of lactone **16** in 30 mL of DMF, along with 0.93 g (6.3 mmol) of potassium thiophenoxide. The mixture was stirred for 12 h, during which time it turned dark brown. The solution was partitioned between 150 mL of ether and 50 mL of 1 N NaOH. The ether layer was dried over K_2CO_3, and the solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel with CH_2Cl_2 as the eluent to give **26a** as an oil in 61% yield: IR (neat) 1750 (C=O), 1625 (C=C), 1190, 855 cm^{-1}; NMR ($CDCl_3$) δ 2.7 (dt, 2, J = 2.8 and 7.2 Hz), 4.3 (t, 2, J = 7.2 Hz), 7.2-7.3 (m, 5), 7.51 (t, J = 2.8 Hz); mass spectrum, m/e 206 (M^+, 100), 161 (25), 147 (71), 129 (27), 109 (10), 77 (12).

Reaction of Lactone 16 with *tert*-Butyl Mercaptan. Formation of 26b. To a 125-mL Erlenmeyer flask was added 0.5 g (2.6 mmol) of lactone **16** in 50 mL of ether, followed by 0.5 g (5 mmol) of *tert*-butyl mercaptan. The mixture was stirred for 12 h at room temperature and then extracted twice with 30 mL of 1 N NaOH. The ether layer was dried over K_2CO_3 and the solvent removed by rotary evaporator. The residue was purified by column chromatography on silica gel with CH_2Cl_2 as eluent. Evaporation of the solvent gave 0.30 g (63%) of light yellow crystalline solid **26c**: mp 120-123 °C; IR (KBr) 1710 (C=O), 1590 (C=C), 1190, 1020, 855 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (s, 9), 3.15 (dt, 2, J = 2.1 and 7.2 Hz), 4.5 (t, 2, J = 7.2 Hz), 7.3 (t, 1, J = 2.1 Hz).

Reaction of Lactone 16 with L-Cysteine. Formation of 26c. To a 125-mL Erlenmeyer flask was added 0.96 g (5 mmol) of lactone **16**, followed by 0.79 g (5 mmol) of L-cysteine hydrochloride in 60 mL of 50% aqueous methanol. The pH was adjusted to 7.0 with 1 N NaOH and the mixture stirred for 12 h at room temperature. The mixture was extracted with 50 mL of ether and the aqueous layer was cooled to -20 °C upon which 0.31 g (20%) of adduct **26c** precipitated: IR (KBr) 3400 (br, NH_2COOH) 1760 (C=O), 1715, 1200, 810 cm^{-1}; NMR (D_2O) δ 2.6 (s, 3, $CH_3SO_3^-$), 2.9-3.4 (m), 4.5 (br, exchangeable with D_2O), 7.21 (t, 1).

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Pyrimidine Acyclic Nucleosides. 5-Substituted 1-[(2-Aminoethoxy)methyl]uracils as Candidate Antivirals

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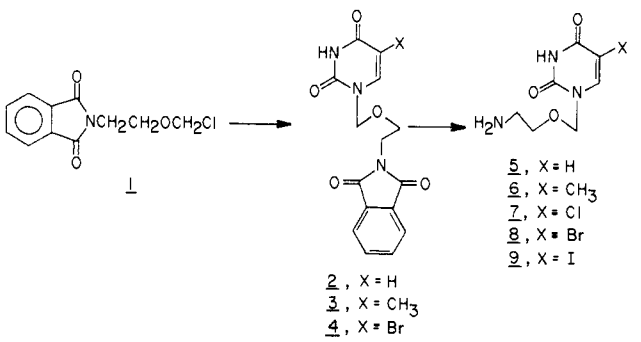
Several 5-substituted analogues of the acyclic aminonucleoside 1-[(2-aminoethoxy)methyl]uracil (**5**) were prepared for evaluation as antivirals. The uracil and thymine analogues were prepared in two steps from *N*-[2-(chloromethoxy)ethyl]phthalimide (**1**). The 5-chloro, 5-bromo, and 5-iodo analogues were prepared by halogenation of **5**. These acyclic aminonucleosides exhibited neither cell toxicity nor antiviral activity. This is compatible with their lack of substrate properties toward herpes simplex virus thymidine kinase.

