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UNSATURATED KETONUCLEOSIDES. SYNTHESIS AND PROPERTIES OF 7-(3,6-DI-*O*-ACETYL-2-DEOXY-β-D-*glycero*-HEX-2-ENOPYRANOSYL-4-ULOSE)THEOPHYLLINE

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ABSTRACT

The synthesis of the title compound (**4**), an unsaturated 4′-ketonucleoside, was accomplished by oxidation of 7-(2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)theophylline. Under mildly alkaline conditions, **4** readily decomposed, whereas it was stable in an acidic medium. Reduction of **4** with sodium borohydride–acetic acid gave 7-(4,6-di-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranosyl)theophylline. A mechanism involving initial complex formation between AcO-6′ and the borohydride ion, followed by intramolecular hydride-transfer to the keto group, is proposed.

INTRODUCTION

Ketodeoxyhexosylpurines possess *in vitro* growth-inhibitory activity on KB cancer cells[1], whereas parent nucleosides are inactive. Some of them also showed significant activity against leukaemia L1210 in mice[2]. 4′-Ketonucleosides were more active than 2′-ketonucleosides, and unsaturated 2′-ketonucleosides showed still higher activity *in vitro*[1] and *in vivo*[2].

In order to obtain information on the biochemical mechanism of action and to elucidate the structural requirements for biological activity of ketonucleosides, the synthesis was undertaken of an unsaturated 4′-ketonucleoside which is the first example of this class of compound.

RESULTS AND DISCUSSION

Two methods of synthesis appeared to be suitable. The first involved acetylation of the free ketonucleoside, followed by rapid elimination of the β-acetoxyl group, a method used to obtain[3] unsaturated 2′-ketonucleosides. However, unsaturated 4′-ketonucleosides could not be obtained by this procedure, due to the lability of the glycosylic bond. The second approach was the oxidation of HO-4′ of a partially acetylated nucleoside, initiating the β-elimination of the acetyl group. This method was successful.

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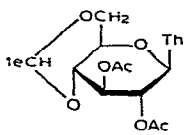
The starting material, 7-(2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl)-theophylline (**1**) was obtained in good yield from 1,2,3-tri-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucose and trimethylsilyltheophylline under the conditions described by Niedballa and Vorbrüggen[4] for the synthesis of pyrimidine nucleosides. N.m.r. data ($J_{1',2'}$ 8.5, $J_{2',3'}$ 8.5, and $J_{3',4'}$ 8.5 Hz) showed that **1** had the β configuration and that it existed in the $^4C_1$ conformation. Compound **1** had λ_{max}^{MeOH} 274 nm, similar to that (273 nm) of 1,3,7-trimethylxanthine and different from those (239 and 267 nm in neutral solution) of 1,3,9-trimethylxanthine, demonstrating that it was a 7-substituted theophylline[5].



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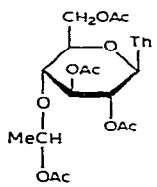
Th = theophylline



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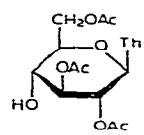

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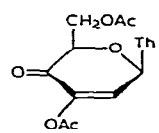

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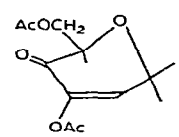

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Acetolysis of **1** with acetic anhydride containing 1% of sulphuric acid gave the crystalline nucleoside **2**. Previous procedures[6,7] for hydrolysing a 4-*O*-(acetoxyethyl) group in glucose derivatives involved treatment with fuming nitric acid in chloroform, followed by the removal of the nitric ester group with acetic acid–zinc dust–iron filings. Mild hydrolysis with acid is a simpler method which gives improved yields. Hydrolysis of **2** with 70% acetic acid (90°, 1 h) gave 7-(2,3,6-tri-*O*-acetyl-β-D-glucosyl)theophylline (**3**, 70% from **1**).

Oxidation of **3** gave the desired, unsaturated carbonyl compound 7-(3,6-di-*O*-acetyl-2-deoxy-β-D-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline (**4**), in crystalline form, by elimination of the β-acetoxyl group. The most satisfactory reagent was methyl sulphoxide and dicyclohexylcarbodi-imide in the presence of dichloroacetic acid[8]. Methyl sulphoxide and acetic anhydride afforded **4**, but also gave a considerable proportion of methylthiomethyl ether; oxidation with ruthenium tetraoxide or chromic anhydride gave low yields.

