mg, 0.1 mmol) and 30% HBr–AcOH (1 mL) was stirred at 25 °C for 24 h and then warmed until all the solid was dissolved and left to stand at room temperature for 7 days. The solution was poured into excess Et_2O, and the solid was collected, redissolved in dilute NH_4OH, and purified by gradient chromatography on a C_{18} reversed-phase silica gel column, using 0.1 M NH_4OAc, pH 7.5, in reservoir A and 1:9 EtOH–0.1 M NH_4OAc, pH 7.5, in reservoir B. The fractions containing 17 (elution time 143 min) and mAPA (8) (elution time 190 min) were collected separately and freeze-dried. Each product was redissolved in dilute NH_4OH (pH 10), a small amount of undissolved gelatinous material was removed by filtration through a bed of silica gel, and the filtrate was freeze-dried. This process was repeated twice to obtain 16 mg (26%) of 17 as a yellow powder: mp 215 °C dec; TLC R_f 0.09 (silica gel, 5:4:1 $CHCl_3$–MeOH–NH_4OH); IR (KBr) ν 3450, 1670–1630, 1610 cm^{-1}; MS m/z calcd 498 (M + 1), found 498. HPLC analysis (C_{18} column, 5% EtOH in 0.1 M NH_4OAc, pH 7.5) revealed a single peak with a retention time of 11.7 min. The weight of mAPA (8) was 16 mg (45% yield); TLC R_f 0.57 (silica gel, 5:4:1 $CHCl_3$–MeOH–NH_4OH).

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Synthesis of Two Cyclopentenyl-3-deazapyrimidine Carbocyclic Nucleosides Related to Cytidine and Uridine

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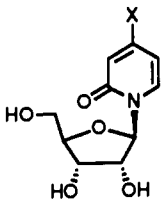
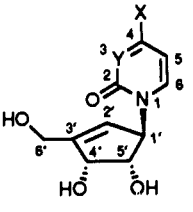
The cytosine analogue of neplanocin A, cyclopentenylcytosine (CPE-C, 3), has significant antitumor and antiviral activity commensurate with the drug's ability to produce a significant depletion of cytidine triphosphate (CTP) levels that result from the potent inhibition of cytidine triphosphate synthetase. Another important antitumor agent, previously identified as a potent inhibitor of the same enzyme, is 3-deazauridine (2). The synthesis of the cyclopentenyl nucleosides 3-deaza-CPE-C (5) and 3-deaza-CPE-U (6) was undertaken in order to investigate the effects of a modified 3-deaza pyrimidine aglycon moiety on the biological activity of the parent CPE-C. These compounds were synthesized via an S_N2 displacement reaction on cyclopenten-1-ol methanesulfonate (10) by the sodium salt of the corresponding aglycon. In each case, separation and characterization of the corresponding N- and O-alkylated products was necessary before final removal of the blocking groups. The target compounds were devoid of in vitro antiviral activity against the HSV-1 and human influenza viruses. Although 3-deaza-CPE-C was nontoxic to L1210 cells in culture, 3-deaza-CPE-U displayed significant cytotoxicity against murine L1210 leukemia in vitro.

Introduction

The bioisosteric replacement of nitrogen by carbon in the pyrimidine heterocycle of the naturally occurring pyrimidine nucleosides cytidine and uridine has generated effective inhibitors of cell growth.[1-4] 3-Deazauridine (2),



1: X = NH_2
2: X = OH



3: X = NH_2, Y = N
4: X = OH, Y = N
5: X = NH_2, Y = CH
6: X = OH, Y = CH

and to a lesser extent 3-deazacytidine (1), produced significant growth inhibition against L-1210 leukemia cells in vitro.[4] The more effective of the two analogues, 3-deazauridine, also increased the survival time of mice bearing either this tumor or the *ara*-C-resistant variety (L-1210/*ara*-C), against which it displayed even better activity.[5] Other important biochemical properties resulting from this change were the increased stability of the glycosylic bond of both 1 and 2, and the inertness of 1 toward deamination by cytidine deaminase (CDA).[6] The primary metabolic effect responsible for the biological activity of 3-deazauridine (2) was determined to be the strong depletion of CTP pools resulting from the inhibition of cytidine triphosphate synthetase by the metabolite 3-deazauridine 5′-triphosphate (3-deaza-UTP).[5,7,8]

Recently, we have discovered that a more radical change in the structure of cytidine, which consisted of replacing the tetrahydrofuran ring by a cyclopentene moiety,[9,10] produced an analogue (CPE-C, 3) which was 3 orders of magnitude more potent than 3-deazauridine (2) as an antitumor agent and whose activity appeared to be commensurate with a sustained reduction of CTP pools.[10-13] The compound also displayed very potent antiviral activity and this was similarly correlated with the inhibition of cytidine triphosphate synthetase.[10,14,15] In support of this

