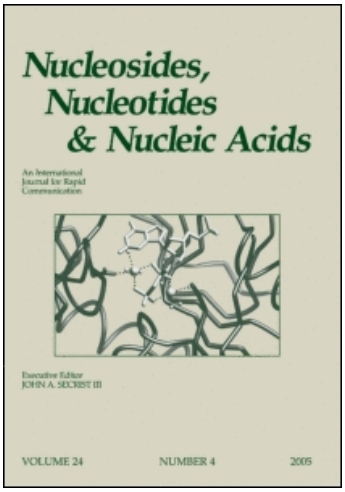


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of C-1'-Branched Acyclic Nucleosides

James A. Linn[a]; James L. Kelley[a]
[a] Division of Organic Chemistry, Burroughs Wellcome Co., Research Triangle Park, NC

To cite this Article Linn, James A. and Kelley, James L.(1993) 'Synthesis of C-1'-Branched Acyclic Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 12: 2, 199 — 213
To link to this Article: DOI: 10.1080/07328319308021206
URL: http://dx.doi.org/10.1080/07328319308021206

NUCLEOSIDES & NUCLEOTIDES, 12(2), 199-213 (1993)

SYNTHESIS OF C-1'-BRANCHED ACYCLIC NUCLEOSIDES

James A. Linn* and James L. Kelley

Division of Organic Chemistry, Burroughs Wellcome Co.
Research Triangle Park, NC 27709

Abstract: Two C-1'-branched acyclic thymine derivatives, 1-[2-hydroxy-1-(2-hydroxyethoxy)ethyl]thymine and 1-[3-hydroxy-1-(2-hydroxyethoxy)-propyl]thymine were synthesized by a novel iodine-activated reaction of a tolylthio derivative with ethylene glycol. This synthetic method provides a potentially versatile synthetic entry to C-1'-branched acyclic nucleosides.

The discovery of the potent antiherpetic activity of acyclovir [9-[(2-hydroxyethoxy)methyl]guanine, Zovirax®] has led to the synthesis of many related compounds.[1-7] Numerous variations in the (2-hydroxyethoxy)methyl side chain of acyclovir have been reported; several side chain analogues have significant antiherpetic activity.[4-7] A few C-1' branched analogues of acyclovir have been described, but none of these exhibit significant antiviral activity.[8-14]

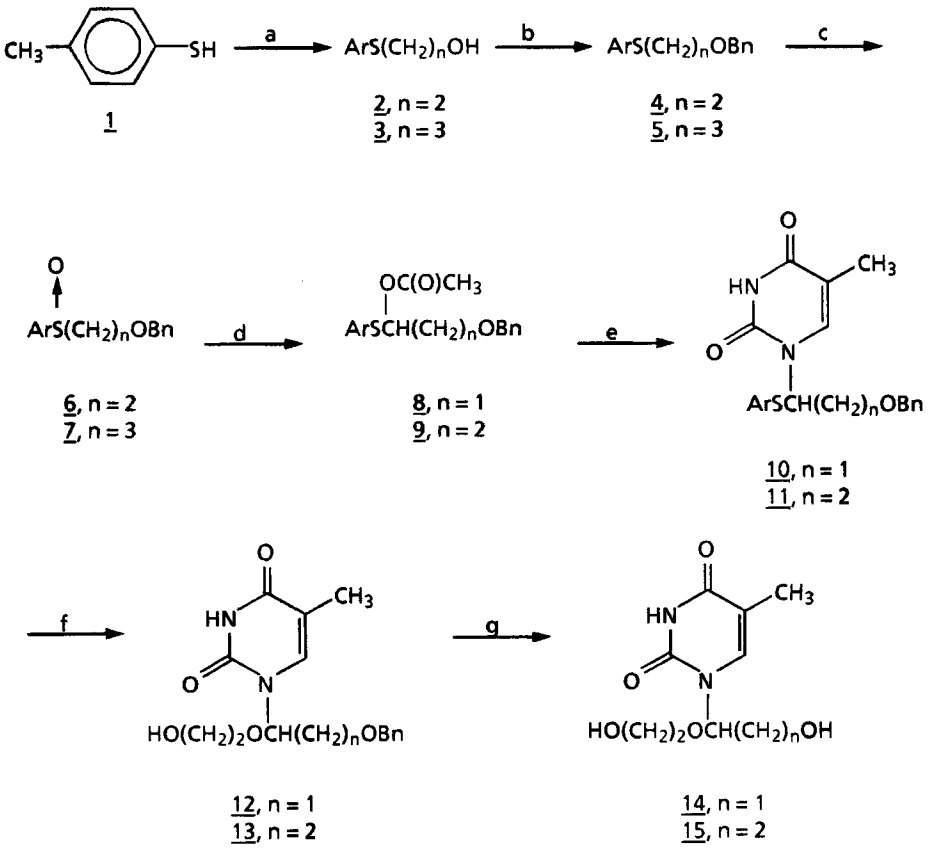
Several synthetic entries to C-1'-branched analogues of acyclic nucleosides have been reported.[8,13,15-29] These methods include Michael-type addition of a heterocycle to an α,β-unsaturated ester;[8,20] alkylation of heterocycles with iodomethyl ethers derived from 1,3-dioxolanes;[15,25] oxidative cleavage of dihydroxy nucleosides;[13,18,24,26-28] oxidative cleavage of a (2,5-dihydro-furan-2-yl)guanine;[13] chlorinolysis of a side chain thionucleoside, followed by reaction with an alcohol;[10,16,21,22] alkylation of heterocycles with chloromethyl ethers derived from higher aldehydes;[17,23] Lewis acid catalyzed condensation of heterocycles with triacetoxy-3-oxaalkanes;[11,19] and trimethylsilyl trifluoromethyl-sulfonate catalyzed reaction of acetals with bis-silylated uracils.[29]

We have developed a new synthesis of the C-1'-branched acyclic thymidines 14 and 15, based in part on the work of McElhinney[21] and Ogilvie.[30] This synthetic method involves a key step in which the C-1'-substituted tolylthio intermediates are activated with iodine in the presence of ethylene glycol to give the O-benzyl acyclic nucleosides 12 and 13. Removal of the O-benzyl groups gives the C-1'-branched acyclic thymidines 14 and 15.

