Moreover the mean of the values shown is not far from the 3.3 kJ mol^{-1} reported by Tanford[7], Gill and Wadso,[9] and Aveyard and Mitchell,[11,12] whose data have, of course, been used here.

Values for the Gibbs energy of hydration (ΔG_{hyd}) of some aliphatic alcohols (a closely related term to ΔG_{soln} through the Gibbs energy of vaporization) have been reported by Butler[16] and are shown in Table III. Given the difficulties inherent in the methods adopted and, hence, the errors associated with ΔG_{hyd} it is tempting to see an oscillation in the values of ΔG_{hyd} too, especially for the lower members of the series. Irregularity of behavior in solution with steady increase in chain length has been reported also by Mukerjee, Mysels, and Kapauan[18] for micelle formation in a series of long-chain alkyl ammonium salts.

It therefore appears that for some, though not all, systems the assumption of a monotonous increase in ΔG_{trs} per methylene group, and thus P, may not be valid. Indeed, if the oscillation in $\Delta(\Delta G_{trs})$ is confirmed, then the linear relationships normally described between $f(P)$ and chain length may be the mean of two other linear relationships, one relating to the substances of odd-numbered chain length and the other to the even-numbered members. If these results are confirmed by studies on other systems (in progress in our laboratory) and by other workers, then the methods for calculation of P, cited earlier, may need to be revised, as will the general application of "Hansch" analysis. These observations may therefore have a significance for such empirically based analyses as QSAR studies or the empirical solubility estimation of Amidon et al.,[17] which depends upon calculated values of P.

We are as yet uncertain about the origin of this phenomenon, but it must lie in the solute–solute or solute–solvent interactions. Since the phenols and the solutes of Tables II and III are all liquids, the kind of irregularities encountered amongst solids cannot provide an explanation, but it is perhaps significant that all the solutes showing oscillations in $\Delta(\Delta G_{trs})$ contain hydroxy groups. It is therefore conceivable that the separate contributions made to ΔG_{soln} in water by the hydroxy function and by the hydrocarbon part of the molecule vary according to some unknown interaction occurring either in the liquid solute or some conformational effect in the solvated molecule. It may also be significant that in the series so far examined, oscillation in these values is confined to the lower members, that is, to those members where ΔG_{trs} and ΔS_{trs} both vary;[13,14] for the higher members whose partition is increasingly "entropy driven", the large ΔS_{trs} contributions to ΔG_{trs}, which are linearly related to chain length, tend to obscure the ΔH_{trs} contribution.[13,14]

Only more detailed experiments on partitioning, performed under carefully controlled conditions, will reveal the general or particular nature of these observations.

Registry No. *m*-Methoxyphenol, 150-19-6; *m*-ethoxyphenol, 621-34-1; *m*-propoxyphenol, 16533-50-9; *m*-butoxyphenol, 18979-72-1; *m*-pentoxyphenol, 18979-73-2; butanol, 71-36-3; pentanol, 71-41-0; hexanol, 111-27-3; heptanol, 111-70-6; butyric acid, 107-92-6; valeric acid, 109-52-4; hexanoic acid, 142-62-1; heptanoic acid, 111-14-8; hexadecane, 544-76-3; dodecane, 112-40-3; octane, 111-65-9; 1-octanol, 111-87-5; water, 7732-18-5.

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9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine: A New Potent and Selective Antiherpes Agent[1]

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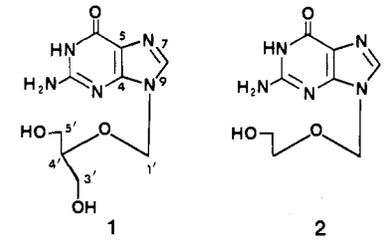
The synthesis of a new acyclic analogue of deoxyguanosine, 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **1**), is described starting from epichlorohydrin via condensation of 2-*O*-(acetoxymethyl)-1,3-di-*O*-benzylglycerol (**5**) with N^2,9-diacetylguanine (**6**). In vitro studies indicate that DHPG is a potent and broad-acting (herpes simplex virus types 1 and 2, cytomegalovirus, and Epstein-Barr virus) antiherpetic agent. In vivo studies indicate its lack of toxicity [LD_{50} (mice) = 1–2 g/kg, ip] and its superiority over acyclovir [oral ED_{50} = 7 (mg/kg)/day vs. 550 (mg/kg)/day in HSV-2 infected mice].

