Studies on the Sodium Borohydride Reduction of Unsaturated Keto Nucleosides. Novel Route to Deoxy Nucleosides

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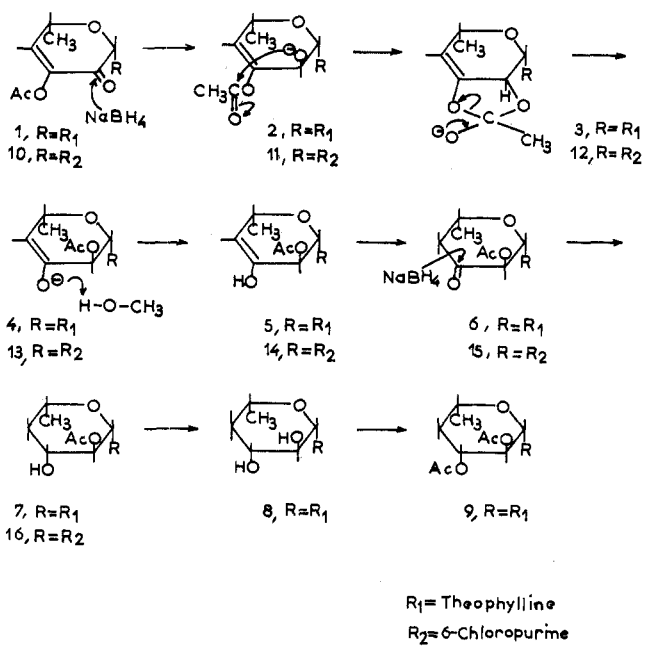
Reduction of α,β-unsaturated (ketohexosyl)purines, which constitute the first examples of unsaturated keto nucleosides, with sodium borohydride gave the corresponding deoxy nucleosides. Contrary to the recently reported (4′,6′-dideoxy-β-L-*glycero*-hex-3′-enopyranosulosyl)purines, which were obtained by acetylation of the corresponding keto nucleosides, the α anomer, subsequently described, was prepared by oxidation of the partially protected deoxyhexosylpurine. The mechanisms of these reductions were established by a study of the NMR spectra of the deoxy nucleosides using $NaBH_4$ in deuterated solvents and sodium borodeuteride in light solvents. 1,2 addition of the hydride was shown to be the mode of reduction of all the studied α- and β-unsaturated keto nucleosides. The ready availability of these unsaturated keto nucleosides provides extremely useful synthetic intermediate nucleosides especially for the preparation of nucleosides containing rare deoxy sugars.

The recent synthesis of the first unsaturated keto nucleosides[1,2,4] permitted the demonstration that these new nucleosides not only exhibit growth inhibitory activity against KB cells[3] but that they may constitute important synthetic intermediates in the nucleoside field owing to their stability in various media.[1-5]

We now report a study of the reduction of the recently synthesized unsaturated β-keto nucleosides **1**[4] and **10**[2] and that of the α isomer (**17**) subsequently described. These metal hydride reductions constitute in addition a new and facile route to deoxyhexosylpurines from (ketohexosyl)purines. It

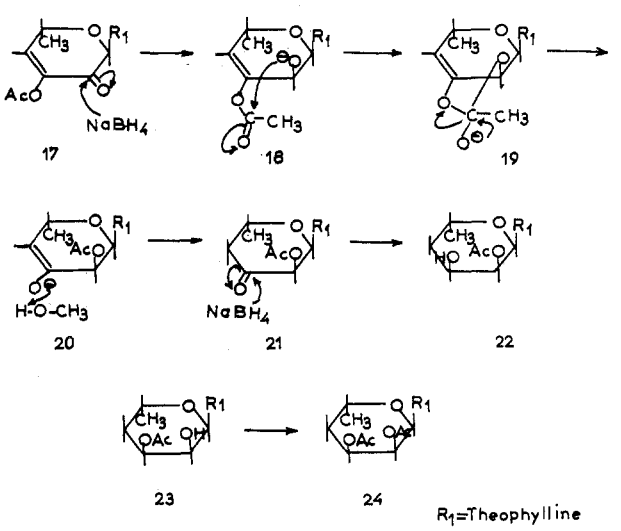
Scheme I



is also important to note that the study of the mechanisms could permit us to establish novel approaches to the synthesis of branched chain sugar nucleosides by nucleophilic addition.

