of t-BuOH. Copper bronze, 1 g, and iodobenzene, 204 g (1 mol), were added, and the mixture was refluxed for 48 h. The mixture was filtered and distilled to yield 141 g of **16**, bp 120–140 °C (10 mm). The distillate was dissolved in i-PrOH and treated with an excess of 70% $HClO_4$ and diluted ($Et_2O$). The $Et_2O$ layer was discarded, and the aqueous and oil layers were treated with an excess of NaOH solution and extracted ($Et_2O$). The extracts were dried (KOH pellets), filtered, and distilled to yield **16**, 50 g (27%), bp 138–140 °C (10 mm). Anal. ($C_{12}H_{11}NO$) C, H, N.

**Method F. Methyl 3-(3-Pyridinyloxy)benzoate (18).** A solution of 3-[3-(trifluoromethyl)phenoxy]pyridine (**17**), 10 g (0.042 mol), in concentrated $H_2SO_4$, 52 g (0.5 mol), was heated on the steam bath for 16 h. The solution was cooled and poured into MeOH, 1 L. The solution was refluxed for 2 h and poured into a large excess of solid $NaHCO_3$. $Et_2O$ was added and the mixture was filtered through filter aid. The organic layer was dried ($MgSO_4$), filtered, and distilled to yield **18**, 6.7 g (70%), bp 173–175 °C (10 mm). Anal. ($C_{13}H_{11}NO_3$) H, N; C: calcd, 68.11; found, 67.54.

**Method G. 2-(3-Pyridinyloxy)benzenamine (19).** A solution of 3-(2-nitrophenoxy)pyridine (**20**), 43 g (0.2 mol), in glacial HOAc, 250 mL, held between 95 and 100 °C, was treated with four portions of Fe filings, 56 g (1 G.A.), and $H_2O$, 105 mL, with stirring. The mixture was held at 100 °C for 1 h and poured into $H_2O$. The aqueous mixture was extracted ($CH_2Cl_2$). The extracts were dried ($MgSO_4$), filtered, and distilled to yield 27 g, bp 125–127 °C (0.3 mm). Recrystallization ($Et_2O$) yielded **19**, 13 g (33%), mp 68–70 °C. Anal. ($C_{11}H_{10}N_2O$) C, H, N.

**Method H. 3-(2-Nitrophenoxy)pyridine (20).** A solution of 3-pyridinol, 47.5 g (0.5 mol; Aldrich Chemical Co.), in $Me_2SO$, 350 mL, was treated with NaH, 21 g (0.5 mol, 57% in mineral oil), in portions under a $N_2$ atmosphere. Copper bronze, 100 mg, and 1-chloro-2-nitrobenzene, 88 g (0.5 mol), were added and, with stirring, the mixture was heated cautiously to 110 °C. The reaction became moderately exothermic and the temperature rose to 145 °C. The mixture was heated at 165 °C for 1 h, cooled, and poured into $H_2O$. The mixture was extracted ($Et_2O$). The extracts were dried ($MgSO_4$), filtered, and distilled to yield **20**, 54 g (50%), bp 140–142 °C (0.6 mm). Anal. ($C_{11}H_8N_2O_3$) C, H, N.

**Method I. 3,3'-Oxybis(pyridine) (23).** A solution of 3,3'-oxybis(pyridine) 1-oxide (**24**), 16.5 g (0.088 mol), in glacial HOAc was heated to 100 °C and Fe, 6.0 g (0.106 G.A.), was added in two equal portions with stirring. The mixture was heated at 100 °C for 1 h, cooled, poured into $H_2O$, and filtered through filter aid. The mixture was treated with a large excess of solid NaOH and extracted repeatedly ($Et_2O$). The extracts were dried ($MgSO_4$), filtered, and distilled to yield **23**, 9.75 g (64.5%), bp 145–147 °C (14 mm). Anal. ($C_{10}H_8N_2O$) C, H, N.

