Synthesis and Properties of Unsaturated Halogeno-ketonucleosides. A New Route to Vinyl- and Epimino-nucleosides

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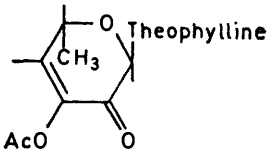
The first synthesis of unsaturated halogeno-ketonucleosides has been accomplished by oxidation of 3',4'-anhydro-hexosylpurines followed by the action of lithium halide on the keto-anhydro-intermediate. Nucleophilic additions to these new compounds were especially studied. Sodium borohydride was shown to add to the carbonyl group providing a new and simple route to unsaturated nucleosides. Hydrazoic acid added to the double bond by a 1,2-addition mechanism, leading to a triazolo-nucleoside. 1,4-Addition of cyclohexylamine followed by intramolecular elimination of bromine afforded an epimino-nucleoside, which constituted the first example of an aziridine derivative in the nucleoside field. The structure of the new compounds obtained was ascertained from a study of their ^1H and ^{13}C n.m.r. spectra.

We have recently reported [1] that sodium borohydride reduction of (3'-*O*-acetyl-4',6'-dideoxy-L-hex-3'-enopyranosulosyl)purines (1) affords 4',6'-dideoxynucleosides. We now report the synthesis of unsaturated and



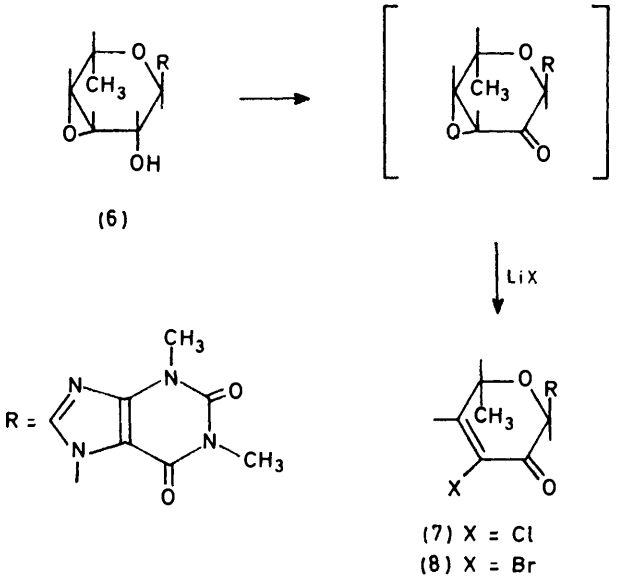
(1)

branched-chain sugar nucleosides by addition of nucleophilic reagents on αβ-unsaturated ketonucleosides. These compounds possess *in vitro* growth inhibitory activity on KB cancer cells [2,3] and number of them significant antitumour activity against leukaemia L 1210 in mice.[4]

Attempts to add nitromethane or amines to the αβ-unsaturated ketonucleosides, by the Michael reaction, were unsuccessful, because of the degradation of 3'-*O*-acetylketonucleosides. This instability in alkaline media may be explained by the probable formation of a 3'-ketonucleoside which undergoes spontaneous β-elimination of the nitrogenous base.

In order to avoid the formation of a 3'-ketonucleoside we tried to obtain αβ-unsaturated ketonucleosides with a halogen in the 3'-position, which should be more stable in alkaline medium. The desired halogeno-nucleosides could be prepared by oxidation of 7-(3',4'-anhydro-6'-deoxy-α-L-*talo*-hexopyranosyl)theophylline (6) with the dimethyl sulphoxide–dicyclohexylcarbodi-imide (DCC) system.[5] The ketonucleosides obtained were then treated with lithium halide according to a recently reported procedure.[6,7] 7-[3'-Chloro- (7) and 7-(3'-bromo-4',6'-dideoxy-α-L-*glycero*-hex-3'-enopyranosulosyl]theophylline (8) could be obtained by action of, successively, lithium chloride and lithium bromide on the epoxy keto-intermediate (Scheme 1), but attempts to obtain unsaturated fluoro- and iodo-nucleosides with lithium fluoride and lithium iodide were unsuccessful.