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hypothesis, the isolated enzyme has been shown to be strongly inhibited by the CPE-C 5'-triphosphate (CPE-CTP) metabolite.[14] The cyclopentene uracil analogue (CPE-U, 4), on the other hand, was totally devoid of biological activity.[9]

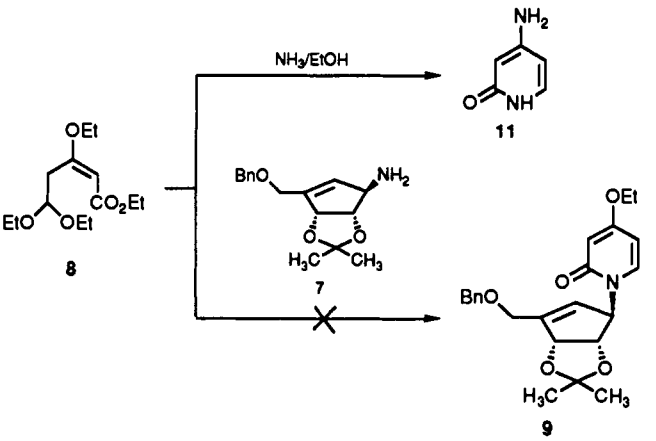
The biological activity of 3-deazauridine undoubtedly is related to the significant change in its aglycon moiety resulting from the removal of the N-3 nitrogen of the pyrimidine ring. The 3-deazauracil ring of 2 is markedly more acidic than uracil and the corresponding triphosphate metabolite (3-deaza-UTP) appears to function efficiently as a competitive substrate–analogue inhibitor of cytidine triphosphate synthetase with respect to UTP.[7] On the other hand, kinetic studies with CPE-CTP revealed that the interaction of this metabolite with the same enzyme is more complex.[14] From a structural viewpoint, however, one could envisage CEP-CTP functioning as a product–analogue inhibitor whose pharmacological activity is related to the cyclopentene carbocycle. This preference for a common biochemical locus for both 3-deazauridine and CPE-C, which results from two rather different structural changes in the molecules of uridine and cytidine, prompted us to consider the synthesis of compounds **5** and **6**, which, in terms of chemical structures, contain elements of both powerful enzyme inhibitors. In addition, despite the fact that CPE-C is a poor substrate for CDA, it is nonetheless deaminated to a significant degree in some species to the inert metabolite CPE-U.[16] The complete resistance of 3-deazacytidine to deamination by CDA[6] led us to consider that if activity was realized for compound **5**, its effectiveness would not be compromised by deamination. The present report describes the synthesis and results on the biological activity of these novel compounds. A preliminary account of this work has been described.[17]

Chemistry

For the preparation of the target carbocyclic nucleosides **5** and **6**, we used a modification of our previously developed method for the synthesis of neplanocin A and related carbocyclic nucleosides.[10,18–20] In this approach, the carbocyclic cyclopenten-1-ol, functionalized as a *p*-toluenesulfonic or methanesulfonic acid ester (e.g., **10**), reacts with the sodium salt of the corresponding heterocyclic base to give the condensation product resulting from an S_N2 displacement.

Of the two heterocyclic bases required for this project, 3-deazacytosine (4-amino-2-oxo-1,2-dihydropyridine, **11**) and 3-deazauracil (4-hydroxy-2-oxo-1,2-dihydropyridine, **14a**), only the latter is commercially available. However, as discussed later, 3-deazauracil was far from ideal for this displacement reaction and, therefore, the protected 4-(benzyloxy)-2-pyridone (**14b**) was employed. We first

Scheme I



obtained 3-deazacytosine (**11**) by the method of Cook et al.,[3] which consisted of the ring closure of the acyclic intermediate **8** with ammonia (Scheme I). Later, in a more efficient and expedient manner, we prepared 3-deazacytosine from **14a** by the method of Bisagni and Hung, which consisted in reacting **14a** with boiling benzylamine, followed by catalytic debenzylation over Pd on charcoal.[21] Finally, protected 4-(benzyloxy)-2-pyridone (**14b**) was prepared in two steps from commercially available 4-nitro-pyridine *N*-oxide according to published procedures.[22,23]

