

2'-Azido-2',3'-dideoxypyrimidine Nucleosides. Synthesis and Antiviral Activity against Human Immunodeficiency Virus¹

James A. Warshaw and Kyoichi A. Watanabe*

Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021. Received March 21, 1989

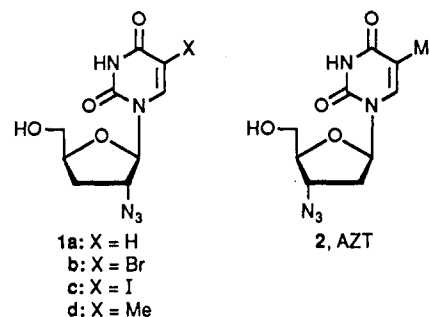
A series of four 2'-azido-2',3'-dideoxypyrimidine nucleosides were synthesized and their activity against human immunodeficiency virus was explored. 2,2'-Anhydro-5-*O*-benzoyluridine (**6a**) was prepared from 5-*O*-benzoyluridine (**5a**) and converted into 3'-deoxy analogue **8a** by imidazolylthiocarbonylation followed by Bu₃SnH reduction. Treatment of **8a** with LiN₃ in DMF followed by saponification afforded 2'-azido-2',3'-dideoxyuridine (**1a**). The 5'-*O*-benzoylated nucleoside **9a** was further converted into the 5-bromo and 5-iodo analogues (**1b** and **1c**) by halogenation and debenzoylation. 2',3'-*O*-Isopropylideneuridine (**3**) was converted in two steps into the thymine nucleoside, which was benzoylated and de-*O*-isopropylidened to afford 5'-*O*-benzoyl-5-methyluridine (**5d**). 2'-Azido-2',3'-dideoxy-5-methyluridine (**1d**) was synthesized from **5d** in a similar manner as that used for the synthesis of **1a** from **5a**. These new nucleosides, closely related to AZT, however, did not exhibit any significant anti-HIV activity in tissue culture using H9 cells.

Human immunodeficiency virus (HIV) has been recognized as the etiologic agent of acquired immunodeficiency syndrome (AIDS).² Nucleoside analogues, such as 3'-azido-3'-deoxythymidine (AZT)³ and other 2',3'-dideoxynucleosides (DDN)⁴ are thus far the most active against this retrovirus in vitro. Although the exact mechanism of action of these nucleoside analogues is not fully understood, Furman et al.⁵ has shown that AZT is converted to its corresponding triphosphate by cellular enzymes and this triphosphate acts as a competitive inhibitor of the reverse transcriptase (RT) of HIV. In addition, selective inhibition of RT was demonstrated due to the higher affinity of AZT triphosphate for the reverse transcriptase than for cellular DNA polymerase α .^{5,6} Furthermore, if incorporated into a growing viral DNA chain, these 2',3'-dideoxynucleoside analogues would halt further DNA synthesis since they lack a 3'-hydroxyl group.^{7,8}

Recently, Lin et al.^{9,10} published the results of the systematic structure-activity relationships of AZT analogues against retroviruses. Of particular interest was the fact that substitution in the 5-position of the pyrimidine ring with either H, Br, or I yielded AZT derivatives with significant anti-HIV activity.¹⁰ Herdewijn et al.¹¹ has also

demonstrated that 2'-azido-2',3'-dideoxyadenosine (with azide in the "up" configuration) has moderate activity against HIV. The above results coupled with another recent publication by Herdewijn et al.¹² revealing that many 3'-substituted 2',3'-dideoxypyrimidine nucleoside analogues are inactive against HIV led to the current investigation.

In an attempt to understand more fully the importance of the 3'-azido group in AZT, we undertook the synthesis of the novel nucleoside analogues **1a**–**1d**. Of special in-



terest should be that compound **1d** is a regioisomer of AZT (2). Consequently, the extent of anti-HIV activity observed in compounds **1a**–**1d** can shed insight into the structural requirements of 2',3'-dideoxynucleosides.