The study of nucleophilic addition was performed with the unsaturated bromo-ketonucleoside (8). Sodium borohydride was shown to add on the carbonyl group, whereas hydrazoic acid added to the double bond by a 1,2-addition mechanism. The case of cyclohexylamine was particularly interesting because this reagent added to (8) by a 1,4-addition mechanism leading to the corresponding epimino-nucleoside, the first example of an aziridine derivative in the case of nucleosides. In addition, this one-step reaction constitutes a new route to epimino-glucosides deriving from hexoses.[8]



SCHEME 1

The synthesis of 7-(3',4'-anhydro 6'-deoxy-α-L-*talo*-hexopyranosyl)theophylline (6) was accomplished by two methods. The first involves the treatment of 7-(6'-deoxy 3',4'-*O*-isopropylidene-α-L-*manno*-hexopyranosyl)theophylline (3) [9] with mesyl chloride and deacetalation by trifluoroacetic acid–methanol (90%) as described by Christensen and Goodman.[10] The 7-(6'-deoxy-4'-*O*-mesyl-α-L-*manno*-hexopyranosyl)theophylline (4) obtained was characterized by the presence of a mesyl group signal in the n.m.r. spectrum (δ 3.3). Treatment of (4) with 2N-sodium methoxide gave the desired anhydronucleoside (6). The structure, 7-(3',4'-

anhydro-6′-deoxy-α-L-*talo*-hexopyranosyl)theophylline (6), was determined by n.m.r. spectroscopy which showed $J_{4',5'}$ 3 Hz, indicating[11] that 2′-, 3′-, 4′-, and 5′-H were in a *cis*-relationship. This was consistent with the *talo*-configuration. A study of Dreiding models showed in addition that (6) was in a half-chair $^0H_1$ conformation.

The synthesis of (6) could also be accomplished by another approach involving the partial benzoylation of 7-(6′-deoxy-α-L-*manno*-hexopyranosyl)theophylline (2) with 12 mol. equiv. of benzoyl chloride in the presence of pyridine–dichloroethane.

Although Chittenden and Buchanan utilized pyridine–dichloromethane for the synthesis of 3′-*O*-benzoyl-4′,6′-*O*-benzylidene-β-D-galactopyranoside,[12] a systematic study of the use of co-solvents with the object of controlling the partial benzoylation of sugars has not been performed. Selective acylations of sugars are usually performed by utilizing low temperatures[13] and small quantities of acylating agents.[14] The use of co-solvents may permit control of the rate of esterification which increases depending on the solvent in the following order: ether < benzene < dichloroethane < acetone < acetonitrile < nitromethane.

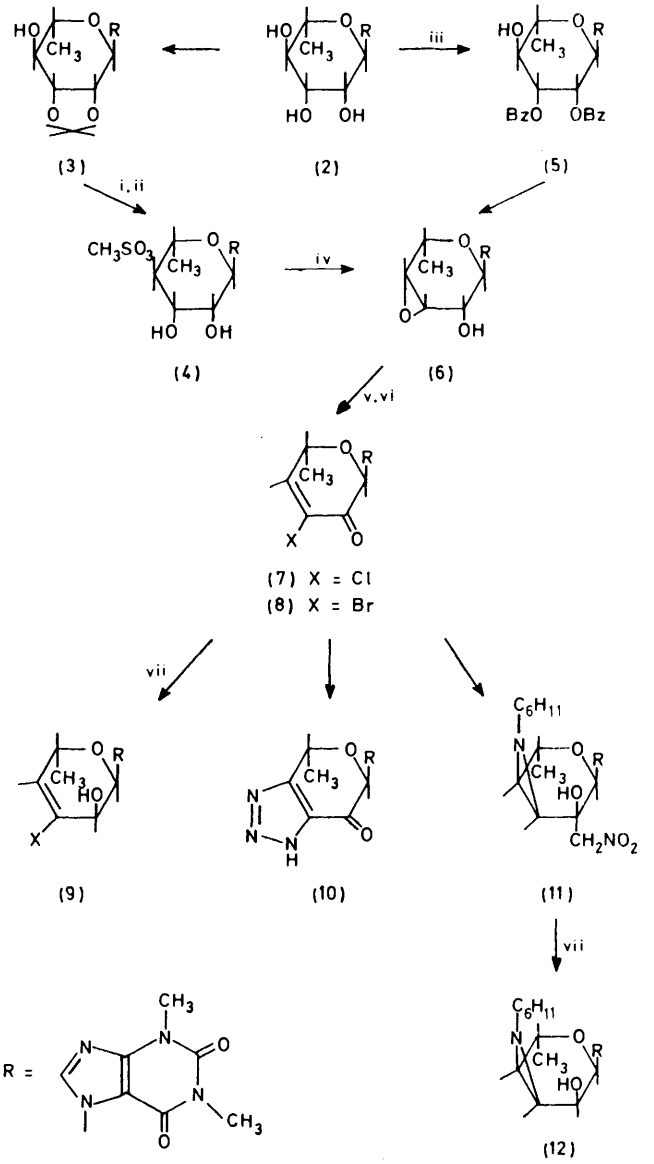
The dibenzoate (5) was isolated and purified. Its structure was determined from the n.m.r. spectrum. In acetone, 4′-H resonated at δ 4 whereas the 2′- and 3′-H signals shifted downfield (δ 6.3 and 5.9, respectively). 7-(6′-Deoxy-2′,3′-*O*-dibenzoyl-α-L-*manno*-hexopyranosyl)theophylline (5) was mesylated, then treated with 2N-sodium methoxide. The theophylline (6) was characterized by spectroscopic and analytical data as being identical with the compound prepared from (3).

