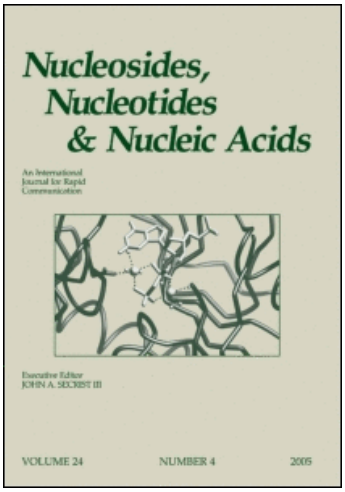

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Synthesis of Purine and Pyrimidine Trihydroxyacyclonucleosides

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SYNTHESIS OF PURINE AND PYRIMIDINE TRIHYDROXYACYCLONUCLEOSIDES

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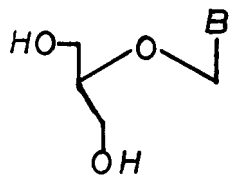
Abstract The [[3-hydroxy-2-bis(hydroxymethyl)-1-propoxy]methyl] derivatives of adenine, guanine, cytosine and thymine have been synthesized and tested against herpesviruses.

Introduction

Nucleoside analogues represent an important group of biologically active molecules (1). Nucleosides in which the cyclic carbohydrate moiety is replaced by acyclic chains have been shown to possess antiviral activity (2,3). We have introduced a novel class of ring-open nucleoside analogues, 1, (4-8) which we (9-12) and others (13-15) have shown to have remarkable activity against herpesviruses. We have found that the introduction of an additional hydroxymethyl group at the 3'-position (2) significantly reduces antiherpetic activity (16). We wish to report the synthesis of the new analogue system 3 in which the hydroxy functions are further removed from the base by the presence of an additional methylene group. The adenine, guanine, cytosine and thymine derivatives of 3 have been prepared and tested for activity against herpesviruses.



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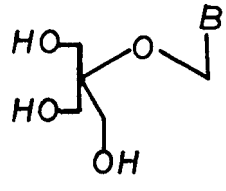

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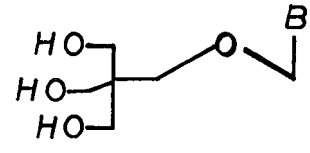

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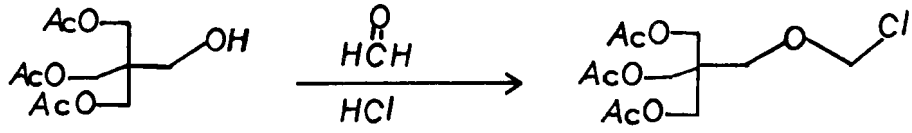
Results and Discussion

The key intermediate for the synthesis of compounds 3 is the chloromethyl ether of pentaerythritol triacetate (5). Pentaerythritol triacetate (4) was prepared according to a previously described procedure (17) and was converted to 5 using paraformaldehyde and HCl.