Before attempting the direct displacement approach, we extensively studied the reaction of carbocyclic cyclopentenyl amine (**7**) with ethyl 3,5,5-triethoxy-3-pentenoate (**8**) under various reaction conditions (Scheme I). Unfortunately, we were unable to detect any formation of the carbocyclic nucleoside **9**, which was considered to be an attractive precursor to both target compounds **5** and **6**. This was an attempt to unambiguously synthesize N-substituted carbocyclic nucleosides, such as **9**, and circumvent the generation of mixtures of N- and O-alkylated products, which were expected to result from the direct displacement approach due to the ambident nucleophilic character of the heterocyclic bases (**11** and **14**). Notwithstanding this anticipated difficulty, the direct approach was attempted and worked reasonably well (Scheme II). When **11** was used as the nucleophile, a 70% yield of an approximately 1:1 mixture of N- and O-alkylated products was obtained. After separation by column chromatography, the structural assignments for **12** and **13** were made by comparison of their NMR (^1H and ^{13}C) spectra with data for known cytosine derivatives. In the ^1H NMR spectra, the typical heterocyclic proton signals of the O-alkylated product (**13**) appeared shifted downfield (0.49–0.79 ppm) relative to the equivalent signals in the N-alkylated product **12**. In addition, the chemical shift of the carbon attached to the heterocyclic base (C-1') in **13** appeared downfield (82.6 vs 66.6 ppm) relative to the corresponding signal from **12**. Other carbon resonances that experienced significant downfield shifts in **13**, relative to those of **12**, were C-3 and C-6 in the heterocyclic base (105.4 vs 99.6 ppm and 147.2 vs 134.2 ppm, respectively). These characteristic trends observed for the N- and O-alkylated products in their proton and carbon NMR resonances are consistent with observations made by other investigators.[24]

(14) Kang, G. J.; Cooney, D. A.; Moyer, J. D.; Kelley, J. A.; Kim, H.-Y.; Marquez, V. E.; Johns, D. G. *J. Biol. Chem.* **1989**, *264*, 713.
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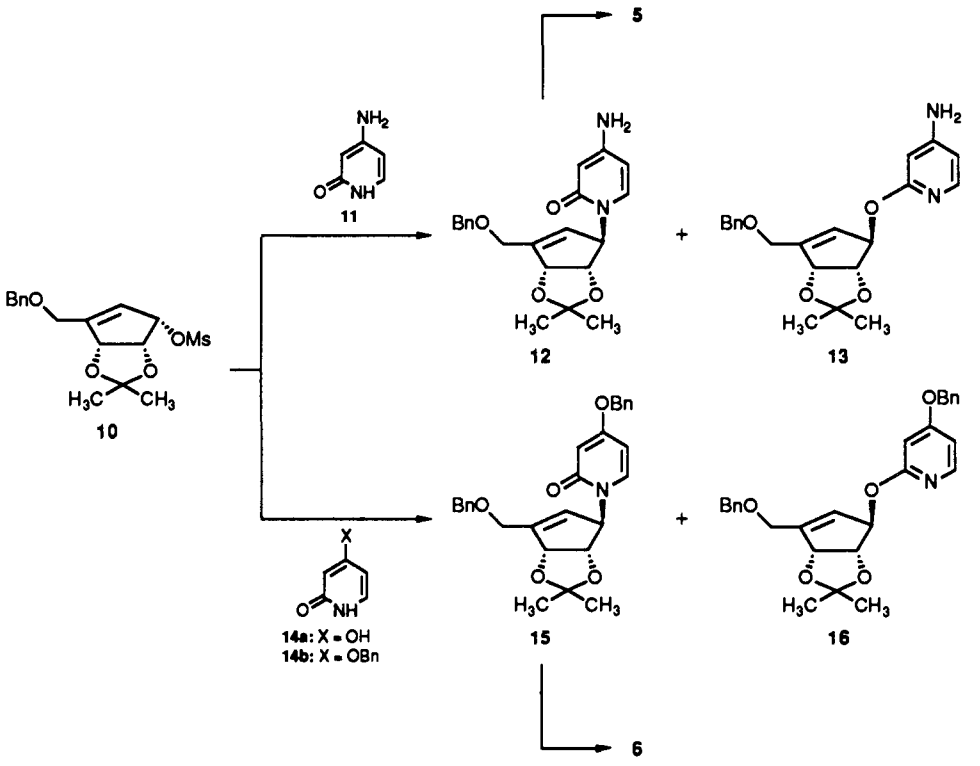
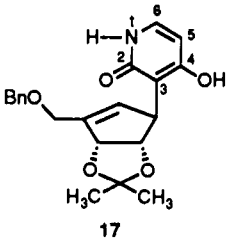
Scheme II



