Nucleic Acid Related Compounds. 107. Efficient Nitration of Uracil Base and Nucleoside Derivatives[1]

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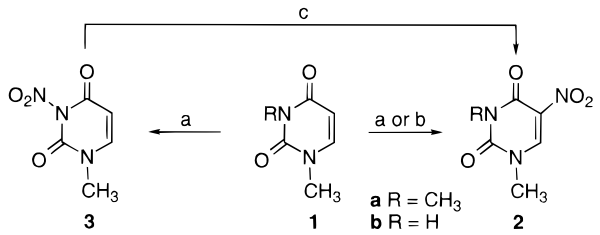
Introduction

The 5′-phosphate ester of 5-nitro-2′-deoxyuridine (**7c**) is a potent mechanism-based inhibitor of thymidylate synthase.[2] Compound **7c**[3] and 1-(β-D-arabinofuranosyl)-5-nitrouracil[4] have antiviral activity, and certain *O*-nitro esters of pyrimidine[5] and purine[6] nucleosides also have biological activity. The 5′-*O*-nitro esters of pyrimidine nucleosides function as good substrates for 5′-modification via S_N2 displacement of nitrate and other transformations.[7,8] Recently, we used 6′-*O*-nitro esters of 2′-substituted homonucleosides to generate 6′-oxyl radicals, which abstract H3′ by 1,5-hydrogen transfer to initiate radical cascade reactions analogous to processes postulated to occur at the active site of ribonucleotide reductases.[9] Reactions of *N*-nitro derivatives of uridine (N3) and inosine (N1) with $^{15}NH_3$ have been utilized to obtain [^{15}N]-nucleosides.[10]

The first synthesis of 5-nitrouridine employed nitration of 2′,3′,5′-tri-*O*-(3,5-dinitrobenzoyl)uridine with fuming nitric/sulfuric acid.[11] Treatment of uracil with nitronium tetrafluoroborate in sulfolane gave 5-nitrouracil in high yield, but uridine and 2′-deoxyuridine (and protected derivatives) failed to give their 5-nitro derivatives.[12] Analogous nitration ($NO_2^+BF_4^-$) of the 5′-phosphates of uridine and 2′-deoxyuridine (chromatographic separation from nitrate esters) and enzymatic dephosphorylation (alkaline phosphatase) gave 5-nitrouridine and 2′-deoxy-5-nitrouridine (∼25%).[12] Coupling of trimethylsilylated 5-nitrouracil with protected 2-deoxy-*erythro*-pentofuranosyl chlorides furnished the corresponding 2′-deoxy-5-nitrouridines in good yields,[13] but separation of anomers was required.[13b] Treatment of a 1,6-disubstituted uracil with nitric acid/acetic acid gave the 5-nitro derivative in 17% yield.[14]

Nitrations of uridine → 5′-*O*-nitrouridine (44%) and 2′-deoxyuridine → 2′-deoxy-5′-*O*-nitrouridine (20%) were effected with fuming nitric acid,[7a] and *O*-nitro esters were obtained with other 2′-deoxynucleosides.[7c,8] However, the strongly acidic conditions resulted in removal of protecting groups such as isopropylidene[7b] and silyl[6b] and gave variable product mixtures.[7] Acetyl nitrate (in situ generation with nitric acid and acetic anhydride) at low temperatures gave higher yields of the *O*-nitro esters,[5,6b,7b,9] but glycosyl cleavage occurred upon attempted nitration of homoadenosine.[9b] We now report efficient nitrations of uracil base and nucleoside derivatives.

Scheme 1[a]



[a] (a) $Cu(NO_3)_2 \cdot 3H_2O/Ac_2O$; (b) fuming HNO_3; (c) H_2SO_4.

Results and Discussion

Treatment of 1,3-dimethyluracil (**1a**) (Scheme 1) with copper(II) nitrate/acetic anhydride[15] at ambient temperature for 48 h gave 1,3-dimethyl-5-nitrouracil (**2a**, 90%). Similar treatment (4 h) of 1-methyluracil (**1b**) gave traces (∼5%, TLC) of 1-methyl-5-nitrouracil (**2b**), but 1-methyl-3-nitrouracil (**3**, 77%) was the major product. Rearrangement of **3** into its 5-nitro isomer **2b** (73%) occurred in concentrated sulfuric acid, and **3** was unstable in alkaline solution. The 5-nitro isomer **2b** (80%) was obtained directly from **1b** with fuming nitric acid.

