obtained α-halo esters were purified by distillation or chromatography, as shown in Table I. Characteristic spectral data for selected typical compounds are as follows.

Chloromethyl *n*-hexanoate (1a): bp 54–57 °C (0.5 mm); IR (neat) 2970, 2930, 1750, 1435, 1135, 1100, 1040 and 720 cm^{-1}; NMR ($CDCl_3$) δ 5.67 (s, 2 H), 2.5 (t, 2 H), 0.8–2.0 (8 H).

Chloromethyl benzoate (1f): IR (neat) 3060, 2990, 1730, 1590, 1490, 1450, 1340, 1300, 1250, 1080, 800, 720 cm^{-1}; NMR ($CDCl_3$) δ 7.0–8.2 (m, 5 H), 5.97 (s, 2 H).

α-Chloroethyl *n*-hexanoate (1h): IR (neat) 2960, 2920, 1750, 1450, 1380, 1270, 1230, 1160, 1050, 1030, 950, 670 cm^{-1}; NMR ($CDCl_3$) δ 6.50 (q, 1 H), 2.33 (t, 2 H), 1.8 (d, 3 H), 0.7–1.7 (9 H).

Soft quaternary salts **3a–k** and **4a–d** were prepared by mixing equimolar amounts of the corresponding **1** or **2** with the amine in acetonitrile at 70 °C. The product was isolated by crystallization. The yields were usually close to quantitative. Characteristic spectral data are as follows.

1-[(*n*-Hexanoyloxy)methyl]-3-acetoxyquinuclidinium chloride (3a): IR ($CHCl_3$) 2950, 1750, 1460, 1365, 1100, 900 cm^{-1}; NMR (D_2O) δ 5.17 (s, 2 H), 3.2–4.4 (9 H), 1.2–3.2 (11 H), 2.1 (s, 3 H), 0.9 (t, 3 H).

1-[(Phenylacetoxy]-3-acetoxyquinuclidinium chloride (3): IR ($CHCl_3$) 2960, 1740, 1460, 1370, 1210, 1120, 1080, 930 cm^{-1}; NMR (D_2O) δ 7.4 (s, 5 H), 5.23 (s, 2 H), 3.90 (s, 2 H), 3.0–4.0 (7 H), 1.8–3.0 (5 H), 2.1 (s, 3 H).

[(Benzoyloxy)methyl]triethylammonium chloride (3f): IR (KBr) 3010, 2990, 1720, 1595, 1450, 1260, 1180, 1110, 1080, 805, 720 cm^{-1}; NMR (D_2O) δ 7.4–8.4 (5 H), 5.50 (s, 2 H), 3.5 (q, 6 H), 1.47 (t, 9 H).

1-[(Benzoyloxy)methyl]-3-acetoxyquinuclidinium bromide (3j): IR (KBr) 2975, 1720, 1600, 1450, 1370, 1240, 1110, 1030, 920, 720 cm^{-1}; NMR (D_2O) δ 7.2–8.2 (5 H), 5.47 (s, 2 H), 2.0–4.3 (12 H), 2.2 (s, 3 H).

1-[(Pivaloyloxy)methyl]-3-acetoxyquinuclidinium chloride (4b): IR (KBr) 2980, 1710, 1370, 1250, 1150, 1110 cm^{-1}; NMR (D_2O) δ 5.23 (s, 2 H), 3.2–4.2 (6 H), 1.9–3.0 (6 H), 2.2 (s, 3 H), 1.3 (s, 9 H).

