5-ALKOXYMETHYL-1-HYDROXYALKYLURACILS WITH POTENTIAL ANTI-HIV ACTIVITY

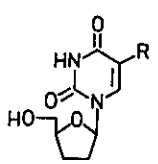
Ahmed E.–S. Abdel–Megied[a], Mohammed S. Motawia[a], Erik B. Pedersen[a], and Carsten M. Nielsen[b]

[a] Department of Chemistry, Odense University, DK–5230 Odense M, Denmark

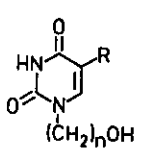
[b] Retrovirus Laboratory, Enterovirus Department, Statens Seruminstitut, Amager Boulevard 80, DK–2300 Copenhagen, Denmark

Abstract – Acid catalyzed etherification of 5-hydroxymethyluracil **(3)** afforded the corresponding 5-alkoxymethyluracils **(4a–h)**. Treatment of the sodium salt of compounds **(4a–g)** with 4-bromobutyl acetate afforded 1,3-bis-(4-acetyloxybutyl)- **(5a–g)** and 1-4-acetyloxybutyluracil derivatives **(6a–g)**. Alkylation of **4h** with 5-chloropentyl benzoate gave 1,3-bis-(5-benzoyloxypentyl)- **(8)** and 1-(5-benzoyloxypentyl)-5-t-butyloxymethyluracil **(9)**. Ammonolysis of **6a–g** and **9** at room temperature gave the corresponding hydroxyalkyl derivatives **(7a–g** and **10)**.

The economic impact of AIDS will be a serious problem if the disease begins to spread rapidly through the general heterosexual population.[1] Even if case loads do not grow rapidly, AIDS will continue to be a serious concern. A major contributor to the expenses in treating this disease is the costly 3'-azido-3'-deoxythymidine (AZT) which represents a first step in the development of pratical chemotherapy against pathogenic human retrovirus. Therefore, it is important to consider low cost compounds as possible candidates with activity against AIDS. At the same time they will offer a new chance to find compounds with less prominent side effects than those observed for AZT.[2]



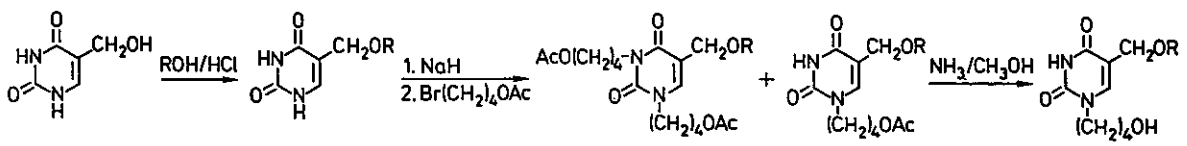
1



2

The synthesis of 1-hydroxyalkyluracils (**2**) will be straightforward and for n = 5 these compounds still have the carbon backbone found in 2',3'-dideoxynucleosides (**1**) which have protective activity against HIV in MT–4, ATH8 and PBM cells.[3,4] Removal of the hydrophilic sugar ring oxygen will increase the lipophilic properties of **2** compared to **1**.[5] The change in lipophilic properties may influence the biological activity and should be compensated. This can easily be done by using proper alkoxymethyl as substituents in the 5-position of **2**. The lipophilic π-parameter has been reported to –0.78 for CH_2OCH_3 and 0.84 for $CH_2OC_4H_9$ which roughly correspond to increments of 0.5 for each CH_2 group.[5] This approach is not overthrown by the steric requirements of the substituent in the 5-position of the uracil since *in vitro* activity against HIV also has been reported for 3'-azido-5-benzyl-2',3'-dideoxyuridine.[6] To choose the alkoxymethyl group for adjusting the lipophilic property of the compounds (**2**) has ordinary common sense because this group can be considered as an ether derivative of the hydroxymethyl group found in naturally occurring hypermodified nucleotides. This has interesting perspectives since it has been claimed that 5-hydroxymethyl-2'-deoxyuridine triphosphate and not thymidine triphosphate, is a substrate for SP10c DNA replication and is present in SP10c phage-infected *Bacillus subtilis*.[7]