**Method J. 3,3'-Oxybis(pyridine) 1-Oxide (24).** A solution of 3-pyridinol, 29.5 g (0.3 mol), in $H_2O$ (100 mL) was treated with KOH, 16.8 g (0.3 mol). Toluene, 500 mL, was added and the mixture was refluxed and stirred, removing $H_2O$ with a Dean–Stark trap until dry. The toluene was removed at reduced pressure. The dry salt was mixed with 3-bromopyridine 1-oxide,[26] 65 g (0.37 mol), and heated cautiously to 140 °C. The reaction became moderately exothermic and warmed to 175 °C. When the exotherm had subsided, the mixture was heated at 180 °C for 0.25 h. After the mixture cooled, $CHCl_3$ and $H_2O$ were added and the mixture was filtered through filter aid. The $CHCl_3$ layer was separated, dried ($MgSO_4$), filtered, and distilled to yield 20.7 g, bp 145–150 °C (0.2 mm). Recrystallization (i-PrOH–$Et_2O$) yielded **24**, 18 g (32%), mp 116–118 °C. Anal. ($C_{10}H_8N_2O_2$) C, H, N.

**Method K. 3,3'-Oxybis(pyridine) 1,1'-Dioxide (25).** This is essentially the method of Ochiai.[27] A solution of 3,3'-oxybis(pyridine) 1-oxide (**24**), 4.2 g (0.0223 mol), in glacial HOAc, 20 mL, was treated with an excess of 30% $H_2O_2$ and heated on the steam bath for 16 h. The mixture was cooled, i-PrOH was added, and the solution was evaporated at reduced pressure. The residue was treated with excess NaOH and extracted ($CHCl_3$). The extracts were dried ($MgSO_4$), filtered, and evaporated to yield **25**, 2.1 g (45%), mp 216–218 °C. Sublimation at 180 °C (0.1 mm) yielded **25**, 1.5 g (33%), mp 220–222 °C. Anal. ($C_{10}H_8N_2O_3$) C, H, N.

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(26) H. J. Den Hertog, C. R. Holder, and W. P. Comb, *Recl. Trav. Chim. Pays-Bas*, **70**, 591 (1951).
(27) E. Ochiai, M. Ishikawa, and S. Zai-Ren, *J. Pharm. Soc. Jpn.*, **64**, 72 (1944); *Chem. Abstr.*, **45**, 8526 (1951).

# Nucleosides Containing Chemically Reactive Groups

Robert D. Elliott,* R. Wallace Brockman, and John A. Montgomery

*Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35255.* *Received October 1, 1980*

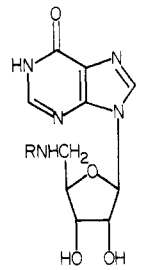
5'-Amino-5'-deoxyinosine (1) and 1-(6-amino-2,5,6-trideoxy-β-D-*erythro*-hexofuranosyl)thymine (**9**) were prepared and substituted on the amino group with chemically reactive functions in an effort to find inhibitors of enzymes that metabolize the corresponding nucleotides. The resulting 5'-substituted methylnitrosoureas **3**, **11a**, and **11b**, bromoacetamides **4** and **13**, phenyl carbamates **5** and **14**, and 4-(fluorosulfonyl)benzamides **6** and **15** were tested for cytotoxicity to H.Ep-2 cells in culture and as inhibitors of incorporation of precursors into nucleic acids of L1210 cells. The inosine derivatives were also evaluated as inhibitors of hypoxanthine phosphoribosyltransferase. Compounds **4**, **6** and **13** showed moderate inhibition of formation of nucleic acids, and compound **4** demonstrated significant cytotoxicity ($ED_{50} < 5$ μg/mL).

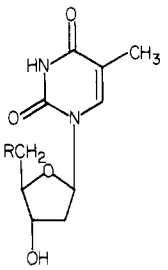
A detailed rationale has been presented for the preparation of nucleosides containing a chemically reactive function attached to C-5' that may act as irreversible inhibitors of enzymes that act on the corresponding nucleotide.[1] This paper describes the synthesis and evaluation of certain derivatives of inosine and thymidine. The reactive functions chosen were the methylnitrosoureido, bromoacetamide, phenyl carbamate, and phenylsulfonyl fluoride.

