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SOME BENZYLIDENE ACETAL DERIVATIVES OF THEOPHYLLINE NUCLEOSIDES†

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ABSTRACT

The reaction of some hexopyranosyltheophylline nucleosides with benzaldehyde in the presence of zinc chloride gave the expected benzylidene acetals. Thus, 7-α-D-mannopyranosyltheophylline gave the 2′,3′:4′,6′-diacetal as a mixture of diastereoisomers, one of which was isolated. The β-D-galacto- and β-D-gluco-pyranosyltheophyllines gave the 4′,6′-acetals, which were characterised as 2′,3′-diesters. Mild, acidic hydrolysis of 7-(4,6-*O*-benzylidene-2,3-di-*O*-mesyl-β-D-glucopyranosyl)theophylline gave 7-(2,3-di-*O*-mesyl-β-D-glucopyranosyl)theophylline, and strongly basic hydrolysis gave 7-(2,3-anhydro-4,6-*O*-benzylidene-β-D-allopyranosyl)theophylline. Ring-opening of this 2′,3′-epoxide with iodide anion afforded mainly 7-(4,6-*O*-benzylidene-2-deoxy-2-iodo-β-D-altropyranosyl)theophylline, which was characterised as the 3′-acetate.

INTRODUCTION

In previous papers[1,2], we described a convenient procedure for the synthesis of theophylline nucleosides[1], and some chemical transformations of 7-β-D-glucopyranosyltheophylline (**6**), including the preparation of a 6′-deoxyhex-5′-enopyranosyl nucleoside[2]. In an attempt to extend these studies to the synthesis of a corresponding 2′,3′-dideoxyhex-2′-enopyranosyl nucleoside (**15**), we prepared certain benzylidene acetals of theophylline nucleosides, including that of 7-β-D-glucopyranosyltheophylline (**8**), as intermediates.

The interest in preparing such unsaturated nucleoside derivatives lies in the fact that they are analogues of cytosinine (**16**), a structural component of the antibiotic blasticidin S[1,2] which possesses anti-tumour activity.

†Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.

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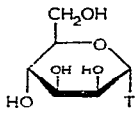

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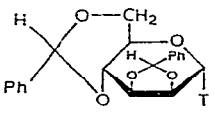

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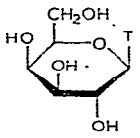

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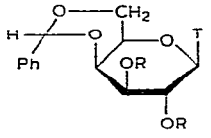

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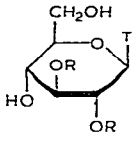

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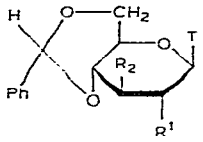
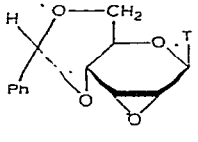


	R^1	R^2
8	OH	OH
9	OAc	OAc
10	OMs	OMs
11	OH	I



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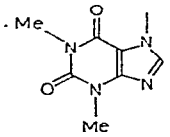
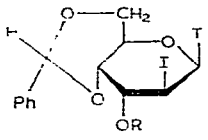
T =





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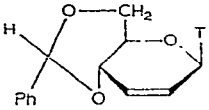

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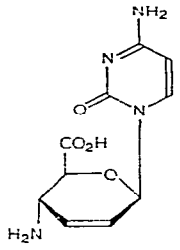

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DISCUSSION

The reaction of 7-α-D-mannopyranosyltheophylline (**1**) with benzaldehyde and zinc chloride gave a mixture from which a dibenzylidene acetal was isolated in low yield (20%). Elemental analysis, and i.r. and ^{1}H-n.m.r. spectra (Table I) were in accord with a dibenzylidene acetal which, by analogy with the benzylidenation of methyl α-D-mannopyranoside[3], was considered to be 7-(2,3:4,6-di-*O*-benzylidene-α-D-mannopyranosyl)theophylline (**2**). The fact that there were only two sharp singlets (τ 3.91, 4.23) for benzylic protons in the ^{1}H-n.m.r. spectra was taken as evidence that only one of the four possible diastereomeric acetals was present. The configuration of the benzylic centre of the 4′,6′-acetal is that shown in **2** (*i.e.*, phenyl equatorial). It is well-established that such acetal rings are formed under thermodynamic control, which favours an equatorial disposition for the phenyl residue[3]. However, it was not possible to assign the configuration at the 2′,3′-benzylic proton (τ 3.91). Foster *et al.*[3] found that an *endo*-2,3-benzylic proton in the corresponding acetal derived from methyl α-D-mannopyranoside resonated at lower field (τ 4.16 in *p*-dioxane) than an