A program initiated to synthesize nucleoside analogues in which the cyclic carbohydrate moiety is replaced by an acyclic side chain has led to the discovery of the potent antiherpetic drug acyclovir (9-[(2-hydroxyethoxy)methyl]guanine, ZOVIRAX).[1,2] Acyclovir possesses potent antiviral activity in cells infected with herpes simplex virus type 1 (HSV-1), but it is essentially nontoxic to uninfected host cells.[2,3] This selective toxicity is related to acyclovir being a unique substrate for HSV-1 encoded thymidine kinase.[4] Phosphorylation to acyclovir monophosphate occurs preferentially in HSV-1 infected cells, with subsequent selective inhibition of viral replication.[2,4]

Synthesis of 5'-amino analogues of certain pyrimidine nucleosides has resulted in 5'-amino-5-iodo-2',5'-dideoxyuridine (AIU), an analogue of thymidine with selective activity against HSV-1.[5,6] AIU is also a unique substrate for HSV-1 encoded thymidine kinase, thereby exhibiting little or no uninfected cell toxicity.[7,8]

Scheme I



Other studies in these laboratories have found a series of pyrimidine acylic nucleosides analogous to acyclovir to have little or no in vitro antiviral activity.[9] In an attempt to find pyrimidine acyclic nucleosides with antiviral activity comparable to acyclovir, a series of 1-[(2-aminoethoxy)methyl]uracils has been synthesized. These compounds possess structural features in common with both AIU and acyclovir. The synthesis and antiviral effect of these compounds against HSV-1 are described in this report.

Chemistry. The 1-[(2-aminoethoxy)methyl]uracils **5-9** were prepared in two or three steps from *N*-[2-(chloromethoxy)ethyl]phthalimide (**1**)[10] (Scheme I). Alkylation

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of a threefold excess of uracil with 1 under the general conditions developed by Baker[11,12] gave only a low yield of 2. We then examined a modification of the silyl Hilbert–Johnson reaction where the silylating solvent was used in the alkylation step[13] with acetonitrile as a cosolvent.[14] After the reaction was refluxed for several days, very little reaction had occurred. However, when a catalytic amount of 4-toluenesulfonic acid[15] was added, 2 was obtained in good yield. The thymine analogue 3 was obtained similarly. A similar one-step nucleoside synthesis has been recently reported by Vorbrüggen.[16]

Bromination of 2 with pyridinium hydrobromide perbromide gave 4 in good yield. Attempted removal of the phthaloyl group with hydrazine gave none of the desired 8. Although phthalhydrazide was isolated, loss of the characteristic pyrimidine ultraviolet absorption indicated that attack of the pyrimidine ring had occurred. In contrast, the uracil moiety of 2 was stable toward hydrazine and gave 5 in good yield. The thymine analogue 6 was obtained by treatment of 3 with methylamine.[17] The ultraviolet spectra substantiated that 5 and 6, and therefore 2 and 3, were the 1-isomers.[12,18]

The 5-halouracils 7–9 were prepared from 5 by reaction with *N*-chlorosuccinimide, with pyridinium hydrobromide perbromide, and with iodine monochloride, respectively. Attempted iodination with iodine failed to give 9 under a variety of conditions.