Treatment of 2′,3′,5′-tri-*O*-acetyluridine (**4a**) with $Cu(NO_3)_2/Ac_2O$[15] gave 2′,3′,5′-tri-*O*-acetyl-3-nitrouridine

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(1) Paper 106: Robins, M. J.; Guo, Z.; Samano, M. C.; Wnuk, S. F. *J. Am. Chem. Soc.*, in press.

(2) (a) Wataya, Y.; Matsuda, A.; Santi, D. V. *J. Biol. Chem.* **1980**, *255*, 5538−5544. (b) Maggiora, L.; Chang, C. C. T.-C.; Torrence, P. F.; Mertes, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 3192−3198.

(3) (a) De Clercq, E.; Descamps, J.; Huang, G.-F.; Torrence, P. F. *Mol. Pharmacol.* **1978**, *14*, 422−430. (b) Washtien, W. L.; Santi, D. V. *J. Med. Chem.* **1982**, *25*, 1252−1255.

(4) Torrence, P. F.; Huang, G.-F.; Edwards, M. W.; Bhooshan, B.; Descamps, J.; De Clercq, E. *J. Med. Chem.* **1979**, *22*, 316−321.

(5) Chwang, T. L.; Fridland, A.; Avery, T. L. *J. Med. Chem.* **1983**, *26*, 280−283.

(6) (a) Chwang, T. L.; Fridland, A.; Verhoef, V. *Biochem. Pharmacol.* **1983**, *32*, 2643−2646. (b) Chwang, T. L.; Williams, R. D.; Schieber, J. E. *Tetrahedron Lett.* **1983**, *24*, 3183−3186.

(7) (a) Lichtenthaler, F. W.; Müller, H. J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 752−753. (b) Lichtenthaler, F. W.; Müller, H. J. *Synthesis* **1974**, 199−201. (c) Lichtenthaler, F. W. In *Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1978; Vol. 1, pp 391−399.

(8) (a) Duschinsky, R.; Eppenberger, U. *Tetrahedron Lett.* **1967**, 5103−5108. (b) Duschinsky, R. In *Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1978; Vol. 1, pp 295−297.

(9) (a) Robins, M. J.; Guo, Z.; Samano, M. C.; Wnuk, S. F. *J. Am. Chem. Soc.* **1996**, *118*, 11317−11318. (b) Robins, M. J.; Guo, Z.; Wnuk, S. F. *J. Am. Chem. Soc.* **1997**, *119*, 3637−3638.

(10) (a) Ariza, X.; Bou, V.; Vilarrasa, J. *J. Am. Chem. Soc.* **1995**, *117*, 3665−3673. (b) Ariza, X.; Farràs, J.; Serra, C.; Vilarrasa, J. *J. Org. Chem.* **1997**, *62*, 1547−1549.

(11) Wempen, I.; Doerr, I. L.; Kaplan, L.; Fox, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 1624−1629.

(12) Huang, G.-F.; Torrence, P. F. *J. Org. Chem.* **1977**, *42*, 3821−3824.

(13) (a) Hubbard, A. J.; Jones, A. S.; Walker, R. T. *Nucleic Acids Res.* **1984**, *12*, 6827−6837. (b) Rao, T. S.; Rando, R. F.; Huffman, J. H.; Revankar, G. R. *Nucleosides Nucleotides* **1995**, *14*, 1997−2008.

(14) Benhida, R.; Aubertin, A.-M.; Grierson, D. S.; Monneret, C. *Tetrahedron Lett.* **1996**, *37*, 1031−1034.

(15) Buchanan, J. G.; Edgar, A. R.; Hutchison, R. J.; Stobie, A.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2567−2571.