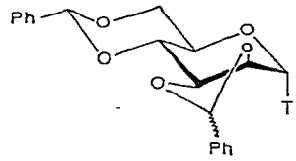
TABLE I

^{1}H-N.M.R. PARAMETERS*

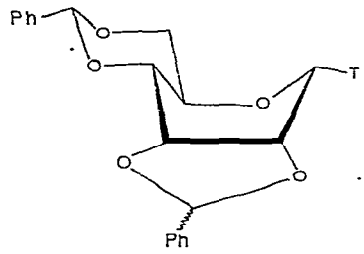
Compound	2[a]	5[b]	9[b]	10[a]	12[c]	13[d]	14[e]
H-1′	3.45d	3.28d	~3.60d	~3.60d	3.62d	3.80d	4.27d
H-2′	4.43t	3.85t	~3.67ot	~3.6o	5.40d	4.51q	5.02q
H-3′	4.93cm	4.30q	4.08cm	4.31ot			4.38osx
H-4′		4.89q					5.33q
H-5′	5.2–6.2o	5.84s	5.4–6.2cm	5.5–6.1cm	6.2–6.4cm	5.0–6.1cm	6.0cm
H-6′a		5.58q			5.82oq		5.50oq
H-6′b		5.82q			6.05q		5.73q
H-8	1.50s	1.44s	1.60s	1.31s	1.94s	1.76s	2.12s
*CH*Ph	4.23s	4.14s	4.27s	4.18os	4.35s	4.15s	4.35s
	3.91s	—	—	—	—	—	—
OAc	—	—	8.02s	—	—	—	7.73s
	—	—	8.13s	—	—	—	—
OMs	—	6.65s?	—	6.66s?	—	—	—
	—	6.92s	—	6.75s	—	—	—
N-Me	6.48s	6.51s	6.50s		6.57s	6.47s	6.41s
	6.58s	6.58s?	6.56s	6.52os	6.69s	6.63s	6.63s
$J_{1',2'}$	7.0	9.0	~9.0	—	~0.5	2.0	2.0
$J_{2',3'}$	~7.5	9.5	~9.0	~9.0	8.5	3.0	3.0
$J_{3',4'}$	—	3.5	—	~9.0	—	—	~2.5
$J_{4',5'}$	—	~1.0	—	—	—	—	~9.5
$J_{5',6'a}$	—	~2.0	—	—	~4.0	—	—
$J_{5',6'b}$	—	~1.5	—	—	~4.5	—	~4.5
$J_{6'a,6'b}$	—	~12	—	—	~10	—	~9.5
$J_{1',3'}$	—	—	—	—	—	~0.5	~0.5

*First-order chemical shifts (τ values) and coupling constants (Hz) at 100 MHz. [a]In pyridine-d_5. [b]In pyridine-d_5 at 70°. [c]In pyridine-d_5 at 90° with hexamethyldisilazane (HMDS) as internal reference standard. [d]In pyridine-d_5 at 60°. [e]In chloroform-*d*. Key: cm, complex multiplet; d, doublet; o, overlapped; q, quartet; s, singlet; sx, sextet; t, triplet.