Results and Discussion

Nucleosides **1a**–**1d** were synthesized according to Scheme I. For the synthesis of **1a**–**1c**, the common intermediate was 5'-*O*-benzoyluridine (**5a**),¹³ which was prepared in three steps from uridine in 41% overall yield (Scheme I) via acetonation, benzoylation, and deacetonation. Conversion of **4a** into 2,2'-anhydronucleoside **6a**, in our hands, was most effectively achieved by treatment with 1.5 equiv of diphenyl carbonate in DMF at 120 °C for 45 min.¹⁴

The highlight of our synthesis of nucleosides **1** entails the first conversion of 2,2'-anhydronucleosides **6** to the corresponding 3'-deoxynucleosides **8** without concomitant cleavage of the 2,2'-anhydro linkage by utilization of the Barton reaction.¹⁵ Thus, reaction of **6a** with 2.1 equiv of

- (1) Nucleosides. 152.
- (2) (a) Gallo, R. C.; Sarin, P. S.; Gelmann, E. P.; Guroff, M. R.; Richardson, E.; Kalyanaraman, V. S.; Mann, D.; Sidhu, G. D.; Stahl, R. E.; Zoller-Pazner, S.; Leibowitch, J.; Popovic, M. *Science* **1983**, *220*, 865. (b) Barre-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868.
- (3) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
- (4) (a) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911. (b) Matsushita, S.; Mitsuya, H.; Reitz, M. S.; Broder, S. *J. Clin. Invest.* **1987**, *80*, 394.
- (5) Furman, P. A.; Fyfe, J. A.; St. Clair, M. H.; Weinhold, K.; Rideout, J. L.; Freeman, G. A.; Lehrman, S. N.; Bolognesi, D. P.; Broder, S.; Mitsuya, H.; Barry, D. W. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8333.
- (6) Waggar, M. A.; Evans, M. J.; Manly, K. F.; Hughes, R. G.; Huberman, J. A. *J. Cell Physiol.* **1984**, *121*, 402.
- (7) Atkinson, M. R.; Deutscher, M. P.; Kornberg, A.; Russell, A. F.; Moffatt, J. G. *Biochemistry* **1969**, *8*, 4897.
- (8) Mitsuya, H.; Jarrett, R. F.; Matsukura, M.; Veronese, F. D. M.; DeVico, A. L.; Sarngadharan, M. G.; Johns, D. G.; Reitz, M. S.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2033.
- (9) Lin, T. S.; Chen, M. S.; McLaren, C.; Gao, Y. S.; Ghazzouli, I.; Prusoff, W. H. *J. Med. Chem.* **1987**, *30*, 440.
- (10) Lin, T. S.; Guo, J. Y.; Schinazi, R. F.; Chu, C. K.; Xiang, J. N.; Prusoff, W. H. *J. Med. Chem.* **1988**, *31*, 336.
- (11) Herdewijn, P.; Pauwels, R.; Baba, M.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 2131.

- (12) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270.
- (13) (a) Shimokawa, S.; Kimura, J.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3357. (b) Ishido, Y.; Nakazaki, N.; Sakairi, N. *J. Chem. Soc., Perkin Trans. I* **1979**, 2088.
- (14) Hampton, A.; Nichol, A. W. *Biochemistry* **1966**, *5*, 2076.

genation over PtO_2 according to the procedure of Scheit,²³ yielded 1-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)thymine (10). Treatment of 10 with 1 equiv of benzoyl chloride in pyridine yielded 1-(5-*O*-benzoyl-2,3-*O*-isopropylidene- β -D-ribofuranosyl)thymine (11) in 58% yield.²⁴ Reaction of 11 with 97% formic acid afforded 5d in 88% yield²⁵ from 11 and 19% overall yield from 3. Conversion of 5d into 1d was performed in a similar manner as that described above for the preparation of 1a from 5a.