As will be seen, the configuration of the molecule appears to have a real effect upon the direction of the attack of the carbonyl group. Thus, it was shown that reduction of both 7-(3′-*O*-acetyl-4′,6′-dideoxy-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (**1**)[4] and its 6-chloropurine derivative (**10**) in methanol led to the saturated dideoxy nucleosides **7** and **16** having an equatorial OH-2′ whereas reduction of the α isomer (**17**) afforded the dideoxy derivative possessing an axial OH-2′ (**23**).

Scheme II



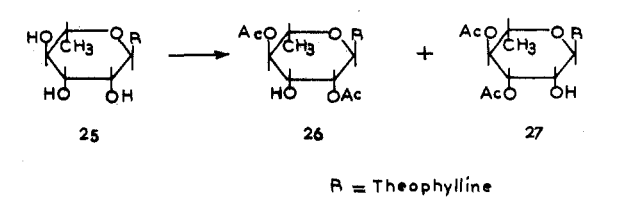
In the NMR spectra the anomeric protons of both **7** and **16** exhibited large coupling constants $J_{1',2'} = J_{2',3'} = 9$ Hz (the H-1′ proton of the starting compounds **1** and **10** exhibited only a singlet) indicating that H-1′, H-2′, and H-3′ are trans diaxial and OH-2′ equatorial. Considering that the bases are in equatorial position to the hexopyranose these correlations are possible only for the β-L-xylo configuration in the 1C conformation.

In the case of **23** the small coupling constant $J_{1',2'} = 1.5$ Hz indicated that OH-2′ was axial. In addition the H-3′ proton was also axial ($J_{3',4'ax} = 11$ Hz) and trans to the equatorial nitrogenous base. These relationships indicated that **23** has the α-L-ribo configuration in the C1 conformation.

Contrary to **1** and **10** which have been obtained by acetylation of the parent 2′-keto nucleosides,[2,6] the α isomer (**17**) was synthesized, as will be seen, by oxidation of the corresponding 3′,4′-diacetate (**27**).

This diacetate could be prepared by acid-catalyzed selective acetylation of 7-(6′-deoxy-α-L-mannohexopyranosyl)theophylline (**25**)[7] using acetic anhydride in the presence of the

Scheme III



etherate complex of boron trifluoride.[8] The reaction was carried out at 50 °C for 30 min and stopped by high vacuum distillation. Under these conditions a mixture of two diacetates (2′,4′- and 3′,4′-diacetate) was formed, but it contains mainly the desired 7-(3′,4′-di-*O*-acetyl-6′-deoxy-α-L-*manno*-hexopyranosyl)theophylline (**27**), as could be established from the nmr spectrum. Purification of the mixture was performed by oxidizing the mixture with the Pfitzner–Moffatt reagent.[14] This procedure gave only one compound which was characterized as 7-(3′-*O*-acetyl-4′,6′-dideoxy-α-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (**17**). The NMR spectrum clearly indicated the conjugated structure of **17.** The H-1′ proton shifted downfield as expected (6.9 ppm instead of 6.4 ppm in the diacetate), also the H-4′ proton resonated at lower field (7.2 ppm) indicating a vinylic proton in β position to the carbonyl. The H-5′ proton was shifted to 4.95 ppm (from 4.2 ppm in **27**) indicating that this proton is vinylogous to a proton in α position to the carbonyl.

All these keto nucleosides are soluble in aqueous methanol. The reaction was carried out at room temperature for compound **1** and at above −50 °C for **10** and **17,** less stable comparatively than **1.**

The reductions appeared to be more stereospecific than those of steroidal enol acetates[9] since no other isomers were detected. The difference in the mode of reduction may be explained by invoking the influence of the base.