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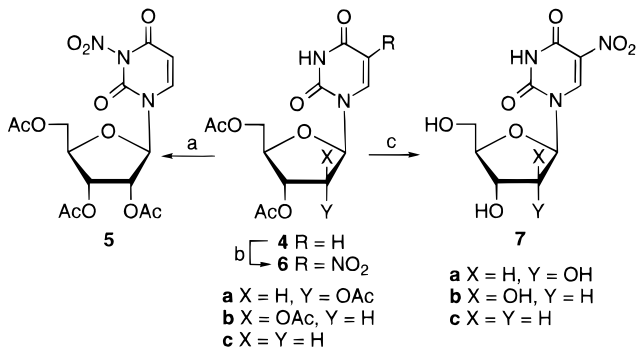
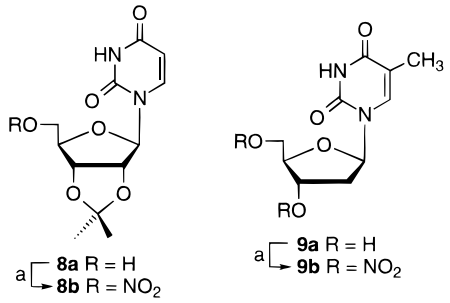
Scheme 2[a]



[a] (a) $Cu(NO_3)_2 \cdot 3H_2O/Ac_2O$; (b) 1-nitropyrazole/TfOH/MeCN; (c) NaOMe/MeOH.

Scheme 3[a]



[a] (a) 1-Nitropyrazole/TfOH/MeCN.

(**5**, quantitative) (Scheme 2). This method complements another procedure for *N*-nitration of nucleosides and amides, in which 1-nitroinosine and 3-nitrouridine derivatives were obtained from protected inosine and uridine with trifluoroacetyl nitrate.[10,16] Treatment of **5** with concentrated sulfuric acid did not produce the rearranged 5-nitrouridine product. Instead, decomposition of **5** occurred in this strong acid medium.

Olah's transfer nitration[17] [1-nitropyrazole (1.5 equiv)/triflic acid (1.5 equiv)/acetonitrile] gave essentially quantitative conversion of **4a** into 2′,3′,5′-tri-*O*-acetyl-5-nitrouridine (**6a**). Deacetylation (NaOMe/MeOH) gave 5-nitrouridine (**7a**, 78% from **4a**). Similar two-stage treatment of the acetylated arabinosyl **4b** and 2′-deoxy **4c** derivatives gave 1-(β-D-arabinofuranosyl)-5-nitrouracil (**7b**, 93%) and 2′-deoxy-5-nitrouridine (**7c**, 58%), respectively.

Analogous treatment of 2′,3′-*O*-isopropylideneuridine (**8a**) (Scheme 3) gave the 5′-*O*-nitro ester **8b** (73%), and thymidine (**9a**) gave 3′,5′-di-*O*-nitrothymidine (**9b**). However, uridine was converted into an unstable mixture (~1:1, ~60%) tentatively assigned as 2′,3′,5′-tri-*O*-nitrouridine and its 5-nitro derivative. Difficulties with purification of nucleoside *O*-nitro esters have been noted previously.[7c]

In summary, copper(II) nitrate/acetic anhydride effected nitration at N3 of uracil derivatives **1b** and **4a** or at C5 of **1a** (which contains a 3-methyl substituent). Treatment of the *N*-nitro heterocycle **3** with sulfuric acid resulted in its rearrangement to 1-methyl-5-nitrouracil (**2b**), but this strong acid treatment resulted in decomposition of the *N*-nitro nucleoside **5**. The Olah reagent gave essentially quantitative nitration at C5 with 2′,3′,5′-tri-*O*-acetyluridine (**4a** → **6a**), its arabinosyl epimer (**4b** → **6b**), and 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**4c** → **6c**) (although the acid-catalyzed glycosyl cleavage of **6c** reduced isolated yields). Deacetylation gave 5-nitrouridine (**7a**, 78%), 1-(β-D-arabinofuranosyl)uracil (**7b**, 93%), and 2′-deoxy-5-nitrouridine (**7c**, 58%) in efficient *overall* yields for the three-stage (acetylation, nitration, and deacetylation) sequences from readily available nucleosides. Olah's reagent effected clean conversion of 2′,3′-*O*-isopropylideneuridine (**8a**) and thymidine (**9a**) into the *O*-nitro esters **8b** and **9b**, respectively, but uridine was converted into an unstable mixture of nitrate esters.