5'-Amino-5'-deoxyinosine[2] (1) and 1-(6-amino-2,5,6-trideoxy-β-D-*erythro*-hexofuranosyl)thymine[3] (**9**) were prepared by literature procedures. These compounds were

(1) J. A. Montgomery, H. J. Thomas, R. W. Brockman, and G. P. Wheeler, *J. Med. Chem.*, **24**, 184 (1981).
(2) A. Hampton, M. Bayer, V. Gupta, and S. Chu, *J. Med. Chem.*, **11**, 1229 (1968).
(3) G. Etzold, G. Kowollik, and P. Langen, *J. Chem. Soc., Chem. Commun.*, 422 (1968). See also German Patent 65936 (1969); *Chem. Abstr.*, **72**, 3726p (1970).

0022-2623/81/1824-0350$01.00/0 





1, R = H
2, R = $CH_3NHCO$-
3, R = $CH_3N(NO)CO$-
4, R = $BrCH_2CO$-
5, R = PhOCO-
6, R = p-$FSO_2$-$C_6H_4$-CO-
7, R = I
8, R = CN
9, R = $NH_2CH_2$-
10, R = $CH_3NHCONHCH_2$-
11a, R = $CH_3N(NO)CONHCH_2$-
11b, R = $CH_3NHCON(NO)CH_2$-
12, R = $CH_3N(NO)CONH$-
13, R = $BrCH_2CONHCH_2$-
14, R = $PhOCONHCH_2$-
15, R = p-$FSO_2$-$C_6H_4$-$CONHCH_2$-

converted to the corresponding methylureidonucleosides (2 and 10) by reaction with methyl isocyanate. Nitrosation of 2 in aqueous acetic acid gave the nitrosourea 3 with no evidence of the formation of the isomeric nitrosourea, whereas nitrosation of 10 in aqueous acetic acid gave a mixture of the 3-methyl-3-nitrosourea 11a and the isomer 11b (4:1). The presence of 11b was established by an examination of the $^1H$ NMR spectrum of the nitrosated product. These results contrast with the single isomer 12 isolated from the nitrosation of 5′-deoxy-5′-(methylureido)thymidine.[4] An attempt to obtain a higher ratio of 11a to 11b by use of anhydrous formic acid as the nitrosation solvent, a technique found to be useful in other cases,[1,5] gave a slightly improved 5:1 ratio of 11a to 11b.

Reaction of 1 and 9 with 4-nitrophenyl α-bromoacetate in dimethylacetamide gave the bromoacetamides 4 and 13. Similar reaction of 1 and 9 with phenyl chloroformate and 4-(flurosulfonyl)benzoyl chloride in dimethylacetamide or dimethylformamide containing a tertiary amine gave the corresponding phenyl urethanes 5 and 14 and sulfonyl fluorides 6 and 15.

**Biological Evaluations.** The bromoacetamido derivative 4 of inosine was quite cytotoxic, decreasing clone formation of H.Ep.-2 cells in culture[6] to 10% of controls at 5 μg/mL. The corresponding thymidine derivative 13 was much less effective, decreasing clone formation to 74% of controls at 20 μg/mL. The phenylcarbamate derivative 5 of inosine was somewhat more effective than 13 decreasing clone formation to 60% of controls at the same concentration.

The inosine derivatives were evaluated as inhibitors of hypoxanthine phosphoribosyltransferase (HPRT).[7] At ten times the substrate concentration, 4 gave a 46% inhibition of the conversion of hypoxanthine to inosinic acid, which increased to 65% inhibition when 4 was preincubated with the enzyme for 1 h prior to addition of the substrate. Compound 6 gave a 40% inhibition of the conversion when preincubated with the enzyme but had no effect otherwise. That the hypoxanthine moiety of these compounds (4 and 6) may be imparting specificity for HPRT is indicated by their inability to inhibit adenine phosphoribosyltransferase with or without preincubation. Although these studies suggest that 4 and 6 are active-site-directed irreversible inhibitors, 6 does not appear to compete effectively enough with hypoxanthine in the reversible binding step to significantly inhibit the conversion to inosinic acid in whole cells. Furthermore, there is no indication that the inhibition of HPRT is related to cytotoxicity, since 6 showed no effect on H.Ep.-2 cells at 20 μg/mL.