3-Acetoxyquinuclidine (5). 3-Quinuclidinol, 25.4 g (0.02 mol), was dissolved at 0 °C in 87 mL (1.08 mol) of pyridine and 31 mL (0.33 mol) of acetic anhydride was added. The solution was heated under reflux for 2 h and the excess pyridine was removed by distillation in vacuo. The residue was dissolved in chloroform and washed with saturated potassium carbonate. The chloroform solution was dried over anhydrous sodium sulfate. Following filtration, the chloroform was removed under reduced pressure to afford a brown-colored liquid. Vacuum distillation of this material gave 23.6 g (0.14 mol, 70%) of **5**: mp 34–36 °C; bp 76–78 °C (0.8 mm); IR (neat) 2950, 2920, 1700, 1435, 1350, 1230, 1020, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.8 (m, 1 H), 2.4–3.6 (6 H), 2.10 (s, 3 H) and 1.1–2.0 (5 H). Anal. ($C_9H_{15}NO_2$) C, H, N.

1-Benzyl-3-acetoxyquinuclidinium chloride (7): mp 205–207 °C; IR (KBr) 2980, 1730, 1365, 1240, 1025, 770, 710 cm^{-1}; ^1H NMR (D_2O) δ 7.6 (s, 5 H), 5.10 (m, 1 H), 4.47 (s, 2 H), 3.2–4.0 (6 H), 2.1 (s, 3 H), 1.8–2.4 (5 H). Anal. ($C_{16}H_{22}ClNO_2$) C, H, N.

Table V. Activity of a Soft Alkylating Agent 1a in P388 Lymphocytic Leukemia[a]

dose, mg/kg	no. of animals	% ILS[b]
400	5	109
200	6	127[c]
100	6	120
50	6	107

[a] One daily dose; total number of doses = 9. Vehicle: saline, administration by ip injection. 1a is NSC 281814D. [b] Percent increase in median survival time as compared to the control group. [c] Activity confirmed by second test.

Competitive Alkylations. a. Determination of Amine Selectivity. To an acetonitrile solution (9 mL) containing 189.0 mg (1.26 mmol) of chloromethyl pivalate (**2**) and 214.2 mg (1.26 mmol) of chloromethyl benzoate (**1f**) was added 212.9 mg (1.25 mmol) of 3-acetoxyquinuclidine (**5**) dissolved in 6 mL of acetonitrile. The solution was heated at 70 ± 0.1 °C for 1 h. The acetonitrile was removed under reduced pressure and the residue obtained was dried in vacuo over anhydrous calcium sulfate. The residue was dissolved in D_2O–acetone-d_6 (~1:2, v/v). The composition of the isolated product mixture was determined by multiple integration (five determinations) of the $\geqslant N^+CH_2O_2CR$ resonance signal of the products at expanded sweep widths (250 Hz). The corresponding very sharp singlet signals were well separated and could easily be integrated.

Using the procedure described for determining the selectivity of 3-acetoxyquinuclidine (**5**) relative to chloromethyl pivalate (**2**) and chloromethyl benzoate (**1f**), triethylamine, pyridine, and 1-methylimidazole were also investigated. The results are shown in Table II.

b. Determination of the Relative Alkylating Reactivity (RAR). The procedure described above was used, mixing 1.26 mmol of **2** and 1.26 mmol of **1a–h** and **6**, respectively, and 1.26 mmol of **5** in acetonitrile. The results are shown in Table IV.

Biology. The screening of **1a** and **1h** were performed by the Drug Evaluation Branch of the NCI. The results are given in Table V.

Synthesis of Some New S-Alkylated Derivatives of 5-Mercapto-2′-deoxyuridine as Potential Antiviral Agents

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A series of S-alkylated derivatives of 5-mercapto-2′-deoxyuridine have been prepared by alkylation of the preformed nucleoside. Two of these compounds, the *S*-propargyl and *S*-allyl derivatives, have shown significant antiviral activity against *Herpes simplex* type 1 in HeLa TK$^-$ cells but appear to be less effective in this assay system than some previously reported 5-substituted 2′-deoxyuridines.