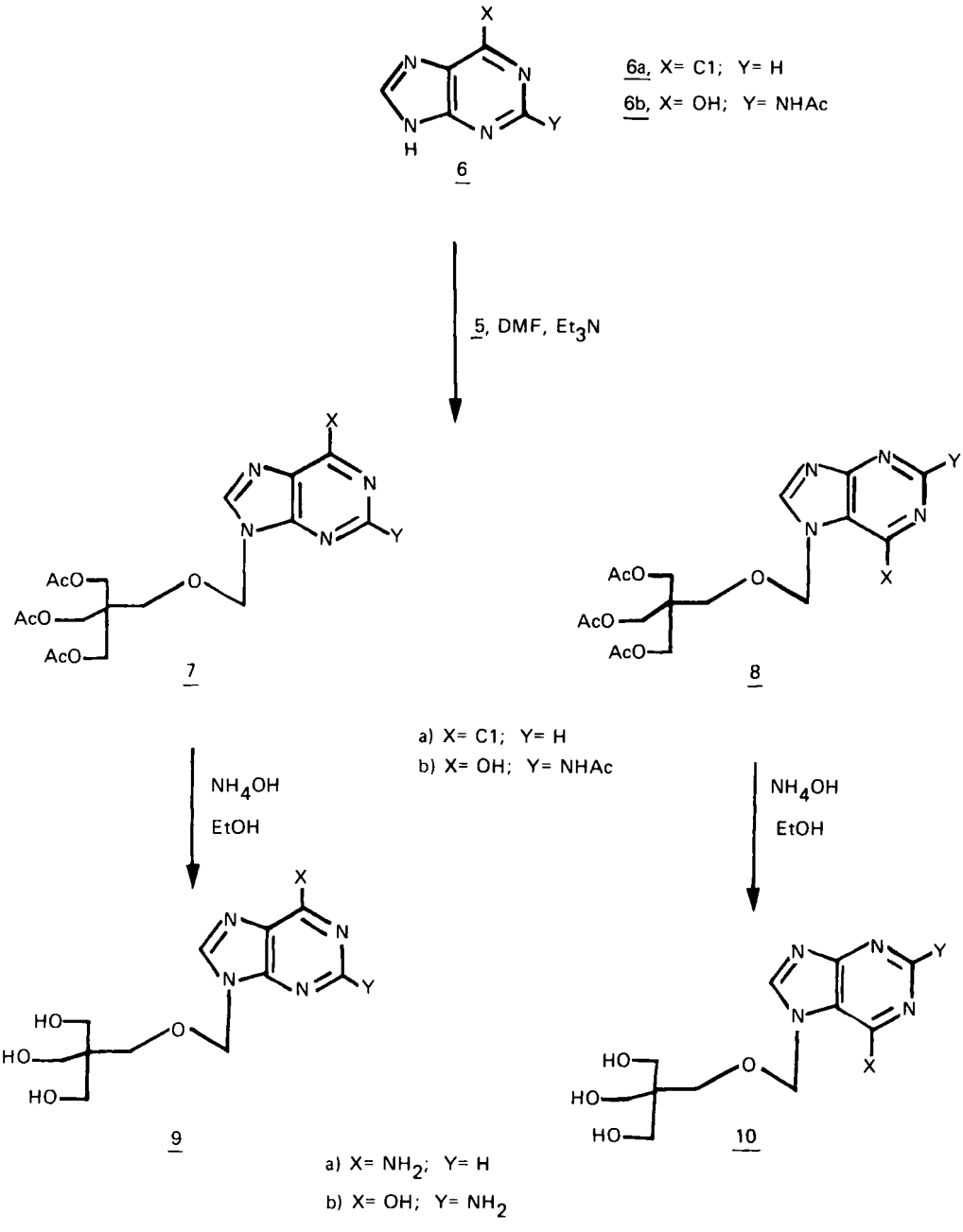


4 5

For the preparation of the adenine derivative (Scheme 1), 5 was condensed with 6-chloropurine in DMF with triethylamine. The N-9 (7a) and N-7 (8a) isomers were obtained in a ratio of 5:1. The isomers were easily separated and converted to their respective adenine derivatives (9a and 10a) with ammonium hydroxide in ethanol. The guanine derivatives 7b and 8b were obtained in a 1:2 ratio by condensing N-acetylguanine with 5. In this case the solution was heated to ensure an acceptable rate of reaction. The isomers were difficult to separate directly but were obtained by crystallization after partial separation by silica gel chromatography. Deprotection was carried out using ammonium hydroxide in ethanol to give 9b and 10b.

The pyrimidine derivatives were prepared using the silylated base procedure (5, 18, 19) and tetrabutylammonium iodide as catalyst (6). The protected products 12 were smoothly deprotected with ammonium hydroxide to give 13.

The physical properties of all new compounds are collected in Table 1, the PMR properties in Table 2 and elemental analyses are summarized in Table 3. The new compounds 7-10, 12 and 13 were submitted for testing against herpesviruses and all were found to have ED-50 values $\geq$ 100 µg/ml for HSV-1, HSV-2 and CMV. Clearly the introduction of the additional methylene group significantly reduced the biological activity. The ED-50 values vs HSV-1 for 1 and 2 where B = guanine are ~0.2 and 50 µg/ml respectively.



