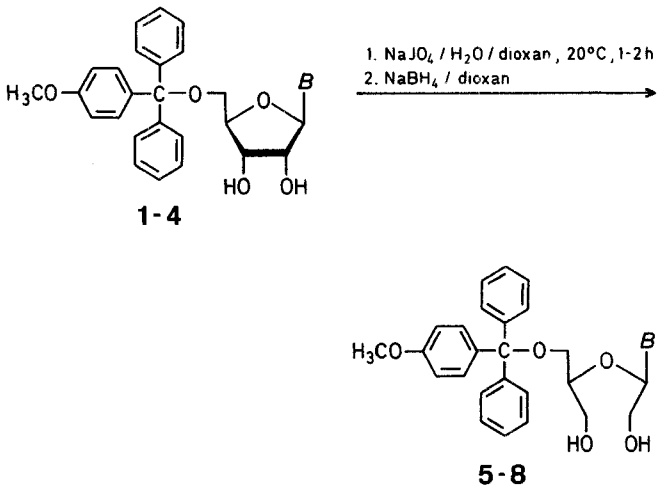

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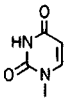
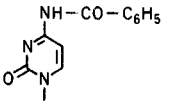
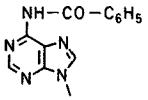
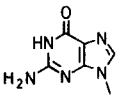
1,5	
2,6	
3,7	
4,8	

Convenient Synthesis of Partially Blocked Oxidized-Reduced Nucleosides

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The preparation and characterization of acyclic nucleoside analogs obtained by their periodate oxidation followed by sodium borohydride reduction was first described by Khym and Cohn[1]. Subsequent publications describe the preparative methods[2,3,4], but the yields of the final products were only 36–56%, because of difficulties in purification.

In the present investigation a simple procedure of oxidation and reduction was developed starting from readily available *N*-acyl-5′-monomethoxytritylnucleosides **1**–**4**[5]. The oxidation of these compounds in aqueous dioxan with a small excess of sodium periodate for 1–2 h at 20°C yielded the dialdehyde derivatives, which were reduced without isolation with sodium borohydride. The reduction proceeded quickly and the purification of the 1′,5′-dihydroxy-4′(*S*)-hydroxymethyl-3′-oxapent-2′(*R*)-yl derivatives **5**–**8** of the common nucleic bases involved a simple extraction with chloroform followed by precipitation with a hexane/ether mixture. Only the adenosine derivative **7** was obtained in crystalline form. The yields in this two-step procedure were 90–95%.

A large excess of sodium borohydride should be avoided in the reduction step as this could cause partial *N*-deacylation which would necessitate the use of chromatography on silica gel to purify the products.

The structures of the newly synthesized compounds **5**–**8** were confirmed by spectral data and microanalyses. The U.V. spectra of **5**–**8** were identical to those of the starting compounds **1**–**4**[5]. The ^{1}H-N.M.R. spectra of compounds **5**–**8** are more complicated than those of the parent nucleosides **1**–**4** due to the diastereotopy of the three HO—CH_2-groups. The presence, however, of two exchangeable triplets assigned to the primary hydroxy groups and of a non-exchangeable triplet due to the 1′-proton by coupling with the adjacent hydroxymethyl group adequately proves the structure **5**–**8**.

These nucleoside analogs may serve as convenient starting compounds in the preparation of various acyclic nucleosides and nucleotides in which the possibility of introduction of different blocking of the hydroxy groups[6] and the preserved chirality at C-4′ is most interesting from a structural point of view.

Table 1. Compounds **5**–**8** prepared

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	U.V. (methanol) λ_{max} [nm] (log ε)
5	95	–[b]	$C_{29}H_{30}N_2O_7$ (518.6)	231 (4.19); 261 (3.95)
6	93	–[b]	$C_{36}H_{35}N_3O_7$ (621.7)	234 (4.37); 259 (4.31); 305 (3.89)
7	90	191–192°	$C_{37}H_{35}N_5O_6$ (645.7)	232 (4.43); 281 (4.31)
8	93	–[b]	$C_{34}H_{37}N_5O_7$ (627.7)	235 (4.23); 255 (4.18); 260 (4.18); 270 (4.06); 281 (4.06)

[a] Satisfactory microanalyses obtained: C ±0.36, H ±0.46, N ±0.35.

[b] Amorphous foam.