Experimental Section

Uncorrected melting points were determined with a microstage block. UV spectra were determined with solutions in MeOH or in H_2O at pH ~2 (0.01 M HCl) and pH ~12 (0.01 M NaOH). ^1H NMR spectra (Me_4Si/Me_2SO-d_6) were determined at 200 MHz, and exchanged ("ex") protons (D_2O) are indicated. HRMS (EI) were determined at 70 eV. Reagent grade chemicals were used, and all solvents were redistilled. MeCN was dried by reflux over and distillation from P_4O_{10}. TLC (visualization with 254 nm light) solvents were S1 [EtOAc/PrOH/H_2O (4:1:2, upper phase), S2 [EtOAc/MeOH (19:1)], and S3 [$CHCl_3$/MeOH (6:1)]. Merck Kieselgel 60 (230−400 mesh) or Dowex 50W (H^+) resin was used for column chromatography. Trifluoromethanesulfonic acid (TfOH), 1-nitropyrazole, 1-methyluracil (**1b**), and 1,3-dimethyluracil (**1a**) are available from Aldrich. Acetylation (Ac_2O/DMAP[18]) of uridine, 1-(β-D-arabinofuranosyl)uracil, and 2′-deoxyuridine gave **4a**,[19] **4b**,[19] and **4c**[18] (quantitative yields) with data as reported. Elemental analyses were determined by the Microanalytical Laboratory at the University of Alberta.

1,3-Dimethyl-5-nitrouracil (2a). Procedure A. A mixture of $Cu(NO_3)_2 \cdot 3H_2O$ (200 mg, 0.83 mmol)/Ac_2O (1.5 mL) was stirred at ambient temperature for 1.5 h, **1a** (100 mg, 0.72 mmol) was added, and stirring was continued for 24 h. $Cu(NO_3)_2 \cdot 3H_2O$ (100 mg, 0.83 mmol) was added, stirring was continued for 24 h, and MeOH (10 mL) was added. After 30 min, volatiles were evaporated. The residue was partitioned (H_2O/$CHCl_3$), and the aqueous layer was extracted ($CHCl_3$, 2×). The combined organic phase was washed (H_2O) and dried ($MgSO_4$). Volatiles were evaporated, and the residue was recrystallized (EtOH) to give **2a** (100 mg, 75%): mp 159−160 °C (lit.[12] mp 158−159 °C); UV (pH 2) max 238, 309 nm (ε 8200, 10 000), min 221, 263 nm (ε 6300, 2500), (pH 12) max 324 nm (ε 17 200), min 265 nm (ε 4000); ^1H NMR δ 3.21 (s, 3H), 3.48 (s, 3H), 9.38 (s, 1H); MS *m*/*z* 185.0437 (100, M^+ = 158.0437). Anal. Calcd for $C_6H_7N_3O_4$: C, 38.93; H, 3.81; N, 22.70. Found: C, 38.79; H, 3.85; N, 22.54.

1-Methyl-3-nitrouracil (3). Treatment of **1b** (500 mg, 3.97 mmol) by procedure A [$Cu(NO_3)_2 \cdot 3H_2O$ (2 g)/Ac_2O (15 mL), 4 h] gave **3** plus a small amount [~5%, TLC (S1 and S3)] of 1-methyl-5-nitrouracil (**2b**). [The aqueous layer was back-extracted with $CHCl_3$ (5×) in order to obtain the noted high yields of **3**.] Recrystallization of the mixture (*i*-PrOH) gave **3** (520 mg, 77%, two crops): mp 100−102 °C; UV (MeOH) max 263 nm (ε 7100), min 230 nm (ε 2000); ^1H NMR δ 3.38 (s, 3H), 5.98 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H); MS *m*/*z* 171.0290 (8, M^+ = 171.0279). Anal. Calcd for $C_5H_5N_3O_4$: C, 35.10; H, 2.95; N, 24.56. Found: C, 34.96; H, 2.96; N, 24.51.

Compound **3** underwent rapid decomposition ($t_{1/2}$ < 2 min) at ambient temperature in aqueous solution at pH ~12.