Results and Discussion

None of the 1-[(2-aminoethoxy)methyl]uracils 5–9 exhibited any significant cytotoxicity at a concentration of 10^{-4} M when tested against Detroit 98 or mouse L cells in cell culture.[19] These compounds were also inactive when examined at 50 μg per disk by means of plaque-inhibition tests against HSV-1 in cell culture.[1,20,21] Little or no activity was observed against two other DNA viruses (vaccinia virus, adenovirus type 5) or a range of RNA viruses comprising rhinovirus 1B, measles, corona, respiratory syncytial virus, and the NWS strain of influenza virus.[1]

As a tool for predicting anti-herpes activity, Fyfe et al. have studied a number of nucleoside analogues as substrates and/or inhibitors of HSV-1 encoded thymidine kinase.[4,22] They have reported that nucleoside analogues in which the anti-herpes activity utilizes the same mechanism of action as acyclovir bind to and are good substrates for HSV-1 encoded thymidine kinase.[4,22] Uracils 5–9 had a low affinity for the thymidine kinase and were inactive as substrates. This lack of substrate properties for HSV-1 encoded thymidine kinase is sufficient to explain the absence of anti-herpetic activity with these pyrimidine acyclic nucleosides. The inactivity of 9 contrasts sharply with the good anti-herpetic activity of the analogous cyclic pyrimidine nucleoside AIU, which is a good substrate for the viral-encoded thymidine kinase.[8]

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. NMR data were recorded on a Varian XL-100-15-FT or T-60 spectrometer using Me_4Si as an internal standard. UV data were obtained on a Unicam SP 800 spectrophotometer. Each analytical sample had spectral data compatible with its assigned structure, gave combustion values for C, H, and N within 0.4% of theoretical, and moved as a single spot on TLC. TLC were performed on Eastman Chromagram sheets of cellulose (C) or silica gel (SG) with fluorescent indicator using C_6H_6–EtOH (5:1, v/v) (solvent 1), C_6H_6–EtOH (10:1, v/v) (solvent 2), EtOAc (solvent 3), CH_3CN–$CHCl_3$ (3:2, v/v) (solvent 4), CH_3CN–H_2O (4:1, v/v) (solvent 5), NH_4OH–H_2O–PrOH (1:1:8, v/v) (solvent 6), or 5% aqueous $(NH_4)_2SO_4$–7.4 M NH_4OH–PrOH (3:3:14, v/v) (solvent 7).

1-[(2-*N*-Phthalimidoethoxy)methyl]uracil (2). Method A. A mixture of 3.41 g (30.4 mmol) of uracil, 4.17 g (30.2 mmol) of K_2CO_3, 50 mL of Me_2SO, and 2.40 g (10.0 mmol) of 1[10] was stirred with protection from moisture for 24 h. The resultant gel was poured over 250 mL of ice–water, acidified to pH 5–6 with 10 mL of AcOH, and extracted with four 100-mL portions of $CHCl_3$. The combined extracts were filtered to remove the insoluble uracil, washed with H_2O, dried ($MgSO_4$), and spin evaporated in vacuo. The residual Me_2SO was removed by repeated coevaporation with EtOH at 95 °C. The residue was triturated with Et_2O to give 2 as white crystals: yield, 0.49 g (15%); mp 197–200 °C. Recrystallization from EtOH gave analytically pure material: yield 0.39 g (13%); mp 203–204 °C; TLC (SG) sol 1; NMR (Me_2SO-d_6) δ 11.22 (br s, 1 H, NH), 7.87 (s, 4 H, ArH), 7.61 (d, 1 H, J = 8.0 Hz, C-6), 5.48 (d, 1 H, J = 8.0 Hz, C-5), 5.08 (s, 2 H, NCH_2O), 3.77 (s, 4 H, CH_2CH_2). Anal. ($C_{15}H_{13}N_3O_5$) C, H, N.

Method B. A mixture of 7.65 g (68.3 mmol) of uracil, 200 mL of hexamethyldisilazane, and 3.6 mL (28 mmol) of trimethylsilyl chloride was refluxed with stirring under N_2 for 18 h. The solution was cooled, 0.76 g (4 mmol) of *p*-toluenesulfonic acid hydrate was added, and the solution was refluxed for 2 h. The reaction was cooled, and a solution of 17.2 g (72 mmol) of 1[10] in 150 mL of CH_3CN was added. The reaction mixture was refluxed with stirring for 18 h and then spin evaporated in vacuo to an oil. The oil was digested with EtOH and spin evaporated in vacuo to give a white solid, which was dispersed in hot EtOH, collected by filtration, and dried: yield 14.5 g (67%). Recrystallization from EtOH/2-MeOEtOH gave 11.2 g (52%) of 2, mp 201–204 °C, which was identical with 2 prepared by method A.