Since the discovery of the anti-herpes activity of 5-iodo-2′-deoxyuridine,[2,3] the first therapeutically employed antiviral nucleoside, a number of other 5-substituted 2′-deoxyuridines have been found to possess significant activity against the *Herpes simplex* virus. These include the clinically effective 5-(trifluoromethyl)[4,5] and 5-ethyl[6] derivatives, as well as the mostly in vitro tested 5-bromo-,[7]

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(2) W. H. Prusoff, M. S. Chen, P. H. Fischer, T.-S. Lin, G. T. Shian, and R. F. Schinazi, *Adv. Ophthalmol.*, **38**, 3–16 (1979).
(3) J. Sugar and H. E. Kaufman in "Selective Inhibitors of Viral Functions", W. A. Carter, Ed., CRC Press, Cleveland, Ohio, 1973, pp 295–311.
(4) C. Heidelberg, *Ann. N.Y. Acad. Sci.*, **255**, 317 (1975).
(5) F. Bigar, *Adv. Ophthalmol.*, **38**, 105–109 (1979).
(6) K.-L. Elze, *Adv. Ophthalmol.*, **38**, 134–139 (1979).

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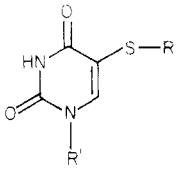
5-cyano-,[8] 5-(thiocyano)-,[9,10] 5-(methoxymethyl)-,[11] 5-(mercaptomethyl)-,[12] 5-(methylamino)-,[13] 5-vinyl-,[14] 5-propyl-,[14] and 5-allyl-2′-deoxyuridines.[14] Recently, several 5-O-alkylated derivatives of 5-hydroxy-2′-deoxyuridine were synthesized and tested; among these, 5-(propynyloxy)-2′-deoxyuridine showed the highest activity against the *Herpes simplex* type 1 virus (HSV-1).[15]

Interest in this laboratory has been for some time directed toward the diverse biological activities of 5-mercapto-2′-deoxyuridine[16] (MUdR, 1) and its derivatives.



1, R = H; R′ = 2-deoxy-β-D-ribofuranosyl
1a, R = H; R′ = H
2, R = $-CH_3$; R′ = 2-deoxy-β-D-ribofuranosyl
3, R = $-CH_2CH{=}CH_2$; R′ = H
4, R = $-CH_2C{\equiv}CH$; R′ = H
5, R = $-CH_2CONH_2$; R′ = H
6, R = $-CH_2CH_2OH$; R′ = H
7, R = $-CH_2CH{=}CH_2$; R′ = 2-deoxy-β-D-ribofuranosyl
8, R = $-CH_2C{\equiv}CH$; R′ = 2-deoxy-β-D-ribofuranosyl
9, R = $-CH_2CONH_2$; R′ = 2-deoxy-β-D-ribofuranosyl
10, R = $-CH_2CH_2OH$; R′ = 2-deoxy-β-D-ribofuranosyl

This nucleoside has been found to be an effective antimetabolite in a variety of test systems,[17] as well as in the preliminary clinical studies against cutaneous neoplasms in man.[18] It has been shown that 1 is phosphorylated by thymidine kinase to 5-mercapto-2′-deoxyuridylic acid which, in turn, is a potent inhibitor of thymidylate synthetase.[19] While 1 showed only borderline activity against HSV-1, its *S*-methyl derivative (2) demonstrated significant anti-herpes activity.[20,21] This was in contrast to the reported inactivity of the analogous 5-methoxy-2′-deoxyuridine.[21] Subsequent studies using ^{14}C-labeled 5-(*S*-methylmercapto)-2′-deoxyuridine indicated that the mode of action of 2 as an antiviral agent is apparently related to its extensive incorporation into the viral DNA.[22] In view of the interesting antineoplastic and antiviral activities, respectively, of 1 and 2 [and also of the 5-(thiocyano) derivative[9,10]], it appeared desirable to synthesize several other *S*-alkyl derivatives, including some of the S analogues of the above-mentioned 5-O-alkylated derivatives of 5-hydroxy-2′-deoxyuridine.[15]