As mentioned earlier, the use of 3-deazauracil (**14a**) for the direct displacement reaction proved to be unwieldy due to the extensive formation of byproducts. One of the isolated compounds that was formed in small amounts was identified by ^{1}H NMR as the C-alkylated product **17**.[25]



Therefore, the presence of four potential sites for alkylation in 3-deazauracil made it necessary to use the protected 4-benzyloxy compound (**14b**), in order to reduce the problem to a two-product mixture as in the previous case with 3-deazacytosine (Scheme II). Using **14b**, the direct displacement reaction afforded a 51% yield of the expected mixture of N- and O-alkylated products in approximately equal amounts. Separation by column chromatography afforded the individual isomers **15** and **16**, which were characterized by their ^{1}H and ^{13}C NMR spectra. As before, the characteristic heterocyclic proton signals of the O-alkylated product **16** were shifted downfield (0.25–1.09 ppm) relative to the equivalent signals in the N-alkylated product **15**. Similarly, the carbon attached to the heterocyclic base (C-1′) in **16** experienced a downfield shift (83.0 vs 67.2 ppm) relative to the equivalent signal in the N-alkylated product **15**. Other carbon resonances, such as C-3 and C-6, experienced similar downfield shifts in **16** relative to the same carbon resonances in **15** (106.8 vs 101.5 ppm and 147.8 vs 134.3 ppm, respectively).

Table I. Inhibition of L1210 Cell Growth (Percent Inhibition)[a]

compd	1000 μM	100 μM	10 μM	1 μM
CPE-C (3)		93	93	93
5	15	0	0	0
6	75	66	45	8

[a] L1210 cells were seeded at 0.15 × 10^5 cell/mL in Fisher's medium containing 10% heat-inactivated horse serum. Cells were exposed to the drugs continuously for 48 h, and the cell number was determined by use of a Coulter counter. Percent inhibition was calculated relative to control cultures which grew to 4.5 × 10^5 cells/mL. The values given are from duplicate determinations.

The simultaneous removal of benzyl and isopropylidene groups in compounds **12** and **15** (BCl_3 at −78 °C) afforded the desired target compounds 3-deaza-CPE-C (**5**) and 3-deaza-CPE-U (**6**). The spectral and analytical data were in agreement with the proposed structures.

Biological Activity

The cytotoxicity of 3-deaza-CPE-C (**5**) and 3-deaza-CPE-U (**6**) was investigated in L1210 tumor cells in direct comparison with the parent antitumor-active CPE-C (**3**). As shown in Table I, the removal of the N-3 nitrogen from the pyrimidine ring of CPE-C completely abolished toxicity. Only at millimolar concentrations was a slight cytotoxic effect observed for 3-deaza-CPE-C. On the other hand, a dose–response effect was observed for 3-deaza-CPE-U in the concentration range between 10^{-3} M and 10^{-6} M. However, 3-deaza-CPE-U was at least 3 orders of magnitude less potent than CPE-C.

From a structure–activity viewpoint it is of interest to correlate the cytotoxic effect of these carbocyclic nucleo-

(24) Bronson, J. J.; Ghazzouli, I.; Hitchcock, M. J. M.; Webb, R. R., II; Martin, J. C. *J. Med. Chem.* **1989**, *32*, 1457.

(25) The characteristic signals that helped identified this compound as a carbocyclic *C*-nucleoside were the following: ^{1}H NMR ($CDCl_3$) δ 10.95 (br s, 1 H, N*H*, D_2O exchanged), 10.46 (s, 1 H, O*H*, D_2O exchanged), 7.32 (m, 5 H, Ph), 7.20 (m, 1 H, H-6, converted to a doublet, J = 6.6 Hz, after D_2O exchange), 5.86 (d, J = 6.6 Hz, 1 H, H-5), 5.30 (s, 1 H, H-2′), 5.22 (d, J = 5.7 Hz, 1 H, H-4′), 4.63 (d, J = 5.7 Hz, 1 H, H-5′), 4.50 (d, J_{AB} = 13.3 Hz, 1 H, PhCH*H*O), 4.35 (d, J_{AB} = 13.3 Hz, 1 H, PhC*H*HO), 4.04 (m, 2 H, H-6′$_{a,b}$).

sides with the presence or absence of the N-3 nitrogen. While CPE-C is a very potent cytotoxic agent, the corresponding uridine analogue (CPE-U, 4) is almost totally devoid of cytotoxicity. This situation is reversed when the N-3 nitrogen is removed: the uridine analogue (3-deaza-CPE-U) is cytotoxic, while the cytosine analogue (3-deaza-CPE-C) is as innocuous as CPE-U. A similar trend was also observed for the riboside analogues, as 3-deazauridine (2) was more potent than 3-deazacytidine (1) against L1210 leukemia in vitro.[4] In this case, however, the difference in potency was only 8-fold ($IC_{50} = 6 \times 10^{-6}$ M and 5×10^{-5} M, respectively),[4] suggesting that the cyclopentene moiety separates more clearly the gap that exists between 3-deazapyrimidine analogues in terms of their biological activity.