Compound **4** had i.r. bands at 1755 and 1780 cm^{-1}, attributable to a normal, saturated ester and to a vinylic ester, respectively. The p.m.r. spectrum ($CDCl_3$) of **4** was consistent with the structure assigned. The signal for H-1′ appeared at δ 6.88 (d, $J_{1',2'}$ 1.7 Hz), and that for H-2′ at δ 7.24 was partly obscured by the residual signal of the solvent. H-5′,6′a,6′b constituted an ABC system (δ 4.3–4.82), but the addition of euroshift F reagent generated an ABX system with H-5′ = X, for which the p.m.r. parameters were determined by the method of Bernstein *et al.*[9]. Moreover, the signal for H-2′ was not now obscured, and it appeared as a triplet due to a long-range coupling with H-5′. Irradiation of the H-5′ resonance caused the H-2′ triplet to collapse to a doublet. Such a five-bond coupling could arise by the mechanism proposed by Anet[10], involving the π-electrons of the unsaturated system.

TABLE I

N.M.R. DATA FOR SOLUTIONS OF **1–4** IN DEUTERIOCHLOROFORM

Compound	Chemical shifts (δ values)										
	H-1′	*H-2′*	*H-3′*	*H-4′*	*H-5′*	*H-6′,6″*	*OAc*	*N-Me*	*H-8*	Me*CH*	*Me*CH
1	5 98	5.75	5 38	4 21		3 5	1.90 2 08	3 43 3.58	7 80	1 35	4.75
2	~6	5 53	5 33	4 67		3.83	1 83 2 01 2 03 2 05	3 35 3 52	7.73	1.28	~6
3	6 13	5 67	5.37	4 55		3.78	1 91 2.10 2 12	3 43 3.60	7 88		
4	6 74	7 24			4 63	4 46	2 0 2 23	3.37 3.57	7 83		
	J values (Hz)[a]										
	1′,2′	*2′,3′*	*3′,4′*	*5′,6′*	*5′,6″*	*6′,6″*	*2′,5′*				
1	8 5	8 5	8 5								
2	9	9.5	8 5								
3	8 5	9	8 5								
4	1.7			2 5	5.6	12 5	1.7				

[a]Relative signs of coupling constants were not determined.

The small value (1.7 Hz) of $J_{1',2'}$ suggests that **4** adopts the sofa conformation **5** with H-1′ perpendicular to the ring. Such a conformation should be favoured, because the bulky sbustituents at C-1′ and C-5′ are equatorial.

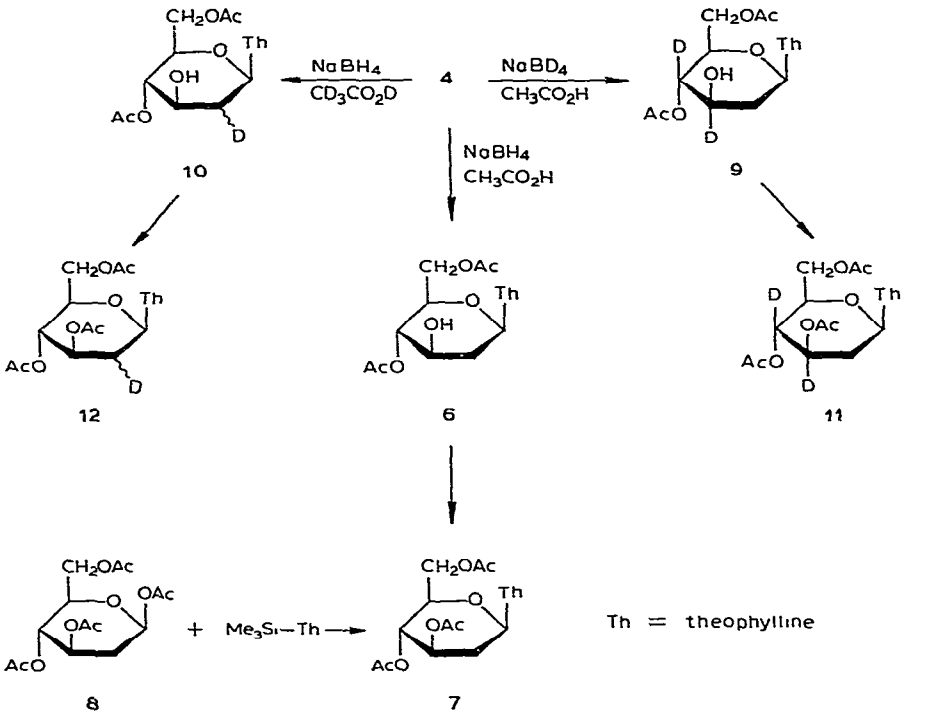
In neutral conditions and in such aprotic solvents as benzene or toluene, **4** was remarkably inert; attempted catalytic hydrogenation, ketal formation, or halogenation failed. In alcoholic solution, **4** was extremely sensitive to nucleophilic attack and decomposed rapidly by elimination of the nitrogeneous base. Thus, treatment with sodium borohydride at −70° led to complete decomposition within 10 min.

