(D_2O) δ 2.4 (t, J = 7 Hz, $-CH_2S$, 2 H), 3.7 (t, J = 7 Hz, CH_2O, 2 H), 6.2 (t, J = 7 Hz, 1′-H, 1 H), 8.2 (s, 6-H, 1 H). Anal. ($C_{11}H_{16}N_2O_6S$) C, H, N.

1-(2′-Deoxy-β-D-ribofuranosyl)-5-(*S*-acetamidomercapto)uracil (9). This material was prepared on the same scale and in a similar manner to that used for the preparation of **7**. Iodoacetamide was used for alkylation, and compound **9** was formed in 78% yield: mp 175–178 °C dec; UV λ_{max} (H_2O) 278 nm (ε 4700), 223 (8400); IR (Nujol) 1608 (C=O), 3350 and 3490 cm^{-1} (NH_2); insufficient sample for NMR. Anal. ($C_{11}H_{15}N_3O_6S$) C, H, N.

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A Direct Method for the Preparation of 2-Hydroxyethoxymethyl Derivatives of Guanine, Adenine, and Cytosine[1a]

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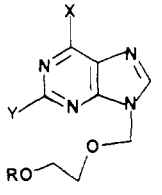
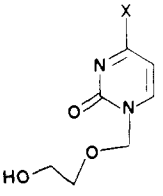
Alkylation of 2-chloro-6-iodopurine with iodomethyl [(trimethylsilyl)oxy]ethyl ether at −63 °C and subsequent treatment of the 9-substituted chloroiodopurine with K_2CO_3 in aqueous dioxane at 25 °C and then with NH_3 under pressure at 150 °C provided 9-[(2-hydroxyethoxy)methyl]guanine (**1a**), a potent antiviral agent against *Herpes simplex* virus type 1, in excellent yield. Its monophosphate (**1g**), which is enzymatically produced from **1a** in the virus-infected cell, was also synthesized. 6-Chloropurine and 4-(methylthio)pyrimidin-2-one anions were similarly alkylated with iodomethyl [(trimethylsilyl)oxy]ethyl ether, and the products (**1f** and **2b**) were transformed by treatment with methanolic NH_3 at 110 °C into 9-[(2-hydroxyethoxy)methyl]adenine (**1b**) and 1-[(2-hydroxyethoxy)methyl]cytosine (**2a**), respectively. The syntheses of these analogues, heretofore difficult to prepare by a simple procedure, have been conveniently accomplished.

The facile synthesis and further elaboration of functionalized 2-hydroxyethoxymethyl derivatives of purines and pyrimidines constitute a goal of considerable dimension. The significance of this objective is suggested by the potent antiviral activity against *Herpes simplex* virus type 1 exhibited by 9-[(2-hydroxyethoxy)methyl]guanine (**1a**,





1a X = OH;[15] Y = NH_2; R = H
b X = NH_2; R = Y = H
c X = I; Y = Cl; R = H
d X = OH;[15] Y = Cl; R = H
e X = Y = Cl; R = H
f X = Cl; R = Y = H
g X = OH;[15] Y = NH_2; R = PO_3H^-

2a X = NH_2
b X = SCH_3

acycloguanosine, Zovirax, Aciclovir, Burroughs-Wellcome)[2-10] and further amplified by the varied biological activity observed with other open-chain riboside analogues, in particular, activity against DNA and RNA viruses[11,12] and substrate or inhibitory activity with different enzymes.[13,14] We describe herein efficient syntheses of 9-[(2-hydroxyethoxy)methyl]guanine (**1a**), 9-[(2-hydroxyethoxy)methyl]adenine (**1b**),[13] and 1-[(2-hydroxyethoxy)methyl]cytosine (**2a**)[3] which embody a general, broadly applicable methodology for the synthesis of open-chain nucleoside analogues.

We have described a convenient method for the preparation of 2-hydroxyethoxymethyl iodide, hydroxyl protected by the trimethylsilyl group, from 1,3-dioxolane and trimethylsilyl iodide.[16] For the synthesis of **1a** we chose a 2-chloro-6-iodopurine precursor, owing to the greater susceptibility of 6-iodopurines toward nucleophilic displacement than the 6-chloro counterparts.[17] Besides, the acylic side chain is pH sensitive and caution should be exercised with it. When the anion of 2-chloro-6-iodo-