Antiviral Activity

The assay procedure will be reported in a later paper.²⁶

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^1H NMR spectra were recorded on a JEOL FX90 spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ) and the signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Values given for coupling constants are first order. IR spectra were recorded on a Perkin-Elmer Model 137 infrared spectrometer. Absorptions are described as vs (very strong), s (strong), m (medium), and br (broad). UV measurements were obtained on an IBM UV-Visible 9430 spectrophotometer (sh, shoulder). Microanalyses were performed by Galbraith Laboratories. Silica gel TLC was performed on Analtech Uniplates with short-wavelength UV light for visualization. Column chromatography was conducted on flash-grade silica gel (Merck 9385, 0.040–0.063 μm).

5'-*O*-Benzoyl-2',3'-*O*-isopropylidene-5-methyluridine (11). To 6.0 g (0.02 mol) of 10 was added 100 mL of BaO-dried pyridine and then 3.1 g (0.02 mol) of benzoyl chloride. The solution was then allowed to stand for 10 h. After this period, the reaction mixture was concentrated in vacuo and then coevaporated three times with EtOH. The residue was then chromatographed over flash silica gel employing gradient elution (liters 1 and 2, 99.5/0.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$, liter 3, 9.85/0.15 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield 4.7 g (58%) of 11 after recrystallization from EtOH: mp 171–173 $^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$) δ 1.32 (s, 3 H, C-Me), 1.51 (s, 3 H, C-Me), 1.61 (d, $J = 0.82$ Hz, 3 H, 5-Me), 4.19–4.64 (m, 3 H, H_4 , 2 H_5), 4.92 (dd, $J_{3,2} = 6.50$ Hz, $J_{3,4} = 3.36$ Hz, 1 H, H_3), 5.06 (dd, $J_{2,3} = 5.82$ Hz, $J_{1,2} = 2.24$ Hz, 1 H, H_2), 5.82 (d, $J_{1,2} = 1.92$ Hz, 1 H, H_1), 7.39–8.10 (m, 6 H, Ar-H, H_6), 11.41 (br s, 1 H, N-H exchangeable). Anal. Calcd ($\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_7$) C, H, N.

5'-*O*-Benzoyl-5-methyluridine (5d). To 4.3 g (0.01 mol) of 11 was added 50 mL of 97% formic acid and the solution was allowed to stand for 3 h. After this time, the reaction mixture was coevaporated twice with EtOH. The crude product was then chromatographed over flash silica gel employing gradient elution (liter 1, 98/2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; liter 2 to end, 9.6/0.4 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield 3.4 g (88%) of 5d: mp 157–159 $^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$) δ 1.60 (s, 3 H, 5- CH_3), 4.00–4.50 (m, 3 H, H_4 , 2 H_5), 4.56–4.75 (m, 2 H, $\text{H}_{2,3}$), 5.34 (d, $J = 3.57$ Hz, 1 H, OH exchangeable), 5.47 (d, $J = 4.97$ Hz, 1 H, OH exchangeable), 5.81 (d, $J_{1,2} = 4.39$ Hz, 1 H, H_1), 7.32–8.10 (m, 6 H, Ar-H, H_6), 11.34 (br s, 1 H, N-H exchangeable). Anal. Calcd ($\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_7$) C, H, N.

5'-*O*-Benzoyl-2,2'-anhydrouridine (6a). To a stirring solution of 5.0 g (0.014 mol) of 5a¹³ in 40 mL of DMF was added 4.6 g (0.02 mol) of diphenyl carbonate and 0.12 g (1.4 mmol) of sodium bicarbonate. The solution was then heated in an oil bath for 45 minutes at 120 $^\circ\text{C}$. After this time, the reaction mixture was