Although compounds 14 and 15 have been prepared by alternate synthetic routes[18-20], the new synthesis described herein provides a potentially more versatile entry to C-1'-branched acyclic nucleosides. Both branching substituents at the C-1'-carbon may be readily varied; the method should be applicable to the preparation of other C-1'-branched acyclic nucleosides by using appropriately substituted arylthio intermediates.

CHEMISTRY

The C-1'-branched acyclic thymine derivatives 14 and 15 were synthesized in seven steps from p-thiocresol(1) as illustrated in Scheme I. The sodium salt of 1 was alkylated with either 2-bromoethanol or 3-bromopropanol to give alcohols 2 and 3 in nearly quantitative yields. The hydroxyl groups were protected by conversion to the benzyl ethers 4 and 5. The sulfide moieties of 4 and 5 were oxidized with hydrogen peroxide in acetic acid to give sulfoxides 6 and 7. These sulfoxides were treated with acetic anhydride and sodium acetate to provide the Pummerer rearrangement products 8 and 9 in 85% and 48% yield, respectively. Coupling of the acetoxymethylsulfides 8 and 9 with bis(O-trimethylsilyl)thymine using stannic chloride in dichloromethane gave 10 and 11 in 84% and 52% yield. The reaction of 10 and 11 with iodine and ethylene glycol in refluxing dichloromethane provided 12 and 13 in 30% and 26% yield. The yields are low due to concomitant cleavage of the side chain to give thymine. Removal of the O-benzyl group of 12 with 10% palladium on carbon and hydrogen in methanol gave 14 in 54% yield. The O-benzyl group of 13 was removed with boron trichloride in dichloromethane to give 15 in 31% yield.



[a] Ar = $C_6H_4CH_3$-4, Bn = $CH_2C_6H_5$. [b](a) $NaOCH_3$, CH_3OH, $Br(CH_2)_nOH$; (b) NaH, BnBr, toluene; (c) 30% H_2O_2, AcOH; (d) Ac_2O, NaOAc; (e) Thymine, HMDS, NH_4SO_4, $SnCl_4$, CH_2Cl_2; (f) I_2, $HOCH_2CH_2OH$, CH_2Cl_2; (g) 10% Pd/C, CH_3OH or BCl_3, CH_2Cl_2.

Scheme 1[a,b]

BIOLOGICAL RESULTS

Compounds 12, 14, and 15 were tested for antiviral activity against three members of the herpes family of viruses (HSV-1, VZV, and HCMV) but were inactive at 100 μM. Additionally, compounds 12-15 were tested for activity against the human immunodeficiency virus Type 1, but were inactive at 100 μM.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Varian XL-200 (^{1}H NMR, 200 MHz; ^{13}C NMR, 50.31 MHz) and a Varian T-60 (^{1}H NMR, 60 MHz) spectrometer. Chemical shift values are reported in parts per million downfield from tetramethylsilane as the internal reference (60 MHz ^{1}H NMR spectra only). UV spectra were recorded on a Unicam SP 800 or a Perkin-Elmer 571 spectrophotometer. Data from the latter was analyzed by a Digital Specialties Microcomputer. Mass spectra (~50 eV) were obtained from Oneida Research Services, Whitesboro, NY, using a Finnegan 4500 TFQ mass spectrometer. Elemental microanalyses were determined by Atlantic Microlabs, Atlanta, GA, and gave combustion values of C,H,N,S within 0.4% of theoretical values. Compounds analyzing for fractional amount(s) of solvent(s) showed the appropriate solvent impurity signals in the ^{1}H-NMR spectra. Preparative flash chromatography[31] was carried out using Silica Gel 60 (40-63 μm, E. Merck No. 9385). Analytical thin-layer chromatography was done using silica gel (200 μ) MK GF (Whatman) plates. Melting points were determined with a Thomas Hoover or Mel-Temp capillary melting point apparatus and are uncorrected.

A plaque reduction assay[32,33] was used to determine inhibitory activity for selected compounds against HSV-1 (strain ICI in Vero cells), VZV (strain 6350 in MRC-5 cells), and HCMV (strain AD169 in HFF cells). Inhibitory activity was measured as an IC_{50} value (50% inhibitory concentration in μM). Inhibition of the HIV-1 (strain IIIB)-mediated cytopathic effect (CPE) in human T-cell lymphotropic virus type 1 transformed MT4 cells was expressed as a reversal of CPE with varying concentrations (μM) of test compound.[34]

2-(4-Tolylthio)ethanol (2).

