2′-Azido-2′,3′-dideoxypyrimidine Nucleosides. Synthesis and Antiviral Activity against Human Immunodeficiency Virus[1]

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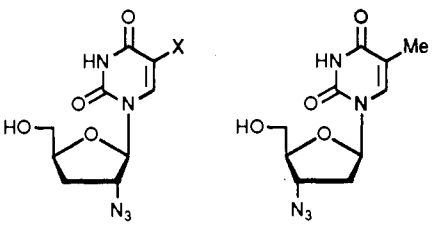
A series of four 2′-azido-2′,3′-dideoxypyrimidine nucleosides were synthesized and their activity against human immunodeficiency virus was explored. 2,2′-Anhydro-5-*O*-benzoyluridine (**6a**) was prepared from 5-*O*-benzoyluridine (**5a**) and converted into 3′-deoxy analogue **8a** by imidazolylthiocarbonylation followed by Bu_3SnH reduction. Treatment of **8a** with LiN_3 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*-isopropylidenated 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 aquired 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 particualr 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 interest 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.



1a: X = H
b: X = Br
c: X = I
d: X = Me

2, AZT

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

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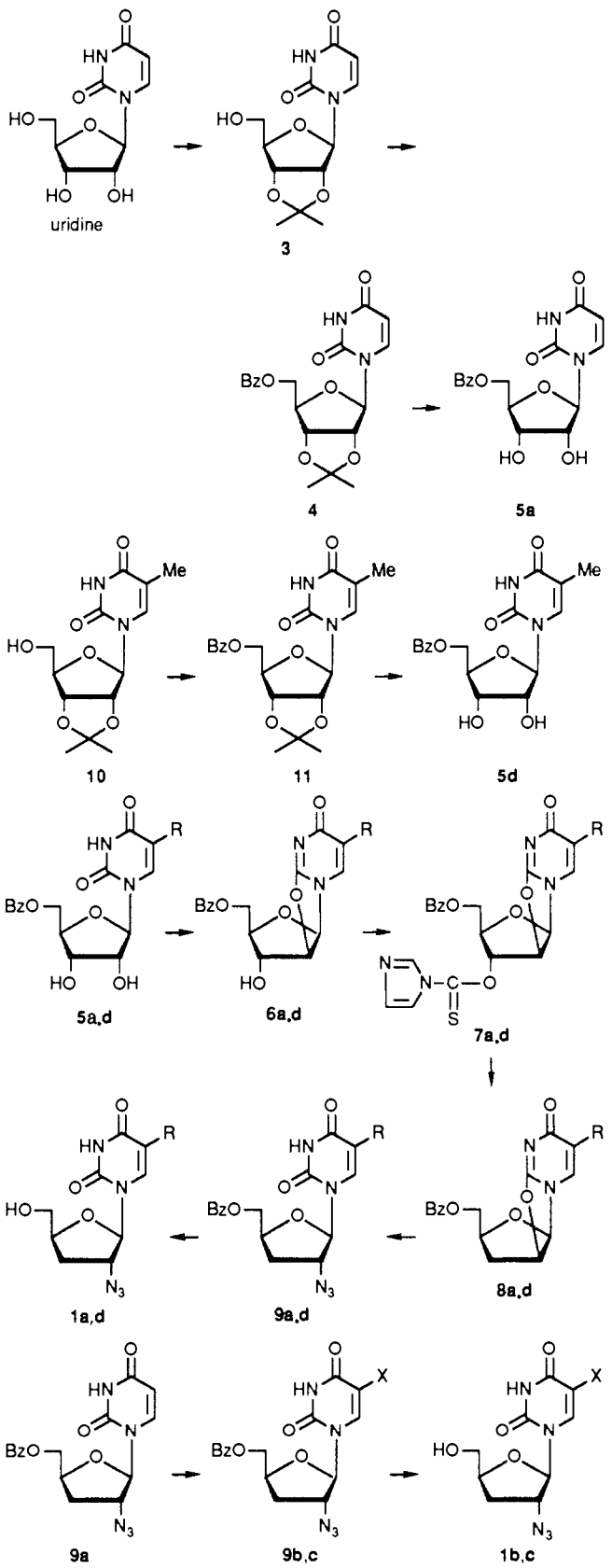
Scheme I