concentrated in vacuo. The crude product was then recrystallized from EtOH to yield 3.01 g (65%) of 6a: mp 198–200 $^\circ\text{C}$ (lit.²⁷ mp 201–202.5 $^\circ\text{C}$); ^1H NMR ($\text{DMSO}-d_6$) δ 4.00–4.55 (m, 4 H, H_3 , H_4 , 2 H_5), 5.29 (d, $J_{2,1} = 5.76$ Hz, 1 H, H_2), 5.84 (d, $J_{5,6} = 7.41$ Hz, 1 H, H_5), 6.11 (br s, 1 H, 3'-OH exchangeable), 6.34 (d, $J_{1,2} = 5.77$ Hz, 1 H, H_1), 7.35–8.0 (m, 6 H, Ar-H, H_6); IR (KBr) 3600–2600 (br, OH), 1730 (s, C=O), 1650 (s), 1620 (s), 1530 (m), 1470 (s), 1270 (m); UV (H_2O) λ_{max} 229, 260 nm (sh). Anal. Calcd ($\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_6 \cdot 1/4 \text{H}_2\text{O}$) C, H, N.

5'-*O*-Benzoyl-5-methyl-2,2'-anhydrouridine (6d) was synthesized in virtually the same manner as 6a to produce 6d, in 67% yield: mp 173–175 $^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$) δ 1.74 (d, $J_{5-\text{Me}-\text{H}_6} = 1.38$ Hz, 3 H, 5-Me), 4.04–4.50 (m, 4 H, H_3 , H_4 , 2 H_5), 5.24 (dd, $J_{2,1} = 5.82$ Hz, $J_{2,3} = 1.34$ Hz, 1 H, H_2), 6.11 (d, $J = 4.39$ Hz, 1 H, 3'-OH exchangeable), 6.32 (d, $J_{1,2} = 5.76$ Hz, 1 H, H_1), 7.37–7.95 (m, 6 H, Ar-H, H_6); IR (KBr) 3290 (m, OH), 1740 (vs, C=O), 1675 (s), 1620 (s), 1555 (vs), 1495 (vs), 1290 (vs); UV (H_2O) λ_{max} 232, 264 nm (sh). Anal. Calcd ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_6 \cdot 1/4 \text{H}_2\text{O}$) C, H, N.

3'-*O*-(Thiocarbonylimidazolyl)-5'-*O*-benzoyl-2,2'-anhydrouridine (7a). To a stirring solution of 1.0 g (3.0 mmol) of 6a in 7.5 mL of DMF was added 1.1 g (6.2 mmol) of 1,1'-thiocarbonyldiimidazole and the solution was allowed to stir for 1 h. After this time, 2 mL of MeCN was added to the precipitate which formed and the crude product was filtered. The precipitate was further purified by trituration with a small quantity of MeOH to yield 1.0 g (76%) of 7a: mp 211–214 $^\circ\text{C}$ dec; ^1H NMR ($\text{DMSO}-d_6$) δ 4.20–4.55 (m, 2 H, 2 H_5), 4.95–5.35 (m, 1 H, H_4), 5.91 (2 d, 2 H, H_5 , H_2), 6.13 (d, $J_{3,4} = 2.19$ Hz, 1 H, H_3), 6.51 (d, $J_{1,2} = 6.03$ Hz, 1 H, H_1), 7.13 (m, 1 H, Im-H), 7.40–8.05 (m, 7 H, Ar-H, H_6 , Im-H), 8.60 (s, 1 H, Im-H); IR (KBr) 1715 (s, C=O), 1645 (vs, C=O), 1545 (m), 1470 (s), 1380 (s), 1325 (s), 1285 (s), 1267 (s), 1247 (s), 1220 (m). UV (MeOH) λ_{max} 226, 259 nm (sh). Anal. Calcd ($\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_6\text{S}$) C, H, N, S.