1-Methyl-5-nitrouracil (2b). A solution of **3** (135 mg, 0.79 mmol) in H_2SO_4 (d = 1.84 g/mL, 1 mL) was allowed to stand at

(16) (a) Romea, P.; Aragonès, M.; Garcia, J.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 7038−7042. (b) Serra, C.; Aragonès, C.; Bessa, J.; Farràs, J.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 7575−7578.

(17) Olah, G. A.; Narang, S. C.; Fung, A. P. *J. Org. Chem.* **1981**, *46*, 2706−2709.

(18) Robins, M. J.; MacCoss, M.; Naik, S. R.; Ramani, G. In *Nucleic Acid Chemistry: Improved and New Synthetic Procedure, Methods and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1986; Vol. 3, pp 58−60.

(19) Brown, D. M.; Todd, A.; Varadarajan, S. *J. Chem. Soc.* **1956**, 2388−2393.

ambient temperature for 30 min [TLC (S3) showed complete conversion of **3** to **2b** plus a small amount of 1-methyluracil (**1b**, < 10%)]. The solution was added *cautiously* to H_2O (10 mL), and this solution was applied to a Dowex 1 × 2 (AcO^-) column. The column was eluted with H_2O, the eluate was concentrated (~5 mL), EtOH (2 mL) was added, and the solution was cooled (~0 °C) overnight to give **2b** (99 mg, 73%): mp 266−267 °C (lit.[12] mp 264−265 °C); UV (pH 2) max 241, 310 nm (ϵ 6600, 9700), min 216, 263 nm (ϵ 3700, 2300), (pH 12) max 325 nm (ϵ 9200), min 271 nm (ϵ 3400); ^{1}H NMR δ 3.41 (s, 3H), 9.32 (s, 1H), 12.02 (br s, 1H, ex); MS *m*/*z* 171.0278 (100, M^+ = 171.0279). Anal. Calcd for $C_5H_5N_3O_4 \cdot H_2O$: C, 31.75; H, 3.73; N, 22.22. Found: C, 31.60; H, 3.79; N, 22.08.

Treatment of **1b** with fuming nitric acid (d = 1.51 g/mL, 4.5 equiv) at ambient temperature for 30 min gave **2b** (85%) with identical data.

2′,3′,5′-Tri-*O*-acetyl-3-nitrouridine (5). Treatment of **4a** (3.7 g, 10 mmol) by procedure A [$Cu(NO_3)_2 \cdot 3H_2O$ (6 g)/Ac_2O (45 mL), 4 h; organic phase ($CHCl_3$) was washed additionally with 2% EDTA/H_2O] gave a colorless oil that was dissolved (benzene) and lyophillized to give **5** (4.14 g, quantitative): UV (MeOH) max 255 nm (ϵ 7200), sh 320 nm (ϵ 1000), min 227 nm (ϵ 3500); ^{1}H NMR δ 2.04, 2.06, 2.08 (3 × s, 3 × 3H), 4.32 (m, 3H), 5.36 (m, 1H), 5.60 (dd, J = 4.0, 6.0 Hz, 1H), 5.94 (d, J = 4.0 Hz, 1H), 6.17 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H); MS *m*/*z* 369.0926 (1, $[M - NO_2]^+$ = 369.0934), 259.0816 (70, $[sugar]^+$ = 259.0818), 158.0187 (1, $[BH_2]^+$ = 158.0202); and other data as reported.[10a]

