A Novel Synthesis of 3'-Deoxy-3'-nitrothymidine *via* Nucleophilic Substitution with Nitrite Anion

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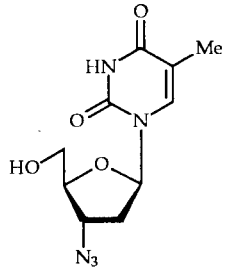
Received October 22, 1994

Nucleophilic substitution at C3' of 1-(2-deoxy-5-*O*-trityl-β-D-*erythro*-pentofuranosyl)-2-methoxy-5-methyl-4(1*H*)-pyrimidinone (**5**) with methyl iodide/triphenylphosphine/diethyl azodicarboxylate gave the expected inverted iodide **6** and minor epimer **7**. Treatment of **6** with lithium nitrite/phloroglucinol yielded the desired nitro derivative **8** and subsequent acidic deprotection afforded the title compound **1**. This represents a novel method for the introduction of a nitro group into the furanosyl moiety of a nucleoside. The nmr spectroscopic techniques (COSY, NOESY, nOe, HMQC and HMBC) were used to determine the stereochemistry at C3' of the nucleosides. Spectral analysis of H-D exchange at the 3'-position of **1** did not indicate the formation of its epimer **10**.

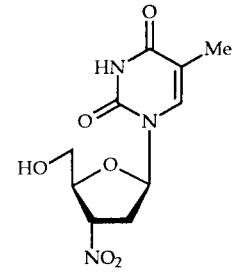
J. Heterocyclic Chem., **32**, 691 (1995).

3'-Azido-3'-deoxythymidine (AZT, zidovudine) is an inhibitor of the reverse transcriptase (RT) of HIV-1 (Human Immunodeficiency Virus type 1), the virus that causes AIDS [1,2]. The nucleoside is metabolized to the triphosphate, which then inhibits the enzyme. Incorporation of the 5'-monophosphate terminates nascent viral DNA. In one crystal and molecular structural study, the azido atoms in AZT were found to be nonlinear and were postulated to occupy the same space as the two oxygen atoms of thymidine 3'-phosphate [3]. Based on these findings and the known delocalization of π-electrons in the azido function of AZT (C3'-N$^-$-N$^+$≡N ↔ C3'-N=N$^+$=N$^-$), 3'-deoxy-3'-nitrothymidine (**1**) can be envisioned as another potential RT inhibitor. The nitro group of **1** contains similar delocalization of π-electrons over the nitrogen and oxygen atoms, and, although the nitro functional group would not occupy an identical space, the calculated volumes [4] of model compounds CH_3NO_2 (48.3 Å^3) and CH_3N_3 (54.8 Å^3) are comparable. The synthesis of **1** is the subject of this paper. During the preparation of our manuscript, a publication of compound **1** appeared in which the synthesis involved oxidation of an appropriately protected 3'-amino- or 3'-oximino-3'-deoxythymidine or coupling of a 3-nitrosugar with persilylated thymine [5]. The 3'-*erythro* stereochemistry of **1** was determined by comparison with the oxidation product obtained from the well characterized 3'-amino-3'-deoxythymidine. The current work, in contrast, undertakes a different synthetic approach and utilizes nmr spectroscopic techniques for characterization of the stereochemistry.

Nitrocarbohydrate chemistry is well established [6-8]. Synthetic methods include condensation of carbohydrate dialdehydes with nitromethane [6], formation of carbohydrate rings from nitroalkanes [7], and, most commonly, introduction of a nitro group to carbohydrates by sequential oxidation of a hydroxyl group, conversion to the oxime and eventual oxidation with 90% hydrogen peroxide (or the derived trifluoroperacetic acid), a chemical that is considered explosive and no longer commerically available [8]. Oxidations with 70% hydrogen peroxide or with perbenzoic acid are unsuccessful [8d]. Failure of the direct introduction of a nitro group by nucleophilic substitution of the iodide or tosylate of a nucleoside with nitrite ion has been reported [9]. Likewise, no one has attempted to perform S_N2 reactions on furanoses.