3'-*O*-(Thiocarbonylimidazolyl)-5'-*O*-benzoyl-5-methyl-2,2'-anhydrouridine (7d) was synthesized in virtually the same manner as 7a to produce 7d in 66% yield, mp 196–200 $^\circ\text{C}$ dec. The material was sufficiently pure to proceed to the next step. 7d: ^1H NMR ($\text{DMSO}-d_6$) δ 1.76 (d, $J_{5-\text{Me}-\text{H}_6} = 1.38$ Hz, 3 H, 5-Me), 4.22–4.47 (m, 2 H, 2 H_5), 4.90–5.25 (m, 1 H, H_4), 5.87 (d, $J_{2,1} = 6.04$ Hz, 1 H, H_2), 6.10 (d, $J_{3,4} = 2.24$ Hz, 1 H, H_3), 6.47 (d, $J_{1,2} = 5.49$ Hz, 1 H, H_1), 7.11 (m, 1 H, Im-H), 7.37–8.12 (m, 7 H, Ar-H, H_6 , Im-H), 8.57 (m, 1 H, Im-H); IR (KBr) 1710 (vs), 1660 (m), 1630 (vs), 1550 (s), 1460 (s), 1380 (s), 1320 (s), 1280 (s), 1260 (vs), 1240 (vs), 1215 (s). UV (MeOH) λ_{max} 230, 256 nm (sh).

3'-Deoxy-5'-*O*-benzoyl-2,2'-anhydrouridine (8a). To 1.23 g (2.8 mmol) of 7a was added 25 mL of dry toluene and 25 mL of dry acetonitrile. To this suspension was added 2.4 g (8.4 mmol) of Bu_3SnH and 50 mg (0.3 mmol) of AIBN. The suspension was then refluxed for 1 h, during which time a clear solution developed. The reaction mixture was then cooled and concentrated in vacuo. The residue was chromatographed over flash silica gel employing a mobile phase of 97.5/2.5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to yield 0.64 g (73%) of 8a after recrystallization from EtOH: mp 124–125 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 2.35–2.87 (m, 2 H, 2 H_5), 4.24 (m, 2 H, 2 H_5), 4.55–4.92 (m, 1 H, H_4), 5.37–5.67 (m, 1 H, H_2), 6.03 (d, $J_{5,6} = 7.4$ Hz, 1 H, H_5), 6.16 (d, $J_{1,2} = 5.49$ Hz, 1 H, H_1), 7.22–8.07 (m, 6 H, Ar-H, H_6); IR (KBr) 3500 (m, H_2O), 1730 (vs, C=O), 1650 (vs, C=O), 1525 (s), 1470 (vs), 1270 (s), 1070 (s); UV (H_2O) λ_{max} 228, 264 nm (sh). Anal. Calcd ($\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_5 \cdot 1/2 \text{H}_2\text{O}$) C, H, N.

3'-Deoxy-5'-*O*-benzoyl-5-methyl-2,2'-anhydrouridine (8d) was synthesized in virtually the same manner as 8a to produce 8d in 47% yield: mp 187–188 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.93 (d, $J_{5-\text{Me}-\text{H}_6} = 1.37$ Hz, 3 H, 5- CH_3), 2.34–2.85 (m, 2 H, 2 H_5), 4.04–4.39 (m, 2 H, 2 H_5), 4.54–4.85 (m, 1 H, H_4), 5.42–5.59 (m, 1 H, H_2), 6.10 (d, $J_{1,2} = 5.76$ Hz, 1 H, H_1), 7.14–7.99 (m, 6 H, Ar-H, H_6); IR (KBr) 1725 (s, C=O), 1670 (s), 1640 (vs), 1550 (vs), 1490 (s), 1280 (s); UV (H_2O) λ_{max} 231, 265 nm (sh). Anal. Calcd ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_5$) C, H, N.

2'-Azido-5'-*O*-benzoyl-2',3'-dideoxyuridine (9a). To 0.4 g (1.3 mmol) of 8a in 8 mL of DMF was added 0.3 g (6.3 mmol) of LiN_3 and 0.4 g (3.8 mmol) of $\text{CF}_3\text{CO}_2\text{H}$ with stirring. The

(23) Scheit, K. H. *Chem. Ber.* 1966, 99, 3884.

(24) Verheyden, J. H. P.; Moffatt, J. G. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; John Wiley and Sons: New York, 1968; Part 1, p 414.

(25) West, B. F. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; John Wiley and Sons: New York, 1968; Part 1, p 313.