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-nitrouracil (6b). Procedure B. Triflic acid (0.66 mL, 1.13 g, 7.5 mmol) was added slowly to a solution of **4b** (1.85 g, 5 mmol) and 1-nitropyrazole (847 mg, 7.5 mmol) in dried MeCN (75 mL) at ambient temperature. Stirring was continued for 72 h [TLC (S1) after 24 h showed ~20% **4b**], volatiles were evaporated, and the residue was dissolved ($CHCl_3$). The solution was washed (H_2O) and dried (Na_2SO_4), and volatiles were evaporated. The residual oil was crystallized (EtOH/*i*-PrOH, 10:1, two crops) to give **6b** (1.98 g, 96%): mp 164−166 °C; UV (MeOH) max 235, 295 nm (ϵ 7800, 8800), min 217, 257 nm (ϵ 6200, 3300); ^{1}H NMR δ 2.00, 2.10, 2.12 (3 × s, 3 × 3H), 4.37 (m, 3H), 5.23 (m, 1H), 5.44 (dd, J = 4.5, 3.0 Hz, 1H), 6.28 (d, J = 4.5 Hz, 1H), 8.88 (s, 1H), 12.3 (br s, 1H, ex); MS *m*/*z* 259.0815 (54, $[sugar]^+$ = 259.0818), 158.0200 (4, $[BH_2]^+$ = 158.0202). Anal. Calcd for $C_{15}H_{17}N_3O_{11}$: C, 43.28, H, 4.13; N, 10.12. Found: C, 43.00; H, 4.14; N, 10.19.

5-Nitrouridine (7a). Treatment of **4a** (1.11 g, 3 mmol) by procedure B (28 h) gave a colorless oil that was dissolved (dried benzene/Δ), frozen (dry ice/acetone), and lyophillized to give **6a** (1.21 g, 97%): mp ~72−73 °C; UV (MeOH) max 235, 297 nm (ϵ 7100, 8100), min 218, 258 nm (ϵ 5500, 3300); ^{1}H NMR δ 2.08 (s, 6H), 2.10 (s, 3H), 4.34 (m, 3H), 5.40 (t, J = 6.0 Hz, 1H), 5.58 (dd, J = 3.5, 6.0 Hz, 1H), 5.97 (d, J = 3.5 Hz, 1H), 9.11 (s, 1H), 12.3 (br s, 1H, ex); MS *m*/*z* 259.0820 (100, $[sugar]^+$ = 259.0818), 158.0204 (6, $[BH_2]^+$ = 158.0202).

Procedure C. A sample of **6a** (400 mg, 0.96 mmol) in NaOMe/MeOH (0.2 M, 30 mL) was stirred at ambient temperature for 30 min (a white precipitate separated immediately). MeOH was added, the resulting solution was neutralized [Dowex-50W (H^+)], and the resin was filtered and washed (MeOH). Volatiles were evaporated from the combined filtrates, and the residue was recrystallized (EtOH, two crops) to give **7a** (220 mg, 80%): mp 188−190 °C (lit.[11] mp 188−190 °C); UV (pH 2) max 236, 306 nm (ϵ 5400, 9400), min 215, 260 nm (ϵ 2200, 500), (pH 12) max 323 nm (ϵ 15 000), min 268 nm (ϵ 4200); ^{1}H NMR[20] δ 5.71 (d, J = 1.8 Hz, 1H), 9.70 (s, 1H), 12.05 (br s, 1H, ex); MS *m*/*z* 158.0195 (15, $[BH_2]^+$ = 158.0202), 133.0505 (24, $[sugar]^+$ = 133.0501). Anal. Calcd for $C_9H_{11}N_3O_8$: C, 37.38; H, 3.84; N, 14.53. Found: C, 37.48; H, 3.85, N, 14.43.

1-(β-D-Arabinofuranosyl)-5-nitrouracil (7b). Treatment of **6b** (3.11 g, 7.5 mmol) in NaOMe/MeOH (0.2 M, 150 mL) by procedure C (1 h) and crystallization (EtOH, three crops) gave a product (2.12 g, 97%) that was recrystallized (EtOH/MeOH or H_2O) to give **7b**: mp 202−205 °C, ~207 °C dec (lit.[4] 197 °C dec); UV (pH 2) max 239, 306 nm (ϵ 7200, 9300), min 216, 262 nm (ϵ 4400, 2400), (pH 12) max 324 nm (ϵ 15 800), min 259 nm (ϵ 4100); (^{1}H NMR[4]); MS *m*/*z* 271.0436 (1, $[M - H_2O]^+$ = 271.0441), 158.0163 (4, $[BH_2]^+$ = 158.0202), 133.0499 (2, $[sugar]^+$ = 133.0501). Anal. Calcd for $C_9H_{11}N_3O_8$: C, 37.38; H, 3.84; N, 14.53. Found: C, 37.41; H, 3.81; N, 14.68.