Sodium methoxide (12.7 g, 0.235 mol) was added in small portions to a stirred solution of 90% p-thiocresol (1) (31.0 g, 0.224 mol) in dry MeOH (250 ml). A solution of 2-bromoethanol (31.0 g, 0.235 mol) in MeOH (50 ml) was added dropwise over 2 h to the thiocresol solution at ambient temperature. After 18 h the volatiles were spin-evaporated *in vacuo*. The residual solid was slurried with 250 ml of EtOAc: hexane (1:2), and the mixture was filtered through a 5-cm pad of Silica Gel 60 (63-200 μm) under reduced pressure. The silica gel pad was

washed with 500 ml of EtOAc:hexane (1:2). The combined filtrates were spin-evaporated in vacuo to give 41 g (99%) of 2 (lit.[21] bp 110-112°C (0.1 mm Hg)) as a golden oil: NMR (60 MHz, $CDCl_3$): δ 7.22 (AB q, 4H, ArH), 3.72 (t, 2H, OCH_2), 3.05 (t, 2H, SCH_2), 2.33 (s, 3H, CH_3), 2.23 (br s, 1H, OH).

3-(4-Tolylthio)propanol (3).

Compound 3 was prepared the same as 2 with a modified work-up. The reaction mixture was spin-evaporated in vacuo, and the residue was partitioned between EtOAc:saturated aqueous $NaHCO_3$ (300 ml:100 ml). Additional H_2O (100 ml) and EtOAc (200 ml) were added. The phases were separated, and the organic phase was washed with saturated $NaHCO_3$ (100 ml) and H_2O (200 ml). The combined aqueous phase was extracted with EtOAc (200 ml), and the combined organic extracts were dried (Na_2SO_4). The organic solution was spin-evaporated in vacuo to give 39.3 g (93%) of crude 3 (lit.[21] bp 130-132°C (0.15 mm Hg))as an amber oil that was 87% pure by NMR: NMR (60 MHz, $CDCl_3$): δ 7.22 (AB q, 4H, ArH), 3.77 (t, 2H, OCH_2), 3.03 (t, 2H, SCH_2), 2.36 (s, 3H, CH_3), 2.00 (br s, 1H, OH), 1.89 (m, 2H, CH_2).

Benzyl 2-(4-tolylthio)ethyl ether (4).

A solution of 2 (40.9 g, 0.224 mol) in dry toluene (400 ml) was added dropwise to pentane-washed NaH (14.5 g, 0.365 mol, 60% oil dispersion). The mixture was stirred for 0.5 h, and a solution of benzyl bromide (45.7 g, 0.267 mol) in dry toluene (100 ml) was added dropwise during 1.25 h. The reaction was refluxed for 1 h and cooled to ambient temperature. The reaction mixture was filtered through a 2-cm-thick pad of Silica Gel 60 (63-200 μm) under reduced pressure. The silica gel pad was washed with 500 ml of EtOAc:hexane (1:4). The combined filtrates were spin-evaporated in vacuo to give 64.9 g of crude 4 as a golden oil. The oil was distilled under high vacuum with a short-path distillation column to give 50.9 g (81%) of 4, bp 123-140°C (0.1 mm Hg): NMR (60 MHz, $CDCl_3$): δ 7.28 (s, 5H, ArH), 7.16 (AB q, 4H, ArH), 4.46 (s, 2H, CH_2Ar), 3.61 (t, 2H, OCH_2), 3.05 (t, 2H, SCH_2), 2.28 (s, 3H, CH_3).

Benzyl 3-(4-tolylthio)propyl ether (5).

A mixture of 3 (36.3 g, 0.199 mol), pentane-washed NaH (11.9 g, 0.298 mol, 60% oil dispersion), and dry toluene (600 ml) was heated to 55°C for 1.5 h. Benzyl bromide (26.1 ml, 0.219 mol) in toluene (100 ml) was added and the reaction was stirred at 55°C for 1 h, then at ambient temperature for 64 h. The reaction mixture was filtered through a 5-cm pad of Silica Gel 60 (63-200 μm), which was washed with 500 ml of EtOAc:hexane (1:4). The combined filtrates were spin-evaporated *in vacuo* to give 52.0 g of a yellow oil. The oil was purified by flash chromatography (80 mm diameter column) using 2 L of hexane, 4 L of EtOAc:hexane (1:24), and 4 L of EtOAc:hexane (1:2) to give 20.2 g (37%) of analytically pure 5: NMR (200 MHz, $CDCl_3$): δ 7.31 (m, 5H, ArH), 7.16 (AB q, 4H, ArH), 4.48 (s, 2H, CH_2Ar), 3.57 (t, 2H, OCH_2), 2.99 (t, 2H, SCH_2), 2.30 (s, 3H, CH_3), 1.90 (m, 2H, CH_2). Anal. ($C_{17}H_{20}OS$) C, H, S.

Benzyl 2-(4-tolylsulfinyl)ethyl ether (6).

Hydrogen peroxide (30%) (3.91 ml, 38.7 mmol) was added at a slow, dropwise rate to a stirred solution of 4 (10.0 g, 38.7 mmol) in AcOH (50 ml). The reaction was heated to 75°C for 0.5 h, and the volatiles were removed by spin evaporation *in vacuo*. The residual liquid was extracted with EtOAc (100 ml), and the organic layer was washed with H_2O (3 x 25 ml) and dried (Na_2SO_4). The organic phase was concentrated under reduced pressure to give a light yellow oil. The oil was purified by flash chromatography (60 mm diameter column) using 2 L of EtOAc:hexane (1:2) and 1.5 L of EtOAc:hexane (1:1). The fractions containing the lower R_f material (Rf=0.41 with EtOAc:hexane (1:1)) were spin-evaporated *in vacuo* to give 6.37 g (60%) of analytically pure 6: NMR (200 MHz, DMSO-d_6): δ 7.44 (AB q, 4H, ArH), 7.30 (m, 5H, ArH), 4.48 (s, 2H, CH_2Ar), 3.71 (m, 2H, OCH_2), 3.05 (m, 2H, SCH_2), 2.35 (s, 3H, CH_3). Anal. ($C_{16}H_{18}O_2S$) C, H, S.