Anhydronucleoside (6) was oxidized with the Moffatt reagent[5] to give an unstable compound which was directly treated with lithium chloride and lithium bromide in DMSO, to give, respectively, the compounds (7) and (8).

The bromo-ketonucleoside (8) was treated with sodium borohydride to afford the unsaturated deoxynucleoside (9). The n.m.r. spectrum of (9) revealed a small coupling constant $J_{1',2'}$ of 2 Hz, indicating an axial–equatorial correlation between 1′- and 2′-H and consequently equatorial addition of the hydride ion to the carbonyl (the 4′-H signal appears at δ 6.3 characteristic of vinylic protons). A 1,2-addition mechanism is therefore preferred for reduction of the unsaturated ketonucleoside (8) and as in the case of the theophylline (1) the hydride ion attacks from the side *trans* to the nitrogenous base.[1]

This reaction constitutes a new and simple route to unsaturated nucleosides.

In order to obtain 4′-amino-4′,6′-dideoxy-nucleosides we added nitrogen nucleophiles to (8). With sodium azide in aqueous ethanol containing ammonium chloride[15] an unexpected 1,2-addition of hydrazoic acid occurred across the double bond to afford a 3′,4′-triazolo-nucleoside. The n.m.r. spectrum of 7-(3′,4′,6′-trideoxy-3′,4′-triazolo-α-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (10) revealed only two protons in the glycosidic ring [δ 6.9 (1′-H) and 5.5 (5′-H)] indicating an unsaturated ketonucleoside. The structure of (10) was confirmed from the u.v. absorption spectrum which showed two chromophores, at 274 nm due to the heterocyclic base and at 252 nm characteristic of 1,2,3-triazoles. As in the case

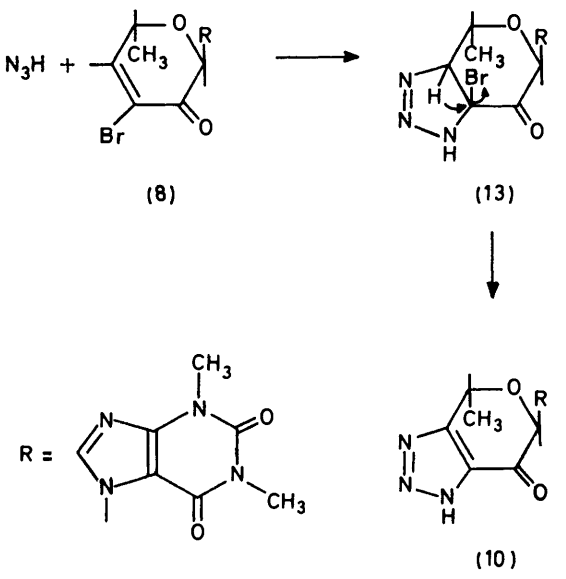


SCHEME 2 Reagents: i, CH_3SO_2Cl; ii, CF_3CO_2H–MeOH; iii, BzCl–C_5H_5N–$C_2H_4Cl_2$; iv, CH_3ONa; v, DMSO–DCC; vi, LiX; vii, $NaBH_4$

of addition of organic azides to olefins with electron-withdrawing substituents,[16] hydrazoic acid should add to the unsaturated bromo-ketonucleoside (8) by the 1,2-addition mechanism to yield a triazoline (13). By elimination of hydrobromic acid, this intermediate afforded the 3′,4′-triazolo-ketonucleoside (10) (Scheme 3).