Of the thymidine derivatives, only 13 showed any significant inhibition of the incorporation of precursors into nucleic acids of L1210 cells.[8] At 50 μg/mL, 13 inhibited the incorporation of [*Me*-$^3H$]thymidine (52%), [5-$^3H$]uridine (60%), and [8-$^{14}C$]adenine (67%) into DNA while only slightly inhibiting the incorporation of the uridine and adenine into RNA. This degree of inhibition of incorporation into DNA, even though significant, is in agreement with the low level of cytotoxicity exhibited by 13 to H.Ep.-2 cells. Efforts are now being devoted to the synthesis of more effective analogues of this type.

## Experimental Section

All evaporations were carried out in vacuo with a rotary evaporatory or by short-path distillation into a dry ice–acetone cooled receiver under high vacuum. Analytical samples were normally dried in vacuo over $P_2O_5$ at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. Compounds containing the nitrosoureido function were also detected with the Greiss reagent. The preparative separations were carried out on Brinkman 2-mm silica gel F-254 plates (8 × 8 in.). All analytical samples were TLC homogeneous. Melting points were determined with a Kofler Heizbank apparatus. The UV absorption spectra were determined in 0.1 N HCl (pH 1), pH 7 buffer, and 0.1 N NaOH (pH 13) with a Cary 17 spectrophotometer: the maxima are reported in nanometers ($\epsilon \times 10^{-3}$). The NMR spectra were determined with a Varian XL-100-15 spectrometer operating at 100.1 MHz in $Me_2SO$-$d_6$ (unless otherwise specified) with tetramethylsilane as an internal reference: chemical shifts (δ, in ppm) quoted in the case of multiplets are measured from the approximate center. The NMR spectrum of 11a and 11b was determined on a Bruker WH400 spectrophotometer operating at 400.1 MHz. The mass spectral data were obtained with a Varian MAT 311A mass spectrometer in the field-desorption mode. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

**5′-Deoxy-5′-(3-methylureido)inosine (2).** A suspension of finely powdered 5′-amino-5′-deoxyinosine[2] (1; 100 mg, 0.340 mmol) in $Me_2NCHO$ (2 mL) was treated with methyl isocyanate (22.1 μL, 0.374 mmol) and stirred vigorously for 20 h. Complete solution occurred after 4 h. The solution was evaporated to dryness at 25 °C and the residue crystallized from hot $H_2O$ (1.5 mL) to give 87 mg (77%) of product: mp ~244 °C dec; UV($H_2O$) $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), in 0.1 N HCl 249 (11.9), in pH 7 248 (12.5), in 0.1 N NaOH 253 (13.4). Anal. ($C_{12}H_{16}N_6O_5 \cdot 0.5H_2O$) C, H, N.

**5′-Deoxy-5′-(3-methyl-3-nitrosoureido)inosine (3).** A solution of 2 (50.0 mg, 0.15 mmol) in $H_2O$ (1 mL) and acetic acid (0.4 mL) at 0 °C was treated over a period of 5 min (Hamilton microsyringe) with a solution of $NaNO_2$ (14.3 mg, 0.207 mmol) in $H_2O$ (50 μL) and stirred at 0 °C for 3.5 h. The crystalline product was collected in an ice-cooled funnel and washed with a small quantity of cold $H_2O$: yield 20 mg (34%); $^1H$ NMR δ 3.1 (s, 3, $CH_3$), 3.4 (s, $H_2O$), 3.6 (m, 2, $CH_2N$), 4.1 (m, 2, $H_{3'}$ and $H_{4'}$), 4.6 (m, 1, $H_{2'}$), 5.3 (d, 1, $C_{2'}$ OH), 5.5 (d, 1, $C_{2'}$ OH), 5.8 (d, 1, $J_{1'2'}$ = 7 Hz, $H_{1'}$), 8.0 (s, 1, $H_2$), 8.3 (s, 1, $H_8$), 8.9 (t, 1, NCONH), 12.5 (s, 1, $H_2$). Anal. ($C_{12}H_{15}N_7O_6 \cdot 2H_2O$) C, N; H: calcd, 4.92; found 4.39.