thiocarbonyldiimidazole (TCDI) in DMF for 1 h gave **7a** in 76% yield. Evidence for the introduction of the thiocarbonylimidazole function into **6a** was revealed from differences observed in the ^{1}H NMR between **6a** and **7a**. Firstly, new absorptions appear at 8.60 and 7.13 ppm in **7a** due to the imidazole group that were not present in **6a**. In addition, the aromatic region integrates for seven protons in **7a** versus six protons in **6a**. Secondly, introduction of the thiocarbonylimidazole group causes strong deshielding of the H-3′ proton in **7a** relative to that of **6a**.[16] In **7a**, H-3′ appears as a doublet at 6.13 ppm ($J_{3',4'}$ = 2.2 Hz), whereas H-3′ in **6a** appears bunched with H-4′, H-5′, and H-5″ in the area of 4.00–4.55 ppm. Evidence for maintenance of the 2,2′-anhydro linkage in **7a** is shown by the paramagnetic shift of H-1′ (6.51 ppm) and the large coupling between the H-1′ and H-2′ protons (6.0 Hz).[17] In addition, the UV[18] and IR[19] spectra of **7a** are indicative of the 2,2′-anhydro structure.

Reaction of **7a** with 3 equiv of tributyltin hydride in the presence of catalytic amounts of α,α'-azobisisobutyronitrile (AIBN) for 1 h yielded 3′-deoxynucleoside **8a** in 73% yield. Evidence for the deoxy structure **8a** comes from spectroscopic studies. In the ^{1}H NMR the absorptions at 8.60 and 7.13 ppm and the other proton in the aromatic region due to the imidazole group in **7a** are no longer present in **8a**. A strong shielding effect is observed for the H-3′ protons (integrated for two protons) in **8a** (multiplet at 2.35–2.87 ppm) relative to H-3′ of **7a** (doublet at 6.13 ppm). Again, the large chemical shift of H-1′ (6.16 ppm), large $J_{1',2'}$ value (5.5 Hz),[17] and the UV[18] and IR[19] spectra are consistent with the 2,2′-anhydro nucleoside structure **8a** for the product.

Introduction of the azide group into **8a** was accomplished by treatment with LiN_3 and 3 equiv of trifluoroacetic acid at 120 °C for 15 h, the procedure similar to that reported by Verheyden et al.[20] The yield of 5′-*O*-benzoyl-2′-azido-2′,3′-dideoxyuridine (**9a**) was 62%. The structure of **9a** was established by the presence of the strong absorption band at 2170 cm^{-1} in the IR, characteristic for the N_3 function. The ^{1}H NMR displayed the loss of the 2,2′-anhydro linkage by observation of the small $J_{1',2'}$ value (1.1 Hz) and the diamagnetic shift of the H-1′ signal (5.81 ppm) of the product as compared to that of **8a** (6.16 ppm). The UV spectral behavior of the product was similar to that of 5′-*O*-benzoyluridine.[13b] De-*O*-benzoylation of **9a** in NH_3/MeOH afforded 2′-azido-2′,3′-dideoxyuridine (**1a**).

Halogenation of **9a** with either Br_2 or I_2 under oxidizing conditions[21] led to **9b** and **9c** in 88% and 86% yields, respectively. Evidence for introduction of halogen at C-5 of the pyrimidine ring is observed by the loss of the H-5 signal in the ^{1}H NMR of **9b** and **9c**. The sizable bathochromic shifts in the long-wavelength UV absorption maxima for these compounds also are consistent with the 5-substitution of the base.[22] Saponification of these nucleosides with NH_3/MeOH led to the desired nucleosides **1b** and **1c**.

