Synthesis of 5-Alkoxymethyl Derivatives of 3′-Amino-2′,3′-dideoxyuridine and Evaluation of their Activity against HIV and Cancer

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Motawia, M. S., Abdel-Megied, A. E.-S., Pedersen, E. B., Nielsen, C. M. and Ebbesen, P., 1992. Synthesis of 5-Alkoxymethyl Derivatives of 3′-Amino-2′,3′-dideoxyuridine and Evaluation of their Activity against HIV and Cancer. – Acta Chem. Scand. 46: 77–81.

5-Alkoxymethyluracils **2a–c** have been prepared by acid-catalyzed etherification of 5-hydroxymethyluracil (**1**). Compounds **1**, **2a–c**, 5-methoxymethyl- and 5-benzyloxymethyl-uracil were silylated and coupled with 1,5-di-*O*-acetyl-3-phthalimido-2,3-dideoxy-β-D-*erythro*-pentofuranose (**3**), in the presence of trimethylsilyl triflate as a catalyst, to give the corresponding 3′-phthalimido-2′,3′-dideoxynucleosides **5a–f** and **6** which on treatment with 33 % methylamine–ethanol afforded the corresponding 3′-amino-2′,3′-dideoxynucleosides **7a–f** and **8** in high yields. Compound **7d** showed colony inhibition when tested against human epidermoid cervical cancer cells. Nucleosides **5a–e**, **7a–f** and **8** did not show any significant activity against HIV-1.

3′-Amino-2′,3′-dideoxyribonucleosides of pyrimidines have been shown to have potential biological activity as antitumor[1–5] and antiviral agents.[6–9] 5-Hydroxymethylpyrimidine deoxyribonucleotides are unique constituents of viral DNA.[10–14] Moreover, the nucleobase itself, 5-hydroxymethyluracil has been detected in methylated base analyses of L cell tRNA[15] and its occurrence in the bacteriophage deoxyribonucleic acids (DNAs) is well known.[11] Therefore, analogues of these unique pyrimidines (5-hydroxymethylribonucleosides) would be potentially useful compounds in AIDS theraphy if they were preferentially incorporated into viral DNA during reverse transcription as selective antiviral agents, especially when they lack the 3′-OH, a prerequisite for the inhibition of DNA elongation. Furthermore, the enzymic transformation of thymidine to 5-hydroxymethyl-2′-deoxyuridine has been demonstrated in *Neurospora* where 5-substituted pyrimidines have been suggested as possible intermediates in the transformation of thymine into RNA pyrimidines.[16]

To the best of our knowledge, the syntheses of only a few 5-substituted ether derivatives of 5-hydroxymethylpyrimidine deoxyribonucleosides have been reported[17] and there is only one example in the literature[6] of the synthesis of a corresponding 3′-amino-2′,3′-dideoxyribonucleoside analogue which was synthesized by a linear route via a 1-(2′-deoxy-β-D-*lyxo*-furanosyl)uracil derivative. However, the need for compounds that may be effective in the therapy of AIDS, and the importance of 5-hydroxymethylpyrimidine deoxyribonucleosides in the biosynthesis as well as the interesting biological activity of 3′-amino-2′,3′- dideoxyribonucleosides of pyrimidines prompted us to synthesize, by a convergent route, some 3′-amino-2′,3′-dideoxyribofuranosyl pyrimidine nucleosides with various alkoxymethyl substituents in the 5-position of the base and to test them for their potential antiviral activity. The HIV virus is known to attack the central nervous system causing dementia and this should be considered when new agents are designed to combat AIDS. We assume that a nucleoside, submitted with a lipophilic alkoxymethyl group, can pass the blood–brain barrier into the cental nervous system relatively easily. This makes the above-mentioned alkoxymethyl-substituted amino nucleosides of potential interest as anti-HIV compounds since 3′-amino-5-ethyl-2′,3′-dideoxyuridine has been reported[18] to show inhibition of replication of HIV in human peripheral blood mononuclear cells (reverse transcriptase assay of supernatants).

The present paper emanates from our recent findings[19] that phthalimide can be directly coupled with 2-deoxy-D-ribose at C-3 using a phosphorus pentaoxide–water–tributylamine reagent in chloroform followed by direct acetylation to give 1,5-di-*O*-acetyl-3-phthalimido-2,3-dideoxy-β-D-*erythro*-pentofuranose (**3**) which we think is a suitable

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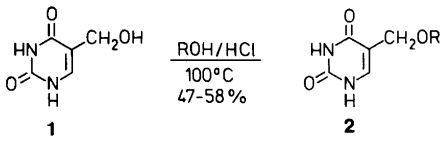
intermediate for elaboration to 3′-amino-2′,3′-dideoxynucleosides and to 3′-amino-2′,3′-dideoxy-*C*-nucleosides. In an alternative route, we have reported[19] the synthesis of **3** in six steps starting from D-xylose. The starting material, 5-hydroxymethyluracil (**1**) was prepared by the method of Cline *et al.*[20] The conversion of **1** into its 5-methoxymethyl and 5-benzyloxymethyl derivatives was carried out by the method of Bubbar and Gupta.[17] The same reaction was utillized for the synthesis of 5-alkoxymethyluracils, **2a–c** (Scheme 1) in yields of 46–58 %.