AZT



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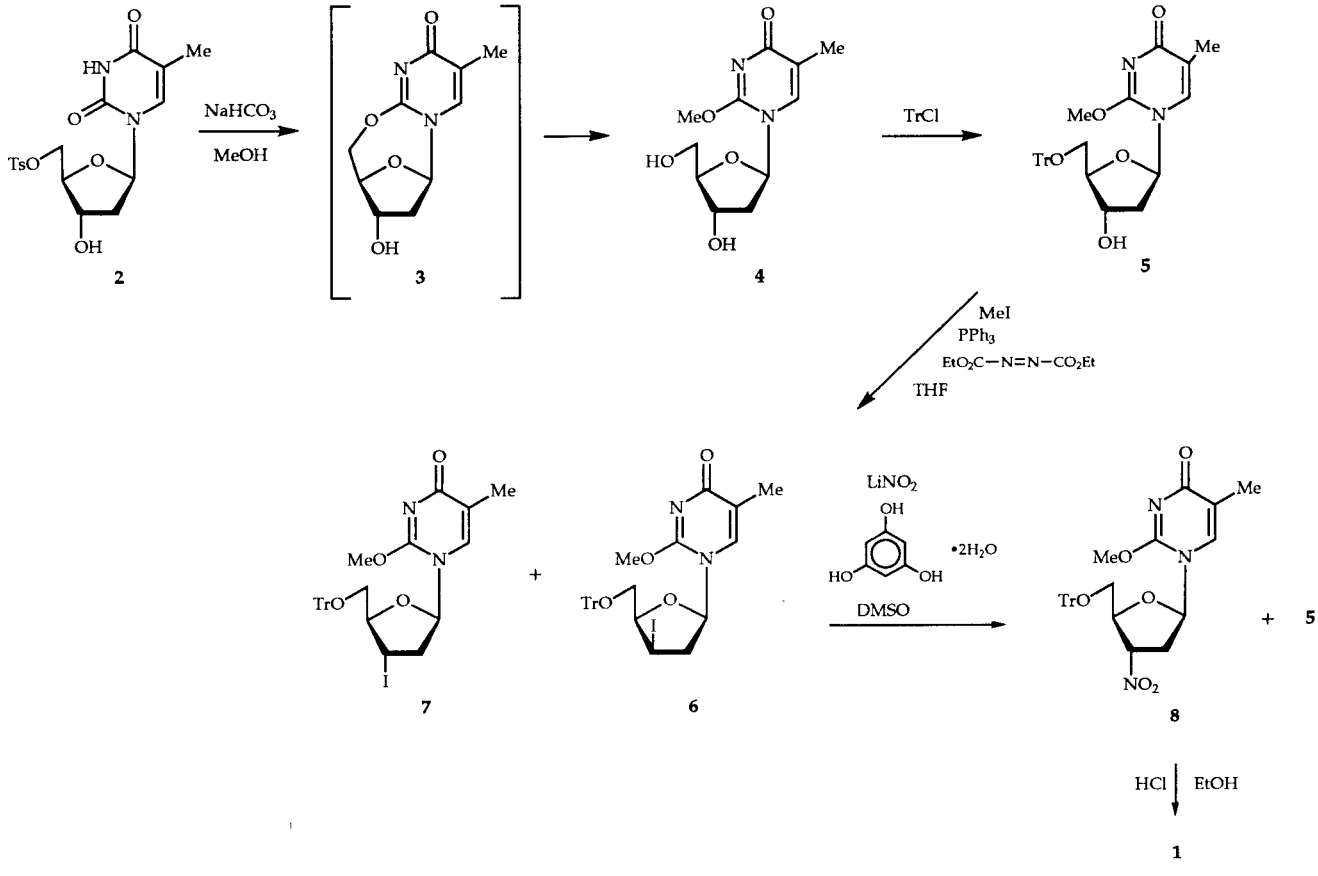
The synthetic strategy of this report utilizes two consecutive nucleophilic substitutions with configurational inversion at the C3'-atom of an appropriately protected thymidine. As shown in Scheme 1, 5'-*O*-tosylthymidine (**2**) [10] was treated with sodium bicarbonate in refluxing methanol to give 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-2-methoxy-5-methyl-4(1*H*)-pyrimidinone (**4**) [11] in 83% yield, presumably *via* cyclic iminoether **3** [12]. The elimination of the acidic *N*3-H of the pyrimidine moiety was to prevent base-catalyzed 2,3'-*O*-anhydro formation in future reactions. To protect the primary OH group at the C5' of the furanose moiety, **4** was tritylated. The resulting nucleoside **5** (64% yield) was reacted with methyl iodide, triphenylphosphine, and diethyl azodicarboxylate (modified Mitsunobu reaction) [13] to afford the 3'-iodo derivatives **6** and **7** (5:1) in 72% yield.