1,2 addition to the unsaturated keto nucleosides **1, 10,** and **17** should lead to the alcoholates **2, 11,** and **18** which undergo acetyl group migration to give the enolates **4, 13,** and **20.** These enols tautomerize to the corresponding 3′-keto nucleosides **6, 15,** and **21** which are further reduced to the deoxy nucleosides **7, 16,** and **22.** The α-deoxy nucleoside **22** undergoes another acetyl migration to give the 3′-acetyl nucleoside **23.**

These mechanisms have been established by a study of the NMR spectra of the deoxy nucleosides obtained by the reduction of **1, 10,** and **17** with $NaBH_4$ in deuterated solvents and of the NMR spectra of the same deoxy nucleosides prepared by using sodium borodeuteride in aqueous methanol.

There are two possible mechanisms to reduce α,β-unsaturated keto nucleosides by sodium borohydride: 1,2- or 1,4-hydride addition. The use of $NaBD_4$ led to deuterio analogues of the deoxy nucleosides. In the case of 1,2 addition only the 2′ and 3′ positions should be labeled whereas labeling of the 2′ and 4′ positions should indicate a 1,4 addition.

Since the NMR signals of compound **8** were not well separated, except for the H-1′, we synthesized the diacetate **9** in whose spectrum all the sugar protons were resolved. The acetylation of **8** was performed with acetic anhydride in pyridine. The disappearance of the H-2′ and H-3′ protons in the spectrum of **9** indicated 1,2-nucleophilic addition to 7-(3′-*O*-acetyl-4′,6′-dideoxy-β-L-*glycero*-hex-3′-enopyranos-2′-ulosyl)theophylline (**1**).[4]

In the NMR spectrum of the compound **16** (Table I, line 4) we also observed the disappearence of the H-2′ signal. Integration showed that two protons resonated at 3.6 ppm. In order to identify these protons we performed the reduction of **10** with $NaBD_4$. The NMR spectrum of the deuterio analogue of **16** indicated disappearance of one of the signals and appearance of a new signal as a ten-peak multiplet corresponding to H-5′. The multiplicity of this signal indicated that both H-4′$_{axial}$ and H-4′$_{equatorial}$ protons are coupled with H-5′. The signal at 3.6 ppm, absent in the spectrum of the deuterio analogue, could then be attributed to the H-3′ proton of **16.** Consequently, as the sodium borodeuteride labeled specifically the 2′ and 3′ positions of 6-chloro-(3′-*O*-acetyl-4′,6′-dideoxy-β-L-*arabino*-hexopyranosyl)purine (**16**) we can deduce that **10** is also reduced by the 1,2-addition mechanism.

