)[14] and *p*-toluenesulfonyl chloride (1.43 g, 7.5 mmol) in pyridine (10 mL) was stirred for 16 h at room temperature and then evaporated. The residue was redissolved in dichloromethane and partitioned with aqueous Na_2CO_3, dried ($MgSO_4$), and evaporated to a yellow oil. Chromatography (CH_2Cl_2) followed by crystallization from diethyl ether–petroleum ether yielded 1.3 g (66%) of **13b**: ^{1}H NMR δ 7.78 (d, 2 H, J = 8.4 Hz, aromatic), 7.37 (d, 2 H, J = 8.6 Hz, aromatic), 4.10 (d, 1 H, J = 5.2 Hz, H-2), 4.05, 3.45 (ABX, 4 H, J_{AX} = 5 Hz, J_{BX} = 11.2 Hz, J_{AB} = 11.4 Hz, H-4, H-6), 3.80 (d, 2 H, J = 5.7 Hz, CH_2OTs), 2.46 (s, 3 H, aromatic CH_3), 2.32 (m, 1 H, H-5), 1.77 (m, 1 H, CH), 0.90 (d, 6 H, J = 6 Hz, CH_3).

9-[(2-Isopropyl-1,3-dioxan-5-yl)methyl]guanine (21). A suspension of the sodium salt of guanine (1.24 mmol), **13b** (3.9 g, 1.24 mmol), and NaI (0.6 g, 4 mmol) in DMF (15 mL) was heated at 100–110 °C for 16 h then cooled, diluted with 20% methanol–dichloromethane (70 mL), filtered through Celite, and evaporated. The residue was chromatographed (15% methanol–CH_2Cl_2), and crystallization from methanol afforded 1.12 g (29%) of **21**: UV λ_{max} (0.1 N HCl) 281 nm (ϵ 7740), 254 (10 900), (0.1 N NaOH) 268 (10 300), sh 254 (9450); ^{1}H NMR δ 7.63 (s, 1 H, H-8), 6.47 (br s, 2 H, NH_2), 4.16 (d, 2 H, H-2'), 4.87, 3.43 (ABX, 4 H, J = 4.7, 11 Hz, H-4', H-6'), 3.75 (d, 2 H, J = 7.3 Hz, CH_2-G), 2.40 (m, 1 H, H-5'), 1.69 (m, 1 H, CH), 0.83 (d, 6 H, J = 6 Hz, CH_3).

9-[3-Hydroxy-2-(hydroxymethyl)prop-1-yl]guanine (23). A solution of **21** (254 mg, 0.87 mmol) in 90% aqueous trifluoroacetic acid was stirred at room temperature for 20 min and then evaporated. The residue was coevaporated 3 times with ethanol, triturated twice with acetone, and the resulting solid crystallized from methanol/water to afford **23** (159 mg, 77%) in two crops: UV λ_{max} (0.1 N HCl) 278 nm (ϵ 7300), 253 (11 000), (0.1 N NaOH) 268 (9990), 254 (9160); ^{1}H NMR δ 7.59 (s, 1 H, H-8), 6.46 (br s, 2 H, NH_2), 4.6 (t, 2 H, OH's), 3.96 (d, 2 H, J = 6.8 Hz, CH_2), 3.34 (m, 4 H, CH_2OH), 2.02 (m, 1 H, CH).

9-[(2-Acetoxyethoxy)methyl]guanine (24). A mixture of 1 (3.0 g, 13.3 mmol) and 4-(dimethylamino)pyridine (0.30 g, 2.5 mmol) in acetic anhydride (100 mL) was vigorously stirred at room temperature for 5 days and then evaporated to dryness. The residue was crystallized from methanol to give 3.48 g (98%) of **24**: UV λ_{max} (methanol) sh 275 nm (ϵ 10 000), 254 (14 000); ^{1}H NMR δ 10.69 (br s, 1 H, NH), 7.83 (s, 1 H, H-8), 6.53 (br s, 2 H, NH_2), 5.37 (s, 2 H, NCH_2O), 4.08 (t, J = 5 Hz, 2 H, CH_2OAc), 3.68 (t, J = 5 Hz, 2 H, CH_2O), 1.97 (s, 3 H, $COCH_3$).