1 **2**

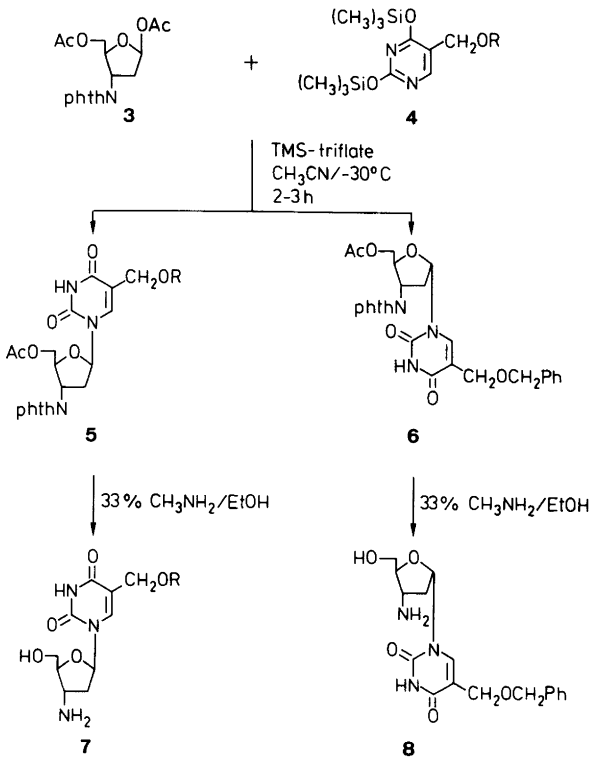
2 a, R = $CH(CH_3)CH_2CH_3$
b, R = $CH_2(CH_2)_8CH_3$
c, R = $CH_2CH_2OCH_2(CH_2)_2CH_3$

Scheme 1.

5-Hydroxymethyluracil (**1**), the ethers **2a–c**, 5-methoxy- and 5-benzyloxy-methyluracil were silyated by the method of Wittenburg[21] to give the corresponding silylated derivatives **4a–f**. Using the reported[22] procedure for nucleoside synthesis with trimethylsilyl triflate (TMS-triflate), the reaction of **3** with the silylated compounds **4a–f** in dry acetonitrile at −30 °C for 2–3 h was easily completed to give an anomeric mixture of the corresponding 3′-phthalimido-2′,3′-dideoxy nucleosides in β:α ratio of 3:2 from which the pure β-anomers **5a–e** were obtained by crystallization from ethanol in yields of 22–35 % (Scheme 2). However, the β-anomer **5f** and its α-anomer **6** were obtained from the corresponding α,β-mixture by fractional crystallization from ethyl acetate in 28, and 16 % yield, respectively.

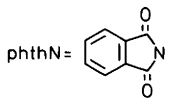
Chromatographic separation of the anomeric mixtures to the corresponding α- and β-anomers proved to be extremely difficult since both anomers has exactly the same R_f value in all the available eluents. Treatment of **5a–f** and **6** with 33 % methylamine in ethanol at reflux temperature for 2–4 h resulted in complete deprotection of both the hydroxy and the amino group to give the corresponding 3′-amino-2′,3′-dideoxynucleosides **7a–f** and **8** in high yields (71–94 %). The α- and β-configurations were determined by ^1H and ^{13}C NMR spectroscopy. Assignments were made based on resonances reported[19] for the α- and β-anomers of similar thymidine nucleosides.

Of the nucleosides **7a–f**, the decyloxymethyl derivative **7d** inhibited colony formation of human epidermoid cervical cancer cells MS751 (ATCC HTB 34). Application of 505 μg prevented all colony formation whereas 51 μg resulted in an inhibition zone of 15 to 18 mm with most of the cells lysed. The colony inhibition was predominantly due to killing of the tumour cells, but the presence of some surviving single cells indicated that the compound may also be an inhibitor of cell division.