The presence of an acetyl group in the 3′ position makes a

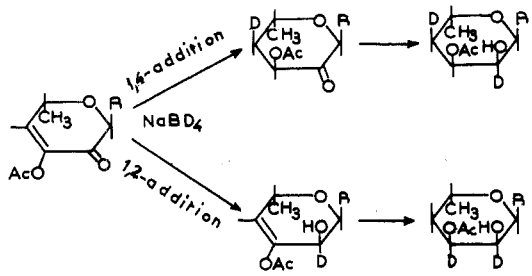
Table I

Line no.	Compd	Hydride	Redn solvent	Deuterio analogue	Chemical shifts, δ[a] H_1'	H_2'	H_3'	H_5'	H_6'	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'ax}$	$J_{3',4'eq}$	$J_{4'ax,5'}$	$J_{4'eq,5'}$	$J_{5',6'}$
1	**9**[b]	$NaBH_4$	CH_3OH/H_2O		6 d	5.7 t	5.1 se		1 d	9	9	10	5			6
2	**9**[b]	$NaBH_4$	CD_3OD/D_2O	Mono-deuterated	6 d	5.7 t	5.1 q		1 d	9	9		5			6
3	**9**[b]	$NaBD_4$	CH_3OH/H_2O	Di-deuterated	6 s				1 d							6
4	**16**[c]	$NaBH_4$	CH_3OH/H_2O		5.7 d	5.1 t	3.6	3.6	1.1 d	9	9					7
5	**16**[c]	$NaBH_4$	CD_3OD/D_2O	Mono-deuterated	5.7 d	5.1 t	3.6	3.6	1.1 d	9	9					7
6	**16**[c]	$NaBD_4$	CH_3OH/H_2O	Di-deuterated	5.7 s			3.6 m	1.1 d					7	2	7
7	**24**[b]	$NaBH_4$	CH_3OH/H_2O		6.7 d	5.9 q	5.5 o	4.2 m	1 d	1.5	3.2	11.5	5			7
8	**24**[b]	$NaBH_4$	CD_3OD/D_2O	Mono-deuterated	6.7 d	5.9 q	5.5 q	4.2 m	1 d	1.5	3.2	11.5				7
9	**24**[b]	$NaBD_4$	CH_3OH/H_2O	Di-deuterated	6.7 s			4.2 m	1 d							7

[a] s, singlet; d, doublet; t, triplet; q, quartet; se, sextet; o, octet; m, multiplet. [b] Solvent C_6D_6. [c] CD_3OD.

1,4-addition mechanism possible (Scheme IV). As the NMR parameters of **23** did not permit us to ascertain the mode of

Scheme IV

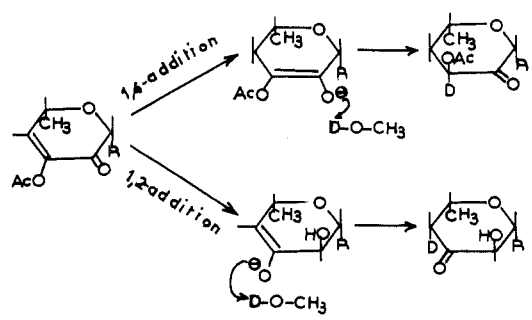


this hydride reduction, we synthesized the diacetate **24.** In the NMR spectrum of this molecule (**24**) we observed the disappearance of H-2′ and H-3′ signals. Consequently, as the 2′ and 3′ positions are labeled, 1,2 addition of the hydride should be also the mode of reduction of 7-(3′-*O*-acetyl-4′,6′-dideoxy-α-L-*glycero*-hex-3′-enopyranosyl-2′-ulosyl)theophylline (**17**).

All these results have been confirmed by a study of the reduction of the unsaturated 2′-keto nucleosides with $NaBH_4$ in deuterated solvents.

1,2 as well as 1,4 additions of hydride would lead to formation of the corresponding enols which react with deuterium from the solvent to form the saturated deuterio analogues (see Scheme V). In the case of 1,4 addition (2′,3′ double bond in the

Scheme V



enolate) the deuterium enters at C-3′ whereas for 1,2 addition (3′,4′ double bond) the reduction yields the 4′-deuterio product.

When **24** was deuterated no change in the multiplicity of H-2′ in the monodeuterated analogue was observed whereas the H-3′ signal (see Table I, lines 7 and 8) was reduced to a quartet indicating the disappearance of the coupling between H-3′ and $H\text{-}4'_{equatorial}$. This implies that C-4′ is labeled by deuterium and consequently that the unsaturated keto nucleoside (**17**) has undergone 1,2 addition.

Reduction of the unsaturated keto nucleoside (**1**) occurs by 1,2 addition. The NMR spectrum of the deuterio analogue of **9** showed (see Table I, line 2) disappearance of the H-3′, $H\text{-}4'_{axial}$ coupling. The H-3′ signal resonated as a quartet indicating that the C-4′ position is labeled by deuterium.