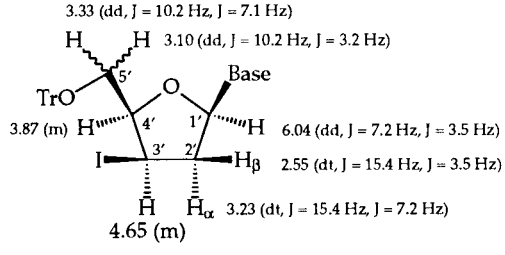
To determine the structures of the epimeric **6** and **7**, COSY, HMQC (proton-detected heteronuclear chemical shift correlation) [14] and HMBC (two-dimensional long-

Scheme 1



range heteronuclear multiple-bond shift correlation) [15] experiments were undertaken to facilitate the complete nmr spectral assignments (Figure 1). Irradiation of H-1' of **6** resonating at δ 6.04 gave 0.4% nuclear Overhauser effect (nOe) to H-3' resonating at δ 4.65, suggesting that H-1' and H-3' were on the same side of the furanose ring; therefore the C3'-*threo* configuration of the thymidine derivative **6** was established. Consequently, the *erythro* configuration was assigned to its epimer **7**, for which irradiation of H-5' resonating at δ 3.30 gave an nOe to H-3' resonating at δ 4.52, as expected. It is reasonable that the nucleophile iodide ion also attacked from the less sterically hindered α-face of the furanose ring to form **7** in the reaction.

The *threo*-3'-iodo derivative **6** was then treated with lithium nitrite in the presence of phloroglucinol (1,3,5-benzenetriol) [16] to give the desired *erythro*-3'-nitro derivative **8** in 36% yield. The infrared spectrum of **8** supports the formation of a C-N bond and the presence of a nitro function (1380 and 1540 cm^{-1}). While the major product formed was the inverted nucleoside **8**, a minor component also was isolated and identified as *erythro*-3'-hydroxylated nucleoside **5** (7% yield). Compound **5** apparently arises from the corresponding unstable 3'-*erythro*-nitrite ester



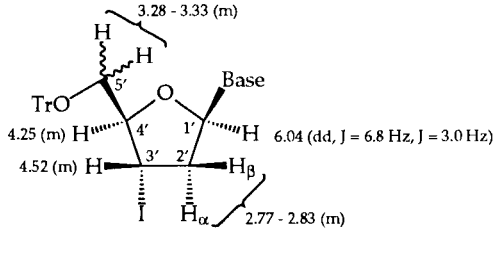
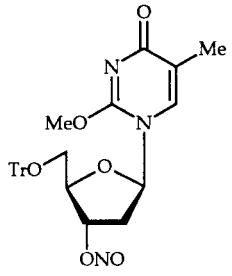


Figure 1. ^1H NMR of **6** and **7** in DMSO-d_6, expressed in δ (ppm) downfield from tetramethylsilane.

intermediate **9**, which in turn is formed as a result of attack by the oxygen atom of the ambident nucleophile NO_2^-. In the present study, reaction in the absence of phloroglucinol gave *only* the alcohol **5** [17].



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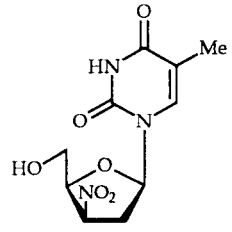
Treatment of the protected nitro derivative **8** with hydrochloric acid/ethanol cleaved both the trityl and methoxy groups to afford the target 3'-deoxy-3'-nitrothymidine (**1**) in 30% yield. The 3'-*erythro* stereochemistry of **1** was confirmed by nOe as follows (since H-3' in DMSO-d_6 overlapped the 5'-OH proton resonating at δ 5.32, deuterium oxide was added to eliminate the 5'-OH proton resonance): irradiation of H-5' resonating at δ 3.67 gave 8.6% nOe to H-3', confirming that H-3' was located at the same side of the furanose ring as H-5', thereby supporting the *erythro* configuration at C3'.