RESULTS AND DISCUSSION

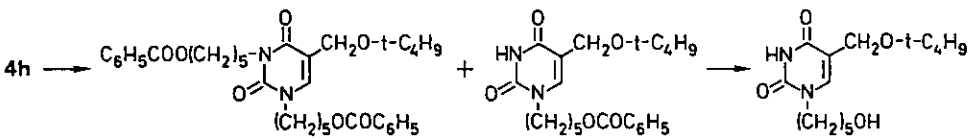


4-7	R
a	CH_3
b	$CH_2CH_2CH_2CH_3$
c	$CH_2CH(CH_3)_2$
d	$CH_2C_6H_5$
e	$CH_2CH_2OCH_2CH_3$
f	4-$CH_3C_6H_4CH_2$
g	$CH(CH_3)C_6H_5$
h	$C(CH_3)_3$

Scheme 1

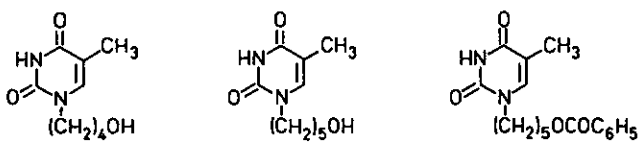
In this report we describe the synthesis of 5-alkoxymethyluracils and their 1-hydroxyalkyl derivatives as shown in Schemes 1 and 2. The starting material 5-hydroxymethyluracil (**3**) was prepared from uracil and paraformaldehyde by the method of Cline and co-workers.[8] In this report 5-alkyloxymethyluracils were prepared by the reaction of 5-hydroxymethyluracil with methanol, *n*-butanol,[9] *iso*-butanol[10] and benzyl alcohol[11] as previously described. The new compounds 5-(2,5-dioxaheptyl)uracil (**4e**), 5-(1-phenylethoxy-

methyl)uracil (**4g**) and 5-t-butoxymethyluracil (**4h**) were obtained by the method of Bubber and Gupta[9] in 50–63% yields whereas 5-(4-methylbenzyloxymethyl)uracil (**4f**) was obtained from **3** and 4-methylbenzyl alcohol by the method of Farkas and Sorm.[11] For preparation of 1-(4-hydroxybutyl)uracil derivatives (**6**), the compounds (**4a–g**) were alkylated with 4-bromobutyl acetate by the method of Sasaki *et al.*[12] In all the reactions, bisalkylation at N1 and N3 inevitably took place along with the formation of the desired 1-(4-acetyloxybutyl)uracil derivatives (**6a–g**). Treatment of **6a–g** with 1:1 mixture of methanol and conc. ammonia at room temperature for 12–24 h resulted in complete deprotection of the hydroxy group and the corresponding 1-(4-hydroxybutyl)uracil derivatives (**7a–g**) were obtained in good yields (Scheme 1).



Scheme 2

The 1-(5-hydroxypentyl)uracil derivative (**10**) was prepared by alkylation of the uracil (**4h**) with 5-chloropentyl benzoate[13] and subsequent deprotection by reaction with ammonia in methanol. The 1-hydroxyalkylthymines (**11**) and (**12**) have previously been prepared and tested for their biological activity against herpes simplex virus[14] and mouse leukemia L 1210,[15] respectively. In this investigation the compound (**12**) was prepared via the corresponding benzoyl derivative (**13**) which was synthesized by alkylation of thymine with 5-chloropentyl benzoate.



The compounds (**6b–g**), (**7a–g**) and (**9–13**) did not show any significant acitivty against HIV when tested in the MT–4 cell system.

Table I. Preparation of Compounds (4–10).