Compound **4** was remarkably stable in acidic conditions (*e.g.*, 0.1M H_2SO_4, room temperature, 48 h), and attempted ionic hydrogenation[11] with triethylsilane–trifluoroacetic acid failed.

When sodium borohydride was added to a solution of **4** in dichloroethane containing glacial acetic acid, fast reduction occurred to give, almost exclusively, 7-(4,6-di-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranosyl)theophylline (**6**), which yielded a crystalline triacetate (**7**).

The n.m.r. spectrum of **6** (Table II) was consistent with the *arabino* configuration and indicated that reduction was accompanied by a 3′→4′ acetyl migration.

Sodium borohydride–acetic acid reduces enamines[12], hydroboronates alkenes[13], and can reductively alkylate cyclic amines[14]. The reductive species is an adduct[14c, 15] $Na[(RCOO)_x\ BH_{4-x}]$, where x = 1–3 depending on the amount of acid used. Aldehydes and especially ketones are reduced[14a] to alcohols relatively slowly by



$NaBH_4$–RCOOH; we have found that saturated ketonucleosides did not react under conditions when **4** was reduced. Thus, the sodium borohydride–acetic acid reduction does not proceed by the mechanism postulated for the unsaturated ketonucleosides in aqueous alcohol, where the reaction is initiated by attack of hydride ion at the carbonyl group[16].

We have therefore examined the reaction of the $NaBH_4$–AcOH system with analogues of **4**, and reduction of **4** with deuterated reagents. Comparison of the n.m.r. spectrum (Table II) of **6** with that of the product **9** obtained by reduction with $NaBD_4$–AcOH indicated the absence of the H-4′ triplet of δ 4.92 and of a proton signal in the region δ 3.8–4.6. Acetylation of **9** caused no changes in this region, indicating deuteration at C-3′. When **4** was reduced with $NaBH_4$–CD_3COOD, the n.m.r. spectrum of the product (**10**) was identical with that of **6**, except that only one proton at C-2′ was observed. In addition, the H-1′ signal became a broadened triplet, due to superposition of two doublets with a large (10.7 Hz) and a small (2.5 Hz) splitting, due to the non-specific deuteration of the axial and equatorial positions at C-2′. No enolization between C-4′ and C-5′ was evident in these experiments.

Saturated ketonucleosides were unchanged after treatment with $NaBH_4$–AcOH. Only 20% of acetone reacted within 5 h, but acetylacetone was completely reduced within 50 min. Unsaturated ketonucleosides containing at least one acetyl group were reduced, but when AcO-3′ was replaced by bromine, no reaction occurred. These