5-Methyl-1-[(2-*N*-phthalimidoethoxy)methyl]uracil (3). A mixture of 6.30 g (50.0 mmol) of thymine, 100 mL of hexamethyldisilazane, and 0.5 mL of trimethylsilyl chloride was refluxed with stirring under N_2 with protection from moisture for 19 h. To the cooled solution was added 1.0 g (5.2 mmol) of 4-toluenesulfonic acid hydrate, followed by the dropwise addition of a solution of 11.92 g (49.8 mmol) of 1[10] in 50 mL of CH_3CN over 5 min. The mixture was refluxed with stirring for 70 h, cooled, and spin evaporated in vacuo. The residual oil was diluted with 200 mL of EtOH, refluxed on the steam bath for 2.5 h, cooled, and spin evaporated in vacuo. The residual white solid was slurried with 200 mL of H_2O, collected, and washed with H_2O: yield 14.5 g (88%); mp 230–234 °C. Two recrystallizations from 2-MeOEtOH gave 3 as white threads: yield 12.33 g (74%); mp 231–234 °C; TLC (SG) sol 2; NMR (Me_2SO-d_6) δ 11.20 (br s, 1 H, NH), 7.87 (s, 4 H, ArH), 7.44 (br s, 1 H, C-6), 5.03 (s, 2 H, NCH_2O), 3.75 (s, 4 H, CH_2CH_2), 1.57 (d, 3 H, CH_3). Anal. ($C_{16}H_{15}N_3O_5$) C, H, N.

5-Bromo-1-[(2-*N*-phthalimidoethoxy)methyl]uracil (4). To a dispersion of 2.00 g (6.34 mmol) of 2 in 8 mL of AcOH was added 3.01 g (9.42 mmol) of pyridinium hydrobromide perbromide in 4 mL of AcOH. The reaction was heated at ~70 °C for 1 h and

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then diluted with 10 mL of H_2O and cooled. The resultant solid was collected, washed with water, and dried: yield 1.83 g (73%); mp 232–238 °C. Recrystallization from THF gave the analytical sample with mp 239–241 °C; TLC (SG) sol 3 and 4; NMR (Me_2SO-d_6) δ 11.72 (br s, 1 H, NH), 8.15 (s, 1 H, C-6), 7.86 (s, 4 H, ArH), 5.08 (s, 2 H, NCH_2O), 3.79 (s, 4 H, CH_2CH_2). Anal. ($C_{15}H_{12}BrN_3O_5$) C, H, N.

1-[(2-Aminoethoxy)methyl]uracil Hydrochloride (5). A mixture of 4.0 mL (124 mmol) of 96% hydrazine, 2.00 g (6.34 mmol) of **2**, and 200 mL of EtOH was refluxed with stirring for 1.25 h. The mixture was cooled and spin evaporated in vacuo at <45 ° C and then four times dispersed in EtOH and evaporated to dryness to remove residual hydrazine. The resultant solid was dispersed in 200 mL of 0.1 N HCl and stirred for 1 h at ambient temperature. The white solid was removed by filtration and washed with water. The combined filtrate and wash were spin evaporated in vacuo to give a light yellow powder, which was recrystallized from aqueous EtOH–C_6H_6. Recrystallization as above gave the analytical sample: yield 0.650 g (46%); mp 226–228 °C; TLC (C) sol 5; UV (0.1 N HCl) λ_{max} 258 nm (ε 9900); UV (0.1 N NaOH) λ_{max} 259 nm (ε 7000); NMR (Me_2SO-d_6) δ 11.25 (br s, 1 H, NH), 8.31 (br s, 3 H, NH_3^+), 7.81 (d, 1 H, J = 8.0 Hz, C-6), 5.63 (d, 1 H, J = 8.0 Hz, C-5), 5.16 (s, 2 H, NCH_2O), 3.75 (t, 2 H, J = 5.0 Hz, OCH_2C), 2.97 (t, 2 H, J = 5.0 Hz, CCH_2N). Anal. ($C_7H_{11}N_3O_3$·HCl) C, H, N.