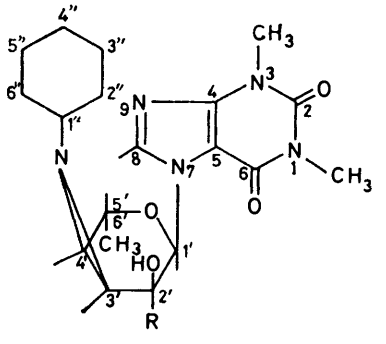
The addition of nitromethane to (8) was accomplished

by using cyclohexylamine rather than sodium methoxide as catalyst. Under these conditions we obtained the cyclohexylaminonucleoside (11), confirmed by its n.m.r. spectrum which revealed between δ 1.3 and 1.5 the



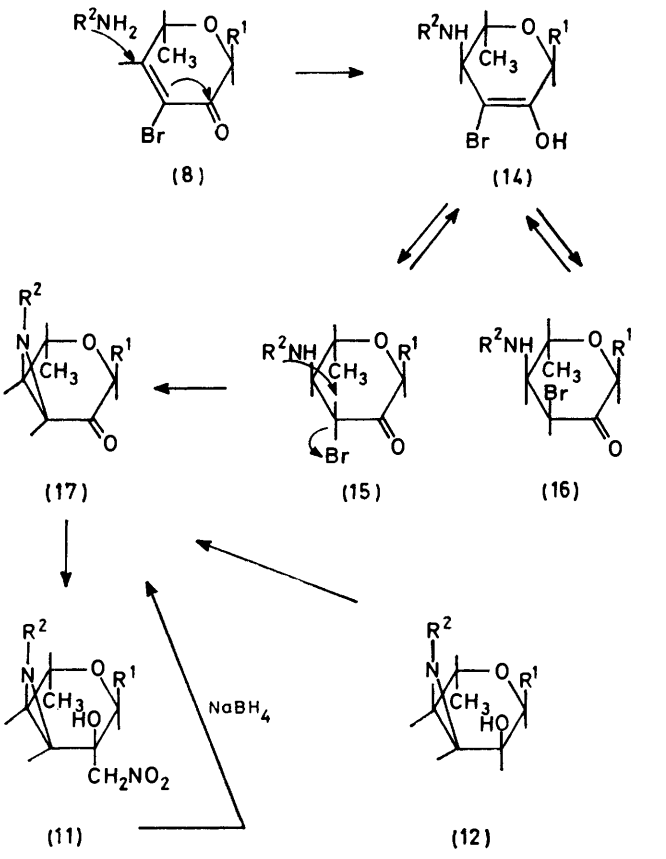
SCHEME 3

signals for the 11 protons of cyclohexylamine. Nevertheless the 1′-H signal, which appeared as a singlet, suggests the possibility of the presence of a carbonyl group in the sugar moiety; we therefore reduced (11)



(11) R = CH_2NO_2
(12) R = H

and obtained 7-(3′,4′-cyclohexylepimino-3′,4′,6′-trideoxy-α-L-*allo*-hexopyranosyl)theophylline (12). In the n.m.r. spectrum of (12) we observed that the 3′- and 4′-H signals were weakly shifted indicating that C-3′ and -4′ were attached to the nitrogen of the cyclohexylamine group forming the epime. In addition the absence of coupling between 4′- and 5′-H, as well as the small



SCHEME 4

value of $J_{1',2'}$ (2 Hz), indicated [11] that 3′- and 4′-H were *cis* to 1′- and 2′-H. These relationships indicated that the epimino-nucleoside (12) had the L-*allo*-configuration.

Thus, a comparative study of the n.m.r. spectra of (11)

^{13}C N.m.r. data for epimino-nucleosides (11) and (12) [a,b]

	Theophylline δ(p.p.m.)					Cyclohexyl δ(p.p.m.)				Epimino-sugar δ(p.p.m.)					
Compound	C-2, -6	C-4	C-5	C-8	NCH_3	C-1″	C-2″, -6″	C-3″, -5″	C-4″	C-1′	C-2′	C-3′, -4′	C-5′	C-6′	CH_2NO
(11)	155,57	148,57	105,96	142,46	28.03	67	31,86	24,39	25,85	76.74	66	41,42	72	17,2	77,46
	151,47				29.85		32,3					41,78			
(12)	155,48	148,88	105.68	141,60	27,94	67,13	32,36	24,44	25,94	77.65	60.85	38,96	71,68	17,29	
					29,81							40,87			