No.	Yield [%]	mp [°C] (solvent)
4e	55	189–190 (ethanol)
4g	63	234–235 (ethanol)
4h	50	261–262 (ethanol)
5a	18	oil
5b	23	oil
5c	9	oil
5d	21	oil
5e	28	oil
5f	19	oil
5g	13	oil
6a	17	82–83 (ether)
6b	34	73–75 (ether)
6c	55	81–82 (ether)
6d	31	89–90 (pet. ether – ether)
6e	28	54–55 (ether)
6f	34	112–113 (ether)
6g	24	80–81 (pet. ether – ether)
7a	91	126–127 (ether)
7b	65	84–85 (ether)
7c	83	102–103 (ether)
7d	83	115–117 (ether)
7e	54	63–65 (pet. ether – ether)
7f	77	98–99 (ether)
7g	74	95–97 (ether)
8	25	oil
9	37	108–109 (ether)
10	77	125–126 (ether)

Table II. ^{1}H–Nmr (250 MHz, $CDCl_3$/TMS) and ms (m/z) of the Compounds (**7a–g** and **10**).

No.	ms (m/z)	^{1}H–nmr, δ–values
7a[a]	228 (M^+, 26) 198 (77) 141 (100)	1.39 (2H, m, CH_2), 1.60 (2H, m, CH_2), 3.24 (3H, s, CH_3), 3.39 (2H, m, $C\underline{H}_2OH$), 3.68 (2H, t, J = 7.0 Hz, CH_2), 4.03 (2H, s, CH_2), 4.47 (1H, t, J = 4.6 Hz, CH_2–O$\underline{H}$), 7.70 (1H, s, 6–H), 11.32 (1H, s, N3–H).
7b	270 (M^+, 1) 198 (100) 141 (54)	0.92 (3H, t, J = 7.3 Hz, CH_3), 1.38 (2H, m, CH_2), 1.59 (4H, m, CH_2), 1.79 (2H, m, CH_2), 2.97 (1H, br s, OH), 3.53 (2H, t, J = 6.6 Hz, CH_2), 3.68 (2H, t, J = 5.8 Hz, $C\underline{H}_2OH$), 3.79 (2H, t, J = 7.2 Hz, CH_2), 4.25 (2H, s, CH_2), 7.29 (1H, s, 6–H), 10.12 (1H, br s, N3–H).
7c	270 (M^+, 2) 198 (100) 141 (29)	0.92 (6H, d, J = 6.6 Hz, CH_3), 1.55–1.98 (5H, m, CH, CH_2), 2.46 (1H, br s, OH), 3.15 (2H, d, J = 6.7 Hz, CH_2), 3.69 (2H, t, J = 6.0 Hz, $C\underline{H}_2OH$), 3.76 (2H, t, J = 7.2 Hz, CH_2), 4.25 (2H, s, CH_2), 7.27 (1H, s, 6–H), 9.72 (1H, br s, N3–H).
7d	304 (M^+, 0.1) 198 (100) 126 (51)	1.57 (2H, m, CH_2), 1.76 (2H, m, CH_2), 2.66 (1H, br s, OH), 3.65 (2H, t, J = 6.0 Hz, $C\underline{H}_2OH$), 3.74 (2H, t, J = 7.2 Hz, CH_2), 4.30 (2H, s, CH_2), 4.60 (2H, s, CH_2), 7.28 (1H, s, 6–H), 7.30–7.35 (5H, m, ArH), 9.94 (1H, br s, N3–H).
7e	286 (M^+, 8) 213 (100) 197 (36)	1.22 (3H, t, J = 7.0 Hz, CH_3), 1.60 (2H, m, CH_2), 1.88 (2H, m, CH_2), 3.50–3.69 (9H, m, CH_2, OH), 3.79 (2H, t, J = 7.0 Hz, CH_2), 4.32 (2H, s, CH_2), 7.41 (1H, s, 6–H).
7f	318 (M^+, 0.4) 198 (100)	1.57 (2H, m, CH_2), 1.75 (2H, m, CH_2), 2.33 (3H, s, CH_3), 2.42 (1H, br s, OH), 3.66 (2H, t, J = 5.8 Hz, $C\underline{H}_2OH$), 3.74 (2H, t, J = 7.2 Hz, CH_2), 4.27 (2H, s, CH_2), 4.56 (2H, s, $C_6H_5C\underline{H}_2$) 7.13–7.26 (5H, m, 6–H, ArH), 9.82 (1H, br s, N3–H).
7g	318 (M^+, 0.2) 198 (100) 126 (42)	1.47 (3H, d, J = 6.4 Hz, CH_3), 1.57 (2H, m, CH_2), 1.75 (2H, m, CH_2), 2.93 (1H, br s, OH), 3.66 (2H, t, J = 6.0 Hz, $C\underline{H}_2OH$), 3.75 (2H, t, J = 7.1 Hz, CH_2), 4.09 (1H, d, J = 13 Hz, CH_2), 4.16 (1H, d, J = 13 Hz, CH_2), 4.52 (1H, q, J = 6.3 Hz, CH), 7.25 (1H, s, 6–H), 7.32–7.62 (5H, m, ArH), 10.13 (1H, br s, N3–H).
10	284 (M^+, 1.7) 227 (100) 211 (36)	1.25 (9H, s, CH_3), 1.35–1.80 (6H, m, CH_2), 1.90 (1H, br s, OH), 3.65 (2H, t, J = 6.0 Hz, $C\underline{H}_2OH$), 3.75 (2H, t, J = 7.2 Hz, CH_2), 4.24 (2H, s, CH_2), 7.20 (1H, s, 6–H), 9.77 (1H, br s, N3–H).