Much effort has been devoted to the synthesis of novel nucleoside analogues as antiherpetic agents,[2] many of which are also toxic to the host. Recently, a few less toxic nucleoside analogues have been shown to be good substrates for the viral-specified thymidine kinase while being poorly phosphorylated by host enzymes.[3] The resulting nucleoside monophosphates are then converted to the triphosphates, which in turn inhibit virus replication by interfering with the viral DNA synthesis while not disrupting uninfected cell DNA synthesis.

This note reports the synthesis and the physical and biological properties of DHPG (**1**),[4,5] an acyclic deoxy-



1 **2**

(1) Contributions 162 and 639 from the Institutes of Bio-Organic Chemistry and Organic Chemistry, Syntex Research.
(2) DeClercq, E. *Biochem. J.* **1982**, *205*, 1.
(3) (a) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B. *Nature (London)* **1978**, *272*, 583. (b) DeClercq, E.; Deschamps, J.; DeSomer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947. (c) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21.
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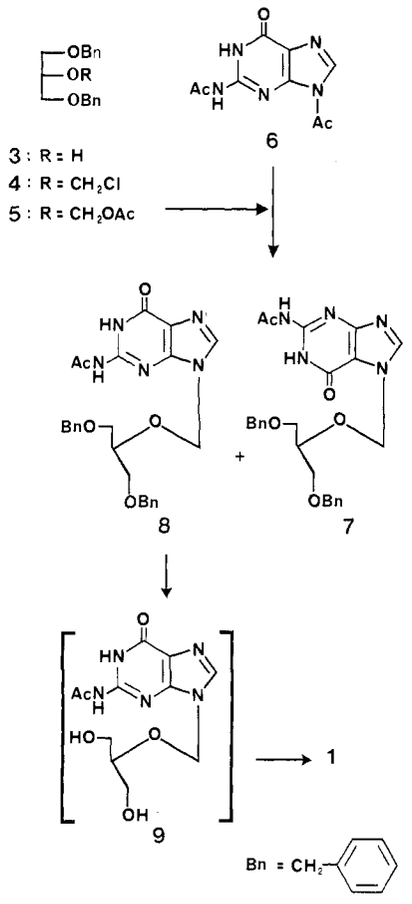
0022-2623/83/1826-0759$01.50/0

Scheme I



guanosine analogue similar to acyclovir (**2**)[3a] but more closely resembling the natural deoxynucleoside in structure.[6] DHPG is a new, uniquely potent, and broadly active antiherpetic agent, substantially devoid of toxicity both in vitro and in vivo.[7] DHPG is also more soluble in water (4.3 vs. 1.2 mg/mL at pH 7.0 and 25 °C)[8] and more bioavailable [19 vs. 4% urinary excretion (5 days) after 20–30 mg/kg oral dose in monkeys][9] than acyclovir.

The synthesis of DHPG (Scheme I) started from epichlorohydrin, which was treated with benzyl alcohol and 50% aqueous NaOH (room temperature, 16 h) to give, after distillation, 1,3-di-*O*-benzylglycerol (**3**) in 63% yield, an improvement over the previously reported synthesis.[10] Chloromethylation of **3** with HCl and paraformaldehyde (methylene chloride, 0 °C, 16 h) gave the chloromethyl ether **4**, which was treated with potassium acetate (acetone, room temperature, 16 h) to yield 2-*O*-(acetoxymethyl)-1,3-di-*O*-benzylglycerol (**5**). Condensation of crude **5** with 1.0 equiv of N^2,9-diacetylguanine (**6**) in the presence of a catalytic amount of *p*-toluenesulfonic acid in sulfolane (95 °C, 72 h) gave a 3:2 mixture of N^2-acetyl-9-[[1,3-bis(benzyloxy)-2-propoxy]methyl]guanine (**8**) and its corresponding N^7 isomer **7**, from which the desired isomer **8** was crystallized from toluene in 31% yield. Debenzylation of **8** over 20% palladium hydroxide on carbon with cyclohexene (refluxing ethanol, 32 h) gave intermediate **9**, which, without isolation, was deacetylated with 1:1 concentrated NH_4OH/methanol (room temperature, 16 h) to furnish an 86% yield (from **8**) of DHPG (**1**).