Chemisty. Previously, the syntheses of *S*-alkyl derivatives of 5-mercaptouracil nucleosides were carried out by a somewhat lengthy synthetic procedure. In each case, 5-mercaptouracil (1a) was first reacted with the appropriate alkyl halide to form the desired 5-S-alkylated derivative. This base was then converted to the corresponding bis(*O*-trimethylsilyl) derivative and coupled with the blocked halogenose, using reaction conditions known to promote the predominant formation of the β-anomeric blocked nucleosides.[16] Purification of the latter (separation from the α-anomer if formed),[23] followed by deblocking, afforded the desired product. However, the preparation of the β-anomeric free mercapto nucleoside 1 is a well-established synthetic procedure[16] and this material can be made readily in substantial quantities. This observation suggested that the selective alkylation of the 5-sulfur atom of this preformed nucleoside might offer a simpler and more direct method for the synthesis of its anomerically pure sulfide derivatives. Since the preparation of a variety of *S*-alkyl derivatives of 5-mercaptouracil has been accomplished via direct alkylation of this base,[16,28] alkylation of the 5-sulfur atom of 1 seemed to hold significant promise.

Whereas the presence of several alternative sites at which alkylation could occur in 1 posed a potential obstacle to the selective alkylation of the 5-sulfur atom, reaction conditions were chosen which would promote selective sulfur alkylation. This was accomplished by exploiting the substantial difference in acidity between the hydroxyl groups present on the pyrimidine and 2′-deoxyribose rings and the much more acidic 5-sulfhydryl group of the pyrimidine ($pK_a = 5.0$).[24] This difference in acidity allowed selective formation of the sulfide anion when a stoichiometric amount of hydroxide ion was used as the base. This, coupled with the inherently greater nucleophilicity of sulfur as compared to oxygen, resulted in highly selective alkylation of the 5-sulfur atom. (It should be mentioned that even in the case of 5-hydroxyuridine selective alkylation at 5-O has been achieved with allyl and propargyl halides.)[25,26] Hence, blocking of the other potential alkylation sites present in 1 proved to be unnecessary.

An additional problem in the alkylation of 1 which had to be considered arose from its tendency to undergo facile autoxidation.[24,27] Previous studies had shown that the nucleoside 1 oxidizes readily to form the corresponding disulfide in aqueous basic solution. Since the alkylation of the sulfur atom of 1 required the use of aqueous base, this dimerization reaction had to be prevented. A 1:1 (volume) solution of 0.1 N NaOH and methanol was found to minimize the tendency of 1 to undergo dimerization and to be a well-suited medium for the alkylation reactions.

(7) W. H. Prusoff and B. Goz, in "Antineoplastic and Immunosuppressive Agents", A. C. Sartorelli and D. G. Johns, Eds., Springer-Verlag, New York, 1975, pp 272–347.
(8) P. F. Torrence, B. Booshan, J. Descamps, and E. De Clercq, *J. Med Chem.*, **20**, 974 (1977).
(9) T. Nagamachi, J.-L. Fourrey, P. F. Torrence, J. A. Waters, and B. Witkop, *J. Med. Chem.*, **17**, 403 (1975).
(10) E. De Clercq, P. F. Torrence, J. A. Waters, and B. Witkop, *Biochem. Pharmacol.*, **24**, 2171 (1975).
(11) J. Meldrum, V. S. Gupta, and J. R. Saunders, *Antimicrob. Agents Chemother.*, **6**, 393 (1974).
(12) V. S. Gupta, G. L. Bubbar, J. B. Meldrum, and J. R. Saunders, *J. Med. Chem.*, **18**, 973 (1975).
(13) T. Y. Shen, J. F. McPherson, and B. O. Linn, *J. Med. Chem.*, **9**, 366 (1966).
(14) Y. C. Cheng, B. A. Domin, R. A. Sharma, and M. Bobek, *Antimicrob. Agents Chemother.*, **10**, 119 (1976).
(15) P. F. Torrence, J. W. Spencer, A. M. Bobst, J. Descamps, and E. De Clercq, *J. Med. Chem.*, **21**, 228 (1978).
(16) M. P. Kotick, C. Szantay, and T. J. Bardos, *J. Org. Chem.*, **34**, 3806 (1969).
(17) K. Baranski, T. J. Bardos, A. Bloch, and T. I. Kalman, *Biochem. Pharmacol.*, **18**, 347 (1969).
(18) S. H. Schwartz, T. J. Bardos, G. H. Burgess, and E. Klein, *J. Med. (Basel)*, **1**, 174 (1970).
(19) T. J. Kalman and T. J. Bardos, *Mol. Pharmacol.*, **6**, 621 (1970).
(20) T. J. Bardos, J. Aradi, Y. K. Ho, and T. I. Kalman, *Ann. N.Y. Acad. Sci.*, **255**, 522 (1975).
(21) M. G. Stout and R. K. Robins, *J. Heterocycl. Chem.*, **9**, 545 (1972).
(22) R. Hardi, R. G. Hughes, Jr., Y. K. Ho, K. C. Chadha, and T. J. Bardos, *Antimicrob. Agents Chemother.*, **10**, 682 (1976).
(23) E. K. Ryu and T. J. Bardos, *J. Heterocycl. Chem.*, **16**, 1049 (1979).
(24) T. J. Bardos and T. I. Kalman, *J. Pharm. Sci.*, **55**, 606 (1966).
(25) B. A. Otter, A. Taube, and J. J. Fox, *J. Org. Chem.*, **36**, 1251 (1971).
(26) B. A. Otter, S. S. Saluja, and J. J. Fox, *J. Org. Chem.*, **37**, 2858 (1972).
(27) T. I. Kalman and T. J. Bardos, *J. Am Chem. Soc.*, **89**, 1171 (1967).