Scheme 1

TABLE 1

Physical Properties of Acyclonucleosides

Compound	Yield (%)	Melting Point (C°)	λmax (nm) 0.1N HCl	H_2O	0.1N NaOH	R_f
7a	49.5	105-107	263	263	264	0.46[a]
8a	9.8		266	267	268	0.33[a]
9a	64	180-181	255	258	258	0.43[b]
10a	53	216-217	270	267	268	0.31[b]
7b	12.7	194-195	259	258	262	0.14[c]
8b	24	140-141	261	262	267	0.32[c]
9b	84	238-240	253	250	265	0.49[d]
10b	80	>290 dec	249	284	280	0.55[d]
12a	50	134-135	264	265	265	0.58[c]
13a	45	142-143	264	265	265	0.07[c]
12b	85	168-171	275	268	267	0.17[c]
13b	64	165-166	275	268	267	0.39[b]

Solvents used were (a) $CHCl_3$-MeOH (95:5) ; (b) $CHCl_3$-MeOH (1:1)

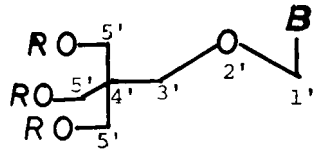
(c) $CHCl_3$-MeOH (9:1) ; (d) iPrOH-NH_4OH-H_2O (7:1:2)

TABLE 2

Proton Magnetic Resonance Data (δ,ppm)

Compound	H-1'	H-3'	H-5'	AcO	Other
5[a]	5.30	3.55	3.94	1.90	
7a[a]	5.64	3.48	3.98	1.92	H-2(8.23);H-8(8.75)
8a[a]	5.78	3.44	3.97	1.88	H-2(8.37);H-8(8.87)
9a[b]	5.50	complex at 3.29			H-2(8.15);H-8(8.23)
10a[b]	5.65	complex at 3.31			H-2(8.20);H-8(8.38)
7b[a]	5.33	3.54	4.08	2.02	AcN(2.33);H-8(7.72)
8b[a]	5.73	3.59	4.04	1.99	AcN(2.43);H-8(7.92)
9b[b]	5.29	complex at 3.29			H-8(7.78)
10b[b]	5.51	complex at 3.27			H-8(8.05)
12a[a]	5.08	3.51	4.03	1.99	H-6(7.06);CH_3(1.89)
13a[b]	5.01	complex at 3.32			H-6(7.54);CH_3(1.76)
12b[a]	5.12	3.47	3.95	1.93	H-5(6.50);H-6(7.55)
13b[b]	5.01	complex at 3.32			H-5(5.72,5.68) H-6(7.59,7.56)

a, $CDCl_3$; b, DMSO-d_6



Experimental

General Methods. Thin-layer chromatographic data (R_f values) are recorded from Merck Kisselgel 60F 254 analytical sheets, column chromatography was performed using Merck silica gel 60 (230-240) packed in glass columns using 15g of silica per gram of crude material. UV spectra were recorded on a Cary 17 spectrometer. Nuclear Magnetic

TABLE 3

Elemental Analyses

Compound	Molecular Formula	Calculated (%) C	H	N	Found (%) C	H	N
7a	$C_{17}H_{21}N_4O_7Cl$	47.62	4.94	13.07	47.47	5.01	12.84
8a	$C_{17}H_{21}N_4O_7Cl$	47.62	4.94	13.07	47.56	5.17	13.12
9a	$C_{11}H_{17}N_5O_4$	46.64	6.05	24.72	46.56	6.05	24.43
10a	$C_{11}H_{17}N_5O_4$	46.64	6.05	24.72	46.58	6.02	24.80
7b	$C_{19}H_{25}N_5O_9$	48.82	5.39	14.98	48.78	5.49	14.87
8b	$C_{19}H_{25}N_5O_9$	48.82	5.39	14.98	48.81	5.48	14.86
9b	$C_{11}H_{17}N_5O_5$ $1.5H_2O$	40.87	6.24	21.66	40.93	5.87	21.40
10b	$C_{11}H_{17}N_5O_5$ H_2O	41.91	6.07	22.21	41.84	5.66	21.76
12a	$C_{17}H_{24}N_2O_9$	51.00	6.04	7.00	51.03	6.01	6.76
13a	$C_{11}H_8N_2O_6$	48.17	6.61	10.21	47.95	6.57	9.96
12b	$C_{16}H_{23}N_3O_8 \cdot 2H_2O$	45.60	6.45	9.97	45.73	5.99	10.03
13b	$C_{10}H_{17}N_3O_5$	46.33	6.61	16.21	46.30	6.64	15.79

Resonance spectra were recorded using a Varian XL-200 spectrometer. Purine and pyrimidine bases were purchased from Sigma Chemical Company and pentaerythritol from Aldrich Chemical Company. C, H and N elemental analyses were performed by Canadian Microanalytical Service.