2′-Deoxy-5-nitrouridine (7c). Treatment of **4c** (3.1 g, 10 mmol) by procedure B (18 h) gave an oil that was dissolved ($CHCl_3$) and chromatographed (silica gel, 1% MeOH/$CHCl_3$). The resulting oil was dissolved (EtOH) and evaporated several times to give a glass that resolidified (after several days) to give **6c** (2.78 g, 78%): UV (MeOH) max 238, 302 nm (ϵ 7200, 8700), min 216, 260 nm (ϵ 4600, 2600); ^{1}H NMR δ 2.08 (s, 6H), 2.56 (m, 2H), 4.28 (m, 2H), 4.38 (m, 1H), 5.23 (m, 1H), 6.10 ("t", J = 6.8 Hz, 1H), 8.98 (s, 1H), 12.21 (br s, 1H, ex); MS *m*/*z* 201.0760 (4, $[sugar]^+$ = 201.0763), 158.0184 (1, $[BH_2]^+$ = 158.0202).

Treatment of **6c** (2.78 g, 7.8 mmol) by procedure C (1 h) gave a yellow powder (1.58 g, 74%, mp 140−143 °C) that was recrystallized (EtOH) to give colorless fine needles of **7c**: mp 154−155 °C (lit.[12] 149−150 °C); UV (pH 2) max 239, 305 nm (ϵ 7800, 9800), min 215, 261 nm (ϵ 4700, 2600), (pH 12) max 324 nm (ϵ 12 900), min 270 nm (ϵ 4300); ^{1}H NMR δ 2.28 ("t", J = 5.8 Hz, 2H), 3.65 (m, 2H), 3.89 ("q", J = 4 Hz, 1H), 4.28 (m, 1H), 5.25 (t, J = 5.5 Hz, 1H, ex), 5.31 (d, J = 6.0 Hz, 1H, ex), 6.06 ("t", J = 5.8 Hz, 1H), 9.52 (s, 1H), 12.12 (br s, 1H, ex); MS *m*/*z* 158.0156 (5, $[BH_2]^+$ = 158.0202), 117.0547 (34, $[sugar]^+$ = 117.0551). Anal. Calcd for $C_9H_{11}N_3O_7$: C, 39.57; H, 4.06; N, 15.38. Found: C, 39.33; H, 4.16; N, 15.23.

2′,3′-*O*-Isopropylidene-5′-*O*-nitrouridine (8b). Treatment of **8a** (852 mg, 3 mmol) by procedure B (20 h) and recrystallization (EtOH, two crops) gave colorless needles of **8b** (685 mg, 73%): mp (166−170 °C, transition) 182−183 °C (lit.[7b] 182−183 °C); UV (MeOH) max 258 nm (ϵ 9800), min 230 nm (ϵ 3000); (^{1}H NMR[7b]); MS *m*/*z* 329.0858 (3, $[MH]^+$ = 329.0860). Anal. Calcd for $C_{12}H_{15}N_3O_8$: C, 43.77; H, 4.59; N, 12.76. Found: C, 43.70; H, 4.66; N, 12.70.

3′,5′-Di-*O*-nitrothymidine (9b). Treatment of **9a** (1.21 g, 5 mmol) by procedure B [TfOH (3 equiv)/1-nitropyrazole (3 equiv), 48 h] gave a yellow oil that was chromatographed (silica gel, 1% MeOH/$CHCl_3$) and recrystallized [hot EtOH/H_2O (1:1, 40 mL)] to give **9b** (640 mg, 39%): mp 124−125 °C (lit.[8b] 131−132 °C); UV (MeOH) max 258 nm (ϵ 9800), min 230 nm (ϵ 3000); (^{1}H NMR[8b]); MS *m*/*z* 332.0598 (7, M^+ [$C_{10}H_{12}N_4O_9$] = 332.0605). Anal. Calcd for $C_{10}H_{12}N_4O_9$: C, 36.15; H, 3.64; N, 16.86. Found: C, 36.01; H, 3.70; N, 17.18.

JO9822939

(20) ^{1}H NMR signals for H2′,3′,4′,5′,5″ were overlapped multiplets, and peaks for the hydroxyl protons were broad, unresolved singlets.