(26) Watanabe, K. A.; Harada, K.; Zeidler, J.; Matulic-Adamic J.; Takahashi, K.; Ren, W.-Y.; Cheng, L.-C.; Fox, J. J.; Chou, T.-C.; Zhu, Q.-Y.; Polsky, B. W.; Gold, J. W. M.; Hardy, W. D.; Armstrong D. J. *Med. Chem.*, submitted for publication (Nucleosides. 154).

(27) Sasaki, T.; Minamoto, K.; Sugiura, T.; Niwa, M. *J. Org. Chem.* 1976, 41, 3138.

reaction mixture was then heated in an oil bath at 120 °C for 15 h. The solution was concentrated in vacuo and the residue was chromatographed over flash silica gel, employing a mobile phase of 98.5/1.5 CH₂Cl₂/MeOH. After pooling of the correct fractions, an oil remained which crystallized from Et₂O. The crude product was then recrystallized from EtOH to yield 0.28 g (62%) of **9a**: mp 160–162 °C; ¹H NMR (CDCl₃) δ 1.91–2.14 (m, 2 H, 2 H₃), 4.27–4.80 (m, 4 H, H₂, H₄, 2 H₅), 5.49 (dd, *J*_{5,6} = 8.23 Hz, *J*_{5,NH} = 2.19 Hz, 1 H, H₅), 5.81 (d, *J*_{1',2'} = 1.1 Hz, 1 H, H_{1'}), 7.32–8.07 (m, 6 H, Ar-H, H₆), 8.57 (br s, 1 H, NH); IR (KBr) 3010 (m), 2170 (s, N₃), 1750 (s, C=O), 1690 (vs, C=O), 1270 (vs), 1110 (s), 710 (s); UV (MeOH) λ_{max} 263 (ε 10 500), 229 nm (15 100). Anal. Calcd (C₁₆H₁₅N₅O₅) C, H, N.

2'-Azido-5'-O-benzoyl-2',3'-dideoxy-5-bromouridine (9b). To 0.28 g (7.8 mmol) of **8a** in 5 mL of dioxane was added 2 mL of 0.5 N HNO₃ and 0.19 g (1.2 mmol) of bromine in 1.4 mL of CCl₄. The reaction mixture was then stirred for 1 h at room temperature. After this time period, the solution was concentrated in vacuo. The residue was then coevaporated with EtOH three times and then recrystallized from EtOH to yield 0.30 g (88%) of **9b**: mp 184–186 °C dec; ¹H NMR (DMSO-*d*₆) δ 1.85–2.40 (m, 2 H, 2 H₃), 4.30–4.75 (m, 4 H, H₂, H₄, 2 H₅), 5.73 (d, *J*_{1',2'} = 2.2 Hz, 1 H, H_{1'}), 7.35–8.10 (m, 6 H, Ar-H, H₆), 11.87 (br s, 1 H, NH exchangeable); IR (KBr) 3015 (m), 2170 (m, N₃), 1735 (vs, C=O), 1620 (m), 1270 (vs), 1130 (s), 705 (s). UV (MeOH) λ_{max} 279 (ε 8100), 227 nm (13 800). Anal. Calcd (C₁₆H₁₄N₅O₅Br·1/4H₂O) C, H, N, Br.

2'-Azido-5'-O-benzoyl-2',3'-dideoxy-5-iodouridine (9c) was synthesized in virtually the same manner as **9b** (except for the substitution of I₂ for Br₂) to produce **9c** in 86% yield: mp 190–192 °C dec; ¹H NMR (DMSO-*d*₆) δ 1.91–2.36 (m, 2 H, 2 H₃), 4.36–4.71 (m, 4 H, H₂, H₄, 2 H₅), 5.72 (d, *J*_{1',2'} = 2.19 Hz, 1 H, H_{1'}), 7.41–8.06 (m, 6 H, Ar-H, H₆), 11.78 (br s, 1 H, NH exchangeable); IR (KBr) 3010 (m), 2140 (m, N₃), 1700 (s, C=O), 1650 (s, C=O), 1600 (m), 1250 (s), 1120 (m), 710 (m). UV (MeOH) λ_{max} 283 (ε 8000), 227 nm (17 600). Anal. Calcd (C₁₆H₁₄N₅O₅I·1/5H₂O) C, H, N, I.