Benzyl 3-(4-tolylsulfinyl)propyl ether (7).

Compound 7 was prepared from 5 (10.0 g, 36.7 mmol), H_2O_2 (30%) (3.71 ml, 36.7 mmol), and AcOH (50 ml) in the same manner as 6. Purification by flash chromatography using EtOAc:hexane (4:5) gave

8.03 g (76%) of 7 as an oil: NMR (200 MHz, $CDCl_3$): δ 7.38 (AB q, 4H, ArH), 7.29 (m, 5H, ArH), 4.46 (s, 2H, CH_2Ar), 3.53 (m, 2H, OCH_2), 2.90 (m, 2H, SCH_2), 2.40 (s, 3H, CH_3), 1.96 (m, 2H, CH_2); (MS): m/e 289 ($M^+ + 1$), 272 ($M^+ - O$), 197 ($M^+ - C_7H_7$), 165 ($M^+ - C_7H_7S$). Anal. ($C_{17}H_{20}O_2S \cdot 0.13\ C_4H_8O_2$) C, H, S.

2-(Benzyloxy)-1-(4-tolylthio)ethyl acetate (8).

A mixture of 6 (6.00 g, 21.9 mmol), anhydrous NaOAc (7.18 g, 87.5 mmol), and Ac_2O was refluxed with stirring for 3 h. The excess Ac_2O was removed by spin evaporation in vacuo. The residue was treated with H_2O (100 ml) and extracted with EtOAc (3 x 100 ml). The combined organic phase was washed with H_2O (50 ml) and dried (Na_2SO_4). The volatiles were removed by spin evaporation in vacuo. The oil was dissolved in hexane (150 ml), and the solution was applied to a flash chromatography column (65 mm diameter) wetted with EtOAc:hexane (1:6). The column was eluted with EtOAc:hexane (1:6), and the fractions containing the major component were combined and spin-evaporated in vacuo to give 5.85 g (85%) of analytically pure 8 as a light yellow oil: NMR (200 MHz, DMSO-d_6): δ7.26 (AB q, 4H, ArH), 7.29 (m, 5H, ArH), 6.11 (dd, 1H, CH), 4.48 (s, 2H, CH_2Ar), 3.62 (m, 2H, OCH_2), 2.29 (s, 3H, CH_3), 2.03 (s, 3H, $C(O)CH_3$); (MS): m/e 316 (M^+), 257 ($M^+ - C_2H_3O_2$), 166 ($M^+ - C_2H_3O_2 - C_7H_7$), 124 ($C_7H_8S^+$), 91 ($C_7H_7^+$). Anal. ($C_{18}H_{20}O_3S$) C, H, S.

3-(Benzyloxy)-1-(4-tolylthio)propyl acetate (9).

A mixture of 7 (5.00 g, 17.3 mmol), anhydrous NaOAc (5.68 g, 69.3 mmol), and Ac_2O (200 ml) was refluxed with stirring for 3 h. The excess Ac_2O was removed by spin-evaporation in vacuo. The residue was treated with H_2O (100 ml) and extracted with EtOAc (3 x 100 ml). The combined organic phase was washed with H_2O (50 ml) and dried (Na_2SO_4). The volatiles were removed by spin evaporation in vacuo, and the residual oil was dissolved in 75 ml of EtOAc:hexane (1:7). This solution was applied to a flash chromatography column (50 mm diameter) wetted with hexane. The column was eluted with EtOAc:hexane (1:7). The fractions containing the major product were combined and spin-evaporated in vacuo to give 2.73 g (48%) of analytically pure 9 as a

light yellow oil: NMR (200 MHz, $CDCl_3$): δ7.30 (m, 5H, ArH), 7.23 (AB q, 4H, ArH), 6.20 (t, 1H, CH), 4.46 (dd, 2H, CH_2Ar), 3.52 (m, 2H, OCH_2), 2.33 (s, 3H, CH_3), 2.06 (m, 2H, CH_2), 2.01 (s, 3H, $C(O)CH_3$); (MS): m/e 330 (M^+), 270 ($M^+ - C_2H_3O_2$), 222 ($M^+ - C_7H_8O$), 166 ($M^+ - C_9H_{10}OS$), 124 ($C_7H_8S^+$), 91 ($C_7H_7^+$). Anal. ($C_{19}H_{22}O_3S$) C, H, S.

1-[2-(Benzyloxy)-1-(4-tolylthio)ethyl]thymine (10).