3-Deaza-CPE-C and 3-deaza-CPE-U were also evaluated for possible antiviral activity against prototype DNA and RNA viruses. Both compounds were completely devoid of antiviral activity against herpes simplex (HSV-1) and human influenza (type A_0) viruses. The minimum cytotoxic concentration (MTC) measured for both compounds was >320 μg/mL against vero host cells, while with MDCK host cells 3-deaza-CPE-U was somewhat more toxic (MTC = 100 μg/mL). No antiviral activity was observed at these concentrations for either compound. This is in sharp contrast with the very marked antiviral activity observed for CPE-C against both DNA and RNA viruses.[10]

Experimental Section

General Procedures. All chemical reagents were commercially available. Proton and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in a Varian XL-200 instrument. The ^{13}C NMR peak positions were determined by reference to dioxane (δ 67.3) and the signs + and − refer to the peaks above or below the base line in the fully decoupled attached-proton test (APT). Proton chemical shifts are expressed as δ values and referenced to Me_4Si. UV spectra were recorded in a Beckman Model 34 spectrophotometer and specific rotations were measured in a Perkin-Elmer Model 241 polarimeter. Positive-ion fast atom bombardment (FAB) mass spectra were obtained by using samples dissolved in a glycerol matrix, and ionization was effected by a beam of xenon atoms derived by neutralizing xenon ions accelerated through 8.6 kV. Normal-phase column chromatography was performed on silica gel (silica gel 60, 230–400 mesh, E. Merck) and analytical TLC was performed on Analtech Uniplates silica gel GF with the solvents indicated for the individual experiments. Elemental analysis were performed by Atlantic Microlab, Inc., Atlanta GA, or by Galbraith Laboratories, Inc., Knoxville, TN.

(1′*R*,4′*R*,5′*S*)-1-[3-[(Benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopenten-1-yl]-4-amino-2-pyridone (12) and (1′*R*,4′*R*,5′*S*)-2-[[3-[(Benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopenten-1-yl]oxy]-4-aminopyridine (13). A solution of 4-amino-2-pyridone (11)[3,21] (0.173 g, 1.57 mmol) in 1.5 mL of anhydrous DMSO was added to a stirred solution of sodium hydride (0.053 g, 80% oil dispersion, 1.74 mmol) in 1.5 mL of DMSO under argon. After 45 min a solution of cyclopentenyl mesylate (10,[19] 0.554 g, 1.56 mmol) in 1.5 mL of DMSO was added, and the resulting mixture was stirred at room temperature for 40 h. The solvent was removed in vacuo and the crude product mixture was passed through a short pad of silica gel and eluted with a mixture of CH_2Cl_2/MeOH (10:1) in order to remove polar impurities. The material collected was rechromatographed over silica gel using the same solvent mixture in a ratio of 6:1 to afford 0.207 g (36%) of 12 and 0.193 g (33%) of 13 [R_f values of 0.48 and 0.72, respectively, on TLC silica gel chromatography (CH_2Cl_2/MeOH, 9:1)].

Compound 12: foam $[\alpha]^{26}_D = -37.76°$ (*c* 1.79, $CHCl_3$); ^1H NMR (Me_2SO-d_6) δ 1.25 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 4.15 (m, 2 H, H-6′$_{a,b}$), 4.37 (d, *J* = 5.9 Hz, 1 H, H-5′), 4.52 (s, 2 H, OCH_2Ph), 5.20 (d, *J* = 5.9 Hz, 1 H, H-4′), 5.25 (d, *J* = 2.3 Hz, 1 H, H-3), 5.54 (bs, 2 H, H-1′, H-2′), 5.67 (dd, *J* = 7.5 Hz, *J*′ = 2.3 Hz, 1 H, H-5), 6.05 (bs, 2 H, NH_2), 6.88 (d, *J* = 7.5 Hz, H-6), 7.20–7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.3, 66.6 (+, C-6′), 66.6 (−, C-1′), 73.0, 83.7 (−, C-5′), 84.6 (−, C-4′), 95.5 (−, C-5), 99.6 (−, C-3), 111.8, 124.7 (−, C-2′), 127.5, 128.2, 134.2 (−, C-6), 137.8, 148.1 (+, C-3′), 155.7 (+, C-2), 163.3 (+, C-4). Anal. ($C_{21}H_{24}N_2O_4 \cdot 0.25H_2O$) C, H, N.