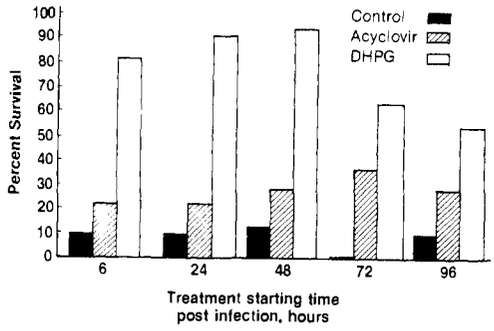


Figure 1. Effect of time of initiation of oral treatment on anti-HSV-2 activities of acyclovir and DHPG in mice. Swiss Webster female mice weighing approximately 20 g each were infected intraperitoneally with 5×10^4 pfu of HSV-2 (G strain). Oral treatments with DHPG or acyclovir at (80 mg/kg)/day or with saline placebo were initiated at 6, 24, 48, 72, or 96 h postinfection with 22 animals per test group. Treatments were once a day for 3 days thereafter. Survivor increase probabilities were evaluated by a two-tailed Fisher exact test. All DHPG treatments, but only the 72-h ACV treatment, increased the percentage of survivors over control in a statistically significant manner ($p < 0.01$); all other ACV treatments were not statistically different from control ($p > 0.05$).

The structure assignments of the isomeric condensation products **7** and **8** were made on the basis of comparison of their corresponding ^{13}C NMR spectra with those of known purines.[11] Additionally, the spectroscopic properties of DHPG (**1**) (UV and NMR) are similar to those of guanosine, indicating that the side chain is indeed attached to the N^9 nitrogen. Finally, the ^1H NMR spectrum of DHPG is identical with that reported.[5b]

Preliminary in vitro assays demonstrated that DHPG is not only active against a wide variety of strains of herpes simplex virus types 1 and 2[12] but is also substantially more potent than acyclovir against human cytomegalovirus and Epstein–Barr virus. The following ED_{50} values were obtained by plaque-reduction assay for four different strains of CMV (DHPG/ACV): BT1943, 1.1/75 μM; Major, 4.8/86 μM; Towne, 1.0/98 μM; AD169, 7.0/95 μM.[12] Additionally, DHPG reduces the number of EBV genome copies in P3HR-1 infected cells (ED_{50} = 1 μM).[12b] Moreover, while the rate of phosphorylation of DHPG by viral-specified thymidine kinase (HSV-1, F strain) is 5 times that of acyclovir, its inhibitory effect on uninfected Vero cell DNA synthesis occurs at a concentration three times higher than that of acyclovir,[12a] indicating a re-

(5) (a) Some of the biological activities of DHPG have been reported independently: Smith, K. O.; Galloway, K. S.; Kennell, W. L.; Ogilvie, K. K.; Radatus, B. K. *Antimicrob. Agents Chemother.* **1982**, *22*, 55. (b) After the original submission of this manuscript, an alternative synthesis and further biological properties of DHPG have been disclosed: Ashton, W. T.; Karkas, J. D.; Field, A. K.; Tolman, R. L. *Biochem. Biophys. Res. Commun.* **1982**, *108*, 1716.

(6) The structural formulas of DHPG (**1**) and intermediates **7–9** have been depicted in a "ribose-like" conformation only to draw attention to the similarity in structure between these compounds and deoxyguanosine.

(7) The LD_{50} in mice is 1–2 g/kg, ip. We thank Dr. N. Ackerman for these data.

(8) We thank Dr. R. G. Bergstrom for these data.

(9) We thank Dr. M. D. Chaplin for the DHPG data. For acyclovir data, see: de Miranda, P.; Krasny, H. C.; Page, D. A.; Elion, G. B. *Am. J. Med.* **1982**, *73*, 31.

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(11) Fischer, P.; Lösch, G.; Schmidt, R. R. *Tetrahedron Lett.* **1978**, 1505.