[a] ^{1}H–Nmr was recorded in DMSO–d_6.

Table III. ^{13}C–Nmr (δ 62.5 MHz, $CDCl_3$)/TMS; δ–values of Compounds (**7a–g** and **10**).

No.	Pyrimidine				N–$(CH_2)_nO$	5–CH_2OR
	C–2	C–4	C–5	C–6		
7a[a]	150.7	163.1	109.3	144.2	25.2, 29.2, 47.3, 60.2	57.2, 66.0,
7b	151.0	163.1	111.8	141.7	25.5, 28.9, 48.4, 61.5	13.7, 19.1, 31.4, 64.4, 70.9
7c[b]	150.8	162.7	111.9	141.4	25.6, 29.0, 48.5, 61.8	19.3, 28.3, 64.7, 74.8
7d	151.1	163.2	111.8	142.2	25.7, 29.1, 48.6, 61.6	64.4, 73.2, 127.9, 128.5, 137.7
7e	151.3	163.5	111.5	142.5	25.7, 29.2, 48.5, 61.7	15.1, 65.1, 66.6, 69.6, 70.3
7f	151.0	163.1	111.6	142.0	25.5, 28.9, 48.4, 61.5	20.9, 64.0, 72.8, 127.8, 128.6, 134.5, 137.4
7g	151.0	163.0	111.9	143.0	25.5, 28.9, 48.4, 61.6	23.7, 62.7, 78.3, 126.0, 127.5, 128.3, 141.7
10	150.6	162.9	110.9	142.9	22.3, 28.3, 31.9, 47.4, 60.5	27.2, 56.0, 72.8

[a] In DMSO–d_6. [b] Recorded at 15 MHz.

EXPERIMENTAL

5-Alkoxymethyluracil derivatives (**4e,g,h**).

Conc. HCl (1 ml) and the compound (**3**) (2 g) were added to the ethanol (100 ml). The suspension was stirred at room temperature for 15 min and then kept on an oil bath for 24 h at 100° C. The reaction mixture became homogeneous after 20–30 min. The reaction mixture was cooled to –20° C and after standing for a few days the crystals were collected by filtration and recrystallized.

5-(4-Methylbenzyloxymethyl)uracil (**4f**).