A mixture of thymine (0.822 g, 6.32 mmol), ammonium sulfate (0.036 g, 0.272 mmol), and hexamethyldisilazane (50 ml) was refluxed for 4 h under N_2. The clear solution was cooled and spin-evaporated in vacuo with minimal exposure to atmospheric moisture. A solution of 8 (1.00 g, 3.16 mmol) in dry CH_2Cl_2 (25 ml) was added to the silylated thymine (oil) at 0°C. A solution of stannic chloride (2.87 ml, 3.16 mmol) in CH_2Cl_2 was added dropwise at 0°C, and the reaction was stirred for 18 h at ambient temperature. The reaction was diluted with CH_2Cl_2 (100 ml) and saturated aqueous $NaHCO_3$ (75 ml) and stirred for 10 min. The mixture was filtered through a pad of Celite, and the pad was washed with CH_2Cl_2 (100 ml). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic phase was washed with H_2O (2 x 50 ml) and dried ($MgSO_4$). The volatiles were spin-evaporated in vacuo to give an amber oil. The oil was dissolved in CH_2Cl_2 (50 ml), and the solution was applied to a flash chromatography column (50 mm diameter) wetted with CH_2Cl_2. The column was eluted with 800 ml of CH_2Cl_2 and 1.5 L of MeOH:CH_2Cl_2 (1:99). The fractions containing the highest R_f major product spot were combined and spin-evaporated in vacuo to give 1.04 g (84%) of 10 contaminated with 2% wt/wt CH_2Cl_2: NMR (200 MHz, $CDCl_3$): δ 8.01 (br s, 1H, NH), 7.55 (m, 1H, J = 1 Hz, H-6), 7.36-7.06 (AB q and m, 9H, ArH), 6.15 (t, 1H, CH), 4.56 (dd, 2H, CH_2Ar), 3.84 (d, 2H, OCH_2), 2.30 (s, 3H, CH_3Ar), 1.91 (d, 3H, J = 1 Hz, thymine CH_3); (MS): m/e 382 (M^+), 259 ($M^+ - C_7H_7S$), 91 ($C_7H_7^+$). Anal. ($C_{21}H_{22}N_2O_3S \cdot 0.11$ CH_2Cl_2) C, H, N, S.

1-[3-(Benzyloxy)-1-(4-tolylthio)propyl]thymine (11).

Compound 11 was prepared the same as 10 except that three molar equivalents of thymine were used. The crude product was an amber oil,

which was applied as a solution in CH_2Cl_2 (150 ml) to a flash chromatography column (70 mm diameter) wetted with CH_2Cl_2. The column was eluted with 2 L of MeOH:CH_2Cl_2 (3:97). The appropriate fractions were combined, and the volatiles were removed by spin evaporation in vacuo to give 4.19 g (52%) of analytically pure 11 as an amber oil: NMR (200 MHz, DMSO-d_6): δ 11.10 (br s, 1H, NH), 7.66 (m, 1H, J = 1 Hz, H-6), 7.26 (m, 5H, ArH), 7.17 (AB q, 4H, ArH), 6.06 (t, 1H, J = 7.6 Hz, CH), 4.39 (s, 2H, CH_2Ar), 3.5 (m, 2H, OCH_2), 2.25 (s, 3H, CH_3Ar), 2.2 (m, 2H, CH_2), 1.76 (d, 3H, J = 1 Hz, thymine CH_3); (MS): m/e 396 (M^+), 123 ($C_7H_7S^+$), 91 ($C_7H_7^+$). Anal. ($C_{22}H_{24}N_2O_3S$) C, H, N.

1-[2-(Benzyloxy)-1-(2-hydroxyethoxy)ethyl]thymine (12).

Ethylene glycol (0.186 ml, 3.33 mmol) was added to a stirred mixture of 10 (0.85 g, 2.22 mmol), iodine (0.563 g, 2.22 mmol), and CH_2Cl_2 (25 ml). The reaction was stirred at ambient temperature for 18 h. The reaction was refluxed for 2 h, and then stirred at ambient temperature for 88 h. After another 5 h of reflux, additional ethylene glycol (0.186 ml, 3.33 mmol) was added followed by 20 h of refluxing. Additional iodine (0.563 g, 2.22 mmol) was added, and the reaction was refluxed for 6 h, followed by the addition of ethylene glycol (0.186 ml, 3.33 mmol). The reaction was refluxed for 40 h and appeared to be complete by TLC (MeOH:CH_2Cl_2 - 5:95). Dichloromethane (100 ml) was added to the dark reaction, and the mixture was added to a flash chromatography column (50 mm diameter) wetted with CH_2Cl_2. The column was eluted with CH_2Cl_2 (1 L), then MeOH:CH_2Cl_2 (2:98; 1 L), then MeOH:CH_2Cl_2 (3:97; 1 L). The major, lower R_f material was collected, and the appropriate fractions were combined and spin-evaporated in vacuo to give 0.30 g of crude 12 as a brown oil. The oil was triturated with Et_2O/acetone/hexane and the volatiles were allowed to evaporate. A light yellow solid was removed from the flask. Recrystallization of the solids from hot Et_2O/acetone (20 ml:10 ml) followed by addition of hexane (10 ml) gave 0.107 g (15%) of analytically pure 12 as a white powder, mp 82-83°C; TLC, MeOH:CH_2Cl_2 (10:90), one spot with R_f = 0.41; UV (pH 1) λ_{max} 266 (ε 8700), λ_{min} 234 (ε 2300) nm; (pH 7) λ_{max} 267 (ε 8500), λ_{min} 234 (ε 2000) nm; (pH 13) λ_{max} 266 (ε 5800), λ_{min} 244 (ε 3200) nm; ^{1}H-NMR (200 MHz, DMSO-d_6):

δ 11.27 (br s, 1H, NH), 7.44 (m, 1H, J = 1 Hz, H-6), 7.27 (m, 5H, ArH), 5.80 (t, 1H, J = 5.7 Hz, OCH), 4.64 (t, 1H, OH), 4.49 (dd, 2H, CH_2Ar), 3.67 (m, 2H, $C\underline{H}_2OH$), 3.45 (m, 4H, 2 x CH_2O), 1.76 (d, 3H, J = 1 Hz, CH_3); ^{13}C-NMR (50.309 MHz, DMSO-d_6): δ 163.71 (C-2), 151.16 (C-4), 137.82 (C-1$'''$), 135.85 (C-6), 128.18/127.49/127.41 (C-2$'''$/C-3$'''$/C-4$'''$), 109.36 (C-5), 82.03 (C-1'), 72.17 (C-4$''$), 70.27 (C-4'), 69.06 (C-2$''$), 59.63 (C-3'), 12.04 (C-7); (MS): m/e 321 (M^++1), 258 (M^+-$C_2H_6O_2$), 199 (M^+-C_8H_9O), 91 ($C_7H_7^+$). Anal. ($C_{16}H_{20}N_2O_5$) C, H, N.