The Chloromethyl Ether 5. Pentaerythritol triacetate 4 (28.5g, 0.109 mole) (prepared according to a previously described procedure (17)), was dissolved in dichloromethane (200ml) in a 500ml three neck, round bottom flask. Paraformaldehyde (4g) and anhydrous calcium chloride (5g) were added. Dry hydrogen chloride gas was bubbled slowly into the solution with stirring for 2h. The reaction mixture was filtered quickly under vacuum over $CaCl_2$. The filtrate was concentrated under high vacuum. The NMR in $CDCl_3$ indicated the material was about 92% pure. Compound 5 was stable on standing and was used directly in the condensation reactions described below.

9-[[3-Acetoxy-2-bis(acetoxymethyl)propoxy]methyl]-6-chloropurine (7a) and 7-[[3-Acetoxy-2-bis(acetoxymethyl)propoxy]methyl]-6-chloropurine (8a)

6-Chloropurine (2.5g, 16.2 mmole) was dissolved in DMF (50ml) and triethylamine (2.5ml) and compound 5 (5g, 16.2 mmole) were added. The reaction mixture was stirred at room temperature for 2h. The solution was collected by filtration and the solvents were removed at reduced pressure. The residue was dissolved in a minimum of chloroform and applied to a silica gel column (15 x 4.5cm) which was eluted first with chloroform and then with 5% methanol in chloroform. The yield of compound 7a after crystallization from a mixture of chloroform-hexane (1:1) was 3.6g (49.5%). Compound 8a was obtained as an oily material in 0.6g (9.8%) yield. The properties of these compounds are collected in Tables 1 to 3.

9-[[3-Hydroxy-2-bis(hydroxymethyl)propoxy]methyl]adenine (9a) and 7-[[3-Hydroxy-2-bis(hydroxymethyl)propoxy]methyl]adenine (10a)

Each isomer 7a and 8a (0.5g, 1.15 mmole) was independently treated with 25ml of concentrated NH_4OH-ethanol (2:1) at room temperature for 16h. The solvents were removed and the residue was applied to a silica gel column which was eluted with chloroform:methanol (1:1). After crystallization from ethanol the yield of compound 9a was 0.215g (64%) and that of compound 10a was 0.177g (53%). Properties of 9a

and 10a are collected in Tables 1 to 3.

9-[[3-Acetoxy-2-bis(acetoxymethyl)propoxy]methyl]-N-acetylguanine (7b) and 7-[[3-Acetoxy-2-bis(acetoxymethyl)propoxy]methyl]-N-acetylguanine (8b).

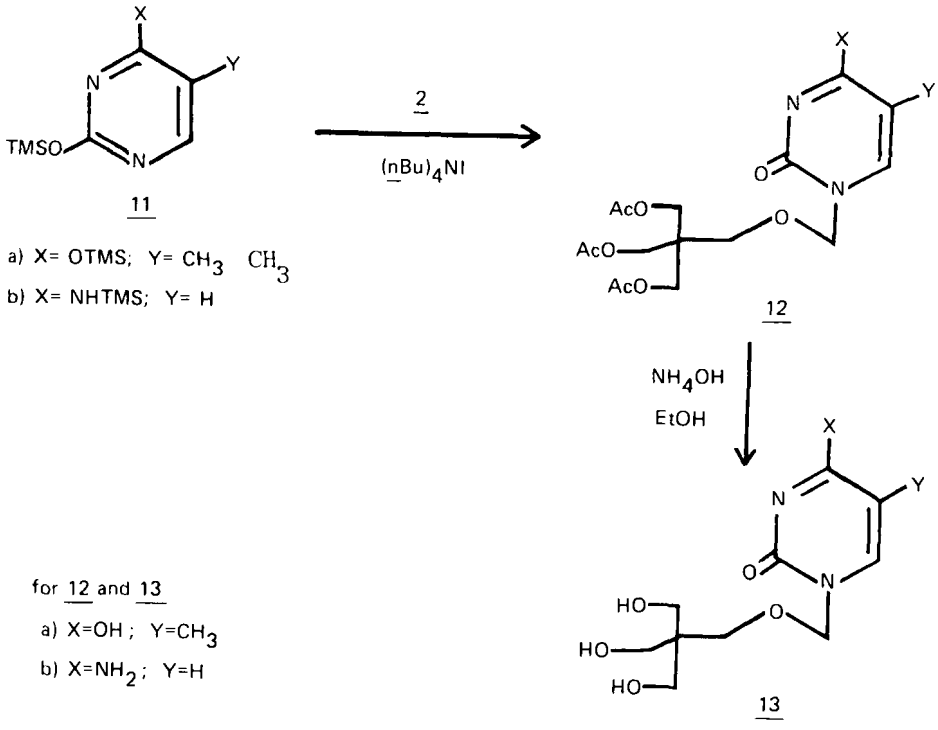
N-Acetylguanine (3.13g, 16.2 mmole) was dissolved in DMF (150ml) and triethylamine (2.5ml) and compound 5 (5g, 16.2 mole) were added. The reaction mixture was stirred at 70° for 5h. The solution was collected by filtration. The solvents were removed and the residue was extracted with chloroform. The extract was applied to a silica gel column which was eluted first with chloroform and then with 5% methanol in chloroform. Fractions containing mainly one of the isomers were combined and evaporated. After crystallization from ethyl acetate:hexane (4:1) 0.95g (12.7%) of compound 7b (slower moving) and 1.8g (24%) of compound 8b (faster moving) were obtained. Properties of compounds 7b and 8b are collected in Tables 1 to 3.