The ^{1}H nmr spectral data of 3'-deoxy-3'-nitrothymidine (**1**) obtained in DMSO-d_6 with added deuterium oxide showed an expected conversion of the coupling pattern associated with 5'-CH_2 at δ 3.67 from a doublet of doublets ($J_{5',OH}$ = 5.2 Hz, $J_{5',4'}$ = 3.7 Hz) to a simple doublet ($J_{5',4'}$ = 3.7 Hz). The resultant DMSO-d_6/deuterium oxide solution was allowed to stand for six months and H-3' was found, as a result of the electron-withdrawing nature of the nitro group, to be sufficiently acidic [18] to have slowly exchanged with deuterium oxide. Proton chemical shifts were identical within experimental error. Integrations were nominally unchanged with the exception of H-3' (δ 5.32), which now integrated for 0.3 proton, indicative of 70% deuterium exchange. The H-4' resonance was observed as a "triplet" superimposed over an apparent weak quartet; the former arose from the 3'D species and the latter derived from the 3'H species. Likewise, the H-2'α and H-2'β resonances also reflected the partial deuterium exchange at the 3'-position. In principle, racemization could have occurred at the C3' chiral center to form a mixture of deuterated **1** and its epimer **10**. Significant ^{1}H nmr spectral differences found in the 3'-epimers such as iodides **6** and **7** would also be expected for nitro compounds **1** and **10**. As evident in Figure 1, the H-3' proton of **7** resonates at a higher field (0.1 ppm) than does the corresponding proton of **6** while the reverse relationship is observed for the adjacent H-4' proton (0.4 ppm). In addition, most noticeably the chemical shifts of H-2'α and H-2'β that are well resolved for **6** (0.7 ppm) merge to cover a 0.1 ppm range for **7**. The spectrum of **1**, however, reveals no evidence of formation of the epimerization product **10**. Furthermore, although the mechanism of H-D exchange was not investigated, the results suggest that the 3'-*erythro* nitro nucleoside **1** is thermodynamically preferred over the 3'-*threo* stereoisomer **10**.



10

The antiviral activity of 3'-deoxy-3'-nitrothymidine (**1**) was assessed in a cell protection assay where HIV-1 causes cytopathic effects to MT4 cells [19]. At concentrations up to 200 μ*M*, **1** did not inhibit viral cell killing in this cell system. This is in accord with literature reports [5] that **1** has minimal activity against HIV.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. The nmr spectra of COSY, NOSEY, nOe, HMQC, and HMBC were acquired on a Varian Unity 400 with a Nalorac Cryogenic Corp Z•SPEC™ MD-400-3 3-mm Micro Dual probe. Chemical shifts are reported as δ (ppm) downfield from tetramethylsilane. Chemical ionization (using methane as initiator) mass spectra were performed by Oneida Research Services, Inc., Whitesboro, NY. Ultraviolet spectra were obtained on a Beckman DU-70 spectrophotometer.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-2-methoxy-5-methyl-4(1*H*)-pyrimidinone (**4**).

A mixture of 35 g (88.3 mmoles) of 5'-*O*-tosylthymidine (**2**) [10] and 11.1 g (132 mmoles) of sodium bicarbonate in 800 ml of methanol was heated at reflux overnight. The mixture was filtered and the filtrate was concentrated to 200 ml. After neutralization with 1 N hydrochloric acid, the mixture was evaporated under reduced pressure, and the residue was chromatographed on silica gel eluted with chloroform followed by chloroform: methanol/95:5, 9:1, and 8:2. The desired fractions were combined and evaporated to give 18.8 g (83%) of **4**, mp 144-147° (lit [7a] mp 143-144°); ^{1}H nmr (DMSO-d_6): δ 1.78 (s, 3H, 5-Me), 2.12-2.17 (m, 2H, H-2'), 3.47-3.66 (m, 2H, H-5'), 3.7-3.8 (m, 1H, H-4'), 3.86 (s, 3H, 2-OMe), 4.19-4.27 (m, 1H, H-3'), 5.03 (t, J = 5.0 Hz, 1H, 5'-OH), 5.26 (d, J = 4.3 Hz, 1H, 3'-OH), 6.08 (t, J = 6.6 Hz, 1H, H-1'), 7.80 (s, 1H, H-6) [20]; uv (*p*H 1): λ max

259 nm (ε 9000), λ min 237 nm (ε 5300); uv (*p*H 13): λ max 257 nm (ε 10000), λ min 239 nm (ε 7400).