(1) (a) This work was presented in part at the 1979 Annual National Meeting of the American Chemical Society, Washington, D.C., Sept. 9–14, 1979, abstract ORGN 22. (b) Address correspondence to University of California at Los Angeles, School of Medicine, Division of Nuclear Medicine, Los Angeles, CA 90024.
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purine,[18] generated with NaH in dry DMF under N_2, was treated with iodomethyl [(trimethylsilyl)oxy]ethyl ether at −63 °C, 2-chloro-9-[(2-hydroxyethoxy)methyl]-6-iodopurine [**1c**; 75% yield; UV λ_{max} (pH 7.0) 283 nm] and the corresponding 7-isomer[19] [10% yield; UV λ_{max} (pH 7.0) 290 nm] were obtained. These compounds are readily separable by chromatography on neutral alumina (0–10% absolute EtOH/$CHCl_3$), with the UV spectra asserting the site of alkylation. In several instances we were able to detect and isolate as minor products the isomeric purines alkylated at position 7. These compounds show a lower R_f on alumina (9:1, $CHCl_3$/EtOH) and display a characteristic bathochromic shift in the ultraviolet spectrum when compared to their 9-substituted counterparts.[20] The presence of a relatively polarizable substituent (e.g., iodo) on the 6 position of the purine appears to direct the increased formation of the 7-isomers. Dropwise addition of a solution of 0.4 mmol of compound **1c** in 120 mL of dioxane to a rapidly stirred aqueous solution of 100 mM K_2CO_3 (120 mL) at room temperature converted it essentially quantitatively to 2-chloro-9-[(2-hydroxyethoxy)methyl]-6-oxopurine [**1d**; UV λ_{max} (pH 7.0) 254; MS m/e 244 (M^+)]. The reaction could be conveniently monitored by UV. We are unaware of any previous preparative use of K_2CO_3 for nucleophilic displacement at C-6 in 6-iodopurine derivatives. Furthermore, the exceptional ease with which nucleophilic displacement of iodide occurs recommends this as a general procedure for carrying out the transformation in the presence of pH-labile groups. Treatment of the analytically pure 2,6-dichloro analogue (**1e**) under similar conditions produced **1d** but in lower yield. The 2-chloro-6-oxo analogue **1d** could be transformed readily into 9-[(2-hydroxyethoxy)methyl]guanine (**1a**) by displacement of the 2-chloro group with NH_3 at 150 °C for 5 h in a steel bomb (80% yield). ^1H NMR, MS, and UV spectra [λ_{max} (pH 7.0) 252, 272 nm (sh)] are wholly consistent with the proposed structure **1a**. For example, the mass spectrum shows the molecular ion m/e 225 (M^+); ions at $M^+ - 30$, $M^+ - 45$, and $M^+ - 59/60$ characteristic of the 2-hydroxyethoxymethyl side chain and the ions at m/e 151, 135, 134, 109, 108, 54, and 43 typical of guanine residues.[21] Previously, the guanosine analogue **1a** was synthesized from β-(chloromethoxy)ethyl benzoate and 2,6-dichloropurine via a four-step sequence, with yields indicated as 41%, "good", and "moderate" for the individual steps in the series. No experimental details were given.[4]

Because phosphorylation of acycloguanosine appears to be necessary for its antiviral activity,[3] a simple means of preparing the monophosphate of **1a** (**1g**; acyclo-GMP) was desirable. Using the general procedure of Imai et al.,[22] we were able to obtain acyclo-GMP in 90–95% yield after chromatography.[23] Treatment with alkaline phosphatase completely hydrolyzed the product to acycloguanosine, as characterized by TLC [isobutyric acid/H_2O/NH_4OH (66:33:1), **1a**, silica gel, R_f = 0.44].