From a mixture of 5-hydroxymethyluracil (4.7 g, 33 mmol), 4-metylbenzyl alcohol (20.7 g, 0.17 mol), benzene (30 ml) and concentrated hydrochloric acid (0.1 ml), the azeotropic mixture of benzene and water was removed by distillation. After the removal of water, the oil-bath temperature was gradually raised to 170° C and held at this temperature for additional 1 h. The crystals which separated on cooling were collected by filtration, washed with ether and recrystallized from dioxane. Yield, 1.2 g (15%); mp 226–227° C. Ms: m/z (%) = 246 (M^+, 0.6); ^1H–nmr (250 MHz, DMSO–d_6/TMS): δ 2.30 (3H, s, CH_3), 3.45 (1H, br s, OH), 4.15 (2H, s, CH_2), 4.45 (2H, s, CH_2), 7.17 (4H, m, ArH), 7.45 (1H, s, 6–H), 10.90 (1H, br s, N1–H), 11.15 (1H, br s, N3–H); ^{13}C–nmr (62.5 MHz, DMSO–d_6/TMS): δ 20.6 (CH_3), 64.0 (CH_2), 71.2 (O–CH_2), 109.0 (C–5), 127.4, 128.6, 135.3, 136.4 (C_6H_4), 140.4 (C–6), 151.2 (C–2), 163.7 (C–4). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.37. Found: C, 63.26; H, 5.82; N, 11.34.

1-(4-Acetyloxybutyl)uracil derivatives (**5a–g**) and (**6a–g**).

A mixture of an 5-alkoxymethyluracil derivative (**4**) (14 mmol) and 50% oil-immersed sodium hydride (680 mg, 14 mmol) in DMF (75 ml) was stirred at 70–80° C for 1 h and cooled to room temperature. 4-Bromobutyl acetate (3.17 g, 16 mmol) was added and the mixture was stirred at room temperature for 24 h (compounds **4a,c** were stirred at 90° C for 2–5 h). Tlc with $CHCl_3/CH_3OH$ (9:1) showed two products and the starting material. The mixture was neutralized with AcOH, evaporated and the residue was partitioned between $CHCl_3$ (100 ml) and water (50 ml). The sparingly soluble starting materials (**4**) was recovered by filtration (0.4–0.9 g). The organic layer was dried over Na_2SO_4, evaporated and chromatographed on silica gel (40 g, 0.04–0.063 mm) with $CHCl_3/CH_3OH$ (98:2) to give 1,3-bis-(4-acetyloxybutyl)uracil derivatives (**5a–g**) in 9–28% yields as oils and 1-(4-acetyloxybutyl)uracil derivatives (**6a–g**) in 17–55% yields as solids.

1-(4-Hydroxybutyl)uracil derivatives (**7a–g**).

Compound (**6**) (5 mmol) in a mixture of MeOH (60 ml) and conc. ammonia (60 ml) was stirred at room temperature for 12–24 h and evaporated. The residue was co-evaporated with ethanol two times, triturated with a small volume of ether and recrystallized.

1,3-Bis(5-benzoyloxypentyl)-5-t-butoxymethyluracil (**8**) *and 1-(5-benzoyloxypentyl)-5-(t-butoxymethyl)uracil* (**9**).

Uracil derivative (**4h**) (2.78 g, 14 mmol) and 50% oil immersed sodium hydride (680 mg, 14 mmol) in DMF (75 ml) was stirred at 70° C for 4 h and then cooled to room temperature. 5-Chloropentyl benzoate (3.17 g, 14 mmol) was added and the mixture was stirred at room temperature for 2 h and then at 90° C for 7 h. After evaporation ice-water (100 ml) was added to the residue and the mixture was neutralized with AcOH under stirring. Unreacted **4h** (0.49 g) was collected by filtration and washed with $CHCl_3$. After extraction of the water phase with $CHCl_3$ (150 ml) the combined $CHCl_3$ phases were evaporated after drying with Na_2SO_4. Preparative silica tlc with $CHCl_3/CH_3OH$ (95:5, v/v) afforded as the first fraction 2.0 g (25%) of 1,3-bis-(5-benzoyloxypentyl)-5-*t*-butoxymethyluracil (**8**) as a colorless oil. Ms: m/z (%) = 578 (M^+, 0.1), 521 (63). ^{1}H–Nmr (250 MHz, $CDCl_3$/TMS: δ 1.25 (9H, s, CH_3), 1.43–1.84 (12H, m, CH_2), 3.76 (2H, t, J = 7.3 Hz, CH_2), 3.98 (2H, t, J = 7.3 Hz, CH_2), 4.22 (2H, s, CH_2), 4.31 (4H, m, CH_2), 7.20 (1H, s, 6–H), 7.41–8.02 (10H, m, C_6H_5). ^{13}C–Nmr (62.5 MHz, $CDCl_3$/TMS): δ 22.3, 22.8, 27.7, 27.9, 40.2, 48.7, 63.7, 63.9 (10 x CH_2), 26.8 (3 x CH_3), 56.2 (CH_2–O), 72.8 ($C(CH_3)_3$), 111.0 (C–5), 138.7 (C–6), 150.2 (C–2), 161.3 (C–4), 127.8, 128.6, 129.5, 131.9 (aryl), 165.3 (C=O).