Anal. Calcd. for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.45; H, 6.26; N, 10.91.

1-(2-Deoxy-5-*O*-trityl-β-D-*erythro*-pentofuranosyl)-2-methoxy-5-methyl-4(1*H*)-pyrimidinone (**5**).

To a mixture of 9.0 g (35 mmoles) of **4** and 20 g of 3Å molecular sieves in 400 ml of dichloromethane were added 13.7 g (49.1 mmoles) of trityl chloride and 5 g (49.4 mmoles) of triethylamine. After stirring at room temperature overnight, the mixture was filtered. The dichloromethane filtrate was washed with water and evaporated *in vacuo*. The residue was then chromatographed on silica gel eluted with chloroform:methanol/98:2 then 95:5 to give 12.2 g (64%) of crude **5** as a solid; ^{1}H nmr (DMSO-d_6): δ 1.50 (s, 3H, 5-Me), 2.15-2.35 (m, 2H, H-2'), 3.13-3.25 (m, 2H, H-5'), 3.85 (s, 3H, 2-OMe), 3.85-3.95 (m, 1H, H-4'), 4.27-4.35 (m, 1H, H-3'), 5.36 (d, J = 5.4 Hz, 1H, 3'-OH), 6.11 (t, J = 6.5 Hz, 1H, H-1'), 7.2-7.4 (m, 15H, three phenyls), 7.60 (s, 1H, H-6).

1-(2,3-Dideoxy-3-iodo-5-*O*-trityl-β-D-*threo*-pentofuranosyl)-2-methoxy-5-methyl-4(1*H*)-pyrimidinone (**6**) and 1-(2,3-Dideoxy-3-iodo-5-*O*-trityl-β-D-*erythro*-pentofuranosyl)-2-methoxy-5-methyl-4(1*H*)-pyrimidinone (**7**).

To a solution of 12.2 g (24.5 mmoles) of **5** in 150 ml of THF were successively added 15.6 g (29.7 mmoles) of triphenylphosphine, 11 g (63.2 mmoles) of diethyl azodicarboxylate, and 9.2 g (64.8 mmoles) of methyl iodide. After stirring at room temperature overnight, methanol (50 ml) was added, and the resulting solution was evaporated to dryness. The residue was chromatographed on silica gel eluted with ethyl acetate:methanol/95:5 to give crude **7** followed by crude **6**. Further column chromatography under the same conditions gave 1.8 g (12%) of **7** and 8.9 g (60%) of **6**, respectively.

Iodide **6** had mp 173-176°; ^{1}H nmr (DMSO-d_6): δ 1.65 (d, $J_{6,Me}$ = 1.1 Hz, 3H, 5-Me), 2.55 (dt, $J_{2'\alpha,2'\beta}$ = 15.4 Hz, $J_{2'\beta,1'}$ = $J_{2'\beta,3'}$ = 3.5 Hz, 1H, H-2'β), 3.10 (dd, $J_{5'a,5'b}$ = 10.2 Hz, $J_{4',5'a}$ = 3.2 Hz, 1H, H-5'a), 3.23 (dt, $J_{2'\alpha,2'\beta}$ = 15.4 Hz, $J_{2'\alpha,1'}$ = $J_{2'\alpha,3'}$ = 7.2 Hz, 1H, H-2'α), 3.33 (dd, $J_{5'a,5'b}$ = 10.2 Hz, $J_{4',5'b}$ = 7.1 Hz, 1H, H-5'b), 3.86 (s, 3H, 2-OMe), 3.87 (m, $J_{3',4'}$ = 4.2 Hz by decoupling with H-5', 1H, H-4'), 4.62-4.67 (m, 1H, H-3'), 6.04 (dd, $J_{1',2'\alpha}$ = 7.2 Hz, $J_{1',2'\beta}$ = 3.5 Hz, 1H, H-1'), 7.25-7.44 (m, 15H, three phenyls), 7.59 (q, $J_{6,Me}$ = 1.1 Hz, 1H, H-6); ^{13}C nmr (DMSO-d_6): δ 13.4 (5-Me), 23.0 (C3'), 43.7 (C2'), 55.4, (2-OMe), 69.7 (C5'), 80.8 (C4'), 86.2 (C1'), 86.5 (C-Tr), 115.0 (C5), 127.3 (C1 of Ph), 128.0 (Ph), 128.4 (Ph), 133.9 (C6), 143.3 (C4 of Ph), 154.8 (C2), 170.3 (C4); uv (*p*H 1): λ max 256 nm (ε 17500), λ min 249 nm (ε 12800); uv (*p*H 13): λ max 260 nm (ε 13500).