2'-Azido-5'-O-benzoyl-2',3'-dideoxy-5-methyluridine (9d) was synthesized in virtually the same manner as **9a** to produce **9d** in 59% yield: mp 121–123 °C; ¹H NMR (CDCl₃) δ 1.66 (d, *J* = 1.1 Hz, 3 H, 5-Me), 1.95–2.37 (m, 2 H, 2 H₃), 4.27–4.85 (m, 4 H, H₂, H₄, 2 H₅), 5.79 (d, *J*_{1',2'} = 1.65 Hz, 1 H, H_{1'}), 7.30–8.12 (m, 6 H, 5-Ar-H, H-6), 8.64 (br s, 1 H, NH); IR (KBr) 3010 (m), 2150 (m, N₃), 1740 (s, C=O), 1700 (s, C=O), 1680 (s, C=O), 1270 (s). UV (MeOH) λ_{max} 268 (ε 10 000), 226 nm (15 500). Anal. Calcd (C₁₇H₁₇N₅O₅) C, H, N.

2'-Azido-2',3'-dideoxyuridine (1a). To 0.5 g (1.4 mmol) of **9a** was added 25 mL of a saturated solution of ammonia in methanol. The reaction mixture was allowed to stand for 24 h. After this time, the solution was concentrated in vacuo. The residue was then recrystallized from EtOH to yield 0.16 g (45%) of **1a**: mp 167–169 °C; ¹H NMR (DMSO-*d*₆) δ 1.65–2.27 (m, 2 H, 2 H₃), 3.32–3.92 (m, 2 H, 2 H₅), 3.97–4.33 (m, 1 H, H₄), 4.37–4.57 (m, 1 H, H₂), 5.17 (t, *J*_{OH-5'} = 5.21 Hz, 1 H, 5'-OH exchangeable), 5.60 (dd, *J*_{5,6} = 8.32 Hz, *J*_{5,NH} = 2.06 Hz, 1 H, H₅), 5.74 (d, *J*_{1',2'} = 1.92 Hz, 1 H, H_{1'}), 7.98 (d, *J*_{6,5} = 8.23 Hz, 1 H, H₆), 11.35 (br s, 1 H, NH exchangeable); IR (KBr) 3600 (m), 3500–3000 (br, OH), 2140 (s, N₃), 1700 (vs, C=O), 1470 (m), 1270 (s), 1125 (s); UV (EtOH)

λ_{max} 263 nm (ε 10 000). Anal. Calcd (C₉H₁₁N₅O₄·1/8H₂O) C, H, N.

2'-Azido-2',3'-dideoxy-5-bromouridine (1b) was synthesized in the same manner as **1a**. After the reaction was allowed to stand for 24 h, the solution was concentrated in vacuo and then coevaporated twice with EtOH. The residue was then taken up in a small quantity of MeCN and chromatographed over flash silica gel, employing a mobile phase of 99/1 CH₂Cl₂/MeOH to yield 0.12 g (55%) of **1b**: mp 148–150 °C; ¹H NMR (DMSO-*d*₆) δ 1.65–2.40 (m, 2 H, 2 H₃), 3.35–4.00 (m, 2 H, 2 H₅), 4.10–4.37 (m, 1 H, H₄), 4.42–4.60 (m, 1 H, H₂), 5.39 (t, *J*_{5'-OH,5'} = 4.94 Hz, 1 H, 5'-OH exchangeable), 5.71 (d, *J*_{1',2'} = 1.37 Hz, 1 H, H_{1'}), 8.57 (s, 1 H, H₆), 11.82 (br s, 1 H, NH exchangeable); IR (KBr) 3500 (m), 3700–2800 (br, OH), 2130 (s, N₃), 1700 (vs, C=O), 1450 (m), 1270 (s), 1120 (s). UV (EtOH) λ_{max} 280 (ε 8800). Anal. Calcd (C₉H₁₀N₅O₄Br) C, H, N.