3 **4** **5** **6** **7** **8**

4, 5, 7 a, R = H
b, R = CH_3
c, R = $CH(CH_3)CH_2CH_3$
d, R = $CH_2(CH_2)_8CH_3$
e, R = $CH_2CH_2OCH_2(CH_2)_2CH_3$
f, R = CH_2Ph



Scheme 2.

Compounds **5a–e**, **7a–f** and **8** were tested for their antiviral activity against HIV-1 in MT-4 cell culture, but no significant activity was observed at non-cytotoxic concentrations.

Experimental

NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz for ^1H and 62.9 MHz for ^{13}C. Microanalyses were carried out at NOVO-NORDISK A/S, Novo Allé, DK-2880 Bagsværd. EI mass spectra were recorded on a Varian MAT 311 A Spectrometer.

5-Alkoxymethyluracils **2a–c**. *General procedure.* A suspension of 5-hydroxymethyluracil[20] (10.0 g, 70 mmol) in 500 ml of the corresponding alcohol and 5 ml of conc. HCl was stirred for 15 min at room temperature. The reaction mixture was kept for 3–24 h at 100 °C on an oil bath. In all instances, the reaction mixture became homogeneous after 20–30 min. The reaction mixture was stored in a refrigerator and the precipitate formed was filtered off, washed with ether and air dried. Recrystallization from MeOH or EtOH afforded pure products.

5-(1-Methylpropoxymethyl)uracil (**2a**). 6.4 g (46 %), m.p. 220–222 °C (EtOH). ^{1}H NMR (Me_2SO-d_6): δ 0.82 (t, 3 H, CH_2CH_3), 1.10 (d, 3 H, $CHCH_3$), 1.40 (m, 2 H, CH_2CH_3), 3.45 (M, 1 H, OCH), 4.12 (s, 2 H, CH_2O), 7.38 (s, 1 H, 6-H), 10.75 (br s, 1 H, NH), 11.07 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 9.6, 19.1, 28.6 [$CH(CH_3)CH_2CH_3$], 61.9 (CH_2O), 75.2 (OCH), 109.7 (C-5), 139.4 (C-6), 151.0 (C-2), 163.4 (C-4). FAB MS (DMSO, SYLF, TCA): *m/z* (%) 199 (18, $M+H^+$), 141 (29), 125 (100), 82 (36), 41 (45), 29 (53). Anal. ($C_9H_{14}N_2O_3$) C, H, N.

5-Decyloxymethyluracil (**2b**). 11.4 g (58 %), m.p. 203–204 °C (MeOH). ^{1}H NMR (Me_2SO-d_6): δ 0.85 (t, 3 H, CH_3), 1.24–1.47 [m, 16 H, $(CH_2)_8$], 3.35 (t, 2 H, OCH_2), 4.04 (s, 2 H, CH_2O), 7.37 (s, 1 H, 6-H), 10.84 (br s, 1 H, NH), 11.09 (br s, 1 H NH). ^{13}C NMR (Me_2SO-d_6): δ 13.8 (CH_3), 22.0, 25.6, 28.6, 28.8, 28.9, 28.9, 29.1, 31.2 [$(CH_2)_8$], 64.2 (CH_2O), 69.4 (OCH_2), 109.2 (C-5), 140.2 (C-6), 151.2 (C-2), 163.7 (C-4). MS: *m/z* (%) 282 (0.1, M^+), 141 (46), 126 (100), 125 (34), 82 (34). Anal ($C_{15}H_{26}N_2O_3$) C, H, N.

5-[2-(n-Butoxy)ethoxymethyl]uracil (**2c**). 8.0 g (47 %), m.p. 194–196 °C (EtOH). ^{1}H NMR (Me_2SO-d_6): δ 0.89 (t, 3 H, CH_3), 1.13–1.40 (m, 4 H, $-CH_2CH_2$), 3.42 (t, 6 H, $OCH_2CH_2OCH_2$), 4.17 (s, 2 H, CH_2O), 7.47 (s, 1 H, 6-H), 10.87 (br s, 1 H, NH), 11.13 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 13.7 (CH_3), 18.8, 31.2 (CH_2CH_2), 64.4 (CH_2O), 68.9, 69.3, 69.9 ($OCH_2CH_2OCH_2$), 108.9 (C-5), 140.2 (C-6), 151.0 (C-2), 163.5 (C-4). MS: *m/z* (%) 242 (2.6, M^+), 141 (100), 125 (59), 57 (47). Anal. ($C_{11}H_{18}N_2O_4$) C, H, N.

