

(D₂O) δ 2.4 (t, J = 7 Hz, -CH₂S, 2 H), 3.7 (t, J = 7 Hz, CH₂O, 2 H), 6.2 (t, J = 7 Hz, 1'-H, 1 H), 8.2 (s, 6-H, 1 H). Anal. (C₁₁H₁₆N₂O₆S) 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} (H₂O) 278 nm (ϵ 4700), 223 (8400); IR (Nujol) 1608 (C=O), 3350 and 3490 cm⁻¹ (NH₂); insufficient sample for NMR. Anal. (C₁₁H₁₆N₂O₆S) C, H, N.

H₁₅N₃O₆S) C, H, N.

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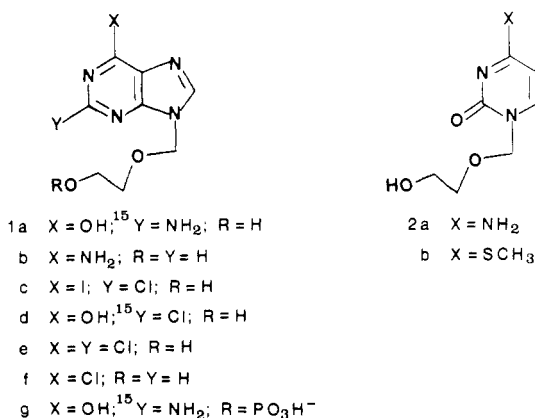
A Direct Method for the Preparation of 2-Hydroxyethoxymethyl Derivatives of Guanine, Adenine, and Cytosine^{1a}

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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 chloriodopurine with K₂CO₃ in aqueous dioxane at 25 °C and then with NH₃ 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 NH₃ 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,



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 acyclic side chain is pH sensitive and caution should be exercised with it. When the anion of 2-chloro-6-iodo-

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- (2) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716.
- (3) Fyfe, J. A.; Keller, P. M.; Furman, P. A.; Miller, R. L.; Elion, G. B. *J. Biol. Chem.* **1978**, *253*, 8721.
- (4) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature (London)* **1978**, *272*, 583.
- (5) Kaufman, H. E.; Varnell, E. D.; Centifanto, Y. M.; Rheinstrom, S. D. *Antimicrob. Agents Chemother.* **1978**, *14*, 842.

- (6) Pavan-Langston, D.; Campbell, R.; Lass, J. *Am. J. Ophthalmol.* **1978**, *86*, 618.
- (7) Field, H. J.; Bell, S. E.; Elion, G. B.; Nash, A. A.; Wildy, P. *Antimicrob. Agents Chemother.* **1979**, *15*, 554.
- (8) Klein, R. J.; Friedman-Kien, A. E.; DeStefano, E. *Antimicrob. Agents Chemother.* **1979**, *15*, 723.
- (9) Park, N.-H.; Pavan-Langston, D.; McLean, S. L.; Albert, D. *Antimicrob. Agents Chemother.* **1979**, *15*, 775.
- (10) Goldman, J. M.; Chipping, P. M.; Agnarsdottir, G.; Brigden, D. *Lancet* **1979**, *1*, 820.
- (11) De Clercq, E.; Descamps, J.; De Sommer, P.; Holý, A. *Science* **1978**, *200*, 563.
- (12) De Clercq, E.; Holy, A. *J. Med. Chem.* **1979**, *22*, 510.
- (13) Schaeffer, H. J.; Gurwara, S.; Vince, R.; Bittner, S. *J. Med. Chem.* **1971**, *14*, 367.
- (14) Coward, J. K.; Sweet, W. D. *J. Med. Chem.* **1972**, *15*, 381.
- (15) This designation is intended only to indicate substitution and not the favored tautomeric form.
- (16) Keyser, G. E.; Bryant, J. D.; Barrio, J. R. *Tetrahedron Lett.* **1979**, 3263.
- (17) With 2,6-dichloropurine, conversion to 2-chlorohypoxanthine requires 1 h of heating in alkali; see, for example, Montgomery, J. A.; Holum, L. B. *J. Am. Chem. Soc.* **1957**, *79*, 2185.

purine,¹⁸ generated with NaH in dry DMF under N₂, 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-isomer¹⁰ [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/CHCl₃), 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, CHCl₃/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 K₂CO₃ (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 K₂CO₃ 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 NH₃ 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/H₂O/NH₄OH (66:33:1), **1a**, silica gel, R_f = 0.44].