[a] Measured in $CDCl_3$ solution with Me_4Si as internal standard. [b] The signals were assigned on the basis of their multiplicities in off-resonance decoupled spectra and by consideration of known substituent effects.

and (12) clearly showed that (11) had an aziridine ring at the 3′ and 4′ positions. On the other hand, the presence of two strongly coupled doublets at δ 5.1 and 5.6 provided evidence that a nitromethyl group was attached to the 2′-position of the nucleoside, and not a carbonyl group as suggested by the reaction of sodium borohydride with (11). In these conditions the addition of nitromethane to (8) in the presence of cyclohexylamine afforded the theophylline (11). The structures of (11) and (12) have also been confirmed by their ^{13}C n.m.r. spectra (Table).

The formation of nucleoside (11) can be explained by a two-step mechanism. First there is a 1,4-addition, as postulated by Cromwell and Cram [17] for the synthesis of an aziridinone, by the action of cyclohexylamine on an αβ-unsaturated halogenoketone followed by addition of nitromethane to the ketone formed.

Addition of cyclohexylamine at C-4 of (8) from the opposite side of the 6-methyl group led to an amino-bromoenol (14) which tautomerized to the *arabino*-ketonucleoside (15) and the *ribo*-ketonucleoside (16). Because the amino and bromo groups were *trans*-diaxial in the *arabino*-isomer (15), intramoledular nucleophilic attack of the amine occurred leading to the cyclohexyl-epimino-ketonucleoside (17) which afforded the 2′-*C*-nitromethyl-epimino-nucleoside (11) by addition of nitromethane. Synthesis of (12) by the action of $NaBH_4$ on (11) can be explained by the elimination of a nitromethyl group leading to the *ribo*-ketonucleoside (17), which was immediately reduced.

EXPERIMENTAL

Solutions were evaporated at 40 °C under reduced pressure. U.v. spectra were measured with a Varian-Techtron model 635 spectrophotometer. I.r. spectra were determined for potassium bromide pellets by use of a Perkin-Elmer model 137 spectrometer. N.m.r. spectra were recorded with a Varian T-60 instrument using tetramethylsilane as internal standard, and decoupling was effected with a Varian T-6059 spin decoupler, using the frequency-sweep mode. Optical rotations were determined with a Roussel–Jouan Quick polarimeter. Reactions were monitored by t.l.c. on Schleicher and Schull plastic sheets. Nucleoside spots were detected by visual examination under u.v. light and by spraying with 30% sulphuric acid and heating at 105 °C. M.p.s are uncorrected. Elemental analysis were obtained from the Laboratoire de Microanalyse du C.N.R.S.

7-(6′-*Deoxy*-4′-O-*mesyl*-α-L-manno-*hexopyranosyl*)*theophylline* (4).—To a solution of 7-(6′-deoxy-2′-,3′-*O*-isopropylidene-α-L-*manno*-hexopyranosyl)theophylline [9] (3) (10 g, 27.7 mmol) in pyridine (150 ml), mesyl chloride (4.68 ml, 60.5 mmol) was added. After 2 h at room temperature, the solution was concentrated. The remaining oil was dissolved in chloroform and washed with water (2 × 50 ml). The organic phase was dried (Na_2SO_4) and evaporated. The syrupy residue was then dissolved in trifluoroacetic acid–methanol (9 : 1 v/v; 50 ml). After 30 min at room temperature the solution was concentrated and the *methylsulphonylnucleoside* (4) crystallized from ethanol (10.1 g, 90%), m.p. 185°; $[\alpha]_D^{20}$ −45° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 274 nm (ε 8 200); $\nu_{max.}$ (KBr) 1 720 (C=O, base) and 1 680 cm^{-1} (base, conjugated C=O); R_F 0.7 [ethyl acetate–MeOH (85 : 15)]; δ(CD_3CO_2D) 8.45, 6.6 (d, $J_{1',2'}$ 7.5 Hz), 3.7 (s), 3.5 (s), 3.3 (s, CH_2SO_2), and 1.6 (d, $J_{5',6'}$ 7 Hz) (Found: C, 41.2; H, 4.65; N, 14.05. $C_{14}H_{20}N_4O_8S$ requires C, 41.6; H, 4.95; N, 13.85%).