1-(5'-O-Acetyl-3'-phthalimido-2',3'-dideoxy-β-D-erythro-pentofuranosyl)-5-alkoxymethyluracils **5a–f** *and the α-anomer* **6**. *General procedure.* To a solution of **3**[19] (6.95 g, 20 mmol) in 100 ml of dry MeCN (refluxed over P_2O_5 and subsequently over CaH_2) were added the silylated uracil derivatives[21] (20 mmol) in 50 ml of dry MeCN and the mixture was cooled to −30 °C. A solution of trimethylsilyl triflate (4 ml, 22 mmol) in 30 ml of dry MeCN was then added dropwise with magnetic stirring over a period of 10 min. The reaction mixture was stirred at −30 °C for 2–3 h. The reaction mixture was diluted with 250 ml of methylene chloride and extracted with ice-cold saturated aq. $NaHCO_3$ solution. The organic phase was separated, washed with cold H_2O (3×150 ml), dried over Na_2SO_4, and evaporated to obtain the crude products which upon crystallization from EtOH or ethyl acetate afforded the pure products **5a–f** and **6**.

1-(5'-O-Acetyl-3'-phthalimido-2',3'-dideoxy-β-D-erythro-pentofuranosyl)-5-hydroxymethyluracil (**5a**). 2.57 (30 %), m.p. 232–234 °C (EtOH). ^{1}H NMR (Me_2SO-d_6): δ 2.07 (s, 3 H, CH_3CO), 2.40 (m, 1 H, 2' β-H), 2.75 (m, 1 H, 2' α-H), 4.20 (m, 4 H, 5'-H, CH_2O), 4.47 (m, 1 H, 4'-H), 4.90 (m, 1 H, 3'-H), 6.55 (t, 1 H, 1'-H), 7.69 (s, 1 H, 6-H), 7.89 (m, 4 H, Ar-H), 11.33 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 20.39 (CH_3CO), 33.97 (C-2'), 48.63 (C-3'), 55.89 (CH_2O), 63.72 (C-5), 77.88 (C-4'), 84.52 (C-1'), 114.66 (C-5), 123.02 (C-4''), 131.51 (C-3''a), 134.38 (C-5''), 136.53 (C-6), 150.19 (C-2), 162.50 (C-4), 167.48 (C=O), 170.19 (CH_3CO). Anal. ($C_{20}H_{19}N_3O_8 \cdot \frac{1}{2}H_2O$) C, H, N.

1-(5'-O-Acetyl-3'-phthalimido-2',3'-dideoxy-β-D-erythro-pentofuranosyl)-5-methoxymethyluracil (**5b**). 2.63 (30 %), m.p. 202–204 °C (EtOH). ^{1}H NMR (Me_2SO-d_6): δ 2.05 (s, 3 H, CH_3CO), 2.44 (m, 1 H, 2' β-H), 2.76 (m, 1 H, 2' α-H), 3.29 (s, 3 H, OCH_3), 4.10 (s, 2 H, CH_2O), 4.23 (m, 2 H, 5'-H), 4.46 (m, 1 H, 4'-H), 4.89 (m, 1 H, 3'-H), 6.52 (t, 1 H, 1'-H), 7.80 (s, 1 H, 6-H), 7.88 (m, 4 H, Ar-H), 11.46 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 20.31 (CH_3CO), 33.87 (C-2'), 48.66 (C-3'), 57.42 (OCH_3), 63.76 (C-5'), 66.07 (CH_2O), 77.94 (C-4'), 84.66 (C-1'), 110.84 (C-5), 123.00 (C-4''), 131.49 (C-3''a), 134.37 (C-5''), 139.01 (C-6), 150.10 (C-2), 162.48 (C-4), 167.46 (C=O), 170.07 ($COCH_3$). Anal. ($C_{21}H_{21}N_3O_8 \cdot \frac{1}{4}H_2O$) C, H, N.

1-(5'-O-Acetyl-3'-phthalimido-2',3'-dideoxy-β-D-erythro-pentofuranosyl)-5-(1-methylpropoxymethyl)uracil (**5c**). 2.5 g (26 %), m.p. 188–190 °C (EtOH). ^{1}H NMR (Me_2SO-d_6): δ 0.86 (t, 3 H, CH_3), 1.14 (d, 3 H, CH_3), 1.47 (m, 2 H, CH_2), 2.06 (s, 3 H, CH_3CO), 2.44 (m, 1 H, 2' β-H), 2.81 (m, 1 H, 2' α-H), 3.42 (m, 1 H, OCH), 4.07–4.35 (m, 4 H, 5'-H, CH_2O), 4.47 (m, 1 H, 4'-H), 4.92 (m, 1 H, 3'-H), 6.54 (t, 1 H, 1'-H), 7.80 (s, 1 H, 6-H), 7.90 (m, 4 H, Ar-H), 11.43 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 9.46 (CH_3), 18.98, 18.98 (CH_2, CH_3), 20.59 (CH_3CO), 33.82 (C-2'), 48.75 (C-3'), 62.06 (CH_2O), 63.82 (C-5'), 75.66 (OCH), 77.91 (C-4'), 84.85 (C-1'), 111.77 (C-5), 122.98 (C-4''), 131.46 (C-3''a), 134.4 (C-5''), 138.5 (C-6), 150.11 (C-2), 162.47 (C-4), 167.43 (C=O), 169.98 ($COCH_3$). Anal. ($C_{24}H_{27}N_3O_8$) C, H, N.