N^2-(*p*-Anisyldiphenylmethyl)-9-[(2-hydroxyethoxy)methyl]guanine (26). A solution of **24** (2.96 g, 11.1 mmol), *p*-anisylchlorodiphenylmethane (4.35 g, 15.6 mmol), triethylamine (4.0 mL, 29 mmol), and 4-(dimethylamino)pyridine (0.30 g, 2.5 mmol) in DMF (50 mL) was heated at 50 °C for 23 h, and then methanol (5 mL) was added. The solution was evaporated to dryness. The residue was dissolved in dichloromethane, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed (1:15 methanol/dichloromethane) to give 5.09 g (85%) of **25** as a foam. A solution of **25** (3.97 g, 7.35 mmol) and concentrated NH_4OH (10 mL) in methanol (50 mL) was kept at room temperature for 3 days and then evaporated to dryness. The residue was crystallized from ethanol to give 2.85 g (78%) of **26**: UV λ_{max} (methanol) 277 nm (ϵ 14 000), 260 (15 400); ^{1}H NMR δ 10.65 (br s, 1 H, NH), 7.69 (br s, 1 H, NH), 7.68 (s, 1 H, H-8), 7.17–7.35 (m, 12 H, aromatic), 6.86 (d, J = 9 Hz, 2 H, aromatic), 4.87 (s, 2 H, NCH_2O), 4.51 (t, J = 5 Hz, 1 H, OH), 3.72 (s, 3 H, OCH_3), 3.21 (m, 2 H, CH_2OH), 2.93 (t, J = 5 Hz, 2 H, CH_2O).

N^2-(*p*-Anisyldiphenylmethyl)-9-[[1,3-dihydroxy-2-(hydroxymethyl)-2-propoxy]methyl]guanine (28). A solution of **26** (1.63 g, 3.28 mmol), dicyclohexylcarbodiimide (2.60 g, 12.6 mmol), and methylphosphonic acid (0.20 g, 2.3 mmol) in dry Me_2SO (150 mL) was magnetically stirred at 18 °C for 4 h and then at room temperature for 18 h. The resulting suspension was cooled to 18 °C, and a solution of oxalic acid dihydrate (90 mg) in methanol (9 mL) was added. The suspension was filtered and the filtrate evaporated to dryness on a Kugelrohr apparatus (60 °C/1 torr). The residue was chromatographed (1:12 methanol/dichloromethane) to give 1.32 g (82%) of **27** as a white foam. A solution of **27** (1.07 g, 2.17 mmol), 37% aqueous formaldehyde (7.8 mL), and 1 N sodium hydroxide (7.8 mL) in THF (50 mL) and water (50 mL) was kept at room temperature for 18 h. Ammonium chloride (1.5 g) was then added and the solution evaporated to approximately 40 mL. The resulting solution plus the precipitated gum was partially dissolved in a mixture of water (200 mL) and dichloromethane (300 mL). The dichloromethane phase was combined with the residual gum and the mixture evaporated to dryness. The residue, preabsorbed onto silica gel (25 g), was chromatographed (1:6 methanol/dichloromethane) to give 0.64 g (53%) of **28** as a white solid. An analytical sample was crystallized from ethanol: UV λ_{max} (methanol) 277 nm (ϵ 13 150), 260 (14 800); ^{1}H NMR δ 10.67 (br s, 1 H, NH), 7.70 (br s, 1 H, NH), 7.65 (s, 1 H, H-8), 7.15–7.35 (m, 12 H, aromatic), 6.85 (d, J = 9 Hz, 2 H, aromatic), 5.01 (s, 2 H, NCH_2O), 4.35 (t, J = 5 Hz, 3 H, OH), 3.72 (s, 3 H, OCH_3), 3.25 (d, J = 5 Hz, 6 H, CH_2OH).

9-[[1,3-Dihydroxy-2-(hydroxymethyl)-2-propoxy]methyl]guanine (29). A solution of **28** (272 mg, 0.49 mmol) in 80% aqueous acetic acid was heated at 80 °C for 2 h and then evaporated to dryness. The residue was triturated with ethyl acetate and then recrystallized from water to give 119 mg (85%) of **29**: UV λ_{max} (methanol) sh 273 nm (ϵ 9300), 253 (13 300), (0.1 N HCl) sh 276 (8500), 256 (12 100), (0.1 N NaOH) 266 (11 200), 256 (11 100); ^{1}H NMR δ 10.62 (br s, 1 H, NH), 7.77 (s, 1 H, H-8), 6.46 (br s, 2 H, NH_2), 5.53 (s, 2 H, NCH_2O), 4.66 (t, J = 5 Hz, 3 H, OH), 3.51 (d, J = 5 Hz, 6 H, CH_2OH).

Plaque Assays. Experiments were conducted with Vero cells infected with HSV-1 (F strain) and then treated with the nucleoside analogue as described previously.[9a] Fifty percent inhibitory doses (ID_{50}) are defined as doses causing a 50% reduction in plaque numbers compared to untreated controls.