The second fraction was 2.01 g (37%) of 1-(5-benzoyloxypentyl)-5-*t*-butoxymethyluracil **(9)**, mp 108–109°C (ether). FAB ms: (DMSO, glycerol, TCA) m/z (%) = 389 (M^+ + 1, 0.8). ^{1}H–Nmr (250 MHz, $CDCl_3$/TMS): δ 1.30 (9H, s, CH_3), 1.45–1.89 (6H, m, CH_2), 3.76 (2H, t, J = 7.4 Hz, CH_2), 4.22 (2H, s, CH_2), 4.33 (2H, t, J = 6.4 Hz, CH_2), 7.21 (1H, s, 6–H), 7.44–8.03 (5H, m, benzoyl), 9.04 (1H, br s, N3–H). ^{13}C–Nmr (62.5 MHz, $CDCl_3$/TMS): δ 23.0, 28.3, 28.7, 48.6, 64.4 (5 x CH_2), 27.5 (3 x CH_3), 56.3 (CH_2), 73.2 ($C(CH_3)_3$), 112.81 (C–5), 140.6 (C–6), 150.4 (C–2), 162.4 (C–4), 128.1, 129.3, 130.1, 132.6 (aryl), 166.3 (C=O). Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.26; N, 7.21. Found: C, 64.84; H, 7.33; N, 7.11.

5-(t-Butoxymethyl)-1-(5-hydroxypentyl)uracil **(10)**.

Compound **(9)** (1.05 g, 2.7 mmol) in a 1:1 mixture (80 ml) of MeOH and conc. ammonia was stirred at room temperature for one week. After evaporation, the residue was partitioned between ethyl acetate (50 ml) and water (25 ml). The aqueous layer was evaporated and the residue was chromatographed on silica gel (60 g, 0.04–0.063 mm) with $CHCl_3/CH_3OH$ (9:1, v/v) to give 0.59 g (77%) of 5-(*t*-butoxymethyl)-1-(5-hydroxypentyl)uracil **(10)**.

1,3-Bis(5-benzoyloxypentyl)thymine and 1-(5-benzoyloxypentyl)thymine **(13)**.

Thymine was alkylated according to the procedure described for alkylation of 5-t-butoxymethyluracil **(4h)**. Unreacted thymine (0.46 g) was collected by filtration. Chromatography of the crude product on a silica column using $CHCl_3/CH_3OH$ (99:1, v/v) gave as the first fraction 1.66 g (23%) of 1,3-bis(5-benzoyloxypentyl)thymine as a colorless oil. Ms: m/z (%) = 506 (M^+, 12), 105 (100). ^{1}H–Nmr (250 MHz, $CDCl_3$/TMS: δ 1.51 (4H, m, CH_2), 1.65–1.88 (8H, m, CH_2), 1.91 (3H, s, CH_3), 3.72 (2H, t, J = 7.2 Hz, CH_2), 3.98 (2H, t, J = 7.3 Hz, CH_2), 4.31 (2H, t, J = 5.9 Hz, CH_2), 4.33 (2H, t, J = 5.8 Hz, CH_2), 6.96 (1H, s, 6–H), 7.43 (4H, t, J = 7 Hz, m–ArH), 7.54 (2H, m, p–ArH), 8.03 (4H, dd, J = 7 and 1.3 Hz, o–ArH). ^{13}C–Nmr (62.5 MHz, $CDCl_3$/TMS): δ 13.0 (CH_3), 23.0, 23.5, 27.3, 28.3, 28.4, 28.7, 41.2, 49.2, 64.5, 64.8 (10 x CH_2), 109.8 (C–5), 128.3, 128.4, 129.5, 129.6, 130.3, 130.5, 132.9, 132.9 (2 x aryl), 138.3 (C–6), 151.4 (C–2), 163.7 (C–4), 166.6 (C=O), peak matching for $C_{29}H_{34}N_2O_6$: Calcd 506.2417. Found: 506.2437.