1-(5'-O-Acetyl-3'-phthalimido-2',3'-dideoxy-β-D-erythro-pentofuranosyl)-5-decyloxymethyluracil (**5d**). 4 g (35 %), m.p. 168–170 °C (EtOH). ^{1}H NMR (Me_2SO-d_6): δ 0.85 (t, 3 H, CH_3), 1.23–1.49 [m, 16 H, $(CH_2)_8$], 2.02 (s, 3 H, CH_3CO), 2.43 (m, 1 H, 2' β-H), 2.77 (m, 1 H, 2' α-H), 3.41 (t, 2 H, OCH_2), 4.13 (s, 2 H, CH_2O), 4.23 (m, 2 H, 5'-H), 4.46 (m, 1 H, 4'-H), 4.90 (m, 1 H, 3'-H), 6.60 (t, 1 H, 1'-H), 7.80 (s, 1 H, 6-H), 7.90 (m, 4 H, Ar-H), 11.50 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 13.94 (CH_3), 20.46 (CH_3CO), 22.13 (CH_2), 25.72 (CH_2), 28.75, 28.94, 29.04, 29.09, 29.20 [$(CH_2)_5$], 31.34 (CH_2), 33.95 (C-2'), 48.87 (C-3'), 63.94 (C-5'), 64.41 (CH_2O), 69.82 (OCH_2), 78.08 (C-4'), 84.93 (C-1'), 111.32 (C-5), 123.14 (C-4''), 131.63 (C-3''a), 134.51 (C-5''), 139.07 (C-6), 150.24 (C-2), 162.65 (C-4), 167.57 (C=O), 170.07 (CH_3CO). Anal. ($C_{30}H_{39}N_3O_8$) C, H, N.

1-(5'-O-Acetyl-3'-phthalimido-2',3'-dideoxy-β-D-erythro-pentofuranosyl)-5-[2-(n-butoxy)ethoxymethyl]uracil (**5e**). 2.37 g (22 %), m.p. 144–146 °C (EtOH). ^{1}H NMR

(Me_2SO-d_6): δ 0.87 (t, 3 H, CH_3), 1.24–1.53 (m, 4 H, CH_2CH_2), 2.03 (s, 3 H, CH_3CO), 2.44 (m, 1 H, 2′ β-H), 2.78 (m, 1 H, 2′ α-H), 3.34–3.57 (m, 6 H, $OCH_2CH_2OCH_2$), 4.18 (s, 2 H, CH_2O), 4.23 (m, 2 H, 5′-H), 4.45 (m, 1 H, 4′-H), 4.89 (m, 1 H, 3′-H), 6.50 (t, 1 H, 1′-H), 7.80 (s, 1 H, 6-H), 7.88 (m, 4 H, Ar-H), 11.46 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 13.62 (CH_3), 18.70 (CH_2), 20.30 (CH_3CO), 31.18 (CH_2), 33.76 (C-2′), 48.70 (C-3′) 63.77 (C-5′), 64.61 (CH_2O), 69.21, 69.30, 69.93 ($OCH_2CH_2OCH_2$), 77.90 (C-4′), 84.76 (C-1′), 111.04 (C-5), 122.98 (C-4″), 131.47 (C-3″a), 134.35 (C-5″), 139.10 (C-6), 150.10 (C-2), 162.50 (C-4), 167.42 (C=O), 170.00 ($COCH_3$). Anal. ($C_{26}H_{31}N_3O_9$) C, H, N.