The stability demonstrated by the 2-hydroxyethoxymethyl group toward NH_3 at high temperature (see, i.e., **1d** → **1a**) has made possible the synthesis of 9-[(2-hydroxyethoxy)methyl]adenine (**1b**)[13] from the corresponding 6-chloropurine analogue **1f**. Similarily, 1-[(2-hydroxyethoxy)methyl]cytosine[3] (**2a**) was produced in 85% yield from 1-[(2-hydroxyethoxy)methyl]-4-(methylthio)-pyrimidin-2-one (**2b**). In all cases, the precursor was made by alkylation of the purine or pyrimidine[24] anion with iodomethyl [(trimethylsilyl)oxy]ethyl ether at −63 °C, followed by treatment with 10% aqueous KF and 10% aqueous $NaHCO_3$ to remove the trimethylsilyl protecting group. The in situ generation of the protected alkylating agent from 1,3-dioxolane and trimethylsilyl iodide again obviates the previously required chloromethylation of a monoprotected ethylene glycol. The great value of the methodology presented here lies in its inherent simplicity and concomitant wide spread applicability. In fact, the highly efficient conversion of 1,3-dioxolane to iodomethyl [(trimethylsilyl)oxy]ethyl ether[16] has facilitated the development of the new syntheses indicated in this work and the preparation of additional series of open-chain nucleoside analogues of potential pharmacological interest.[25]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance (^1H NMR) spectra were recorded on a Varian EM-390 or XL-100 spectrophotometer using tetramethylsilane as an internal standard. ^{31}P NMR spectra were obtained on a Varian Associates XL-100-15 NMR system equipped with a Digital NMR-3 data system, operating at 40.5 MHz for ^{31}P and 100 MHz for ^1H. Broad-band proton decoupling centered at about δ 4.0 was used. Deuterium from the D_2O solvent was used for field frequency stabilization. Phosphoric acid (85%) in a concentric capillary (2-mm o.d.) was used as primary ^{31}P reference. All spectra were obtained using 16K data points and a 2500-Hz bandwidth. Ultraviolet absorption spectra were obtained on a Beckman Acta M VI spectrophotometer. Mass spectra were run on a Varian MAT CH-5 spectrometer (10 and 70 eV) or a Varian MAT 731 spectrometer (field desorption) coupled with a 620i computer and a STATOS recorder. Microanalyses were preformed by Josef Nemeth and his staff. Thin-layer chromatograms were run on EM aluminum oxide F-254 neutral type E plates (thickness 0.25 mm) or EM silica gel F-254 plates (thickness 0.25 mm). Column chromatography utilized ICN neutral alumina (activity grade 1). Where analyses are indicated by the symbols of the elements, analytical results are within ±0.4% of the theoretical values.

2-Hydroxyethoxymethyl Derivatives. General Procedure. Trimethylsilyl iodide (1.1 mmol) was added to cyclohexene (0.5 mL) at 0 °C; after 10 min, the solution was cooled to −78 °C. 1,3-Dioxolane (1.1 mmol) in cyclohexene (0.5 mL) was similarly cooled to −78 °C and, after 10 min, the cooled trimethylsilyl iodide solution was added in one portion. The transfers were done by means of a syringe through serum caps in order to minimize contact with moisture. A solution of 6-chloropurine, 2 chloro-6-iodopurine,[18] or 4-(methylthio)pyrimidin-2-one[24] (1.0 mmol) in DMF (14 mL) was added to NaH (100 mg, 50% dispersion, 1.5 mmol) under a nitrogen atmosphere with evolution of hydrogen gas. After 15 min, the solution was cooled to −63 °C (CO_2–$CHCl_3$)

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(19) 2-Chloro-7-[(2-hydroxyethoxy)methyl]-6-iodopurine: ^1H NMR [$(CD_3)_2CO$] δ 3.69 (s, 4, OCH_2), 5.98 (s, 2, NCH_2O), 8.79 (s, 1, purine CH); MS m/e 354 (M^+).

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(23) Acyclo-GMP (**1g**). In the nondecoupled ^{31}P NMR spectrum, the phosphate ^{31}P resonance displays a characteristic triplet: δ 3.91 ($^3J_{PH}$ = 5.7 Hz). Proton-decoupled spectrum: δ 3.91 (s). The spectra were recorded in D_2O, adjusted to pH 9 by the addition of $(CH_3)_4N^+OH^-$ (nucleotide concentration, 15 mM; EDTA concentration, 2 mM).

(24) 4-(Methylthio)pyrimidin-2-one was prepared according to the procedure of Delia, T. J.; Olsen, M. J.; Brown, G. B. *J. Org. Chem.* **1965**, *30*, 2766.

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and the cooled 1,3-dioxolane-trimethylsilyl iodide reaction mixture added in one portion via syringe. The entire reaction mixture was stirred and warmed to room temperature over a period of 3 h, at which time aqueous KF (100 mg/mL, 2 mL) and aqueous $NaHCO_3$ (75 mg/mL, 2 mL) were added. After 30 min, the solvent was removed in vacuo and the residue was extracted with $CHCl_3$ (3 × 50 mL). The chloroform layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by chromatography on neutral alumina (100:1 ratio, alumina/product) using a gradient elution of 0–10% EtOH/$CHCl_3$.