TABLE II

N.M R. DATA FOR COMPOUNDS 6–12

Compound	Chemical shifts (δ values)									
	H-1′	H-2′	H-2″	H-3′	H-4′	H-5′	H-6′ H-6″	OAc	NMe	H-8
6 ($CDCl_3$)	6 13	2.8 ——1.98		4.5–3.7	4 92	4.5 ——3 7		2 08 2.17	3.42 3 61	7.92
(CD_3OD)	6.10	2 6	2.2	4 5–3 8	4.97	4.5 ——3.8		2 02 2.12	3.32 3.52	8.23
7 ($CDCl_3$)	6 21	2.80	2 18	5.5 ——— 5.0		4 55——3.8		2 05 2.07 2 08	3.40 3 60	7.93
9 (CD_3OD)	6.10	2 6	2.2			4.5 ——3 8		2 02 2 12	3 32 3 52	8 23
10 (CD_3OD)	6.10	2.7 ——2.2		4.5–3 8	4 97	4 5 ——3.8		2 02 2.12	3 32 3 52	8 23
11 ($CDCl_3$)	6.21	2 80	2.18			4 5 ——3 8		2.05 2 07 2.08	3.40 3.60	7.93
12 ($CDCl_3$)	6 21	2 8 ——2 2		5 5 ——— 5.0		4 55——3 8		2.05 2 07 2 08	3.40 3.60	7.93

	J values (Hz)[a]						
	1′,2′	1′,2″	2′,2″	2′,3′	2″,3′	3′,4′	4′,5′
6 ($CDCl_3$)	2.5	10.5				9 5	9 5
(CD_3OD)	2.5	10 7	12	5	9.5	9 5	9.5
7 ($CDCl_3$)	2 2	10 5	12	4	10		

[a]Relative signs of coupling constants were not determined.

results strongly suggest that reduction is initiated by hydride attack on the enol-acetate[17]. It is of interest that isopropenyl acetate remained unchanged after exposure to $NaBH_4$–AcOH for 24 h, showing the inertness of an isolated enolacetate group towards attack by hydride ion.

Thus, rapid reduction may occur with compounds containing structural elements which coordinate the reducing agent and permit intramolecular hydrogen addition. When a solution of **4** was added to a solution of $Na[(AcO)_3BH]$ generated by stirring sodium borohydride with glacial acetic acid solution until evolution of H_2 ceased, only very slow reduction occurred in spite of the excess of hydride. Thus, preformed $Na[(AcO)_3BH]$ cannot reduce **4**. When the reduction was carried out by the inverse-addition method and a large excess of acetic acid was used, the initial, slow reaction was stopped and no further reduction occurred, because acetic acid competed with the nucleoside acetoxyl groups to form a complex with the boro-hydride ion.

A Dreiding model of **4** shows that, in the complexed AcO-6′, the hydride is situated favourably for transfer to the 4′-keto group and this explains the preferential attack from the more-hindered side of the molecule. Thus, the reduction of **4** could involve (*1*) formation of a co-ordinated boron–oxygen bond at AcO-6′, (*2*) intramolecular hydride transfer to C-4′, (*3*) 3′→4′ acetyl migration, (*4*) intra- or intermolecular reduction of the enol group at C-3′, and (*5*) protonation either concomitantly or subsequently.

Further studies are necessary to ascertain the role of AcO-3′ when 6′-deoxynucleosides are reduced.

EXPERIMENTAL

General methods. — U.v. spectra were measured with a Varian UV-VIS M 635 spectrophotometer, i.r. spectra (KBr pellets) with a Perkin–Elmer 137 spectrometer, and n.m.r. spectra (internal Me_4Si) with a Varian T-60 instrument. Optical rotations were determined with a Roussel–Jouan Quick polarimeter. Melting points are uncorrected. T.l.c. was performed on silica gel F 1500 LS 254 (Schleicher–Schüll), and silica gel 60 PF (Merck) was used for p.l.c. with *A* ethyl acetate and *B* ethyl acetate–ethanol (8:2).

General procedure for acetylation. — To 15 ml of acetic anhydride at 100° (bath) was added 1 g of sodium acetate, and the mixture was stirred until all of the acetate had dissolved. The alcohol was added during 15 min and, after a further 1 h at 100°, the excess of acetic anhydride was decomposed by methanol. Volatile materials were evaporated off and the residue was triturated in water to remove sodium acetate. The remaining solid was collected and crystallised.