*1-(5′-O-Acetyl-3′-phthalimido-2′,3′-dideoxy-*β*-D-erythro-pentofuranosyl)-5-benzyloxymethyluracil* (**5f**). 2.9 g (28 %), m.p. 180–182 °C (EtOAc). ^{1}H NMR (Me_2SO-d_6): δ 1.99 (s, 3 H, CH_3CO), 2.46 (m, 1 H, 2′ β-H), 2.79 (m, 1 H, 2′ α-H), 4.15–4.30 (m, 4 H, 5′-H, CH_2O), 4.43–4.61 (m, 3 H, 4′-H, OCH_2), 4.89 (m, 1 H, 3′-H), 6.52 (t, 1 H, 1′-H), 7.29–7.45 (m, 5 H, phenyl-H), 7.84–7.97 (m, 5 H, 6-H, phth-H), 11.52 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 20.28 (CH_3CO), 33.80 (C-2′), 48.69 (C-3′), 63.75 (C-5′), 64.14 (CH_2O), 71.49 (OCH_2), 77.92 (C-4′), 84.79 (C-1′), 110.98 (C-5), 122.98 (C-4‴, phth), 127.30 (C-4″, phenyl), 127.28, 128.11 (C-2″, C-3″, phenyl), 131.47 (C-3a‴, phth), 134.34 (C-5‴, phth), 138.23 (C-1″, phenyl), 139.22 (C-6), 150.08 (C-2), 162.50 (C-4), 167.44 (C=O), 169.99 (CH_3CO). Anal. ($C_{27}H_{25}N_3O_8$) C, H, N.

*1-(5-O-Acetyl-3-phthalimido-2,3-dideoxy-*α*-D-erythro-pentofuranosyl)-5-benzyloxymethyluracil* (**6**). 1.66 g (16 %), m.p. 202–204 °C (EtOAc). ^{1}H NMR (Me_2SO-d_6): δ 2.00 (s, 3 H, CH_3CO), 2.74 (m, 2 H, 2′-H), 4.14–4.23 (m, 2 H, 5′-H), 4.29 (s, 2 H, CH_2O), 4.61 (s, 2 H, OCH_2), 4.82–4.89 (m, 2 H, 3′-H and 4′-H), 6.34 (t, 1 H, 1′-H), 7.27–7.47 (m, 5 H, phenyl-H), 7.87 (m, 4 H, phth-H), 7.96 (s, 1 H, 6-H), 11.51 (br s, 1 H, NH). ^{13}C NMR (Me_2SO-d_6): δ 20.40 (CH_3CO), 32.94 (C-2′), 49.39 (C-3′), 63.97 (C-5′), 64.28 (CH_2O), 71.49 (OCH_2), 76.48 (C-4′), 83.97 (C-1′), 111.31 (C-5), 123.02 (C-4‴, phth), 127.39 (C-4″, phenyl), 127.40 (C-2″, phenyl), 128.15 (C-3″, phenyl), 131.47 (C-3‴a, phth), 134.43 (C-5‴, phth), 137.62 (C-1″, phenyl), 138.29 (C-6), 150.17 (C-2), 162.47 (C-4), 167.54 (C=O), 170.0 (CH_3CO). Anal. ($C_{27}H_{25}N_3O_8 \cdot \frac{1}{2}H_2O$) C, H, N.

3′-Amino-2′,3′-dideoxy-5-alkoxymethyluridines **7a–f** *and* α*-Anomer* **8**. *General procedure.* To a stirred suspension of compounds **5a–f** or **6** (5.6 mmol) in 50 ml of 99.9 % EtOH were added 100 ml of 33 % $MeNH_2$ in absolute ethanol at room temperature. After 5 min the clear solution obtained was refluxed at 90 °C for 2–4 h. The reaction mixture was cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (40 g, 0.040–0.063 mm) with CH_2Cl_2–MeOH (9:1 v/v) to remove all of the impurities and the column was then eluted with MeOH to obtain the pure products **7a–f** and **8**.

3′-Amino-2′,3′-dideoxy-5-hydroxymethyluridine (**7a**). 1.14 g (79 %), m.p. 201–202 °C. ^{1}H NMR (Me_2SO-d_6): δ 2.05 (m, 2 H, 2′-H), 3.39 (m, 1 H, 3′-H), 3.55–3.68 (m, 3 H, 4′-H, 5′-H), 4.14 (s, 2 H, CH_2O), 6.12 (t, 1 H, 1′-H), 7.78 (s, 1 H, 6-H). ^{13}C NMR (Me_2SO-d_6): δ 40.57 (C-2′), 51.08 (C-3′), 56.01 (CH_2O), 61.06 (C-5′), 83.65 (C-1′), 87.59 (C-4′), 113.88 (C-5), 136.96 (C-6), 150.30 (C-2), 162.74 (C-4). MS: *m/z* (%) 257 (0.3, M^+), 116 (48), 72 (30), 56 (36), 18 (100). Anal. ($C_{10}H_{15}N_3O_5 \cdot \frac{1}{2}H_2O$) C, H, N.