6-Chloro-9-[(2-hydroxyethoxy)methyl]purine (1f): 72% yield; mp 149–150 °C dec ($CHCl_3$–CCl_4); NMR [$(CD_3)_2CO$] δ 3.68 (s, 4, OCH_2), 5.83 (s, 2, NCH_2O), 8.62 (s, 1, purine CH), 8.71 (s, 1, purine CH); MS *m/e* 198 (M^+ – HCHO), 183 (M^+ – C_2H_5O), 168 (M^+ – $C_2H_4O_2$), 167 (M^+ – $C_2H_5O_2$), 155 (M^+ – $C_3H_5O_2$), 154 (M^+ – $C_3H_6O_2$), 45 (B, $C_2H_5O^+$). Anal. ($C_8H_9ClN_4O_2$) C, H, N.

2-Chloro-9-[(2-hydroxyethoxy)methyl]-6-iodopurine (1c): 75% yield; mp 162–162.5 °C ($CHCl_3$–CCl_4); NMR [$(CD_3)_2CO$] δ 3.71 (s, 4, OCH_2), 5.79 (s, 2, NCH_2O), 8.63 (s, 1, purine CH); MS *m/e* 354 (M^+), 336 (M^+ – H_2O), 324 (B, M^+ – HCHO), 309 (M^+ – C_2H_5O), 294 (M^+ – $C_2H_4O_2$), 293 (M^+ – $C_2H_5O_2$), 280 (M^+ – $C_3H_6O_2$), 153 (M^+ – $C_3H_6O_2$ – I); UV λ_{max} (pH 7.0) 283 mm. Anal. ($C_8H_8ClIN_4O_2$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-4-(methylthio)pyrimidin-2-one (2b): 75% yield; mp 73–74 °C (benzene–petroleum ether); NMR ($CDCl_3$) δ 2.54 (s, 3, CH_3), 3.76 (s, 4, OCH_2), 5.31 (s, 2, NCH_2O), 6.22 (d, *J* = 7.5 Hz, 1, 5-H), 7.47 (d, *J* = 7.5 Hz, 1, 6-H); MS *m/e* 171 (M^+ – C_2H_5O), 156 (M^+ – $C_2H_4O_2$), 155 (M^+ – $C_2H_5O_2$), 143 (M^+ – $C_3H_5O_2$), 142 (M^+ – $C_3H_6O_2$), 75 (B, $C_3H_7O_2^+$). Anal. ($C_8H_{12}N_2O_3S$) C, H, N.

2,6-Dichloro-9-[(2-hydroxyethoxy)methyl]purine (1e): 80% yield; mp 119–120 °C ($CHCl_3$–CCl_4); NMR ($CDCl_3$) δ 3.71 (s, 4, OCH_2), 5.69 (s, 2, NCH_2O), 8.22 (s, 1, purine CH); MS *m/e* 262 (M^+), 244 (M^+ – H_2O), 232 (B, M^+ – HCHO). Anal. ($C_8H_8Cl_2N_4O_2$) C, H, N.

9-[(2-Hydroxyethoxy)methyl]guanine (Acycloguanosine, 1a). To 120 mL of a 100 mM aqueous solution of K_2CO_3 at room temperature was added dropwise with efficient stirring a solution of 143 mg (0.4 mmol) of 2-chloro-9-[(2-hydroxyethoxy)-methyl]-6-iodopurine (**1c**) in 120 mL of dioxane over a period of 90 min, and the reaction mixture was stirred for another 30 min at the same temperature. The solution was carefully neutralized with 1 N HCl and concentrated at room temperature on a rotary evaporator. The residue was applied to a DEAE-cellulose column and eluted first with water, followed by a gradient of triethylammonium bicarbonate, pH 8.5 (0.0–0.3 M). The appropriate fractions were combined and the solvent evaporated. The residue was washed with $CHCl_3$, and the product, 2-chloro-9-[(2-hydroxyethoxy)methyl]-6-oxopurine [**1d**; UV λ_{max} (pH 7.0) 254; MS *m/e* 244 (M^+). Anal. ($C_8H_9ClN_4O_3$) C, H], was treated with liquid NH_3 at 150 °C for 5 h in a steel bomb. The residue was washed with a minimum amount of cold water to remove NH_4Cl and recrystallized from EtOH/H_2O, giving 72 mg (80% yield) of 9-[(2-hydroxyethoxy)methyl]guanine (**1a**): ^1H NMR [$(CD_3)_2SO$] δ 3.50 (m, 4, OCH_2), 4.62 (br, 2, NH or OH), 5.36 (s, 2, NCH_2O), 6.47 (s, 2, NH or OH), 7.80 (s, 1, purine CH); MS *m/e* 225 (M^+), 195 (M^+ – HCHO), 181 (M^+ – C_2H_4O), 180 (M^+ – C_2H_5O), 165 (M^+ – $C_2H_4O_2$), 164 (M^+ – $C_2H_5O_2$), 151 (B, M^+ – $C_3H_6O_2$). Anal. ($C_8H_{11}N_5O_3 \cdot 0.33H_2O$) C, H, N.