(12) (a) Smee. D. F.; Martin, J. C.; Verheyden, J. P. H.; Matthews, T. R., submitted for publication in *Antimicrob. Agents Chemother.* (b) Cheng, Y.-C.; Huang, E.-S.; Lin, J.-C.; Mar, E.-C.; Pagano, J. S.; Dutschman, G.; Grill, S., submitted for publication in *Proc. Natl. Acad. Sci. U.S.A.*

(13) Ames salmonella/microsome plate test and mitotic gene conversion assay with yeast strain D_4 by Litton Bionetics, Inc.

markably high therapeutic index for DHPG. Additionally, DHPG did not show mutagenic activity in the Ames test.[13]

Subsequent in vivo studies demonstrated even more forcefully the superiority of DHPG. Oral treatment of mice infected ip with HSV-2 (G strain) required only 7 (mg/kg)/day of DHPG vs. 550 (mg/kg)/day of acyclovir to reduce by 50% the mortality of drug-treated as compared to placebo-treated animals (oral dosage initiated 1 day postinfection and continued once daily for 3 more days).[12a]

A similar study indicated that oral treatment [80 (mg/kg)/day] with DHPG can be postponed as late as 96 h postinfection while still giving a 55% increase in survival, whereas identical treatment with acyclovir did not significantly increase survival over placebo-treated control (Figure 1).

The potent and broad activity of DHPG against many members of the herpes family, coupled with high water solubility and bioavailability, could, if maintained in the clinic, provide a safe and powerful drug against a wide range of herpes virus infections.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian HA-100 (^{1}H NMR, 100 MHz) and a Bruker WM-300 (^{1}H NMR, 300 MHz; ^{13}C NMR, 75.453 MHz), and chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Ultraviolet spectra were recorded in nanometers from solutions in methanol on a Cary-14 spectrometer. Spectroscopic data and elemental analyses were obtained by the Syntex Analytical Research Division. Melting points were determined on a hot-stage microscope and are corrected.

1,3-Di-*O*-benzylglycerol (3).[10] A solution of sodium hydroxide (300 g, 7.5 mol) in water (280 mL) was added over 10 min to benzyl alcohol (1.1 kg, 10.6 mol). The mixture was cooled to 25 °C, and then epichlorohydrin (306 g, 3.31 mol) was added with rapid stirring over 30 min. Vigorous stirring was continued for 16 h. The mixture was then diluted with water (2 L) and extracted with toluene (3 × 4 L). The toluene extract was washed with water (500 mL), dried over Na_2SO_4, and evaporated to an oil, which was distilled on a wiped film evaporator to yield 563 g (63%) of **3**.

***N*^{2}-Acetyl-9-[[1,3-bis(benzyloxy)-2-propoxy]methyl]guanine (8).** Hydrogen chloride gas (dried through concentrated H_2SO_4) was bubbled into a stirred mixture of paraformaldehyde (117 g, 3.9 mol) and **3** (486 g, 1.8 mol) in methylene chloride (4.8 L) at 0 °C until all the solid dissolved (3 h). The resulting solution was stored at 0 °C for 16 h, dried over $MgSO_4$, and then evaporated to give **4** as a very unstable clear oil. The clear oil was then added dropwise to a stirred mixture of potassium acetate (600 g, 6.1 mol) in acetone (4.3 L). The mixture was stirred for 16 h at room temperature and then filtered and evaporated. The residual oil was dissolved in toluene (2.4 L). The resulting solution was washed with saturated $NaHCO_3$ (1.5 L) and water (2 × 500 mL), dried over Na_2SO_4, and evaporated to give 650 g of **5** as a marginally stable pale yellow oil: ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.3 (s, 10 H, aromatic), 5.34 (s, 2 H, OCH_2O), 4.48 (s, 4 H, benzylic), 3.95 (p, J = 6 Hz, 1 H, CHO), 3.53 (d, J = 6 Hz, 4 H, CH_2O), 1.93 (s, 3 H, CH_3).