Compound 13: foam; $[\alpha]^{26}_D = -55.4‰$ (*c*, 0.80, $CHCl_3$); ^1H NMR (Me_2SO-d_6) δ 1.25 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 4.10 (bs, 2 H, H-6′$_{a,b}$), 4.50–4.55 (m, 3 H, H-5′, OCH_2Ph), 5.14 (d, *J* = 5.4 Hz, 1 H, H-4′), 5.64 (bs, 1 H, H-1′), 5.77 (d, *J* = 1.6 Hz, 1 H, H-3), 5.81 (bs, 1 H, H-2′), 6.00 (bs, 2 H, NH_2), 6.16 (dd, *J* = 5.7 Hz, *J*′ = 1.6 Hz, 1 H, H-5), 7.20–7.40 (m, 5 H, Ph), 7.60 (d, *J* = 5.7 Hz, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ 26.1, 27.5, 66.7 (+, C-6′), 72.7, 82.6 (−, C-1′), 83.4 (−, C-5′), 83.9 (−, C-4′), 94.1 (−, C-5), 105.4 (−, C-3), 112.0, 126.7 (−, C-2′), 127.4, 127.5, 128.2, 138.0, 147.5 (+, C-3′), 147.2 (−, C-6), 155.0 (+, C-2), 164.4 (+, C-4). Anal. ($C_{21}H_{24}N_2O_4$) C, H, N.

(1′*R*,4′*R*,5′*S*)-1-[3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-1-yl]-4-amino-2-pyridone (5, 3-Deaza-CPE-C). A solution of 12 (0.178 g, 0.48 mmol) in 3.5 mL of dry CH_2Cl_2 was stirred at −78 °C under a nitrogen atmosphere. This solution was treated with 1.9 mL of a 1 M solution of BCl_3 in CH_2Cl_2 and stirred at −78 °C for 90 min. During a 30-min period, the solution was allowed to slowly warm to 0 °C at which time 3 mL of MeOH was added. The solution was then concentrated in vacuo and coevaporated three more times with MeOH. The crude product mixture was dissolved in 20 mL of water and treated with 3 mL of 30% aqueous ammonium hydroxide prior to lyophilization. Reversed phase (C-18) column chromatography using 5% aqueous MeOH as eluant afforded 0.048 g (41%) of 5 as a white amorphous powder: $[\alpha]^{25}_D = -93.32°$ (*c* 0.28, H_2O); UV (H_2O) λ_{max} 274 (sh, log ε 3.88), 261 (log ε 3.96), 218 nm (log ε 4.47); ^1H NMR (Me_2SO-d_6 + D_2O) δ 3.74 (t, *J* = 5.5 Hz, 1 H, H-5′), 4.04 (bs, 2 H, H-6′$_{a,b}$), 4.31 (d, *J* = 5.7 Hz, 1 H, H-4′), 5.31 (d, *J* = 2.4 Hz, 1 H, H-3), 5.43 (bd, *J* = 1.8 Hz, 1 H, H-2′), 5.53 (m, 1 H, H-1′), 5.75 (dd, *J* = 7.5 Hz, *J*′ = 2.4 Hz, 1 H, H-5), 6.99 (d, *J* = 7.5 Hz, 1 H, H-6); ^{13}C NMR (D_2O) δ 59.0 (+, C-6′), 65.2 (−, C-1′), 73.1 (−, C-5′), 77.8 (−, C-4′), 94.5 (−, C-5), 102.2 (−, C-3), 126.8 (−, C-2′), 135.2 (−, C-6), 148.4 (+, C-3′), 158.5 (+, C-2), 165.1 (+, C-4); FAB mass spectrum, *m/z* (relative intensity) 331 (MH + glycerol, 6), 239 (MH^+, 100), 111 (b + 2 H, 73). Anal. ($C_{11}H_{14}N_2O_4$) C, H, N.