9-[(2-Hydroxyethoxy)methyl]adenine (1b). A solution of 6-chloro-9-[(2-hydroxyethoxy)methyl]purine (**1f**; 130 mg, 0.13 mmol) in methanol (5 mL) was saturated with NH_3 at 0 °C in a sealable tube. The reaction tube was sealed and heated at 110 °C for 18 h. The solvent was removed in vacuo, and the residue was extracted with hot acetone (50 mL). The acetone was filtered and, upon concentration, a colorless solid precipitated: 80–90% yield; mp 199.5–200 °C, lit. 198–199 °C;[13] NMR [$(CD_3)_2SO$] δ 3.52 (m, 4, OCH_2), 4.57 (t, *J* = 4 Hz, 1, OH), 5.55 (s, 2, NCH_2O), 7.15 (s, 2, NH_2), 8.10 (s, 1, purine CH), 8.20 (s, 1, purine CH); MS *m/e* 209 (M^+), 179 (M^+ – HCHO), 164 (M^+ – C_2H_5O), 149 (B, M^+ – $C_2H_4O_2$), 148 (M^+ – $C_2H_5O_2$), 135 (M^+ – $C_3H_6O_2$). Anal. ($C_8H_{11}N_5O_2$) C, H, N.

1-[(2-Hydroxyethoxy)methyl]cytosine (2a). A solution of 1-[(2-hydroxyethoxy)methyl]-4-(methylthio)pyrimidin-2-one (**2b**; 38 mg, 0.18 mmol) in methanol (5.5 mL) was saturated with NH_3 at 0 °C and similarly heated at 110 °C for 24 h. The solvent was removed in vacuo, and the residue was extracted with hot acetone (50 mL). The acetone was filtered and, upon concentration, a colorless solid precipitated: 85% yield; mp 158–159 °C; NMR [$(CD_3)_2SO$] δ 3.37 (br, 1, NH or OH), 3.48 (s, 4, OCH_2), 5.05 (s, 2, NCH_2O), 5.68 (d, *J* = 7.5 Hz, 1, 5-H), 7.08 (br, 2, NH or OH), 7.56 (d, *J* = 7.5 Hz, 1, 6-H); MS *m/e* 185 (M^+), 167 (M^+ – H_2O), 155 (M^+ – HCHO), 140 (B, M^+ – C_2H_5O), 125 (M^+ – $C_2H_4O_2$), 124 (M^+ – $C_2H_5O_2$), 111 (M^+ – $C_3H_6O_2$). Anal. ($C_7H_{11}N_3O_3 \cdot 0.125H_2O$) C, H, N.

Acycloguanosine Monophosphate (Acyclo-GMP,[3] 1g). Pyrophosphoryl chloride[26] (45 μL, 0.32 mmol) was slowly added to a cooled, stirred suspension (0 °C) of acycloguanosine (**1a**; 14.4 mg, 64 μmol) in *m*-cresol (1 mL). After 5 h at 0–5 °C, the reaction was quenched by the rapid addition of ice and, immediately thereafter, carefully neutralized with a chilled solution of 0.5 M $NaHCO_3$. After extraction with ether (3 × 20 mL), the colorless solution was evaporated to dryness under vacuum at 20 °C. The residue was then chromatographed on a column of DEAE-cellulose with a linear gradient of 0.0 to 0.35 M triethylammonium bicarbonate, pH 8.0. The fractions containing the product were pooled and evaporated to dryness at 20 °C as indicated above, giving 90–95% of pure acyclo-GMP as judged by TLC, ^1H NMR, and ^{31}P NMR:[23] ^1H NMR (D_2O) δ 3.53–3.95 (m, 4, OCH_2), 5.45 (s, 2, NCH_2O), 7.87 (s, 1, purine CH).

Biological Activity. Compounds reported in this paper have been previously subjected to biological evaluation.[2-10,13] Acycloguanosine (**1a**) has been recently introduced as a potent and selective antiviral agent against *Herpes simplex* virus type 1 (HSV-1) in cell culture systems,[2-4] in animals models infection in the brain, skin, and eye, and pneumonia due to HSV in man.[10] **1a** also inhibits multiplication of varicella-zoster virus, cytomegalovirus, and B virus, but has no effect on vaccine virus, adenovirus type 5, and a wide range of RNA viruses.[4]

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