3′-Amino-2′,3′-dideoxy-5-methoxymethyluridine (**7b**). 1.15 g (76 %), m.p. 140–142 °C. ^{1}H NMR (Me_2SO-d_6): δ 2.08 (m, 2 H, 2′-H), 3.22 (s, 3 H, OCH_3), 3.41 (m, 1 H, 3′-H), 3.56–3.71 (m, 3 H, 4′-H, 5′-H), 4.04 (s, 2 H, CH_2O), 6.08 (t, 1 H, 1′-H), 8.0 (s, 1 H, 6-H). ^{13}C NMR (Me_2SO-d_6): δ 40.73 (C-2′), 50.47 (C-3′), 57.20 (OCH_3), 60.47 (C-5′), 66.23 (CH_2O), 83.87 (C-1′), 87.59 (C-4′), 109.70 (C-5), 139.38 (C-6), 150.20 (C-2), 162.74 (C-4). MS: *m/z* (%) 271 (1, M^+), 116 (100), 72 (62), 56 (46). Anal. ($C_{11}H_{17}N_3O_5 \cdot \frac{1}{2}H_2O$) C, H, N.

3′-Amino-2′,3′-dideoxy-5-(1-methylpropoxymethyl)uridine (**7c**). 1.25 g (71 %), m.p. 124–126 °C. ^{1}H NMR (Me_2SO-d_6): δ 0.83 (t, 3 H, CH_3), 1.07 (d, 3 H, CH_3), 1.41 (m, 2 H, CH_2), 2.07 (m, 2 H, 2′-H), 3.39 (m, 2 H, 3′-H, OCH), 3.59 (m, 4 H, 5′-H, CH_2O), 4.10 (m, 1 H, 4′-H), 6.09 (t, 1 H, 1′-H), 7.91 (s, 1 H, 6-H). ^{13}C NMR (Me_2SO-d_6): δ 9.44 (CH_3), 18.98 (CH_3), 28.55 (CH_2), 40.67 (C-2′), 50.74 (C-3′), 60.73 (C-5′), 62.13 (CH_2O), 75.35 (OCH), 83.77 (C-1′), 87.60 (C-4′), 110.93 (C-5), 138.37 (C-6), 150.16 (C-2), 162.59 (C-4). MS: *m/z* (%) 313 (0.03, M^+), 116 (100), 72 (40), 56 (21). Anal. ($C_{14}H_{23}N_3O_5 \cdot H_2O$) C, H, N.

3′-Amino-2′,3′-dideoxy-5-decyloxymethyluridine (**7d**). 1.87 g (84 %), m.p. 95–97 °C. ^{1}H NMR (Me_2SO-d_6): δ 0.86 (t, 3 H, CH_3), 1.24–1.48 [m, 16 H, $(CH_2)_8$], 2.06 (m, 2 H, 2′-H), 3.36 (t, 2 H, OCH_2), 3.41–3.83 (m, 4 H, 3′-H, 4′-H, 5′-H), 4.07 (s, 2 H, CH_2O), 6.08 (t, 1 H, 1′-H), 7.94 (s, 1 H, 6-H). ^{13}C NMR (Me_2SO-d_6): δ 13.86 (CH_3), 22.03 (CH_2), 25.60 (CH_2), 28.64 (CH_2), 28.82, 28.93, 28.98, 29.09 [$(CH_2)_4$], 31.23 (CH_2), 40.76 (C-2′), 50.73 (C-3′), 60.71 (C-5′), 64.46 (CH_2O), 69.48 (OCH_2), 83.84 (C-1′), 87.69 (C-4′), 110.23 (C-5), 138.85 (C-6), 150.16 (C-2), 162.65 (C-4). MS: *m/z* (%) 397 (0.3, M^+), 116 (100), 72 (27), 56 (24). Anal. ($C_{20}H_{35}N_3O_5$) C, H, N.

*3′-Amino-2′,3′-dideoxy-5-[2-(*n*-butoxy)ethoxymethyl]uridine* (**7e**). 1.55 g (77 %), yellow gum. ^{1}H NMR (Me_2SO-d_6): δ 0.87 (t, 3 H, CH_3), 1.15–1.52 (m, 4 H, CH_2CH_2), 2.06 (m, 2 H, 2′-H), 3.35–3.69 [m, 8 H, 3′-H, 4′H, 5′-H, $O(CH_2)_2OCH_2$], 4.11 (s, 2 H, CH_2O), 6.08 (t, 1 H, 1′-H), 7.97 (s, 1 H, 6-H). ^{13}C NMR (Me_2SO-d_6): δ 13.66 (CH_3), 18.73 (CH_2), 31.21 (CH_2), 40.73 (C-2′), 50.63 (C-3′), 60.62 (C-5′), 64.78 (CH_2O), 69.02, 69.32, 69.94

($OCH_2CH_2OCH_2$), 83.83 (C-1'), 87.64 (C-4'), 110.04 (C-5), 139.06 (C-6), 150.15 (C-2), 162.67 (C-4). MS: *m/z* (%) 357 (2.7, M^+), 116 (100), 72 (41), 56 (28).