Thymidine Kinase Assay. The assay was performed by the methods of Doberson and Greer,[19] using HSV-1 (strain F)-affinity-purified kinase.[20] Reaction mixtures contained 100 mM Tris·HCl (pH 7.5), 50 mM KCl, 2 mM $MgCl_2$, 1 mM dithiothreitol, 25 mM NaF, 1 mg BSA/mL, 0.5 mM [γ-^{32}P]ATP (20 μCi/μM), 0.2 mM nucleoside analogue, and enzyme in a 0.1 mL volume. The [γ-^{32}P]ATP required for the assay was from ICN Chemical and Radioisotope Div., Irvine, CA; thymidine came from Sigma Chemical Co., St. Louis, MO. The thymidine kinase affinity gel required for enzyme purification was prepared by the Cheng procedure.[21] and the results from the deoxynucleoside kinase assays were expressed as relative phosphorylation rates, a method that has been used by others.[20,22]

Animal Studies. Swiss-Webster female mice (Simonsen Laboratories, Gilroy, CA), weighing approximately 20 g each, were infected intraperitoneally with 5×10^4 PFU of HSV-2 (strain G). This challenge was approximately equivalent to 10 50% lethal doses. DHPG and the nucleoside analogues were administered subcutaneously once a day for 4 days starting 24 h postinfection. Deaths were recorded for 21 days after infectin.

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Synthesis and Antiviral Activity of Certain Nucleoside 5′-Phosphonoformate Derivatives

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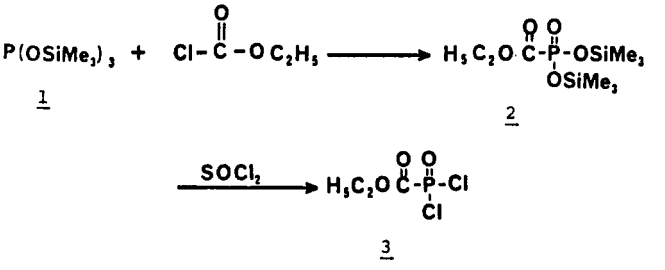
(Ethoxycarbonyl)phosphonic dichloride (**3**) was synthesized by chlorination of bis(trimethylsilyl) (ethoxycarbonyl)phosphonate with thionyl chloride. Adenosine 5′-(ethoxycarbonyl)phosphonate (**4**), guanosine 5′-(ethoxycarbonyl)phosphonate (**5**), 2′-deoxyadenosine 5′-(ethoxycarbonyl)phosphonate (**18**) and 2′-deoxyguanosine 5′-(ethoxycarbonyl)phosphonate (**19**) were synthesized by coupling of compound **3** with adenosine, guanosine, 2′-deoxyadenosine, and 2′-deoxyguanosine, respectively. Alkaline treatment of **4**, **5**, **18**, and **19** gave the corresponding adenosine 5′-(hydroxycarbonyl)phosphonate (**14**), guanosine 5′-(hydroxycarbonyl)phosphonate (**15**), 2′-deoxyadenosine 5′-(hydroxycarbonyl)phosphonate (**20**), and 2′-deoxyguanosine 5′-(hydroxycarbonyl)phosphonate (**21**). Treatment of **4** and **5** with methanolic ammonia resulted in the production of adenosine 5′-(aminocarbonyl)phosphonate (**12**) and guanosine 5′-(aminocarbonyl)phosphonate (**13**), respectively. The nucleotide analogue **20** exhibited the most potent antiviral activity of this group of nucleotide tested in vitro and was most active against herpes viruses especially HSV-2. The nucleotide analogue **21** had lower, but significant, activity against HSV-2. All of the compounds tested were nontoxic to confluent Vero cells at concentrations as high as 5000 μM.

Compounds which selectively inhibit virus specific functions but have little effect on host cells have been the target of many recent investigations.[1,2] Phosphonoformate (Foscarnet), an analogue of pyrophosphate, has been found to be a potent antiviral agent.[3] Phosphonoformate inhibits viral reverse transcriptase[4] and DNA polymerase[5] and is active against herpes simplex virus (HSV-1)[6,7] and certain other viruses.[8–10] Recently, elimination of replication of human T-cell lymphotropic virus type III (HTLV-III) with phosphonoformate at a nontoxic dose has been reported.[11,12] This study showed that the activity of reverse transcriptase of HTLV-III has been reduced drastically by phosphonoformate. Beldekas and co-workers studied the effect of foscarnet on the nature and frequency of T-cell differentiation defect seen in AIDS and in certain people with LAS.[13] These investigators reported that foscarnet permits T-cell colony growth and expansion in the cell culture.

Phosphonoformate has been used topically for treatment of HSV-1 infection in laboratory animals with satisfactory results.[14] Phosphonoformate has also been used in a 3% cream formulation, which is not irritating to the skin, and in clinical testing shortens the time mucocutaneous HSV-1 and HSV-2 lesions require to reach the stage of crusting and reduces the appearance of new vesicles.[15] Topical treatment of recurrent genital herpes with foscarnet cream has also been claimed to accelerate healing in man.[16]

Scheme I



1 2 3

It appears that phosphonoformate binds to the pyrophosphate "well" of the viral DNA and RNA polymerase.[4,5]

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