**5′-[(Bromoacetyl)amino]-5′-deoxyinosine (4).** A stirred suspension of 1 (50.0 mg, 0.170 mmol) in $Me_2NAc$ (15 mL) was treated over a period of 2 min with 4-nitrophenyl α-bromoacetate[9]

(4) T. Lin, P. Fischer, G. Shiau, and W. Prusoff, *J. Med. Chem.*, **21**, 130 (1978).
(5) T. P. Johnston, G. S. McCaleb, P. S. Opliger, and J. A. Montgomery, *J. Med. Chem.*, **9**, 892 (1966).
(6) L. L. Bennett, Jr., P. A. Allan, J. W. Carpenter, and D. L. Hill, *Biochem. Pharmacol.*, **25**, 517 (1976).
(7) D. L. Hill, *Biochem. Pharmacol.*, **19**, 545 (1970).
(8) R. W. Brockman, S. C. Shaddix, M. Williams, and R. F. Struck, *Cancer Treat. Rep.*, **60**, 1317 (1976).
(9) D. W. Russell, *Biochem. J.*, **78**, 696 (1961).

(46.5 mg, 0.179 mmol) and stirred for 30 min. The resulting solution was evaporated to dryness at 25 °C and the residual glass triturated with $Et_2O$ (10 mL) to give **4** as a yellow powder, which was collected and washed with $Et_2O$: yield 67.4 mg (97%); mp ~200 °C dec; UV ($H_2O$) $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), in 0.1 N HCl 248 (10.5), in pH 7 249 (10.3), in 0.1 N NaOH 253 (11.0). Anal. ($C_{12}H_{14}BrN_5O_5$) C, H, N.

**5'-Deoxy-5'-[(phenoxycarbonyl)amino]inosine (5).** A stirred suspension of **1** (50.0 mg, 0.170 mmol) in $Me_2NAc$ (4 mL) containing $Et_3N$ (26.1 μL, 0.187 mmol) was treated over a period of 10 min with phenyl chloroformate (23.9 μL, 0.187 mmol) and stirred for 1 h. The solution was filtered and evaporated to dryness. The residue was triturated first with $Et_2O$ and then with $CHCl_3$ and dried in vacuo to give **5** as a solvate with $CHCl_3$ and $Et_2O$: yield 57 mg (75%); $^1H$ NMR δ 1.19 (t, $CH_3$ of $Et_2O$), 3.45 (m, $H_{5'}$), 4.09 (m, 2, $H_{3'}$ and $H_{4'}$), 4.64 (m, 1, $H_{2'}$), 5.45 (d, 2, $O_{2'}$ H and $O_{3'}$ H), 5.91 (d, 1, $J_{1',2'}$ = 5.4 Hz, $H_{1'}$), 7.26 (m, 5, $C_6H_5$), 8.05 (m, 2, N*H*$CH_2$, $H_2$), 8.32 (H of $CHCl_3$), 8.34 (s, $H_8$). Anal. ($C_{17}H_{17}N_5O_6 \cdot 0.4CHCl_3 \cdot 0.1Et_2O$) C, H, N.

**5'-Deoxy-5'-[[4-(fluorosulfonyl)benzoyl]amino]inosine (6).** A suspension of **1** (100 mg, 0.375 mmol) in $Me_2NCHO$ (2 mL) containing diisopropylethylamine (84.7 μL, 0.487 mmol) was treated in portions under $N_2$ with 4-(fluorosulfonyl)benzoyl chloride (109 mg, 0.487 mmol) and stirred for 2.5 h. The solution was poured into $H_2O$ (40 mL), filtered to remove a solid impurity, and evaporated to dryness. The residue was stirred with $H_2O$ (2 mL) containing one drop of 1 N HCl until a homogeneous white powder formed (ca. 20 h). The product was collected and washed successively with 0.1 N HCl, $H_2O$, and $Et_2O$: yield 77 mg (45%); mp ~227 °C dec; UV ($H_2O$–$Me_2SO$, 23:2), $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), in 0.1 N HCl 237 (18.4), in pH 7 237 (18.5), in 0.1 N NaOH 243 (20.4); MS, *m/e* 454 [$(M + 1)^+$]. Anal. ($C_{17}H_{16}FN_5O_7S \cdot 0.3H_2O$) C, H, N.