For the synthesis of the thymine (AZT) analogue **1d**, 2′,3′-*O*-isopropylideneuridine (**3**) was used as the starting material. Hydroxymethylation of **3**, followed by hydro-

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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% yield[25] 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. ^{1}H 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 CH_2Cl_2/MeOH, liter 3, 9.85/0.15 CH_2Cl_2/MeOH) to yield 4.7 g (58%) of **11** after recrystallization from EtOH: mp 171–173 °C; ^{1}H NMR (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 ($C_{20}H_{22}N_2O_7$) 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 coevaportated twice with EtOH. The crude product was then chromatographed over flash silica gel employing gradient elution (liter 1, 98/2 CH_2Cl_2/MeOH; liter 2 to end, 9.6/0.4 CH_2Cl_2/MeOH) to yield 3.4 g (88%) of **5d**: mp 157–159 °C; ^{1}H NMR (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, $H_{2',3'}$), 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 ($C_{17}H_{18}N_2O_7$) C, H, N.

5'-*O*-Benzoyl-2,2'-anhydrouridine (6a). To a stirring solution of 5.0 g (0.014 mol) of **5a**[13] 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 °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 °C (lit.[27] mp 201–202.5 °C); ^{1}H NMR (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 ($C_{16}H_{14}N_2O_6 \cdot {}^1/_4H_2O$) 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 °C; ^{1}H NMR (DMSO-d_6) δ 1.74 (d, $J_{5\text{-Me},H_6}$ = 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 ($C_{17}H_{16}N_2O_6 \cdot {}^1/_4H_2O$) 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 °C dec; ^{1}H NMR (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 ($C_{20}H_{16}N_4O_6S$) 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 °C dec. The material was sufficiently pure to proceed to the next step. **7d**: ^{1}H NMR (DMSO-d_6) δ 1.76 (d, $J_{5\text{-Me},H_6}$ = 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 CH_2Cl_2/MeOH to yield 0.64 g (73%) of **8a** after recrystallization from EtOH: mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 2.35–2.87 (m, 2 H, 2 $H_{3'}$), 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 ($C_{16}H_{14}N_2O_5 \cdot {}^1/_2H_2O$) 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 °C; ^{1}H NMR ($CDCl_3$) δ 1.93 (d, $J_{5\text{-Me},H_6}$ = 1.37 Hz, 3 H, 5-CH_3), 2.34–2.85 (m, 2 H, 2 $H_{3'}$), 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 ($C_{17}H_{16}N_2O_5$) 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 CF_3CO_2H with stirring. The