9-[[3-Hydroxy-2-bis(hydroxymethyl)propoxy]methyl]guanine (9b) and 7-[[3-Hydroxy-2-bis(hydroxymethyl)propoxy]methyl]guanine (10b).

Compounds 7b and 8b (0.38g, 0.81 mmole) were separately treated with 25ml of concentrated NH_4OH-ethanol (2:1) at room temperature for 16h. The solvents were removed and the residue was crystallized from water-ethanol (1:4) giving 0.2g (82%) of compound 9b and 0.19g (78%) of compound 10b. Properties of 9b and 10b are collected in Tables 1 to 3.

1-[[3-Acetoxy-2-bis(acetoxymethyl)propoxy]methyl]thymine (12a)

Thymine (2g, 15.9 mmole) and ammonium sulfate (1g) were added to hexamethyldisilazane (60ml). The mixture was heated at reflux with exclusion of moisture until the solution became clear. The solvent was removed at reduced pressure and the residue was dried under vacuum. The residue was dissolved in dichloromethane (50ml) and $(nBu)_4NI$ (63mg, 0.17 mmole) and chloromethyl ether 5 (6.2g, 20 mmole) were added. The mixture was heated at reflux for 2h. The solution was cooled to room temperature and diluted with water (10ml) and methanol (60ml). After stirring for 2 minutes the solvents were removed at reduced pressure and the residue was dissolved in dichloromethane (75ml). The solution



Scheme 2

was washed with saturated NaCl (aq), water and dried over Na_2SO_4. The solvent was removed and the residue was applied to a silica gel column which was washed with 5% methanol in chloroform. After crystallization from ether-ethanol (4:1), 3.2g (50%) of compound 12a was obtained. Properties are collected in Tables 1 to 3.

1[[3-Hydroxy-2-bis(hydroxymethyl)propoxy]methyl]thymine (13a)

This procedure was similar to that for the deprotection of compounds 7a and 8a, except that chloroform:methanol (85:15) was used for silica gel chromatography. The product was crystallized from ethanol:ethyl acetate(1:1) giving a 45% yield of compound 13a. Properties are collected in Tables 1 to 3.

1-[[3-Acetoxy-2-bis(acetoxymethyl)propoxy]methyl]cytosine (12b)

This procedure is similar to that for compound 12a except that the dichloromethane solution of the final product was not washed with saturated NaCl in water but was directly applied to a silica gel column which was washed with chloroform:methanol (9:1). After crystallization from ethanol:ethyl acetate (1:1) an 85% yield of 12b was obtained. Properties are collected in Tables 1 to 3.

1-[[3-Hydroxy-2-bis(hydroxymethyl)propoxy]methyl]cytosine (13b)

This procedure is similar to that for the deprotection of 7b and 8b except that 13b was crystallized from ethyl acetate:ethanol (1:2) and was obtained in a 64% yield. Properties are collected in Tables 1 to 3.

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