**1-[2,5,6-Trideoxy-6-(3-methylureido)-β-D-*erythro*-hexofuranosyl]thymine (10).** 5'-Deoxy-5'-iodothymidine (**7**) was prepared from thymidine and methyl triphenoxyphosphonium iodide by the procedure of Verheyden and Moffatt.[10] Treatment of **7** with NaCN gave the cyano derivative **8** which was hydrogenated in the presence of palladium oxide on barium sulfate to give 1-(6-amino-2,5,6-trideoxy-β-D-*erythro*-hexofuranosyl)thymine[3] (**9**). A solution of **9** (60 mg, 0.235 mmol) in $Me_2NCHO$ (1 mL) was treated with methyl isocyanate (15.3 μL, 0.258 mmol), stirred for 3 h, filtered, and evaporated to dryness. A solution of the residue in warm EtOH (2 mL) was filtered and evaporated to dryness. The residue was triturated with EtOAc (2 mL), collected, and dried at 100 °C in vacuo ($P_2O_5$): yield 57 mg (74%); mp 185 °C; UV (EtOH) $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), in 0.1 N HCl 267 (10.2), in pH 7 267 (9.60), in 0.1 N NaOH 267 (7.57); MS, *m/e* 312 ($M^+$). Anal. ($C_{13}H_{20}N_4O_5 \cdot 0.2H_2O \cdot 0.2EtOH$) C, H, N.

**1-[2,5,6-Trideoxy-6-(3-methyl-3-nitrosoureido)-β-D-*erythro*-hexofuranosyl]thymine (11a). A.** A solution of **10** (33.0 mg, 0.102 mmol) in 50% aqueous HOAc (1 mL) was cooled in an ice bath and treated gradually over a period of 5 min with a solution of $NaNO_2$ (9.66 mg, 0.140 mmol) in 40 μL of $H_2O$. The solution was stirred at 0 °C for 2.5 h and lyophilized. The residue was stirred with $H_2O$ (0.4 mL) at 0 °C and, the insoluble product was collected by filtration and washed with a small quantity of cold $H_2O$: yield 17 mg (49%); mp indefinite. This compound, although homogeneous by TLC on silica gel, $CHCl_3$–MeOH (5:1), was found by $^1H$ NMR to contain ~20% of the isomeric 1-[2,5,6-trideoxy-6-(3-methyl-1-nitrosoureido)-β-D-*erythro*-hexofuranosyl]thymine (**11b**): $^1H$ NMR (values assigned to **11a** unless otherwise specified) δ 1.8 (s, 5-$CH_3$), 1.9 (s, 5-$CH_3$ of **11b**), 1.5–2.2 (m, $H_{2'}$ and $H_{5'}$), 2.8 (d, *C*$H_3$NH of **11b**), 3.1 (s, $CH_3$NNO), 3.2–3.5 (m, $H_{6'}$), 3.6 (m, $H_{4'}$ of **11b**), 3.7 (m, $H_{4'}$), 3.8 (m, $H_{6'}$ of **11b**), 4.0 (m, $H_{3'}$, of **11b**), 4.1 (m, $H_{3'}$), 5.3 (m, $C_{3'}$ OH), 6.2 (t, $H_{1'}$), 7.5 (s, $H_6$), 8.6 (m, MeN*H* of **11b**), 8.8 (t, $CH_2$N*H*), 11.3 (s, $H_3$). Anal. ($C_{13}H_{19}N_5O_6$) C, H, N.