2'-Azido-2',3'-dideoxy-5-iodouridine (1c) was synthesized in the same manner as **1a**. After the reaction was allowed to stand for 24 h, the solution was concentrated in vacuo. The residue was then taken up in a small quantity of MeCN and chromatographed over flash silica gel employing a mobile phase of 99/1 CH₂Cl₂/MeOH to yield 0.11 g of crude product. This crude material was then rechromatographed over flash silica gel employing a mobile phase of 1/1 EtOAc/CH₂Cl₂ to yield 65 mg (55%) of **1c**: mp 152–154 °C; ¹H NMR (DMSO-*d*₆) δ 1.65–2.30 (m, 2 H, 2 H₃), 3.35–3.95 (m, 2 H, 2 H₅), 4.08–4.36 (m, 1 H, H₄), 4.40–4.55 (m, 1 H, H₂), 5.35 (t, *J*_{5'-OH,5'} = 4.48 Hz, 1 H, 5'-OH exchangeable), 5.69 (d, *J*_{1',2'} = 0.90 Hz, 1 H, H_{1'}), 8.59 (s, 1 H, H₆), 11.71 (br s, 1 H, NH exchangeable); IR (KBr) 3600 (m), 3600–2700 (br, OH), 2160 (s, N₃), 1700 (vs, C=O), 1450 (m), 1270 (s), 1125 (s); UV (EtOH) λ_{max} 285 nm (ε 7500). Anal. Calcd (C₉H₁₀N₅O₄I·1/5H₂O) C, H, N.

2'-Azido-2',3'-dideoxy-5-methyluridine (1d) was synthesized in the same manner as **1a**, to give **1d** in 44% yield: mp 167–169 °C; ¹H NMR (DMSO-*d*₆) δ 1.75 (d, *J*_{5-Me-H⁶} = 0.83 Hz, 3 H, 5-CH₃), 1.78–2.39 (m, 2 H, 2 H₃), 3.36–3.92 (m, 2 H, 2 H₅), 4.00–4.33 (m, 1 H, H₄), 4.33–4.56 (m, 1 H, H₂), 5.21 (t, *J* = 5.22 Hz, 1 H, 5'-OH exchangeable), 5.74 (d, *J*_{1',2'} = 2.47 Hz, 1 H, H_{1'}), 7.85 (d, *J*_{6-5-Me} = 1.37 Hz, 1 H, H-6), 11.34 (br s, 1 H, NH exchangeable); IR (KBr) 3500 (m), 2150 (s, N₃), 1710 (vs, C=O), 1675 (vs, C=O), 1275 (m), 1220 (m), 1100 (s). UV (EtOH) λ_{max} 267 (ε 9400). Anal. Calcd (C₁₀H₁₃N₅O₄) C, H, N.

Acknowledgment. This investigation was supported in part by grants from the National Institute of Allergy and Infectious Diseases and the National Cancer Institute, NIH, U.S.D.H.H.S. (Grants Nos. AI-26056 and CA-08748). We thank Drs. Bruce W. Polsky and Jonathan W. M. Gold of the Laboratory of Medical Microbiology, Memorial Sloan-Kettering Cancer Center, for the anti-HIV assay of compounds **1a–1d**.

Registry No. **1a**, 126543-45-1; **1b**, 126543-49-5; **1c**, 126543-50-8; **1d**, 126543-51-9; **5a**, 54618-06-3; **5d**, 120649-55-0; **6a**, 24877-18-7; **6d**, 126578-22-1; **7a**, 126578-21-0; **7d**, 126543-52-0; **8a**, 126543-46-2; **8d**, 126543-53-1; **9a**, 126543-47-3; **9b**, 126543-55-3; **9c**, 126543-56-4; **9d**, 126543-54-2; **10**, 2073-43-0; **11**, 126543-48-4; uridine, 58-96-8.