Anal. Calcd. for $C_{30}H_{29}N_2O_4I$; C, 59.22; H, 4.80; N, 4.60; I, 20.86. Found: C, 59.10; H, 5.12; N, 4.52, I, 20.79.

Iodide **7** had mp 109°; ^{1}H nmr (DMSO-d_6): δ 1.56 (d, $J_{6,Me}$ = 0.8 Hz, 3H, 5-Me), 2.77-2.83 (m, 2H, H-2'), 3.28-3.33 (m, 2H, H-5'), 3.86 (s, 3H, 2-OMe), 4.20-4.30 (m, $J_{3',4'}$ = 9.4 Hz by decoupling with H-5', 1H, H-4'), 4.45-4.60 (m, 1H, H-3'), 6.04 (dd, J = 6.8 Hz, J = 3.0 Hz, 1H, H-1'), 7.2-7.4 (m, 15H, three phenyls), 7.69 (q, $J_{6,Me}$ = 0.8 Hz, 1H, H-6); uv (ethanol): λ max 255 nm (ε 11700), λ min 246 nm (ε 11000), sh 230 nm (ε 17500); uv (*p*H 1): λ max 259 nm (ε 14700), λ min 242 nm (ε 12400); uv (*p*H 13): λ max 217 nm (ε 76400), sh 259 nm (ε 21100).

Anal. Calcd. for $C_{30}H_{29}N_2O_4I$•0.2 $C_4H_8O_2$: C, 59.09; H, 4.93; N, 4.47; I, 20.27. Found: C, 59.12; H, 5.11; N, 4.46; I, 20.24. [The presence of a small amount of ethyl acetate in this sample was apparent from the ^{1}H nmr spectrum δ 1.16 (t, 3H), 1.97 (s, 3H), 4.05 (q, 2H).]

1-(2,3-Dideoxy-3-nitro-5-*O*-trityl-β-D-*erythro*-pentofuranosyl)-2-methoxy-5-methyl-4(1*H*)-pyrimidinone (**8**).

A mixture of 1.0 g (1.64 mmoles) of **6**, 180 mg (3.4 mmoles) of lithium nitrite, and 550 mg (3.4 mmoles) of phloroglucinol dihydrate in 8 ml of DMSO was stirred at room temperature for 3 days. The reaction was poured onto water, and the precipitate was collected by filtration. (Material remaining in the filtrate was not pursued.) The solid was partitioned between ethyl acetate and water. The organic phase was separated, dried over magnesium sulfate, and evaporated to dryness. The residue was chromatographed on silica gel eluted with ethyl acetate followed by ethyl acetate:methanol/98:2 to give 0.36 g (36%) of **8** and then 60 mg (7%) of **5**.

Compound **8** had mp 78°; ir (nujol): 1630 cm^{-1} (C=O), 1540, 1380 (C-NO_2); ^{1}H nmr (DMSO-d_6): δ 1.55 (d, $J_{6,Me}$ = 1 Hz, 3H, 5-Me), 2.6-2.8 (m, 1H, H-2'a), 3.0-3.25 (m, 1H, H-2'b), 3.3-3.4 (m, 2H, H-5'), 3.84 (s, 3H, 2-OMe), 4.5-4.6 (m, 1H, H-4'), 5.4-5.5 (m, 1H, H-3'), 6.21 (d, J = 7 Hz, 1H, H-1'), 7.2-7.4 (m, 15H, three phenyls), 7.62 (q, J = 1 Hz, 1H, H-6); uv (ethanol): λ max 217 nm (ε 69100), λ min 251 nm (ε 17400); uv (*p*H 1): λ max 258 nm (ε 10300), λ min 240 nm (ε 8000); uv (*p*H 13): λ max 250 nm (ε 10800).