Table 2. ^{1}H-N.M.R. Spectra[a] (DMSO-d_6, 25°C, δ [ppm], J [Hz] of Compounds **5–8**

Product	6-H, 5-H, 8-H, 2-H	Trityl Group $C(C_6H_5)_2$	$H_3CO—C_6H_4$	NH, OH[b]	*N*-Acyl groups	1′-H	2′-H, 2″-H, 3′-H, 4′-H, 4″-H	5′-H, 5″-H
5	7.63 (d, J = 8.0) 5.51 (d, J = 8.0)	7.3–7.2 (m)	7.16 (d, J = 8.9) 6.86 (d, J = 8.9), 3.73 (s)	11.35 (br.s), 5.12 (t, J = 5.9), 4.74 (t, J = 5.3)	–	5.79 (t, J = 5.8)	3.70–3.36 (m)	2.95 (m)
6	8.14 (d, J = 7.5)[c]	7.4–7.19 (m)	7.15 (d, J = 8.9), 6.85 (d, J = 8.9), 3.68 (s)	11.32 (br.s), 5.17 (t, J = 5.9), 4.77 (t, J = 5.5)	8.02 (d, J = 7.3) 7.63 (t, J = 7.3), 7.52 (t, J = 7.3)	5.99 (t, J = 5.0)	3.65–3.35 (m)	2.99 (m)
7	8.74 (s), 8.67 (s)	7.24–7.02 (m)	6.94 (d, J = 8.9), 6.78 (d, J = 8.9), 3.68 (s)	11.20 (br.s), 5.29 (t, J = 6.0), 4.85 (t, J = 5.5)	8.05 (d, J = 7.2), 7.64 (t, J = 7.2), 7.55 (t, J = 7.2)	6.04 (t, J = 6.1)	4.16–3.40 (m)	2.83 (m)
8	8.18 (s)	7.25–7.07 (m)	6.97 (d, J = 8.9), 6.79 (d, J = 8.9), 3.70 (s)	12.11 (br.s), 11.75 (br.s), 5.22 (t, J = 6.0)	2.85 (m, J = 6.7), 1.10 (d, J = 6.7), 1.09 (d, J = 6.7)	5.70 (t, J = 6.1)	3.98–3.35 (m)	2.80 (m)

[a] The traditional numbering system of nucleosides is preserved for the analogs **5–8** in order to underline their similarity.
[b] Exchangeable with D_2O.
[c] 5-H is overlapped by the signals of aromatic groups.

U.V.-Absorption spectra: Cary Recording Spectrometer (Model 118) of Applied Phys. ^{1}H-N.M.R. spectra: Bruker WM 250. Chromatography: T.L.C. on thin layer plates silica gel F LS 254 of Schleicher & Schüll. The substances were dried in a vacuum dessicator over phosphorus pentoxide. Melting points are not corrected.

Oxidation and Reduction of 1–4; General Procedure:
To a solution of the nucleoside **1–4** (5 mmol) in a mixture of dioxan (50 ml) and water (10 ml), a solution of sodium periodate (5.3 mmol) in water (10 ml) is added with stirring at 20°C. A precipitate of $NaIO_3$ is formed during or after the addition. The suspension is stirred at 20°C for 1–2 h. This time is needed for completion of the reaction according to checking by T.L.C. in chloroform/methanol (9/1). The dialdehyde derivatives move faster than the parent nucleosides which show an R_f of 0.4 for compounds **1** and **4** and R_f 0.6 for compounds **2** and **3**. Dioxan (50 ml) is then added, the suspension stirred for 10 min at 20°C, filtered, and the cake washed with dioxan (30 ml). To the combined filtrates sodium borohydride (5 mmol) is added and the mixture is stirred for 10–20 min at 20°C [the products **5–8** move slower than the parent nucleosides **1–4** on T.L.C. (9/1 chloroform/methanol)]. After addition of acetone (1 ml) and stirring for 5 min at 20°C the mixture is neutralized with 30% acetic acid and then evaporated to a volume of approximately 30–40 ml. This solution is shaken with chloroform (100 ml) and water (50 ml). The aqueous layer is again treated with chloroform (50 ml). The combined organic layers are washed with water (50 ml) and then dried with sodium sulfate. The filtrate is evaporated to dryness to yield an amorphous solid, except with the adenosine derivative **7** which crystallized and showed on treatment with acetone an m.p. of 191–192°C. The residue is then dissolved in a small amount of dichloromethane and added dropwise to a 2/1 hexane/ether (200 ml). The precipitate is collected, washed with the same solvent mixture, and dried. The characteristics of compounds **5–8** are presented in Tables 1 and 2.

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