1-[3-(Benzyloxy)-1-(2-hydroxyethoxy)propyl]thymine (13).

Iodine (2.26 g, 8.92 mmol) was added to a solution of 11 (1.77 g, 4.46 mmol), ethylene glycol (0.75 ml, 13.4 mmol) and CH_2Cl_2 (50 ml). The solution was refluxed for 18 h. The reaction was complete by TLC (MeOH:CH_2Cl_2-1:9). Methanol (25 ml) was added to the reaction and then 15 g of Silica Gel 60 (63-200 μm) was added to the dark solution. The volatiles were removed by spin evaporation in vacuo, and the residual solids were applied to a flash chromatography column (50 mm diameter) wetted with CH_2Cl_2. The column was eluted with MeOH:CH_2Cl_2 (2:98; 1.5 L), and then with MeOH:CH_2Cl_2 (5:95; 1.5 L). The major, intermediate R_f spot was collected, and the appropriate fractions were combined and spin-evaporated in vacuo to give 0.46 g of crude 14 as a dark oil. The oil was dissolved in 50 ml of MeOH:CH_2Cl_2 (2:98), and the solution was re-chromatographed as described above. The appropriate fractions were collected, combined, and spin-evaporated in vacuo to give 0.39 g (26%) of 13 as a light amber oil; TLC, MeOH:CH_2Cl_2 (5:95), one spot with R_f = 0.27; UV (pH 1) λ_{max} 267 (ε 8200), λ_{min} 234 (ε 1700) nm; (pH 7) λ_{max} 267 (ε 8800), λ_{min} 234 (ε 2400) nm; (pH 13) λ_{max} 267 (ε 7200), λ_{min} 246 (ε 5200) nm; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 11.29 (br s, 1H, NH), 7.49 (m, 1H, J = 1 Hz, H-6), 7.31 (m, 5H, ArH), 5.78 (t, 1H, OCH), 4.62 (t, 1H, OH), 4.42 (s, 2H, CH_2Ar), 3.6-3.3 (m, 4H, 2 x OCH_2), 3.17 (m, 2H, $C\underline{H}_2OH$), 2.05 (m, 2H, CH_2), 1.77 (d, J = 1 Hz, 3H, CH_3); (MS): m/e 335 (M^++1), 289 (M^+ - C_2H_5O), 209 (M^+ - $C_5H_5N_2O_2$), 199 (M^+ - $C_9H_{11}O$), 91 (C_7H_7+). Anal. ($C_{17}H_{22}N_2O_5 \cdot 0.29\ CH_4O \cdot 0.29\ H_2O$) C, H, N.

1-[2-Hydroxy-1-(2-hydroxyethoxy)ethyl]thymine (14).

A mixture of 12 (0.72 g, 2.25 mmol), 5% Pd on carbon (0.20 g) and MeOH (25 ml) was shaken in the presence of H_2 at 45 psi, on a Parr hydrogenation apparatus, for 18 h. The reaction was recharged with 10% Pd on carbon (0.2-0.3 g) three times during the course of 3 days until the reaction was complete by TLC. The reaction mixture was filtered through a pad of Celite, and the pad was rinsed with MeOH. The combined filtrate was spin-evaporated in vacuo to give 14 as a waxy, white solid. The solid was recrystallized from hot EtOH (35 ml) by dilution with Et_2O (100 ml) to give 0.28 g (54%) of analytically pure 14 as a white solid, mp 196.5-197.5°C (lit.[19] mp 200-201°C); TLC, MeOH:CH_2Cl_2 (2:8), one spot with R_f = 0.52; UV (pH 1) λ_{max} 267 (ε 8500), λ_{min} 234 (ε 2000) nm; (pH 7) λ_{max} 266 (ε 8600), λ_{min} 233 (ε 1800) nm; (pH 13) λ_{max} 267 (ε 6000), λ_{min} 244 (ε 3500) nm; ^{1}H-NMR (200 MHz, DMSO-d6): δ 11.21 (br s, 1H, NH), 7.43 (m, 1H, J = 1 Hz, H-6), 5.57 (t, 1H, OCH), 5.04 (br t, 1H, OH), 4.62 (br t, 1H, OH), 3.63-3.35 (m, 6H, 3 x OCH_2), 1.77 (d, 3H, J = 1 Hz, CH_3); ^{13}C-NMR (50.309 MHz, DMSO-d6): δ 163.81 (C-2), 151.34 (C-4), 136.07 (C-6), 109.11 (C-5), 84.08 (C-1'), 70.17/61.16/59.64 (C-4'/C-3'/C-2"), 12.08 (C-7); (MS): m/e 231 (M^++1), 213 (M^+ - OH), 199 (M^+ - CH_2OH), 169 (M^+ - C_2H_5O), 126 ($C_5H_5N_2O_2^+$). Anal. ($C_9H_{14}N_2O_5$) C, H, N.