Anal. Calcd. for $C_{30}H_{29}N_3O_6$•0.5 $C_4H_8O_2$: C, 67.24; H, 5.82; N, 7.35. Found: C, 67.06; H, 5.65; N, 7.19. [The presence of ethylacetate in this sample was apparent from the ^{1}H nmr spectrum δ 1.16 (t, 3H), 1.97 (s, 3H), 4.05 (q, 2H).]

3'-Deoxy-3'-nitrothymidine (**1**).

A solution of 0.4 g (0.76 mmoles) of **8** and four drops of concentrated hydrochloric acid in 10 ml of ethanol was heated at 80° for 40 minutes. After neutralization with 1 *N* sodium hydroxide, the solution was evaporated under reduced pressure. The residue was chromatographed on silica gel eluted with ethyl acetate to afford 40 mg (30%) of **1**, mp 152-154°; cims: m/z 272 (MH^+); ^{1}H nmr (DMSO-d_6): δ 1.76 (d, $J_{6,Me}$ = 1.2 Hz, 3H, 5-Me), 2.47 (ddd, $J_{2'\alpha,2'\beta}$ = 14.8 Hz, $J_{2'\beta,3'}$ = 8.3 Hz, $J_{2'\beta,1'}$ = 8.1 Hz, 1H, H-2'β), 2.87 (ddd, $J_{2'\alpha,2'\beta}$ = 14.8 Hz, $J_{2'\alpha,1'}$ = 6.3 Hz, $J_{2'\alpha,3'}$ = 2.8 Hz, 1H, H-2'α), 3.67 (dd, $J_{5',OH}$ = 5.2 Hz, $J_{5',4'}$ = 3.7 Hz, 2H, H-5'), 4.40 (apparent q, $J_{3',4'}$ = $J_{4',5'}$ = 3.7 Hz, 1H, H-4'), 5.30-5.34 (m, 2H, H-3' and 5'-OH), 6.27 (dd, $J_{1',2'\beta}$ = 8.1 Hz, $J_{1',2'\alpha}$ = 6.3 Hz, 1H, H-1'), 7.67 (q, $J_{6,Me}$ = 1.2 Hz, 1H, H-6), 11.35 (s, 1H, NH); ^{1}H nmr (deuterium oxide): δ 1.76 (d, J = 1.3 Hz, 3H, 5-Me), 2.45-2.57 (m, 1H, H-2'a), 2.96-3.03 (m, 1H, H-2'b), 3.78 (m, 2H, H-5'), 4.49 (q, J = 3.8 Hz, 1H, H-4'), 5.23-5.28 (m, 1H, H-3'), 6.25 (dd, J = 7.6 Hz, J = 6.6 Hz, 1H, H-1'), 7.53 (q, J = 1.3 Hz, H-6) [21]; ^{13}C nmr (DMSO-d_6): δ 12.3 (5-Me), 35.1 (C-2'), 61.6 (C-5'), 82.9 (C-4'), 84.0 (C-1'), 85.5 (C-3'), 109.9 (C-5), 135.9 (C-6), 150.5 (C-2), 163.7 (C-4); uv (ethanol): λ max 264 nm (ε 9500), λ min 233 nm (ε 2500); uv (*p*H 1): λ max 265 nm (ε 9300), λ min 234 nm (ε 2300); uv (*p*H 13): λ max 218 nm (ε 37900), sh 262 nm (ε 10700).

Anal. Calcd. for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49. Found: C, 44.04; H, 4.90; N, 15.37.

Acknowledgment.

Dr. J. A. Bentley is thanked for determining the volumes of methyl azide and nitromethane, M. H. St. Clair for HIV-1 data; D. Minick for obtaining infrared spectra; G. A. Freeman, S. R.

Shaver, and J. Kelly-Hart for technical assistance; and D. Tabon Staton for the structural drawings and artwork. Many helpful suggestions provided by Drs. C. W. Andrews, M. Cory, G. E. Martin, and A. Spaltenstein during the preparation of this manuscript are also gratefully acknowledged.

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