**B.** A solution of **10** (75 mg, 0.240 mmol) in 97% formic acid (0.5 mL) was cooled in an ice bath, treated in portions with solid $NaNO_2$ (49.7 mg, 0.720 mmol), stirred for 2 h, and lyophilized. A solution of the residue in $H_2O$ (4 mL) was treated with Amberlite IR-120 ($H^+$) resin, filtered (charcoal), and lyophilized. A solution of the solid in MeOH was purified on a thick plate using 5:1 $CHCl_3$–MeOH as eluate. The major band was extracted with MeOH (70 mL) and the solvent was removed in vacuo. A solution of the residue in EtOH (1 mL) was filtered and evaporated to a gum, which was triturated with $H_2O$ (0.5 mL) to give a white crystalline solid: yield 27 mg (33%). An $^1H$ NMR of this product indicated **11a** containing ~15% of **11b**. This mixture was confirmed by HPLC, μBondapak $C_{18}$ column (Waters), $H_2O$–$CH_3CN$ (90:10), flow rate 1.5 mL/min; retention time of **11a**, 16.95 min; **11b**, 21.15 min; MS *m/e* 341 ($M^+$). Anal. ($C_{13}H_{19}N_5O_6$) C, H, N.

**1-[6-[(Bromoacetyl)amino]-2,5,6-trideoxy-β-D-*erythro*-hexofuranosyl]thymine (13).** A solution of **9** (50 mg, 0.196 mmol) in $Me_2NAc$ (5 mL) was cooled in an ice bath, treated with 4-nitrophenyl α-bromoacetate[6] (53.5 mg, 0.206 mmol), and stirred at 25 °C for 30 min. The solution was evaporated to dryness at 25 °C and the residue stirred with $Et_2O$ (10 mL) until a homogeneous powder formed. The product was collected and washed with $Et_2O$: yield 68 mg (92%); mp 205 °C dec; UV($H_2O$) $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), in 0.1 N HCl 267 (9.50), in pH 7 266 (9.50), in 0.1 N NaOH 267 (7.25). Anal. ($C_{13}H_{18}BrN_3O_5$) C, H, N.

**1-[2,5,6-Trideoxy-6-[(phenoxycarbonyl)amino]-β-D-*erythro*-hexofuranosyl]thymine (14).** A vigorously stirred suspension of **9** (50.0 mg, 0.196 mmol) in $Me_2NAc$ (1 mL) containing *N,N*-diisopropylethylamine (34.1 μL, 0.196 mmol) was treated gradually over a period of 5 min with phenyl chloroformate (27.6 μL, 0.216 mmol). The solution was stirred for 2 h and evaporated to dryness at 25 °C. A solution of the residue in $CHCl_3$ (3 mL) was filtered and evaporated to dryness. The gummy residue was triturated with $Et_2O$, dried, and triturated with $H_2O$ (1 mL) to give a homogeneous white powder. The product was collected and washed with cold $H_2O$: yield 58 mg (79%); mp 202 °C; UV($H_2O$–$Me_2SO$, 21:4), $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), in 0.1 N HCl 266 (9.55), in pH 7 266 (9.71), in 0.1 N NaOH 267 (8.61). Anal. ($C_{18}H_{21}N_3O_6$) C, H, N.

**1-[2,5,6-Trideoxy-6-[[4-(fluorosulfonyl)benzoyl]amino]-β-D-*erythro*-hexofuranosyl]thymine (15).** A stirred suspension of **9** (50.0 mg, 0.196 mmol) in $Me_2NAc$ (1 mL) containing *N,N*-diisopropylethylamine (34.1 μL, 0.196 mmol) was treated in portions with 4-(fluorosulfonyl)benzoyl chloride (54.7 mg, 0.245 mmol), stirred for 4 h, and evaporated to dryness at 25 °C. The residue was triturated with $Et_2O$ (2 × 4 mL), dried, and triturated with 0.1 N HCl (3 mL) to give a white powder, which was collected and washed with $H_2O$ and $Et_2O$: yield 68 mg (77%); mp 238 °C; UV ($H_2O$–$Me_2SO$, 21:4), $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), in 0.1 N HCl 257 (10.9), in pH 7 257 (11.1), in 0.1 N NaOH 268 sh (8.10). Anal. ($C_{18}H_{20}FN_3O_7S \cdot 0.5H_2O$) C, H, N.

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(10) J. Verheyden and J. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).