1-[3-Hydroxy-1-(2-hydroxyethoxy)propyl]thymine (15).

A solution of 1N boron trichloride (10 ml) in CH_2Cl_2 was added slowly to a stirred solution of 13 (0.30 g, 0.90 mmol) in CH_2Cl_2 (5 ml) at -78°C under N_2. After 3 h at -78°C, the reaction was quenched by dropwise addition of a mixture of MeOH: CH_2Cl_2 (10 ml:10 ml). The reaction was adjusted to pH 7.2 with Et_3N, warmed to ambient temperature, and stirred for 18 h. The volatiles were removed by spin evaporation in vacuo. The residual solids were treated with H_2O (3 x 20 ml) and EtOH (20 ml); the volatiles were removed by spin evaporation in vacuo. The solid was dissolved in EtOH:H_2O (30 ml: 30 ml) and 7 g of Rexyn 201 (OH) strong anion exchange resin was added to the solution. Additional resin (3 x 7 g) was added in successive treatments over a 24-h period until a $AgNO_3$ test for chloride ion was negative. The mixture was filtered and the resin beads were washed

with MeOH (150 ml). The filtrate was spin-evaporated in vacuo and the oily residue was co-evaporated with EtOH (2 x 50 ml) to give 0.51 g of a crude white solid. The solid was dissolved in MeOH (25 ml), and 2 g of Silica Gel 60 was added to the solution. After spin evaporation in vacuo the residual solids were added to a flash column (30 mm diameter) wetted with CH_2Cl_2. The column was eluted with MeOH:CH_2Cl_2 (5:95) and the appropriate fractions containing product were combined and spin-evaporated in vacuo to give 0.243 g of a white solid. Recrystallization of the solid from acetone/EtOH gave triethylamine hydrochloride, which was removed by filtration. The mother liquor was evaporated to a colorless oil (0.105 g), which crystallized after 24 h. The solid was dissolved in hot Et_2O (20 ml)/acetone (2 ml), and the turbid mixture was treated with a small amount of $MgSO_4$ and filtered. Hexane (3 ml) was added to the filtrate to initiate crystallization. The solids were collected and dried at 65°C under vacuum to give 0.046 g (21%) of 15, mp 106-109°C (lit.[18,20] mp 115-116°C and lit.[11] mp 94-95°C); TLC, MeOH:CH_2Cl_2 (2:8), one spot with R_f = 0.62; UV (pH 1) λ_{max} 267 (ε 9600), λ_{min} 234 (ε 2500) nm; (pH 7) λ_{max} 268 (ε 9200), λ_{min} 234 (ε 2000) nm; (pH 13) λ_{max} 266 (ε 6700), λ_{min} 245 (ε 4100) nm; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 11.22 (br s, 1H, NH), 7.46 (m, 1H, J = 1 Hz, H-6), 5.73 (dd, 1H, J = 7.2 and 7.6 Hz, OCH), 4.61 (t, 1H, OH), 4.54 (t, 1H, OH), 3.6-3.3 (m, 6H, 3 x OCH_2), 1.85 (m, 2H, CH_2), 1.77 (d, 3H, J = 1 Hz, CH_3); ^{13}C-NMR (75.43 MHz, DMSO-d_6): δ 163.79 (C-2), 151.03 (C-4), 135.80 (C-6), 109.69 (C-5), 81.79 (C-1'), 69.84 (C-5'), 59.63 (C-4' or C-3'), 56.45 (C-3' or C-4'), 37.14 (C-2'), 12.10 (CH_3); (MS): m/e 245 (M^++1), 199 (M^+-C_2H_4OH), 183 (M^+-$C_2H_5O_2$), 126 ($C_5H_6N_2O_2^+$). Anal. ($C_{10}H_{16}N_2O_5$) C, H, N.

ACKNOWLEDGEMENTS

The authors thank J.H. Chan for the synthesis procedure for alkylation of thiocresol; J.W.T. Selway, M. St.Clair, and K.K. Biron for the antiviral tests; and R. Crouch, A. Ragouzeos, and J. Miller for the NMR spectra. We acknowledge the assistance of J. Wilson, J. Appleton, A. Gunter, S. Jones, and D. Eagleson in preparation of the manuscript, and thank L. Mansberg for proofreading the manuscript.