The second fraction was 0.97 g (22%) of 1-(5-benzoyloxypentyl)thymine **(13)**, mp 125-126°C (ether). Ms: m/z (%) = 316 (M^+, 38), 105 (100). ^{1}H–Nmr (250 MHz, $CDCl_3$/TMS): δ 1.50 (2H, m, CH_2), 1.71–1.85 (4H, m, CH_2), 1.90 (3H, s, CH_3), 3.73 (2H, t, J = 7.1 Hz, CH_2), 4.33 (2H, t, J = 6.3 Hz, CH_2), 7.00 (1H, s, 6–H), 7.45 (2H, t, J = 8 Hz, m–ArH), 7.56 (1H, m, p–ArH), 8.03 (2H, d, J = 8 Hz, o–ArH), 9.92 (1H, s, N3–H). ^{13}C–Nmr (62.5 MHz, $CDCl_3$/TMS): δ 12.1 (CH_3), 22.8, 28.1, 28.5, 48.0, 64.3 (5 x CH_2), 110.5 (C–5), 128.2, 129.3, 130.1, 132.7 (aryl), 140.1 (C–6), 150.9 (C–2), 164.3 (C–4), 166.4 (C=O). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.58; H, 6.44; N, 8.75.

1-(5-Hydroxypentyl)thymine (**12**).

Deprotection of **13** was performed in a similar manner as for **10** to afford **12**: mp 142–143°C (Lit.,[15] mp 140–142°C).

Table IV. Microanalyses or Peak Matchings of Compounds (**4–10**).

No.	Molecular formula	Calcd			Found		
		C	H	N	C	H	N
4e	$C_9H_{14}N_2O_4$	50.46	6.59	13.08	50.38	6.77	13.08
4g	$C_{13}H_{14}N_2O_3$	63.40	5.73	11.38	63.48	5.85	11.41
4h	$C_9H_{14}N_2O_3$	54.53	7.12	14.11	54.67	7.34	14.24
5a	$C_{18}H_{28}N_2O_7$	384.1896			384.1885		
5b	$C_{21}H_{34}N_2O_7$	426.2366			426.2387		
5c	$C_{21}H_{34}N_2O_7$	426.2366			426.2370		
5d	$C_{24}H_{32}N_2O_7$[a]						
5e	$C_{21}H_{34}N_2O_8$	442.2315			442.2330		
5f	$C_{25}H_{34}N_2O_7 \cdot \frac{1}{4}H_2O$	62.68	7.26	5.84	62.84	7.28	5.76
5g	$C_{25}H_{34}N_2O_7$[b]						
6a	$C_{12}H_{18}N_2O_5$	53.32	6.71	10.36	53.17	6.77	10.46
6b	$C_{15}H_{24}N_2O_5$	57.67	7.74	8.97	57.55	7.77	9.37
6c	$C_{15}H_{24}N_2O_5$	57.67	7.74	8.97	57.60	7.79	8.92
6d	$C_{18}H_{22}N_2O_5$	62.42	6.40	8.08	62.57	6.51	8.04
6e	$C_{15}H_{24}N_2O_6 \cdot \frac{1}{4}H_2O$	54.13	7.42	8.42	54.38	7.35	8.65
6f	$C_{19}H_{24}N_2O_5$	63.32	6.71	7.77	63.36	6.83	7.66
6g	$C_{19}H_{24}N_2O_5$	63.32	6.71	7.77	62.96	6.69	7.86
7a	$C_{10}H_{16}N_2O_4$	52.62	7.07	12.27	52.24	7.10	12.15
7b	$C_{13}H_{22}N_2O_4$	57.76	8.20	10.36	57.64	8.21	10.27
7c	$C_{13}H_{22}N_2O_4$	57.76	8.20	10.36	57.64	8.26	10.23
7d	$C_{16}H_{20}N_2O_4 \cdot \frac{1}{4}H_2O$	62.22	6.69	9.07	62.15	6.70	9.06
7e	$C_{13}H_{22}N_2O_5 \cdot \frac{1}{4}H_2O$	53.69	7.80	9.63	53.77	7.68	9.63
7f	$C_{17}H_{22}N_2O_4$	64.14	6.97	8.80	64.54	7.16	8.81
7g	$C_{17}H_{22}N_2O_4$	64.14	6.97	8.80	64.56	7.19	8.90
8	$C_{33}H_{42}N_2O_7 \cdot H_2O$	66.42	7.43	4.69	66.54	7.14	4.61
9	$C_{21}H_{28}N_2O_5$	64.93	7.26	7.21	64.84	7.33	7.11
10	$C_{14}H_{24}N_2O_4$	59.13	8.50	9.85	59.00	8.57	9.78