Concerning the monoacetate **23,** the presence of an acetyl group in the 3′ position seems inconsistent with a complete reduction of the unsaturated ketone (successive addition of two hydride ions). It is indeed established that the first attack leads to the enol acetate **18.** In these conditions the mode of reduction of this molecule should be a 1,4-addition mechanism. But this 1,4 addition is inconsistent with the evidence inferred from the isotopic labeling of the molecule.

The presence of the acetyl in the 3′ position could be explained by a migration of this group from the 2′-axial (**22**) to the more stable 3′-equatorial position (**23**).

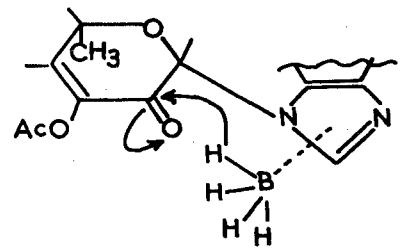


Figure 1.

Concerning the nucleophilic additions to the 3′-keto nucleosides **6, 15,** and **21,** it is well known that in the case of the α-substituted cyclohexanones the axial attack on the carbonyl group is generally favored and $NaBH_4$ reduction gives mainly the equatorial alcohol.[12] This is in accordance with the results of the hydride addition on the intermediate keto nucleosides **6, 15,** and **21,** which gave exclusively the equatorial alcohol as was clearly shown by the coupling constants of their NMR spectra.

The stereospecific axial attack could be explained in the case of **6** and **15,** which possess an equatorial 2′-acetyl, by the proximity of the nitrogeneous base. In the case of **21** the cis-axial 2′-acetyl group and the 4′-axial proton prevent the equatorial attack.

The unusual attack of hydride ion exclusively from the most hindered side in the case of the unsaturated β-keto nucleosides **1** and **10** may consequently be explained by invoking intramolecular participation of a neighboring group. Thus, as in the case of methyl hexopyranosuloses,[13] this group controls the direction of the reduction. Preference of the hydride for an approach cis to the base support the view that either the base or one of its functional groups participates in the formation of the complex with $NaBH_4$ which reduces the carbonyl stereospecifically (Figure 1).

The study of the NMR spectrum of the α-keto nucleoside **17** shows that, contrary to the reduction of **1** and **10,** the hydride attacks from the side trans to the nitrogeneous base. This could signify the nonparticipation of the purine in the reduction of **17.** So, as we have previously mentioned, the hydride approaches cis to the aglycon when the base controls the direction of the reduction.

Considering the stability and the facile preparation of the unsaturated ketohexose nucleosides[5] this novel approach to the synthesis of deoxy nucleosides, especially those containing rare deoxy sugars, provides a direct route to a variety of compounds possessing considerable biological interest.

Experimental Section

Solutions were evaporated at 40 °C under diminished pressure. Uv spectra were measured with a Varian-Techtron Model 635 spectrophotometer. Ir spectra were determined for potassium bromide pellets by use of a Perkin-Elmer Model 137 spectrometer. NMR 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.

The gas–liquid chromatography of acetylated nucleosides was carried out using a Perkin-Elmer Model 990 instrument, with hydrogen flame ionization. Columns were packed with 100–200 mesh Gas-Chrom Z (Applied Sciences Laboratories Inc.) coated with 10% SE-30.

Reactions were monitored by TLC on Schleicher and Schull plastic sheets using (A) ethyl acetate and (B) chloroform–acetone (80/20). Nucleoside spots were detected by visual examination under uv light and by spraying with 30% sulfuric acid and heating at 105 °C. PLC was carried out on plates (20 × 40 cm) coated to a depth of 5 mm with Keiselgel GF_{254} (Merck) admixed with 15% of $CaSO_4$, using ethyl acetate.

Melting points were uncorrected. Elemental analysis were obtained from the Laboratoire de Microanalyse du CNRS.