1-[(2-Aminoethoxy)methyl]-5-methyluracil Hydrochloride (6). A solution of 3.05 g (9.26 mmol) of **3** and 100 mL of 40% aqueous $MeNH_2$ was stirred at ambient temperature for 48 h and then spin evaporated in vacuo. The residual syrup was thrice dissolved in EtOH and reevaporated. The syrup was dissolved in a minimum of EtOH, and Et_2O was added to incipient tubidity. Ten milliliters of HCl-saturated MeOH was added in 1-mL portions to give solids, which were then diluted with Et_2O to a 240-mL volume. The solvent was decanted from the solids, and the Et_2O wash was thrice repeated. The solids were collected and dried: yield 1.99 g (91%); mp 220–225 °C. Since this material contained some phthalimide impurity, it was dissolved in 50 mL of H_2O and washed with Et_2O. The aqueous solution was spin evaporated in vacuo at <40 °C, EtOH was added to the residue, and it was reevaporated to give a white solid that was recrystallized from EtOH: yield 0.566 g (26%); mp 223–225 °C. A second crop yielded 0.365 g (42% total), mp 222–224 °C. An additional recrystallization gave the analytical sample: mp 226–227 °C; TLC (C) sol 6; UV (0.1 N HCl) λ_{max} 265 nm (ε 8600), UV (0.1 N NaOH) λ_{max} 265 nm (ε 6400); NMR (Me_2SO-d_6) δ 9.00 (br s, 3 H, NH_3^+), 7.67 (s, 1 H, C-6), 5.13 (s, 2 H, NCH_2O), 3.75 (t, 2 H, J = 5.0 Hz, OCH_2C), 2.97 (t, 2 H, J = 5.0 Hz, CCH_2N), 1.79 (s, 3 H, CH_3). Anal. ($C_8H_{13}N_3O_3$·HCl) C, H, N.

1-[(2-Aminoethoxy)methyl]-5-chlorouracil Hydrochloride Hydrate (7). A magnetically stirred mixture of 0.500 g (2.26 mmol) of **5**, 0.339 g (2.49 mmol) of *N*-chlorosuccinimide, and 3.5 mL of AcOH was heated at ~70 °C for 1.5 h. The mixture was filtered hot and let stand at ambient temperature overnight. The resultant crystals were collected, washed with a minimum of EtOH, and dried to give 0.450 g (73%) of a crystalline solid which was one spot on TLC. The solid was dissolved in aqueous EtOH, decolorized (Norit), and concentrated by boiling with continued addition of C_6H_6. Two recrystallizations in this manner gave analytically pure material: yield 0.249 g (40%); mp 224–226 °C; TLC (C) sol 7; UV (0.1 N HCl) λ_{max} 273 nm (ε 8500), UV (0.1 N NaOH) λ_{max} 273 nm (ε 5800); NMR (Me_2SO-d_6) δ 9.04 (br s, 3 H, NH_3^+), 8.26 (s, 1 H, C-6), 5.13 (s, 2 H, NCH_2O), 3.73 (t, 2 H, J = 5.0 Hz, OCH_2C), 2.96 (t, 2 H, J = 5.0 Hz, CCH_2N). Anal. ($C_7H_{10}ClN_3O_3$·HCl·H_2O) C, H, N, Cl.