*7-(2,3-Di-*O*-acetyl-4,6-*O*-ethylidene-β-*D*-glucopyranosyl)theophylline* (**1**). — Theophylline (6 g, 33 mmol) was suspended in 1,2-dichloroethane, and hexamethyldisilazane (18 ml) and chlorotrimethylsilane (0.315 ml) were added. The mixture was boiled under reflux with exclusion of moisture until all of the solid had dissolved; it was then concentrated to dryness, and traces of hexamethyldisilazane were removed by repeated distillation of toluene from the residue. The residue and 1,2,3-tri-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucose[18] (9.96 g, 30 mmol) were dissolved in acetonitrile (180 ml), and $SnCl_4$ (1.17 ml, 10 mmol) was added. The mixture was kept at 85° for 2 h; the reaction was monitored by t.l.c. After dilution with chloroform (200 ml), the mixture was shaken with saturated, aqueous $NaHCO_3$ (100 ml), filtered, washed with water, dried, and concentrated. The residue was crystallised from ethanol to give **1** (9.7 g) as needles, m.p. 175–176°, $[\alpha]_D^{20}$ −9° (*c* 0.1, methanol), λ_{max}^{MeOH} 274.5 nm (ε 8220).

Anal. Calc. for $C_{19}H_{24}N_4O_9$: C, 50.4; H, 5.31; N, 12.38. Found: C, 49.5; H. 5.49; N, 12.40.

*7-[4-*O*-(1-Acetoxyethyl)-2,3,6-tri-*O*-acetyl-β-*D*-glucopyranosyl]theophylline* (**2**). — To a stirred mixture of acetic anhydride (45 ml) and sulphuric acid (0.45 ml), **1** (5 g) was slowly added at 0°. After 1 h at room temperature, the solution was

poured into ice and water (500 ml) containing sodium acetate, and neutralised with sodium carbonate. The product was extracted with chloroform, and the extract was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated to dryness, to give **2** which was sufficiently pure for the next step. Crystallisation from ethanol gave fine needles, m.p. 170–171°, $[\alpha]_D^{20}$ +12.5° (*c* 0.1, methanol), λ_{max}^{MeOH} 273 nm (ε 10,800).

Anal. Calc. for $C_{23}H_{30}N_4O_{12}$: C, 49.82; H, 5.41; N, 10.11. Found: C, 49.99; H, 5.43; N, 10.35.

*7-(2,3,6-Tri-*O*-acetyl-β-*D*-glucopyranosyl)theophylline* (**3**). — A solution of **2** in 70% acetic acid (60 ml) was kept for 1 h at 90°, cooled, diluted with water (150 ml), and extracted with chloroform. The extract was successively washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. The product, which could not be crystallised, was purified by precipitation from solution in ethyl acetate with pentane, to give **3** as an amorphous powder (3.4 g, 70% from **1**), $[\alpha]_D^{20}$ −4.5° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 8150).

Anal. Calc. for $C_{19}H_{24}N_4O_{10}$: C, 48.70; H, 5.13; N, 11.96. Found: C, 48.34; H, 5.15; N, 11.98.

*7-(3,6-Di-*O*-acetyl-2-deoxy-β-*D*-*glycero*-hex-2-enopyranosyl-4-ulose)theophylline* (**4**). — To a solution of **3** (3.276 g, 7 mmol) and dicyclohexylcarbodi-imide (4.33 g, 21 mmol) in ethyl acetate (8.75 ml) were added methyl sulphoxide (5.25 ml) and dichloroacetic acid (0.29 ml, 3.5 mmol). The mixture was kept at room temperature for 10 min. Ethyl acetate (35 ml) was added, and then a solution of oxalic acid (1.26 g, 15 mmol) in methanol (5.25 ml). After 15 min, *N,N'*-dicyclohexylurea was removed, the filtrate was washed successively with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated to dryness. A solution of the residue in ethyl acetate (8 ml) was filtered and concentrated, and the residue was crystallised from methanol–pentane and recrystallised from ethyl acetate–pentane to give **4** (1.52 g, 55%), m.p. 140° (dec.), $[\alpha]_D^{20}$ −2° (*c* 0.1, carbon tetrachloride); $\lambda_{max}^{CCl_4}$ 280 nm (ε 8880); ν_{max}^{KBr} 1780 (C = O, enol acetate) and 1755 cm^{-1} (acetate).

Anal. Calc. for $C_{17}H_{18}N_4O_8$: C, 50.30; H, 4.44; N, 13.80. Found: C, 50.22; H, 4.56; N, 13.83.