7-(2′,3′-*Dibenzoyl*-6′-*deoxy*-α-L-manno-*hexopyranosyl*)*theophylline* (5).—To a solution of 7-(6′-deoxy-α-L-*manno*-hexopyranosyl)theophylline [18] (2) (1 g, 3 mmol) in pyridine (10.5 ml), dichloroethane (66 ml) and benzoyl chloride (3.45 ml, 36 mmol) were added. The reaction was stopped after 3 min by addition of methanol (40 ml). The solution was stirred during 40 min, then evaporated, and the residue was dissolved in chloroform (100 ml) and washed with water (50 ml). The organic phase was dried (Na_2SO_4) and evaporated. The oil obtained was dissolved in chloroform, applied to a silica gel (Merck 60) column (diam. 2 cm) packed in chloroform, and eluted with chloroform until the disappearance of methyl benzoate. Elution was continued with chloroform–acetone (250 ml; 9 : 1 v/v) and finally with ethyl acetate (300 ml). The *dibenzoyl nucleoside* (5) was isolated after evaporation of the solvents as a semi-crystalline compound (1.12 g, 70%), $[\alpha]_D^{20}$ −75° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 274 nm (ε 8 000); $\nu_{max.}$ (KBr) 1 740 cm^{-1} (C=O); R_F 0.65 (ethyl acetate); δ(CD_3COCD_3) 8.4 (s), 7.0 (d, $J_{1',2'}$ 9 Hz), 6.3 (q, $J_{2',3'}$ 3 Hz), 5.9 (t, $J_{3',4'}$ 3 Hz), 3.4 (s), 3.2 (s), and 1.6 (d, $J_{5',6'}$ 7 Hz) (Found: C, 60.1; H, 5.15; N, 10.15. $C_{27}H_{26}N_4O_8$ requires C, 60.65; H, 4.85; N, 10.5%).

7-(3′,4′-*Anhydro*-6′-*deoxy*-α-L-talo-*hexopyranosyl*)*theophylline* (6).—(a) To a solution of (5) (534 mg, 1 mmol) in pyridine (10 ml) mesyl chloride (0.156 ml, 2 mmol) was added. After 2 h at room temperature the mixture was concentrated and the residue was dissolved in chloroform and washed with water (2 × 25 ml). The organic phase was dried (Na_2SO_4) and evaporated to give a syrup (602 mg, 1 mmol) which was dissolved in methanol (8 ml)–2N-sodium methoxide (0.75 ml, 1.5 mmol) and stirred during 20 min at room temperature. The solution was then neutralized with Amberlite IR 120 and evaporated to give directly the *anhydronucleoside* (6) as a solid which was recrystallized from methanol to give pure (6) (0.28 g, 90%), m.p. 203°; $[\alpha]_D^{20}$ −70° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 275 (ε 8 000) $\nu_{max.}$ (KBr) 1 720 (C=O, base), 1 670 (base, conjugated C=O), and 3 300 cm^{-1} (HO) ; R_F 0.45 [$CHCl_3$–MeOH (9 : 1)]; δ[$(CD_3)_2NCDO$] 8.4 (s), 6.1 (d, $J_{1',2'}$ 8.70 Hz), 4.8 (q, $J_{2',3'}$ 1.5 Hz), 4.5 (octet, $J_{4',5'}$ 3 Hz), 3.5 (s), 3.3 (s), and 1.4 (d, $J_{5',6'}$ 7 Hz) (Found: C, 50.5; H, 5.25; N, 18.1. $C_{13}H_{16}N_4O_5$ requires C, 50.65; H, 5.2; N, 18.2%).

(b) 7-(6′-Deoxy-4′-mesyl-α-L-*manno*-hexopyranosyl)-theophylline (4) (10 g, 25 mmol) were suspended in methanol (400 ml) and 2N-sodium methoxide (13.6 ml, 27.2 mmol) was added. After 30 min at room temperature the nucleoside was dissolved and the anhydronucleoside (6) was collected by filtration. Recrystallization from ethanol–water gave pure (7 g, 90%); the product was identical in all respects with that obtained by method (a).