7-(3′-*O*-acetyl-4′,6′-dideoxy-α-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (17). A solution of 7-(6′-deoxy-α-L-*manno*-hexopyranosyl)theophylline (**27**,[7] 1.5 g, 4.5 mmol) in methanol (30 ml) was evaporated to dryness in vacuo. The semicrystalline material was then dissolved in acetic anhydride (60 ml, 588 mmol) and boron trifluoride etherate (36 μl, 2.65 mmol) was added. The solution was heated for 30 min at 50 °C and the solvents removed by high vacuum distillation. The obtained dark yellow oil containing a mixture of di- and triacetyl nucleosides was dissolved in ethyl acetate and purified by preparative TLC using ethyl acetate. Two faster moving major bands were detected by ultraviolet absorption. The slower moving of these bands was eluted with acetone to give a semicrystalline material which was dissolved in benzene (16 ml) and Me_2SO (16 ml). Dicyclohexylcarbodiimide (DCC, 2.8 g, 13.5 mmol) and dichloroacetic acid (0.3 ml, 3.75 mmol) were added[14] and the mixture was kept for 10 min at room temperature. Ethyl acetate (100 ml) and oxalic acid (1.2 g) dissolved in methanol were added and the mixture was stirred for 20 min.

Dicyclohexylurea was filtered off and the filtrate was washed with water (3 × 50 ml) and evaporated to a syrup. The crude material was dissolved in ethyl acetate and chromatographed on a silica gel (Merck 0.05–0.2 mm) column eluted with ethyl acetate (500 ml). Evaporation gave a syrup which crystallized at 0 °C from chloroform–methanol (1:5) to give **17** (0.391 g). The purity of the keto nucleoside was ascertained by GLC at 270 °C (retention time 1.5 min): mp 162–165 °C; $[\alpha]^{20}D$ −170° (*c* 0.1, $CHCl_3$); uv λ_{max} (MeOH) 273 nm (ε 10 000); R_f 0.7 (ethyl acetate); ν_{max} (KBr) 1740 cm^{-1} (acetyl); δ (CD_3COCD_3) 7.2 (d, $J_{4',5'}$ = 2 Hz), 6.9 (s), 4.9 (o, $J_{5',6'}$ = 7 Hz).

Anal. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.73; H, 4.59; N, 16.09. Found: C, 51.73; H, 4.68; N, 16.45.

7-(3′-*O*-Acetyl-4′,6′-dideoxy-α-L-*ribo*-hexopyranosyl)theophylline (23). To a solution of **17** (348 mg, 1 mmol) in chloroform (2 ml), methanol (7.5 ml) and water (0.5 ml) were added. The mixture was cooled to −50 °C and sodium borohydride (300 mg, 7.85 mmol) was added. After storage at −50 °C for 4 min, chloroform (20 ml) was added and the mixture was washed with water (10 ml). Evaporation of the solvents gave a syrup which was purified by preparative TLC using ethyl acetate The major band at R_f 0.4 was eluted with acetone to give a syrup which crystallized from ethanol–pentane and recrystallized from ethanol (150 mg): mp 172–174 °C (sublimed at 164 °C), $[\alpha]^{20}D$ +70° (*c* 0.1, MeOH); R_f 0.4 (ethyl acetate); λ_{max} 274 nm (ε 7400); NMR δ (CD_3COOD) 6.4 (d, $J_{1',2'}$ = 1.5 Hz), 5.3 (o, $J_{2',3'}$ = 3, $J_{3',4'ax}$ = 11 Hz), 1.5 (d, $J_{5',6'}$ = 7 Hz).

Anal. Calcd for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.68; N, 15.9. Found: C, 51.15; H, 5.57; N, 16.4.

The acetylation of **23** with acetic anhydride in pyridine gave 7-(2′,3′-di-*O*-acetyl-4′,6′-dideoxy-α-L-*ribo*-hexopyranosyl)theophylline (**24**) as a syrup: $[\alpha]^{20}D$ = +92 (*c* 0.1, ethanol); λ_{max} 274 nm (ε 7900); NMR (C_6D_6) acetyl δ 1.56, 1.62.