The stability demonstrated by the 2-hydroxyethoxymethyl group toward NH₃ at high temperature (see, i.e., **1d** \rightarrow **1a**) has made possible the synthesis of 9-[(2-hydroxyethoxy)methyl]adenine (**1b**)¹³ from the corresponding 6-chloropurine analogue **1f**. Similarly, 1-[(2-hydroxyethoxy)methyl]cytosine³ (**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 pyrimidine²⁴ anion with iodomethyl [(trimethylsilyl)oxy]ethyl ether at -63 °C, followed by treatment with 10% aqueous KF and 10% aqueous NaHCO₃ 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 ether¹⁶ 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. ³¹P 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 ³¹P and 100 MHz for ¹H. Broad-band proton decoupling centered at about δ 4.0 was used. Deuterium from the D₂O solvent was used for field frequency stabilization. Phosphoric acid (85%) in a concentric capillary (2-mm o.d.) was used as primary ³¹P 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 performed 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 $\pm 0.4\%$ 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-one²⁴ (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 (CO₂-CHCl₃)

- (18) Eliot, G. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1956**, *78*, 3508.
- (19) 2-Chloro-7-[(2-hydroxyethoxy)methyl]-6-iodopurine: ¹H NMR [(CD₃)₂CO] δ 3.69 (s, 4, OCH₂), 5.98 (s, 2, NCH₂O), 8.79 (s, 1, purine CH); MS m/e 354 (M^+).
- (20) Robins, R. K.; Godefroi, E. F.; Taylor, E. C.; Lewis, L. R.; Jackson, A. *J. Am. Chem. Soc.* **1961**, *83*, 2574.
- (21) McCloskey, J. A. In "Basic Principles in Nucleic Acid Chemistry"; Academic Press: New York, **1974**; Vol. 1, p 209.
- (22) Imai, K.; Fujii, S.; Takanohashi, K.; Furukawa, Y.; Masuda, T.; Honjo, M. *J. Org. Chem.* **1969**, *34*, 1547.
- (23) Acyclo-GMP (**1g**). In the nondecoupled ³¹P NMR spectrum, the phosphate ³¹P resonance displays a characteristic triplet: δ 3.91 ($^3J_{\text{PH}}$ = 5.7 Hz). Proton-decoupled spectrum: δ 3.91 (s). The spectra were recorded in D₂O, adjusted to pH 9 by the addition of (CH₃)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.
- (25) Bryant, J. D.; Keyser, G. E.; Barrio, J. R. *J. Org. Chem.* **1979**, *44*, 3733.
- (26) Crofts, P. C.; Downie, I. M.; Heslop, R. B. *J. Chem. Soc.* **1960**, 3673.

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 NaHCO₃ (75 mg/mL, 2 mL) were added. After 30 min, the solvent was removed in vacuo and the residue was extracted with CHCl₃ (3 × 50 mL). The chloroform layers were combined, dried over MgSO₄, 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/CHCl₃.

6-Chloro-9-[(2-hydroxyethoxy)methyl]purine (1f): 72% yield; mp 149–150 °C dec (CHCl₃–CCl₄); NMR [(CD₃)₂CO] δ 3.68 (s, 4, OCH₂), 5.83 (s, 2, NCH₂O), 8.62 (s, 1, purine CH), 8.71 (s, 1, purine CH); MS *m/e* 198 (M⁺ – HCHO), 183 (M⁺ – C₂H₅O), 168 (M⁺ – C₂H₄O₂), 167 (M⁺ – C₂H₅O₂), 155 (M⁺ – C₃H₅O₂), 154 (M⁺ – C₃H₆O₂), 45 (B, C₂H₅O⁺). Anal. (C₈H₉ClN₄O₂) C, H, N.

2-Chloro-9-[(2-hydroxyethoxy)methyl]-6-iodopurine (1c): 75% yield; mp 162–162.5 °C (CHCl₃–CCl₄); NMR [(CD₃)₂CO] δ 3.71 (s, 4, OCH₂), 5.79 (s, 2, NCH₂O), 8.63 (s, 1, purine CH); MS *m/e* 354 (M⁺), 336 (M⁺ – H₂O), 324 (B, M⁺ – HCHO), 309 (M⁺ – C₂H₅O), 294 (M⁺ – C₂H₄O₂), 293 (M⁺ – C₂H₅O₂), 280 (M⁺ – C₃H₅O₂), 153 (M⁺ – C₃H₆O₂ – I); UV λ_{max} (pH 7.0) 283 nm. Anal. (C₈H₈ClIN₄O₂) C, H, N.