Table I. Antiviral Activity Results

compd (100 μM)	virus HSV-1 titer, pfu/mL
none (control)	3.8×10^7
3	6.5×10^7
4	3.7×10^7
7	5.3×10^6
8	1.4×10^6
10	3.8×10^7
2	5.2×10^6

Additionally, the use of a nitrogen atmosphere and the addition of excess alkylating agent to the basic solution of 1 immediately after addition of the base aided in the prevention of this side reaction. Separation of the nucleoside products from the inorganic salts formed in the reaction was accomplished by gel-filtration chromatography.

In order to facilitate the spectral characterization of the alkylated nucleosides formed in this work, each of the reagents to be used for the alkylation of 1 was first used to form a sulfide by reaction with the corresponding pyrimidine base 1a. In contrast to the nucleoside alkylations, these reactions were carried out in dry methanol using sodium methoxide as the base. The proton magnetic resonance, infrared, and ultraviolet spectral characteristics of the resulting products were consistent with those anticipated for the pyrimidine sulfides **3**, **4**, and **5**, respectively. The synthesis and properties of *S*-(2-hydroxyethyl)-5-mercaptouracil have been previously described.[28]

The assigned structures of the S-alkylated nucleosides (**7–10**) are based upon correct elemental analyses, ultraviolet spectra which are similar to those reported for other authentic S-alkylated 2′-deoxy-5-mercaptouridines,[16] as well as infrared and NMR spectral data which established the presence of the appropriate S-substituent groups ($-CH_2CH{=}CH_2$, **7**; $-CH_2C{\equiv}CH$, **8**; $-CONH_2$, **9**; $-CH_2CH_2OH$, **10**) and were consistent with the β-anomeric configuration (pseudotriplet at 6.2 ppm in the NMR).[29] Further, thin-layer chromatography in several systems showed only a single spot for each of these nucleosides. It was noted, however, that the *S*-propargyl nucleoside gradually darkened when exposed to air on storage.