REFERENCES

1. 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*, 5716-5720.
2. Schaeffer, H.J.; Beauchamp, L.; de Miranda, P.; Elion, G.B.; Bauer, D.J.; Collins, P. *Nature (London)* **1978**, *272*, 583-585.
3. Elion, G.B. In *Antiviral Chemotherapy: New Directions for Clinical Application and Research*, Mills, J., Corey, L. Eds.; Elsevier: New York, 1986; pp 118-137.
4. Remy, R.J.; Secrist, J.A. III *Nucleosides and Nucleotides* **1985**, *4*, 411-427.
5. Chu, C.K.; Cutler, S.J. *J. Heterocycl. Chem.* **1986**, *23*, 289-319.
6. Kelley, J.L. In *Topics in Medicinal Chemistry*, Spec. Publ. No. 65; Leeming, P.R., Ed.; Royal Society of Chemistry: London, **1988**; pp 189-212.
7. Diana, G.D.; Pevear, D.; Young, D.C. *Annu. Rep. Med. Chem.* **1989**, *24*, 129-137.
8. Scheiner, P.; Geer, A.; Bucknor, A.M.; Gadler, H.; Price, R.W. *Nucleosides and Nucleotides* **1989**, *8*, 1441-1451.
9. Golbraikh, A.A.; Betins, J.; Balodis, J.; Zhuk, R.A.; Nikiforovich, G.V. *Nucleic Acids Res.* **1989**, *17*, 7965-7977.
10. McElhinney, R.S.; McCormick, J.E.; Bibby, M.C.; Double, J.A.; Atassi, G.; Dumont, P.; Pratesi, G.; Radacic, M. *Anti-Cancer Drug Design* **1989**, *4*, 191-207.
11. Shchaveleva, I.I.; Smirnov, I.P.; Kochetkova, S.V.; Tsilevich, T.L.; Khorlin, A.A.; Gottikh, B.P.; Florent'ev, V.L. *Bioorg. Khim.* **1988**, *14*, 824-827.
12. Kochetkova, S.V.; Tsilevich, T.L.; Smirnov, I.P.; Shchaveleva, I.L.; Khorlin, A.A.; Gottikh, B.P.; FLorent'ev, V.L. *Bioorg. Khim.* **1988**, *14*, 820-823.
13. McGee, D.P.C.; Martin, J.C. *Can. J. Chem.* **1986**, *64*, 1885-1889.
14. Fyfe, J.A.; McKee, S.A.; Keller, P.M. *Mol. Pharmacol.* **1983**, *24*, 316-323.
15. Bryant, J.D.; Keyser, G.E.; Barrio, J.R. *J. Org. Chem.* **1979**, *44*, 3733-3734.

16. Lucey, N.M.; McCormick, J.E.; McElhinney, R.S. *J. Chem. Soc., Perkin Trans 1,* **1990**, *3*, 795-802.
17. Farr, R.A.; Bey, P.; Sunkara, P.S.; Lippert, B.J. *J. Med. Chem.* **1989**, *32*, 1879-1885.
18. Mikhailov, S.N.; Efimtseva, E.V. *Khim. Geterotsikl. Soedin USSR* **1988**, *7*, 947-951.
19. Zavgorodnii, S.G.; Efimtseva, E.V.; Mikhailov, S.N.; Tsilevich, T.L.; Yavorskii, A.E.; Florentév, V.L. *Khim. Geterotsikl. Soedin USSR* **1988**, *2*, 223-228.
20. Scheiner, P.; Geer, A.; Bucknor, A.-M.; Imbach, J.-L.; Schinazi, R.F. *J. Med. Chem.* **1989**, *32*, 73-76.
21. McCormick, J.E.; McElhinney, R.S. *J. Chem. Res.* (M) **1983**, *14*, 1736-1769.
22. McCormick, J.E.; McElhinney, R.S. *J. Chem. Res.* (M) **1981**, *12*, 256-281.
23. Schaeffer, H.J. U.S. Patent 4,199,574, 1980.
24. Lerner, L.M.; Rossi, R.R. *Biochemistry* **1972**, *11*, 2772-2777.
25. Barrio, J.R.; Bryant, J.D.; Keyser, G.E. *J. Med. Chem.* **1980**, *23*, 572-574.
26. Kumar, A.; Walker, R.T. *Tetrahedron* **1990**, *46*, 3101-3110.
27. Oivanen, M.; Lönnberg, H.; Kazimierczuk, Z.; Shugar, D. *Nucleosides and Nucleotides* **1989**, *8*, 133-144.
28. Herdewijn, P.; Van Aerschot, A.; Busson, R.; Claes, P.; De Clercq, E. *Nucleosides and Nucleotides* **1991**, *10*, 1525-1549.
29. Tietze, L.F.; Krach, T.; Beller, M.; Arlt, M. *Chem. Ber.* **1991**, *124*, 2019-2024.
30. Ogilvie, K.K.; Nguyen-Ba, N.; Hamilton, R.G. *Can. J. Chem.* **1984**, *62*, 1622-1627.
31. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem* **1978**, *43*, 2923-2925.
32. Collins, P.; Appleyard, G.; Oliver, N.M. *Am. J. Med.* **1982**, 733 (1A), 380.
33. Biron, K.K.; Stanat, S.C.; Sorrell, J.B.; Fyfe, J.A.; Keller, P.M.; Lambe, C.U.; Nelson, D.J. *Proc. Natl. Acad. Sci. USA* **1985**, 82, 2473.
34. Averett, D.R. *J. Virol. Methods* **1989**, 23, 263.

Appendix

Analytical Data

	Calc'd				Found			
No.	C	H	N	S	C	H	N	S
5	74.96	7.40	—	11.77	75.06	7.40	—	11.69
6	70.04	6.61	—	11.68	69.86	6.65	—	11.58
7[a]	70.18	7.07	—	10.69	69.92	7.05	—	10.99
8	68.33	6.37	—	10.13	68.22	6.43	—	10.06
9	69.06	6.71	—	9.70	69.01	6.72	—	9.62
10[b]	64.71	5.72	7.15	8.18	64.81	5.75	6.86	8.24
11	66.64	6.10	7.07	—	66.54	6.14	6.96	—
12	59.99	6.29	8.74	—	59.88	6.31	8.72	—
13[c]	59.52	6.86	8.03	—	59.52	6.66	7.83	—
14	46.95	6.13	12.17	—	46.87	6.16	12.10	—
15	49.18	6.60	11.47	—	49.26	6.62	11.42	—

[a] Compound 7 analyzed with 0.13 mole of EtOAc.
[b] Compound 10 analyzed with 0.11 mole of CH_2Cl_2.
[c] Compound 13 analyzed with 0.29 mole of CH_3OH and 0.29 mole of H_2O.

Received 9/28/92
Accepted 11/23/92