1-[(2-Hydroxyethoxy)methyl]-4-(methylthio)pyrimidin-2-one (2b): 75% yield; mp 73–74 °C (benzene–petroleum ether); NMR (CDCl₃) δ 2.54 (s, 3, CH₃), 3.76 (s, 4, OCH₂), 5.31 (s, 2, NCH₂O), 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⁺ – C₂H₅O), 156 (M⁺ – C₂H₄O₂), 155 (M⁺ – C₂H₅O₂), 143 (M⁺ – C₃H₅O₂), 142 (M⁺ – C₃H₆O₂), 75 (B, C₃H₇O₂⁺). Anal. (C₈H₁₂N₂O₃S) C, H, N.

2,6-Dichloro-9-[(2-hydroxyethoxy)methyl]purine (1e): 80% yield; mp 119–120 °C (CHCl₃–CCl₄); NMR (CDCl₃) δ 3.71 (s, 4, OCH₂), 5.69 (s, 2, NCH₂O), 8.22 (s, 1, purine CH); MS *m/e* 262 (M⁺), 244 (M⁺ – H₂O), 232 (B, M⁺ – HCHO). Anal. (C₈H₈Cl₂N₄O₂) C, H, N.

9-[(2-Hydroxyethoxy)methyl]guanine (Acycloguanosine, 1a). To 120 mL of a 100 mM aqueous solution of K₂CO₃ 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 CHCl₃, 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. (C₈H₉ClN₄O₃) C, H], was treated with liquid NH₃ at 150 °C for 5 h in a steel bomb. The residue was washed with a minimum amount of cold water to remove NH₄Cl and recrystallized from EtOH/H₂O, giving 72 mg (80% yield) of 9-[(2-hydroxyethoxy)methyl]guanine (1a): ¹H NMR [(CD₃)₂SO] δ 3.50 (m, 4, OCH₂), 4.62 (br, 2, NH or OH), 5.36 (s, 2, NCH₂O), 6.47 (s, 2, NH or OH), 7.80 (s, 1, purine CH); MS *m/e* 225 (M⁺), 195 (M⁺ – HCHO), 181 (M⁺ – C₂H₄O), 180 (M⁺ – C₂H₅O), 165 (M⁺ – C₂H₄O₂), 164 (M⁺ – C₂H₅O₂), 151 (B, M⁺ – C₃H₆O₂). Anal. (C₈H₁₁N₅O₃·0.33H₂O) 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 NH₃ 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 [(CD₃)₂SO] δ 3.52 (m, 4, OCH₂), 4.57 (t, *J* = 4 Hz, 1, OH), 5.55 (s, 2, NCH₂O), 7.15 (s, 2, NH₂), 8.10 (s, 1, purine CH), 8.20 (s, 1, purine CH); MS *m/e* 209 (M⁺), 179 (M⁺ – HCHO), 164 (M⁺ – C₂H₅O), 149 (B, M⁺ – C₂H₄O₂), 148 (M⁺ – C₂H₅O₂), 135 (M⁺ – C₃H₆O₂). Anal. (C₈H₁₁N₅O₂) 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 NH₃ 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 [(CD₃)₂SO] δ 3.37 (br, 1, NH or OH), 3.48 (s, 4, OCH₂), 5.05 (s, 2, NCH₂O), 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⁺ – H₂O), 155 (M⁺ – HCHO), 140 (B, M⁺ – C₂H₅O), 125 (M⁺ – C₂H₄O₂), 124 (M⁺ – C₂H₅O₂), 111 (M⁺ – C₃H₆O₂). Anal. (C₇H₁₁N₃O₃·0.125H₂O) C, H, N.

Acycloguanosine Monophosphate (Acyclo-GMP, ³1g). Pyrophosphoryl chloride²⁶ (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 NaHCO₃. 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 ³¹P NMR;²³ ¹H NMR (D₂O) δ 3.53–3.95 (m, 4, OCH₂), 5.45 (s, 2, NCH₂O), 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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