(1′*R*,4′*R*,5′*S*)-1-[3-[(Benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopenten-1-yl]-4-(benzyloxy)-2-pyridone (15) and (1′*R*,4′*R*,5′*S*)-2-[[3-[(Benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopenten-1-yl]oxy]-4-(benzyloxy)pyridine (16). A solution of 4-(benzyloxy)-2-pyridone[23] (0.2 g, 1 mmol) in dry DMF (4 mL) was treated with NaH (0.03 g, 80% oil dispersion, 1 mmol) and maintained with stirring under an argon atmosphere at 40 °C. After 30 min, a solution of cyclopentenyl mesylate (10,[19] 0.3 g, 0.85 mmol) in 3 mL of DMF was added and the reaction mixture was stirred vigorously at 80 °C for 48 h. DMF was removed in vacuo and the resulting brown paste was passed through a short pad of silica gel and eluted with a mixture of CH_2Cl_2/MeOH (2:1), in order to remove polar impurities. The material collected was chromatographed over silica gel using a mixture of CH_2Cl_2/MeOH (98:2) as eluant. This system provided partially pure compounds 15 and 16. The partially pure *N*-nucleoside (15) was rechromatographed over silica gel with a mixture of ether/ethyl acetate (1:1) as eluant to provide 0.107 g (27.4%) of pure 15 as a colorless glass (R_f = 0.3 in the same system). The partially pure *O*-nucleoside (16) was also rechromatographed over silica gel using the same solvent mixture in a 4:1 ratio to give 0.089 g (23%) of pure 16 as a colorless glass (R_f = 0.31 in the same system).

Compound 15: glass; $[\alpha]^{25}_D = -14.08°$ (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 4.24 (bs, 2 H, H-6′$_{a,b}$), 4.54 (d, *J* = 5.3 Hz, 1 H, H-5′), 4.61 (s, 2 H, OCH_2Ph), 4.98 (s, 2 H, OCH_2Ph), 5.21 (d, *J* = 5.7 Hz, 1 H, H-4′), 5.65 (bs, 2 H, H-1′, H-2′), 5.93 (dd, *J* = 7.6 Hz, *J*′ = 2.7 Hz, 1 H, H-5), 6.03 (d, *J* = 2.7 Hz, 1 H, H-3), 6.95 (d, *J* = 7.6 Hz, 1 H, H-6), 7.25–7.50 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.3. 66.7 (+, C-6′), 67.2 (−, C-1′), 70.3, 83.7 (−, C-5′), 84.6 (−, C-4′), 98.4 (−, C-5), 101.5 (−, C-3), 112.3, 123.9 (−, C-2′), 127.7, 128.4, 128.7, 134.3 (−, C-6), 135.1, 137.8, 149.3 (+, C-3′), 163.9 (+, C-2), 167.1 (+, C-4). Anal. ($C_{28}H_{29}NO_5 \cdot 0.25H_2O$) C, H, N.

Compound 16: glass; $[\alpha]^{25}_D = -78.86°$ (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 4.19 (bs, 2 H, H-6′$_{a,b}$), 4.58 (s, 2 H, OCH_2Ph), 4.69 (d, *J* = 5.6 Hz, 1 H, H-5′),

5.06 (s, 2 H, OCH_2Ph), 5.21 (d, J = 5.7 Hz, 1 H, H-4'), 5.80 (bs, 1 H, H-1'), 5.94 (bs, 1 H, H-2'), 6.28 (d, J = 2.0 Hz, 1 H, H-3), 6.57 (dd, J = 6.0 Hz, J' = 2.0 Hz, 1 H, H-5), 7.25–7.45 (m, 10 H, Ph), 8.04 (d, J = 6.0 Hz, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ 26.1, 27.5, 66.8 (+, C-6'), 69.8, 72.8, 83.0 (-, C-1'), 83.4 (-, C-5'), 83.9 (-, C-4'), 95.2 (-, C-5), 106.8 (-, C-3), 112.2, 126.4 (-, C-2'), 127.5, 127.7, 128.3, 128.4, 128.7, 135.8, 138.0, 147.8 (+, C-3'), 147.8 (-, C-6), 164.8 (+, C-2), 167.0 (+, C-4). Anal. ($C_{28}H_{29}NO_5$) C, H, N.