7-(3′-*Chloro*-3′,4′,6′-*trideoxy*-α-L-glycero-*hex*-3′-*enopyranos*-2′-*ulosyl*)*theophylline* (7).—To a solution of (6) (4 g, 13 mmol) in dimethyl sulphoxide (64 ml), DCC (13.46 g, 64.7 mmol), ethyl acetate (40 ml), and dichloroacetic acid (1.45 ml, 13 mmol) were added and the mixture was kept for 15 min at room temperature. It was then cooled to 0 °C and diluted by the addition of ethyl acetate (120 ml). Oxalic acid was added to destroy the excess of DCC and dicyclohexyurea was removed by filtration. Ethyl acetate

was evaporated and lithium chloride (3.8 g, 90 mmol) was added to the remaining DMSO solution which was heated at 45° and stirred during 15 min. After dilution with water (700 ml) the nucleoside was extracted with chloroform (3 × 20 ml). The organic phase was dried (Na_2SO_4) and evaporated to a syrup which crystallized from ethanol. The unsaturated *ketonucleoside* (7) (1.45 g, 40%) was recrystallized from methanol, m.p. 148°; $[\alpha]_D^{20}$ +7.5° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 272 (ε 8 500) and 255 nm (9 200); $\nu_{max.}$ (KBr) 1 720 (C=O, base) and 1 670 cm^{-1} (base, conjugated C=O); R_F 0.54 (ethyl acetate); δ($CDCl_3$) 7.6 (s), 7.3 (d, $J_{4',5'}$ 3.5 Hz), 6.8 (s), 4.8 (s), 3.6 (s), 3.4 (s), and 1.6 (d, $J_{5',6'}$ 7 Hz) (Found: C, 48.05; H, 4.1; N, 17.3. $C_{13}H_{13}ClN_4O_4$ requires C, 48.05; H, 4.0; N, 17.25%).

7-(3′-*Bromo*-3′,4′,6′-*trideoxy*-α-L-glycero-*hex*-3′-*enopyranos*-2′-*ulosyl*)*theophylline* (8).—The procedure for (7) was utilized for the preparation of (8) from (6) (4 g, 13 mmol). The only difference consists in the use of lithium bromide (7 g, 80 mmol) instead of lithium chloride. The *bromoketonucleoside* (8) (3.60 g, 75%) was crystallized from ethanol and recrystallized from ethanol–chloroform (95 : 5), m.p. 171—172°; $[\alpha]_D^{20}$ −10° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 267 nm (ε 11 200); $\nu_{max.}$ (KBr) 1 715 (C=O, base) and 1 670 cm^{-1} (base, conjugated C=O); R_F 0.6 (ethyl acetate); δ($CDCl_3$) 7.6 (s), 7.5 (d, $J_{4',5'}$ 3 Hz), 6.8 (s), 4.8 (octet), 3.6 (s), 3.4 (s), and 1.5 (d, $J_{5'6'}$ 7 Hz) (Found: C, 41.9; H, 3.5; N, 14.5. $C_{13}H_{13}BrN_4O_4$ requires C, 42.3; H, 3.5; N, 15.15%).

7-(3′-*Bromo*-3′,4′,6′-*trideoxy*-α-L-erythro-*hex*-3′-*enopyranosyl*)*theophylline* (9).—Bromo-ketonucleoside (8) (369 mg, 1 mmol) was dissolved in chloroform (2.5 ml)–methanol (7.5 ml). Sodium borohydride (150 mg, 4 mmol) was added and the mixture stirred at room temperature for 10 min. Water (30 ml) was added and the mixture extracted with ethyl acetate (2 × 50 ml). The organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. The unsaturated *deoxynucleoside* (9) (0.25 g, 65%) was crystallized from benzene and recrystallized from methanol, m.p. 166°; $[\alpha]_D^{20}$ +157.5° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 274 nm (ε 8 500); $\nu_{max.}$ (KBr) 1 720 (C=O, base), 1 670 (base, conjugated C=O), and 1 640 cm^{-1} (C=C); R_F 0.63 (ethyl acetate); δ($CDCl_3$) 8 (s), 6.5 (d, $J_{1',2'}$ 2 Hz), 6.3 (d, $J_{4',5'}$ 3 Hz), 4.5 (m), 4.4 (d), 3.5 (s), 3.3 (s), and 1.4 (d, $J_{5',6'}$ 7 Hz) (Found: C, 40.75; H, 4.35; N, 14.6. $C_{13}H_{15}BrN_4O_4,H_2O$ requires C, 40.15; H, 4.35; N, 14.4%).