[a] FAB (glycerol, TCA): m/z (%) = 461 ($M^+ + 1$, 0.4), 91 (100).

[b] FAB (glycerol, TCA): m/z (%) = 475 ($M^+ + 1$, 1.2), 105 (100).

ACKNOWLEDGEMENTS

Danish Natural Science Research Counsil, Assurandør-Societetet in Denmark, and Egyptian Ministry of Higher Education are gratefully acknowledged for their support.

REFERENCES

1. D. E. Bloom and G. Carliner, *Science*, 1988, **239**, 604.
2. D. D. Richman, M. A. Fischl, M. H. Grieco, M. S. Gottlieb, P. A. Volberding, O. L. Laskin, J. M. Leedom, J. E. Groopman, D. Mildvan, M. S. Hirsch, G. G. Jackson, D. T. Durack, and S. Nusinoff-Lehrmann, *N. Engl. J. Med.*, 1987, **317**, 192.
3. P. Herdewijn, J. Balzarini, E. De Clercq, R. Pauwels, M. Baba, S. Broder, and H. Vanderhaeghe, *J. Med. Chem.*, 1987, **30**, 1270.
4. C. K. Chu, R. F. Schinazi, B. H. Arnold, D. L. Cannon, B. Doboszewski, V. B. Bhadti, and Z. Gu, *Biochem. Pharmacol.*, 1988, **37**, 3543.
5. C. Hansch and A. Leo, *Substitution Constants for Correlation Analysis in Chemistry and Biology*, John Wiley & Sons, New York, 1979.
6. B. P. Griffith, S. H. Chu, Z. H. Chen, D. Herring, and G. D. Hsiung, *International Conference on AIDS*, Stockholm, 1988, Abstr. No. 3020.
7. M. Dosmar and H. Witmer, *Current Microbiol.*, 1979, **2**, 361.
8. R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, 1959, **81**, 2521.
9. G. L. Bubbar and V. S. Gupta, *Can. J. Chem.*, 1970, **48**, 3147.
10. M. S. Motawia, A. E.–S. Abdel–Megied, E. B. Pedersen, C. M. Nielsen, and P. Ebbesen, *Acta Chem. Scand.*, 1992, **46**, 71.
11. J. Farkas and F. Sorm, *Coll. Czech. Chem. Commun.*, 1969, **34**, 1696.
12. T. Sasaki, K. Minamoto, T. Suzuki, and S. Yamashita, *Tetrahedron*, 1980, **36**, 865.
13. M. E. Synerholm, *J. Am. Chem. Soc.*, 1947, **69**, 2581.
14. J. Reefschläger, G. Herrmann, H. Jennrich, and N. Frost, *Acta virol.*, 1985, **29**, 185.
15. Y. F. Shealy, C. A. O'Dell, and M. C. Thorpe, *J. Heterocycl. Chem.*, 1981, **18**, 383.

Received, 26th September, 1991