(1'*R*,4'*R*,5'*S*)-1-[3-(Hydroxymethyl)-4,5-dihydroxy-2-cyclopenten-1-yl]-4-hydroxy-2-pyridone (6, 3-Deaza-CPE-U). A solution of protected nucleoside 15 (0.245 g, 0.534 mmol) in dry CH_2Cl_2 was stirred at -78 °C under a nitrogen atmosphere. This solution was treated with 3.2 mL of a 1 M solution of BCl_3 in CH_2Cl_2 and stirred at -78 °C for 3.5 h. Methanol (5 mL) was added and the solution was allowed to reach room temperature. The solution was concentrated in vacuo and coevaporated three more times with MeOH. The residual compound was dissolved in water (6 mL) and lyophilized. Reversed-phase (C-18) column chromatography with 5% aqueous methanol as eluant afforded 0.041 g (32%) of the desired target compound 6 as a white amorphous powder; $[\alpha]^{25}_D$ = -55.6° (c 1.34, H_2O); UV (H_2O, pH 1) λ_{max} 280 nm (log ϵ 3.65), UV (H_2O, pH 11) λ_{max} 268 (sh, log ϵ 3.80), 255 nm (log ϵ 3.91); ^1H NMR (CD_3OD) δ 4.01 (t, J = 5.5 Hz, 1 H, H-5'), 4.55 (bs, 2 H, H-6'$_{a,b}$), 5.70 (d, J = 5.7 Hz, 1 H, H-4'), 5.70 (bd, J = 1.8 Hz, 1 H, H-2'), 5.77 (m, 1 H, H-1'), 5.83 (d, J = 2.6 Hz, 1 H, H-3), 6.07 (dd, J = 7.5 Hz, J' = 2.6 Hz, 1 H, H-5), 7.33 (d, J = 7.6 Hz, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6) δ 58.6 (+, C-6'), 64.3 (-, C-1'), 72.5 (-, C-5'), 77.4 (-, C-4'), 98.2 (-, C-5), 100.2 (-, C-3), 124.0 (-, C-2'), 135.4 (-, C-6), 151.1 (+, C-3'), 163.3 (+, C-2), 166.2 (+, C-4); FAB mass spectrum, m/z (relative intensity) 332 (MH + glycerol, 3), 240 (MH^+, 100), 112 (b + 2 H, 98). Anal. ($C_{11}H_{13}NO_5$) C, H, N.

Biological Tests. In vitro cytotoxicity evaluations were performed by Dr. Richard L. Cysyk and Ms. Nancy M. Malinowski of the Laboratory of Biological Chemistry, DTP, DCT, NCI. Antiviral activity evaluations were conducted under NIH purchase order 263-MD-610174 at Southern Research Institute, Birmingham, AL, under the direction of Dr. William Shannon and Ms. Gussie Arnett.

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Potential Anti-AIDS Agents. Synthesis and Antiviral Activity of Naphthalenesulfonic Acid Derivatives against HIV-1 and HIV-2

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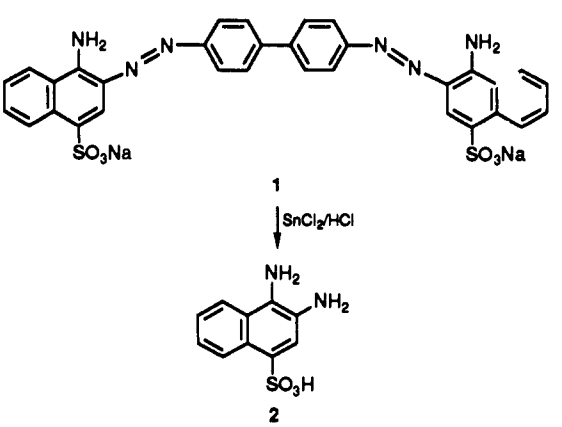
Certain naphthalenesulfonic acid analogues have been synthesized and evaluated for their inhibitory effects on HIV-1- and HIV-2-induced cytopathogenicity, HIV-1 giant cell formation, and HIV-1 reverse transcriptase (RT) activity. A bis(naphthalenedisulfonic acid) derivative having a biphenyl spacer emerged as the most potent and selective inhibitor of virus-induced cytopathogenicity in MT-4 cells. The ED_{50} values for this compound were 7.6 and 36 μM for HIV-1 and HIV-2, respectively. No toxicity to the host cells was detected at 98 μM. This compound also inhibited giant cell formation and was superseded in potency by a bis(naphthalenedisulfonic acid) derivative having a flexible decamethylene spacer. In the cell-free RT assay, a long-chain amide derivative exhibited the most inhibition of RT. All the compounds that achieved complete inhibition of virus-induced cytopathogenicity at concentrations not toxic to host cells were derivatives of 4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid. These analogues represent new leads for the development of anti-HIV agents.

Since the discovery of a retrovirus as the causative agent for AIDS,[1,2] only 3'-azido-2',3'-dideoxythymidine (AZT) has gained wide-scale FDA approval for treatment of patients with AIDS and ARC.[3] However, AZT use has been associated with toxicity,[4] resumption of viral replication,[5] the occurrence of cell to cell virus transmission,[6] and the emergence of AZT-resistant HIV-1 strains during prolonged therapy.[7] It has been demonstrated that common mutations in the HIV-1 reverse transcriptase gene can confer resistance to AZT.[8] Many nucleoside analogues with potential anti-AIDS activities have been reported[9-16] and the mechanism of action of most dideoxynucleosides is established.[17] It is pertinent to note that, so far, this approach has proved to be incapable of completely halting

Scheme I



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