A mixture of **5** (650 g from above), diacetylguanine (423 g, 1.8 mol), *p*-toluenesulfonic acid (4 g, 21 mmol), and sulfolane (500 mL) was heated with stirring at 95 °C. After 48 h, additional *p*-toluenesulfonic acid (4 g, 21 mmol) was added. After 72 h, the mixture was diluted with toluene (4 L) and filtered. The filtrate was passed through silica gel eluting with toluene, dichloromethane, and then 2% methanol/methylene chloride to yield the isomeric mixture of **7** and **8** as a viscous oil. Crystallization from toluene gave 262 g (31%) of **8**: mp 145–146 °C; UV λ_{max} 282 nm (ϵ 11 710), 257 (16 570); ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 8.13 (s, 1 H, H-8), 7.35–7.20 (m, 10 H, aromatic), 5.59 (s, 2 H, H-1′), 4.41 (s, 4 H, benzylic), 4.05 (m, 1 H, H-4′), 3.41 (m, 4 H, H-3′, H-5′), 2.18 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) δ 173.42 (CO), 154.84 (C-6), 148.69 (C-4), 147.93 (C-2), 139.93 (C-8), 138.08, 128.10, 127.30, 127.15 (aromatic), 120.26 (C-5), 76.86 (C-4′), 72.26 (C-1′, benzylic), 69.69 (C-3′, C-5′), 23.68 (CH_3). Anal. ($C_{25}H_{27}N_5O_5$) C, H, N.

***N*^{2}-Acetyl-7-[[1,3-bis(benzyloxy)-2-propoxy]methyl]guanine (7).** A 2:3 mixture of **7** and **8** (1.5 g) was chromatographed over silica gel eluting with 1:15 methanol/methylene chloride to yield 0.19 g of **7** after recrystallization from ethyl acetate: mp 133–134 °C; UV λ_{max} 280 nm (ϵ 10 190), 263 (13 900); ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 8.34 (s, 1 H, H-8), 7.35–7.20 (m, 10 H, aromatic), 5.80 (s, 2 H, H-1′), 4.42 (s, 4 H, benzylic), 4.14 (p, J = 6 Hz, 1 H, H-4′), 3.48 (m, 4 H, H-3′, H-5′), 2.19 (s, 3 H, CH_3); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) δ 173.31 (CO), 157.47 (C-4), 152.46 (C-6), 147.09 (C-2), 144.92 (C-8), 138.16, 128.10, 127.24, 127.14 (aromatic), 111.01 (C-5), 76.55 (C-4′), 74.79 (C-1′), 72.17 (benzylic), 69.69 (C-3′, C-5′), 23.63 (CH_3). Anal. ($C_{25}H_{27}N_5O_5$) C, H, N.

9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine (1). A mixture of **8** (350 g, 0.73 mol), 20% palladium hydroxide on carbon (25 g), cyclohexene (8.1 L), and ethanol (3.6 L) was heated at reflux under N_2. After 8 and 24 h, additional catalyst (5 g) was added. After 32 h, the solution was cooled to room temperature and filtered. The solid residue was boiled in water (2 L) and then filtered over a filter aid. The filter cake was washed with boiling water (1 L). The filtrate was evaporated, and the residue was triturated with methanol (800 mL) to give 199 g (92%) of crude **9**. A solution of **9** (105 g, 0.35 mol), 56% ammonium hydroxide (800 mL), and methanol (800 mL) was kept at 25 °C for 16 h and then evaporated. The residue was triturated with methanol (500 mL) and then recrystallized from water (700 mL) to yield 84.5 g (94%) of **1**: mp >300 °C (water); UV λ_{max} (methanol) sh 270 nm (ϵ 9040), 254 (12 880); ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 10.64 (br s, 1 H, NH), 7.81 (s, 1 H, H-8), 6.50 (s, 2 H, NH_2), 5.44 (s, 2 H, H-1′), 4.63 (p, J = 6 Hz, 1 H, H-4′), 3.35 (m, H-3′, H-5′); ^{13}C NMR (75.453 MHz, Me_2SO-d_6) δ 156.87 (C-6), 153.78 (C-2), 151.27 (C-4), 137.62 (C-8), 116.40 (C-5), 80.00 (C-4′), 71.48 (C-1′), 60.90 (C-3′, C-5′). Anal. ($C_9H_{13}N_5O_4$) C, H, N.

Acknowledgment. We thank Drs. John G. Moffatt and Howard J. Ringold for their advice and support.

Registry No. **1**, 82410-32-0; **3**, 6972-79-8; **4**, 74564-16-2; **5**, 84245-11-4; **6**, 3056-33-5; **7**, 84222-48-0; **8**, 82410-30-8; **9**, 84960-04-3; benzyl alcohol, 100-51-6; epichlorohydrin, 106-89-8.