3-Amino-2,3-dideoxy-5-benzyloxymethyluridine (**7f**). 1.82 g (94%), yellow gum. ^{1}H NMR (Me_2SO-d_6): δ 2.09 (m, 2 H, 2'-H), 3.40–4.13 (m, 4 H, 3'-H, 4'-H, 5'-H), 4.18 (s, 2 H, CH_2O), 4.50 (s, 2 H, OCH_2), 6.10 (t, 1 H, 1'-H), 7.26–7.34 (m, 5 H, Ar-H), 8.03 (s, 1 H, 6-H). ^{13}C NMR (Me_2SO-d_6): δ 40.67 (C-2'), 50.61 (C-3'), 60.63 (C-5'), 64.39 (CH_2O), 71.29 (OCH_2), 83.88 (C-1'), 87.60 (C-4'), 110.04 (C-5), 127.24 (C-4''), 127.32 (C-2''), 128.12 (C-3''), 138.40 (C-1''), 139.24 (C-6), 150.16 (C-2), 162.70 (C-4). MS: *m/z* (%) 347 (0.03), 116 (71), 108 (100), 72 (32), 56 (26).

*1-(3'-Amino-2',3'-dideoxy-α-*D-erythro*-pentofuranosyl)-5-benzyloxymethyluracil* (**8**). 1.4 g (72%), yellow gum. ^{1}H NMR (Me_2SO-d_6): δ 1.82 (m, 1 H, 2' β-H), 2.55 (m, 1 H, 2' α-H), 3.41–3.94 (m, 4 H, 3'-H, 4'-H, 5'-H), 4.20 (s, 2 H, CH_2O), 4.52 (s, 2 H, OCH_2), 6.08 (t, 1 H, 1'-H), 7.27–7.34 (m, 5 H, Ar-H), 8.13 (s, 1 H, 6-H). ^{13}C NMR (Me_2SO-d_6): δ 40.11 (C-2'), 51.89 (C-3'), 61.79 (C-5'), 64.30 (CH_2O), 71.31 (OCH_2), 85.01 (C-1'), 87.82 (C-4'), 110.01 (C-5), 127.28 (C-4''), 127.39 (C-2''), 128.15 (C-3''), 138.34 (C-1''), 140.09 (C-6), 150.31 (C-2), 162.78 (C-4). MS: *m/z* (%) 347 (0.03, M^+), 116 (100), 72 (42), 56 (22).

Cancer test procedure. The compounds were tested by a modification of the Sykes colony inhibition assay.[23] The bottom of a 50 mm diameter petri dish was covered with a feeder layer of 5 ml, 5% agar in tissue culture medium MEM with 10% fetal calf serum. On top of this were placed 30000 human epidermoid cervical cancer cells, MS751 (ATCC HTB 34) dispersed as single cells in 2 ml of a 4% agar with the same medium. 10 µl of an ethanol dilution of the compound were applied to a 5 mm diameter Whatman filter disc and the culture incubated for 14 days at 37 °C with 5% CO_2. The width of the zone around the disc where cell colony formation was inhibited was recorded in mm. Tests in duplicate were carried three times.

Anti-HIV assay procedure. Nucleoside analogues were examined for possible antiviral activity using HIV-1 (strain HTLV IIIB)-infected MT-4 cells as the target system. For screening studies MT-4 cells were incubated with the virus for 2 h, washed and thereafter added in a proportion of 1:10 to uninfected MT-4 cells, which had been preincubated with the test compound in the growth medium for 2 h. Compounds were screened using a concentration in the medium of 0.33 mM. In cases of low solubility a 1:3 dilution of saturated solution was used (**5a–e**, **7d**). Cultures were maintained for one week in parallel with virus-infected control cultures with no added compound. Expression of HIV in the culture medium was quantified by HIV antigen detection ELISA. Compounds mediating less than 20% reduction of antigen expression were considered to lack bilogical activity. Compounds mediating a reduction of 20% or more were examined for cytotoxic potential using concentration-dependent inhibition of MT-4 cell proliferation as measure of cytotoxicity. A 20% inhibition of cell growth relative to control cultures was considered significant. Cytotoxicity TD_{50}: **7d**, 0.06×saturated. The compound was finally re-examined for antiviral activity in the highest sub-toxic concentration observed.

Acknowledgements. The Danish Natural Science Research Council and *Assurandør-Societetet* are gratefully acknowledged for their support.

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Received March 4, 1991.