7-(4′,6′-Dideoxy-β-L-*xylo*-hexopyranosyl)theophylline (8). Sodium borohydride (210 mg, 6.3 mmol) was added to a stirred solution of 7-(3′-*O*-acetyl-4′,6′-dideoxy-β-L-*glycero*-hex-3′-enopyranosulosyl)theophylline (**1**,[4] 310 mg, 1 mmol) in methanol (10 ml). After 2 min water was added (10 ml) and the mixture was extracted with ethyl acetate (3 × 20 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. 7-(4′,6′-Dideoxy-β-L-*xylo*-hexopyranosyl)-theophylline (**8**, 180 mg) was crystallized from ethanol: mp 213–214 °C; $[\alpha]^{20}D$ +5° (*c* 0.1, acetone); R_f 0.55 (*t*-BuOH–H_2O); λ_{max} 275 nm (ε 7300).

Anal. Calcd for $C_{13}H_{18}N_4O_5$: C, 50.25; H, 5.81; N, 18.05. Found: C, 50.14; H, 5.80; N, 18.05.

7-(2′,3′-Di-*O*-acetyl-4′,6′-dideoxy-β-L-*xylo*-hexopyranosyl)theophylline (9). Compound **8** (1,0 g, 3.22 mmol) was dissolved in a mixture of acetic anhydride (5 ml) and pyridine (10 ml). After 45 min at room temperature, the mixture was evaporated in vacuo, and toluene was distilled from the syrupy residue which then crystallized from ethanol to give **9** (1.2 g, 95%): mp 210–211 °C; $[\alpha]^{20}D$ +25° (*c* 0.1, acetone); λ_{max} 274 nm (ε 7510); ir C=O (acetyl) 1740 cm^{-1}; R_f 0.54 (ethyl acetate).

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.58; N, 14.4. Found: C, 51.96; H, 5.61; N, 14.68.

6-Chloro-9-(2′-*O*-acetyl-4′,6′-dideoxy-β-L-*xylo*-hexopyranosyl)purine (16). The same procedure was used as for compound **21** except that 150 mg (0.46 mmol) of **10** was used and the solution was stirred for 20 min at −50 °C. After evaporation of the solvents the crude material crystallized from chloroform to give pure **16** (90 mg): mp 186 °C; $[\alpha]^{20}D$ 0 (*c* 0.1, MeOH); λ_{max} 264 nm (ε 6500).

Anal. Calcd for $C_{13}ClH_{15}N_4O_4$: C, 47.8; H, 4.6; N, 17.15. Found: C, 48.28; H, 4.76; N, 17.19.

The deuterio analogue was crystallized from chloroform, mp 190 °C, λ_{max} 264 nm (ε 8000).

Anal. Calcd for $C_{13}ClH_{13}D_2N_4O_4$: C, 47.5; H, 5.17; N, 17.04. Found: C, 47.02; H, 4.61; N, 16.62.

The acetylation of this deuterio nucleoside with acetic anhydride in pyridine gave 6-chloro-9-(2′,3′-di-*O*-acetyl-2′,3′-dideuterio-4′,6′-dideoxy-β-L-*xylo*-hexopyranosyl)purine, which crystallized from ethanol, mp 153°C.

Anal. Calcd for $C_{15}ClH_{15}D_2N_4O_5$: C, 48.58; H, 4.58; N, 15.11. Found: C, 48.63; H, 4.59; N, 15.43.

Preparation of Deuterio Analogues. These analogues were prepared by using deuterated or light solvents either with sodium borohydride or with sodium borodeuteride. The procedure applied was identical with that used for compounds **23**, **8**, and **16**.

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Registry No.—**1**, 39848-20-9; **8**, 60195-84-8; **9**, 60195-85-9; **10**, 50615-83-3; **16**, 60195-86-0; **16**-d_2, 60195-87-1; **16**-d_2Ac, 60195-88-2; **17**, 60251-49-2; **23**, 60195-89-3; **24**, 60195-90-6; **27**, 60209-47-4.

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