Reduction of **4** *with sodium borohydride–acetic acid.* — (*a*) *By inverse addition.* To a solution of **4** (200 mg, 0.5 mmol) and glacial acetic acid (0.48 ml, 8.4 mmol) in 1,2-dichloroethane (4.5 ml), sodium borohydride (80 mg, 2.1 mmol) was added with stirring and exclusion of moisture. After 30 min, excess of hydride was decomposed with water (2 ml), and the aqueous layer was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and concentrated. Methanol was repeatedly evaporated from the residue to remove boric acid. The product was then purified by p.l.c. (solvent *B*) to give 7-(4,6-di-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranosyl)theophylline (**6**; 152 mg, 75%), which could not be crystallized, but was obtained as an amorphous powder by precipitation from solution in ethyl acetate with pentane; **6** had $[\alpha]_D^{20}$ −0.7° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 8100).

Anal. Calc. for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.36; N, 13.65. Found: C, 49.55; H, 5.41; N, 12.99.

The same procedure was used for reduction with sodium borodeuteride–acetic acid and sodium borohydride–acetic acid-d_4.

In an analogous experiment, $CDCl_3$ was used as solvent and the reduction was monitored by n.m.r. spectroscopy. The triplet of H-4′ at δ 4.92 appeared immediately, showing that acetyl migration occurred during the reduction and not during the work-up.

For experiments with a large excess of acetic acid, **4** (20 mg, 0.05 mmol) was dissolved in acetic acid (0.5 ml), and sodium borohydride (8 mg, 0.21 mmol) was added. The initial, slow reaction stopped within a few minutes, when dissolution of the borohydride was complete.

(*b*) *By direct addition.* A mixture of 1,2-dichloroethane (0.25 ml), glacial acetic acid (0.048 ml, 0.84 mmol), and sodium borohydride (8 mg, 0.21 mmol) was stirred with exclusion of moisture until hydrogen evolution had ceased. A solution of **4** (20 mg, 0.05 mmol) in 1,2-dichloroethane (0.2 ml) was then added. T.l.c. showed very slow reaction. After 24 h, only traces of **6** and ~90% of theophylline were recovered.

*7-(3,4,6-Tri-*O*-acetyl-2-deoxy-β-*D*-*arabino*-hexopyranosyl)theophylline* (**7**). — (*a*) Acetylation of **6** (45 mg) with acetic anhydride–sodium acetate and crystallisation of the product from ethanol gave **7** as needles (35 mg), m.p. 187–188°, $[\alpha]_D^{20}$ −2° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 9100).

Anal. Calc. for $C_{19}H_{24}N_4O_9$: C, 50.44; H, 5.31; N, 12.39. Found: C, 50.10; H, 5.31; N, 12.25.

(*b*) Tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose (**8**, ~90% β-anomer; 2 g, 6.02 mmol) and trimethylsilyltheophylline [obtained from 1.2 g (6.7 mmol) of theophylline] in acetonitrile (35 ml) were treated with $SnCl_4$ (0.24 ml, 2 mmol) at 85° for 1 h. Work-up, as described for **1**, gave a mixture of two nucleosides in a ratio of ~85:15 (t.l.c., solvent *A*). The faster-moving, major component was obtained pure by crystallisation from ethanol. Recrystallisation from ethanol gave **7** (985 mg), m.p. 187–187.5°, $[\alpha]_D^{20}$ −2° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 9150), which was identical (i.r. and n.m.r. spectra) with the product in (*a*).

*7-(2-Deoxy-β-*D*-arabino-hexopyranosyl)theophylline* (**13**). — Compound **7** (40 mg) was treated for 3 h at room temperature with methanolic ammonia saturated at 0°. The solution was concentrated, and the residue was triturated with a small amount of chloroform to remove acetamide. The insoluble mass was collected, and crystallised from methanol to give **13** (27 mg), which decomposed at 233–240°; $[\alpha]_D^{20}$ +3° (*c* 0.1, 80% methanol); λ_{max}^{MeOH} 274 nm (ε 9100); λ_{max}^{Ph1} 274 nm (ε 9700); $\lambda_{max}^{Ph\ 13}$ 274 nm (ε 9750).

Anal. Calc. for $C_{13}H_{18}N_4O_6$: C, 47.86; H, 5.52; N, 17.18. Found: C, 47.91; H, 5.61; N, 17.02.

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