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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 CH_2Cl_2/MeOH. After pooling of the correct fractions, an oil remained which crystallized from Et_2O. The crude product was then recrystallized from EtOH to yield 0.28 g (62%) of **9a**: mp 160–162 °C; ^1H NMR ($CDCl_3$) δ 1.91–2.14 (m, 2 H, 2 $H_{3'}$), 4.27–4.80 (m, 4 H, $H_{2'}$, $H_{4'}$, 2 $H_{5'}$), 5.49 (dd, $J_{5,6}$ = 8.23 Hz, $J_{5,NH}$ = 2.19 Hz, 1 H, H_5), 5.81 (d, $J_{1',2'}$ = 1.1 Hz, 1 H, $H_{1'}$), 7.32–8.07 (m, 6 H, Ar-H, H_6), 8.57 (br s, 1 H, NH); IR (KBr) 3010 (m), 2170 (s, N_3), 1750 (s, C=O), 1690 (vs, C=O), 1270 (vs), 1110 (s), 710 (s); UV (MeOH) λ_{max} 263 (ϵ 10500), 229 nm (15100). Anal. Calcd ($C_{16}H_{15}N_5O_5$) 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 HNO_3 and 0.19 g (1.2 mmol) of bromine in 1.4 mL of CCl_4. 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 $H_{3'}$), 4.30–4.75 (m, 4 H, $H_{2'}$, $H_{4'}$, 2 $H_{5'}$), 5.73 (d, $J_{1',2'}$ = 2.2 Hz, 1 H, $H_{1'}$), 7.35–8.10 (m, 6 H, Ar-H, H_6), 11.87 (br s, 1 H, NH exchangeable); IR (KBr) 3015 (m), 2170 (m, N_3), 1735 (vs, C=O), 1620 (m), 1270 (vs), 1130 (s), 705 (s). UV (MeOH) λ_{max} 279 (ϵ 8100), 227 nm (13800). Anal. Calcd ($C_{16}H_{14}N_5O_5Br \cdot {}^1/_4H_2O$) 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 I_2 for Br_2) 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 $H_{3'}$), 4.36–4.71 (m, 4 H, $H_{2'}$, $H_{4'}$, 2 $H_{5'}$), 5.72 (d, $J_{1',2'}$ = 2.19 Hz, 1 H, $H_{1'}$), 7.41–8.06 (m, 6 H, Ar-H, H_6), 11.78 (br s, 1 H, NH exchangeable); IR (KBr) 3010 (m), 2140 (m, N_3), 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 (17600). Anal. Calcd ($C_{16}H_{14}N_5O_5I \cdot {}^1/_5H_2O$) 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 ($CDCl_3$) δ 1.66 (d, J = 1.1 Hz, 3 H, 5-Me), 1.95–2.37 (m, 2 H, 2 $H_{3'}$), 4.27–4.85 (m, 4 H, $H_{2'}$, $H_{4'}$, 2 $H_{5'}$), 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, N_3), 1740 (s, C=O), 1700 (s, C=O), 1680 (s, C=O), 1270 (s). UV (MeOH), λ_{max} 268 (ϵ 10000), 226 nm (15500). Anal. Calcd ($C_{17}H_{17}N_5O_5$) 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 allow 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 $H_{3'}$), 3.32–3.92 (m, 2 H, 2 $H_{5'}$), 3.97–4.33 (m, 1 H, $H_{4'}$), 4.37–4.57 (m, 1 H, $H_{2'}$), 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, H_5), 5.74 (d, $J_{1',2'}$ = 1.92 Hz, 1 H, $H_{1'}$), 7.98 (d, $J_{6,5}$ = 8.23 Hz, 1 H, H_6), 11.35 (br s, 1 H, NH exchangeable); IR (KBr) 3600 (m), 3500–3000 (br, OH), 2140 (s, N_3), 1700 (vs, C=O), 1470 (m), 1270 (s), 1125 (s); UV (EtOH) λ_{max} 263 nm (ϵ 10000). Anal. Calcd ($C_9H_{11}N_5O_4 \cdot {}^1/_8H_2O$) 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 CH_2Cl_2/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 $H_{3'}$), 3.35–4.00 (m, 2 H, 2 $H_{5'}$), 4.10–4.37 (m, 1 H, $H_{4'}$), 4.42–4.60 (m, 1 H, $H_{2'}$), 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, H_6), 11.82 (br s, 1 H, NH exchangeable); IR (KBr) 3500 (m), 3700–2800 (br, OH), 2130 (s, N_3), 1700 (vs, C=O), 1450, (m), 1270 (s), 1120 (s). UV (EtOH) λ_{max} 280 (ϵ 8800). Anal. Calcd ($C_9H_{10}N_5O_4Br$) 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 CH_2Cl_2/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/CH_2Cl_2 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 $H_{3'}$), 3.35–3.95 (m, 2 H, 2 $H_{5'}$), 4.08–4.36 (m, 1 H, $H_{4'}$), 4.40–4.55 (m, 1 H, $H_{2'}$), 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, H_6), 11.71 (br s, 1 H, NH exchangeable); IR (KBr) 3600 (m), 3600–2700 (br, OH), 2160 (s, N_3), 1700 (vs, C=O), 1450 (m), 1270 (s), 1125 (s); UV (EtOH) λ_{max} 285 nm (ϵ 7500). Anal. Calcd ($C_9H_{10}N_5O_4I \cdot {}^1/_5H_2O$) 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-H^6} = 0.83 Hz, 3 H, 5-CH_3), 1.78–2.39 (m, 2 H, 2 $H_{3'}$), 3.36–3.92 (m, 2 H, 2 $H_{5'}$), 4.00–4.33 (m, 1 H, $H_{4'}$), 4.33–4.56 (m, 1 H, $H_{2'}$), 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, N_3), 1710 (vs, C=O), 1675 (vs, C=O), 1275 (m), 1220 (m), 1100 (s). UV (EtOH) λ_{max} 267 (ϵ 9400). Anal. Calcd ($C_{10}H_{13}N_5O_4$) C, H, N.

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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.