Biological Screening Results. Preliminary screening of some of the above compounds at 100 μM concentration against HSV-1 (strain KOS) in HeLa TK$^-$ cells was conducted in the laboratory of Dr. Yung-chi Cheng according to the previously reported assay method.[14] The results, summarized in Table I, indicate that the *S*-allyl- and *S*-propargyl-substituted nucleosides, **7** and **8**, respectively, possess significant inhibitory activities, while the corresponding bases **3** and **4** were inactive at the concentration tested. Compound **7** was comparable in potency to the "lead compound", *S*-Me-MUdR (**2**), while the *S*-propargyl derivative **8** was significantly more active than **2**. However, the reduction of virus titer caused by a 100 μM concentration of compound **8** in this assay appears to be similar to that obtained with 2 μM iodo-2′-deoxyuridine.[14] Although **8** was not cytotoxic at 100 μM, it caused 50% growth inhibition of HeLa cells at 300 μM. It is interesting to recall that *S*-Me-MUdR (**2**) showed substantially greater antiviral activity against HSV-1 grown in mouse L cells than against the same virus grown in monkey kidney (CV-1) cells.[20] It appears that the HSV-1/HeLa TK$^-$ system has relatively low sensitivity to the antiviral action of this series of compounds.

(28) E. K. Ryu, Ph.D. Thesis, State University of New York at Buffalo, 1976.
(29) M. G. Robins and R. K. Robins, *J. Am. Chem. Soc.*, 87, 4934 (1965).

Experimental Section

The various alkyl halides used in this work were purchased from the Aldrich Chemical Co., Milwaukee, Wis. Authentic 5-mercaptouracil and 5-mercapto-2′-deoxyuridine were prepared by literature method.[16] Ultraviolet spectra were obtained using a Beckman Model 25 spectrophotometer, infrared spectra were obtained using a Perkin-Elmer 197 spectrophotometer, and NMR spectra were determined using Varian T-60 and HA-100 instruments. Me_4Si was used as an internal standard for spectra determined in Me_2SO solution, and DSS served as a standard in D_2O solution. Microanalyses were carried out by Atlantic Microlab (Altanta, GA), and melting points (uncorrected) were obtained on a Mel Temp instrument.

5-(*S*-Allylmercapto)uracil (3). To a solution of 1.15 g of sodium (0.05 g-atom) in 150 mL of dry methanol was added 7.2 g (0.05 mol) of 5-mercaptouracil. A solution of 8.6 mL of allyl bromide (12.1 g, 0.10 mol) in 10 mL of methanol was added and the mixture was allowed to stir overnight. The resulting precipitate was collected, washed with water and then cold ethanol, and dried in vacuo over P_2O_5 to give 7.4 g (81%) of **3**. Recrystallization from ethanol afforded an analytical sample: mp 231–234 °C dec; UV λ_{max} (0.1 N NaOH) 293 nm (ε 7300); IR ν_{max} 1590 cm^{-1} (–C=C); NMR (Me_2SO-d_6) δ 3.3 (d, J = 9 Hz, CH_2, 2 H), 4.7–6.0 (m, $CH{=}CH_2$, 3 H), 7.5 (s, 6-H, 1 H). Anal. ($C_7H_8N_2O_2S$) C, H, N.

5-(*S*-Propargylmercapto)uracil (4). From a similar reaction of 7.2 g (0.05 mol) of 5-mercaptouracil and 14.8 g (0.10 mol) of an 80% solution of propargyl bromide in toluene was obtained 7.3 g (80%) of **4**. Recrystallization from methanol afforded an analytical sample: mp 215–217 °C dec; UV λ_{max} (0.1 N NaOH) 292 nm (ε 7000); IR (Nujol) ν_{max} 3236 cm^{-1} (–C≡CH); NMR (Me_2SO-d_6) δ 3.0 (t, J = 2 Hz, C≡CH, 1 H), 3.6 (d, J = 2 Hz, $-CH_2C{\equiv}C$, 2 H), 7.2 (s, 6-H, 1 H). Anal. ($C_7H_6N_2O_2S$) C, H, N.