7-(3′,4′,6′-*Trideoxy*-3′,4′-*triazolo*-α-L-glycero-*hex*-3′-*enopyranosulosyl*)*theophylline* (10).—To a solution of sodium azide (325 mg, 5 mmol) and ammonium chloride (120 mg, 6.3 mmol) in water (2 ml) and ethanol (6 ml) unsaturated ketonucleoside (8) (370 mg, 1 mmol) was added and the mixture stirred at room temperature. After complete dissolution, water (12 ml) was added and the solution neutralized with Amberlite IR 120. The nucleoside was extracted with chloroform (3 × 25 ml) and the organic phase dried (Na_2SO_4) and evaporated. Triazolonucleoside (10) (0.20 g, 70%) was crystallized from ethanol, m.p. 204—205°; $[\alpha]_D^{20}$ −12.5° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 274 (ε 10 200) and 252 nm (10 600); $\nu_{max.}$ (KBr) 1 740 (C=O) and 1 680 cm^{-1}; R_F 0.7 [ethyl acetate–MeOH (85 : 15)]; δ(CD_3CO_2D) 8.2 (s), 6.9 (s), 5.5 (q, $J_{5',6'}$ 7 Hz), 3.6 (s), 3.3 (s), and 1.8 (d) (Found: C, 46.9; H, 4.05; N, 29.85. $C_{13}H_{13}N_7O_4$ requires C, 47.1; H, 3.9; N, 29.6%).

7-(3′,4′-*Cyclohexylamino*-3′,4′-*dideoxy*-2-C-*nitromethyl*-α-L-ribo-*hexopyranosyl*)*theophylline* (11).—To a solution of unsaturated ketonucleoside (8) (370 mg, 1 mmol) in nitromethane (10 ml), cyclohexylamine (1.15 ml, 10 mmol) was added. After 60 min at room temperature the solution was neutralized with 12N-hydrochloric acid (0.7 ml), then diluted with chloroform (30 ml). The organic phase was washed with water (5 ml), dried, and evaporated. Cyclohexane (2 × 10 ml) was distilled from the residue which crystallized as a hydrochloride (0.25 g, 70%) from propan-2-ol–concentrated hydrochloric acid (0.2 ml), m.p. 158° (decomp.); $[\alpha]_D^{20}$ 120° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 276 nm (ε 7 600); R_F 0.8 (ethyl acetate); δ (C_5D_5N) 8.6 (s), 6.5 (s), 5.6 (d, $^2J_{CH_2NO_2}$ 13 Hz), 5 (d), 3.5 (s), 3.3 (s), 3.1 (d, $J_{3',4'}$ 6.5 Hz), 2.1 (d) and 1.5 (d, $J_{5',6'}$ 7 Hz) (Found: C, 45.9; H, 5.75; N, 15.95; Cl, 12.75. $C_{20}H_{28}N_6O_6,2HCl$ requires C, 46.05; H, 5.75; N, 16.15; Cl. 13.6%).

7-(3′,4′-*Cyclohexylepimino*-3′,4′,6′-*trideoxy*-α-L-galacto-*hexopyranosyl*)*theophylline* (12).—Sodium borohydride (380 mg, 10 mmol) was added to a stirred solution of nitronucleoside (11) (390 mg, 0.75 mmol) in methanol (2 ml). After 10 min water (20 ml) was added and the mixture was extracted with ethyl acetate (3 × 25 ml). The organic phase was dried (Na_2SO_4), then evaporated to dryness. *Epimino-nucleoside* (12) (0.26 g, 66%) was crystallized from ethanol, m.p. 156—157°; $[\alpha]_D^{20}$ +155° (*c* 0.1 in MeOH); $\lambda_{max.}$ (MeOH) 274 (ε 8 400); $\nu_{max.}$ (KBr) 1 720 (C=O, base) and 1 680 cm^{-1} (base, conjugated C=O); R_F 0.7 (ethyl acetate); δ(CD_3NO_2) 8 (s), 6 (d, $J_{1',2'}$ 2 Hz), 4.4 (q $J_{5',6'}$ 7 Hz), 4.1 (q, $J_{2',3'}$ 7 Hz), 3.4 (s), 3.2 (s), 2.5 (t, $J_{3',4'}$ 6.5 Hz), 1.9 and 1.5 (d) (Found: C, 58.5; H, 7.0; N, 17.9. $C_{19}H_{27}N_5O_4$ requires C, 58.6; H, 6.95; N, 18.0%).

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