1-[(2-Aminoethoxy)methyl]-5-bromouracil Hydrobromide Hydrate (8). To a magnetically stirred dispersion of 4.00 g (18.0 mmol) of **5** in 35 mL of AcOH was added 6.8 g (21 mmol) of pyridinium hydrobromide perbromide and 10 mL of AcOH. This mixture was heated at ~60 °C for 1 h and cooled on ice. The solids were collected and washed with acetone. Dilution of the filtrate with acetone gave a second crop. The combined crops were recrystallized from aqueous EtOH: yield 4.94 g (75%). Four recrystallizations from aqueous EtOH–C_6H_6 gave the analytically pure material: yield 2.62 g (40%); mp 184–186 °C dec; TLC (C) sol 7; UV (0.1 N HCl) λ_{max} 276 nm (ε 8800), UV (0.1 N NaOH) λ_{max} 275 nm (ε 5900); NMR (Me_2SO-d_6) δ 8.90 (br s, 3 H, NH_3^+), 8.34 (s, 1 H, C-6), 5.18 (s, 2 H, NCH_2O), 3.75 (t, 2 H, J = 5.0 Hz, OCH_2C), 3.02 (t, 2 H, J = 5.0 Hz, CCH_2N). Anal. ($C_7H_{10}BrN_3O_3$·HBr·H_2O) C, H, N, Br.

1-[(2-Aminoethoxy)methyl]-5-iodouracil Hydrochloride Hydrate (9). A stirred mixture of 1.00 g (4.51 mmol) of **5**, 5.0 mL of AcOH, 7.3 g (45 mmol) of iodine monochloride, and 2 mL of 0.1 N HCl was heated at ~80 °C for 1 h. The mixture was cooled, diluted with 100 mL of H_2O, and extracted with $CHCl_3$ until the halogen color was no longer intense. The remaining halogen was removed by stirring the aqueous solution with cyclohexene. The layers were separated, and the aqueous layer was spin evaporated in vacuo at <40 °C to 20 mL. One-hundred milliliters of EtOH was added, and the solution was concentrated by boiling with the continued addition of C_6H_6. Concentration to 75 mL followed by cooling gave white crystals, which were collected and dried: yield 10.70 g (42%). A second recrystallization gave analytically pure material: yield 0.56 g (34%); mp 236–239 °C; TLC (C) sol 6; UV λ_{max} (0.1 N HCl) 283 nm (ε 7200), UV (0.1 N NaOH) λ_{max} 277 nm (ε 5300); NMR (Me_2SO-d_6) δ 9.11 (br s, 4 H, NH_3^+, NH), 8.32 (s, 1 H, C-6), 5.15 (s, 2 H, NCH_2O), 3.75 (t, 2 H, J = 5.0 Hz, OCH_2C), 2.97 (t, 2 H, J = 5.0 Hz, CCH_2N). Anal. ($C_7H_{10}IN_3O_3$·HCl·H_2O) C, H, N, Cl, I.

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Sulfonate Analogues of Adenosine Nucleotides as Inhibitors of Nucleotide-Binding Enzymes

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2-(Adenin-9-yl)ethanesulfonic acid (**1**), 3-(adenin-9-yl)propanesulfonic acid (**2**), 9-(5-deoxy-β-D-ribofuranosyl)-adenine-5′-sulfonic acid (**3**), and 9-(3-deoxy-β-D-arabinofuranosyl)adenine-3′-sulfonic acid (**4**) were prepared by reaction of the corresponding chlorides by sodium sulfite (**1**–**3**) or by reaction of an epoxide with sodium hydrogen sulfite (**4**). They inhibited a typical nucleotide-binding enzyme, horse liver alcohol dehydrogenase, with inhibition constants in the range of 0.18–4.9 mM at pH 8, 25 °C.

Adenosine nucleotide analogues in which the monophosphate ester is replaced by a sulfonate group are of interest as inhibitors of nucleotide-binding enzymes. Furthermore, they are precursors of sulfonate esters, which are mild alkylators and could be active-site-directed alkylators of such enzymes.[1,2] Under physiological condi-

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