5-(*S*-Acetamidomercapto)uracil (5). 5-Mercaptouracil, 2.88 g (0.02 mol), was added to 20 mL of 1 N NaOH. Iodoacetamide (7.4 g, 0.04 mol) was added to the mixture, which was stirred overnight under a nitrogen atmosphere. The resulting yellow-white precipitate was isolated by filtration and recrystallized from water to give 3.56 g (89%) of **5**: mp 286–290 °C dec; UV λ_{max} (0.1 N NaOH) 293 nm (ε 6890); IR (Nujol) ν_{max} 1610 ($-CONH_2$), 3350 and 3500 cm^{-1} (NH_2); NMR (Me_2SO-d_6) δ 3.3 (s, $-CH_2C(=O)$, 2 H), 7.0–7.4 (br, $-NH_2$, 2 H), 7.6 (d, J = 4 Hz, 6-H, 1 H), 10.1–10.5 (m, 1,3-H, 2 H). Anal. ($C_6H_7N_3O_3S$) C, H, N.

1-(2′-Deoxy-β-D-ribofuranosyl)-5-(*S*-allylmercapto)uracil (7). The β-anomer of 5-mercapto-2′-deoxyuridine (1; 0.10 g, 0.30 mmol) was dissolved in 5 mL of methanol under nitrogen, and 4.1 mL (0.41 mmol) of 0.1 N NaOH and then 0.10 mL (0.14 g 1.1 mmol) of allyl bromide were added. The solution was allowed to stir at room temperature overnight. Evaporation of the solvent in vacuo afforded a pale yellow liquid which crystallized upon the addition of ether to give a white solid (mixed salt and nucleoside), which was collected by filtration (0.15 g), mp 60 °C dec. Chromatography on Sephadex-15 of the mixture afforded analytically pure **5**: yield 0.093 g (83%); mp 149–151 °C; UV λ_{max} (H_2O) 280 nm (ε 5080), 206 (9500); IR (Nujol) 1595 cm^{-1} (–C=CH_2); NMR (D_2O) δ 3.3 (d, J = 6 Hz, $-SCH_2-$, 2 H), 6.2 (t, J = 6 Hz, 1′-H, 1 H), 8.0 (s, 6-H, 1 H). Anal. ($C_{12}H_{16}N_2O_5S$) C, H, N.

1-(2′-Deoxy-β-D-ribofuranosyl)-5-(*S*-propargylmercapto)uracil (8). This material was prepared on the same scale and in a manner similar to that used for the preparation of **7**. Propargyl bromide was used for alkylation and compound **8** formed in 86% yield: mp 104–106 °C; UV λ_{max} (H_2O) 281 nm (ε 5100); IR (Nujol) 3230 cm^{-1} (C≡CH); NMR (D_2O) δ 3.6 (t, J = 2 Hz, –C≡CH, 1 H), 3.9 (t, J = 2 Hz, $-CH_2C{\equiv}C$, 2 H), 6.3 (t, J = 6 Hz, 1′-H, 1 H), 8.2 (s, 6-H, 1 H). Anal. ($C_{12}H_{14}N_2O_5S$) C, H, N.

1-(2′-Deoxy-β-D-ribofuranosyl)-5-[*S*-(2-hydroxyethyl)mercapto]uracil (10). This material was prepared on the same scale and in a similar manner to that used for the preparation of **7**. 2-Bromoethanol was used for alkylation, and compound **10**, which is mildly hygroscopic, formed in 90% yield: mp 79–82 °C; UV λ_{max} (H_2O) 279 nm (ε 4900); IR (Nujol) 3450 cm^{-1} (–OH); NMR

(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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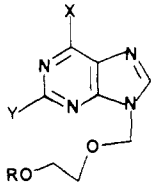
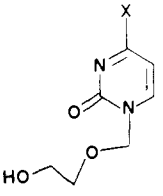
Alkylation of 2-chloro-6-iodopurine with iodomethyl [(trimethylsilyl)oxy]ethyl ether at −63 °C and subsequent treatment of the 9-substituted chloroiodopurine with K_2CO_3 in aqueous dioxane at 25 °C and then with NH_3 under pressure at 150 °C provided 9-[(2-hydroxyethoxy)methyl]guanine (**1a**), a potent 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.
(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.

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