exo-benzylic proton (τ 4.46 in *p*-dioxane). However, both diastereomers of the acetal **2** were not obtained, and therefore assignment of configuration in the manner of Foster *et al.*[3] was not possible. The observed value (7.0 Hz) of $J_{1',2'}$ in the ^{1}H-n.m.r. spectrum of **2** was far too large for an equatorial–equatorial orientation of H-1′ and H-2′, as found in the $^4C_1$ conformation, which would give rise to a relatively small coupling (1–2 Hz). The 2′,3′-*O*-benzylidene group evidently causes gross distortion of the $^4C_1$ conformation (**2a**). The two coupling constants available ($J_{1',2'}$ 7.0, $J_{2',3'}$ 7.5 Hz) suggest the $^{1,4}B$ conformation (**2b**) or a related skew form, in which the dihedral angles $\phi_{1H,2H}$ (~180°) and $\phi_{2H,3H}$ (~0°) would result in coupling constants of the observed magnitude. It has been shown previously that the large C-1′ theophylline group prefers an equatorial position due to both electronic factors, namely the reverse anomeric effect[4], and steric factors. As a result, α-D-mannopyranosyltheophylline (**1**) adopts preferentially the alternative $^1C_4$ conformation, in which the theophylline group is equatorial[1].



2a



2b

The reaction of 7-β-D-galactopyranosyltheophylline (**3**) with benzaldehyde and zinc chloride gave a good yield of a single 4′,6′-benzylidene acetal (**4**), the structure of which was clearly indicated by the ^{1}H-n.m.r. spectrum of the derived 2′,3′-di-*O*-mesyl derivative (**5**), which was largely first order, and the observed coupling constants indicated that the $^4C_1$ conformation was predominant in solution. The observed value of $J_{4',5'}$ (~1.0 Hz) is particularly characteristic of galactopyranosides in this conformation.

The corresponding derivatives (**8** and **10**) of 7-β-D-glucopyranosyltheophylline (**6**) and the derived 7-(2,3-anhydro-4,6-*O*-benzylidene-β-D-allopyranosyl)theophylline (**12**) were reported previously by Todd *et al.*[5]. The 4′,6′-benzylidene acetal **8** was further characterized as its 2′,3′-di-acetate (**9**) and, in addition, the 2′,3′-di-*O*-mesyl derivative **10** was further characterized by methanolysis of the acetal function to give 7-(2,3-di-*O*-mesyl-β-D-glucopyranosyl)theophylline (**7**).

The *allo* configuration of the epoxide **12** followed from two points additional to those cited by Todd *et al.*[5]. Firstly, in the ^{1}H-n.m.r. spectrum of **12**, the signal for H-1′ appeared as a narrow doublet (τ 3.62, $J_{1',2'}$ ~0.5 Hz), which is indicative[6] of a *trans* relationship between H-1 and H-2. Since the anomeric configuration is known to be β, the position of the epoxide ring is therefore clearly defined as below the plane of the pyranoside ring. Secondly, the ring-opening of epoxides in sterically constrained systems generally proceeds stereoselectively to give mainly the product arising from *trans*-diaxial ring-opening[7]. The epoxide **12** reacted with sodium iodide under mildly acidic conditions to give one major product (>85%, t.l.c.), which was isolated crystalline. The ^{1}H-n.m.r. spectrum of the derived acetate was in agreement with that expected for 7-(3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-iodo-β-D-altropyranosyl)-theophylline (**14**), consistent with *trans*-diaxial ring-opening. A minor product formed together with **14** could not be isolated, but was probably 7-(4,6-*O*-benzylidene-3-deoxy-3-iodo-β-D-glucopyranosyl)theophylline (**11**), since the corresponding methyl glycoside of the epoxide **12** gives 20% of the 3-deoxy-3-iodoglucoside under these conditions[8].

The 2-iodo-*altro* derivative **13** was potentially a readily available precursor of the 2′-unsaturated nucleoside **15**. However, both the procedures reported by Stevens *et al.*[9] and Lemieux *et al.*[8] gave complex mixtures when applied to **13**. Similarly, treatment of the 2′,3′-di-*O*-mesyl derivative **10** with either sodium iodide and zinc

dust in boiling *N,N*-dimethylformamide or with potassium ethylxanthate in boiling 1-butanol[10] gave dark syrups containing several components. Fox *et al.*[11] obtained similar results when attempting to prepare an analogue of cytosine, a related 2′-ene.

EXPERIMENTAL

General methods. — For procedures, see Ref. 1.

7-(2,3:4,6-Di-O-benzylidene-α-D-mannopyranosyl)theophylline (**2**). — Crushed, fused zinc chloride (4.0 g) was stirred with redistilled benzaldehyde (20 ml) until dissolution was complete (2–3 h), 7-α-D-mannopyranosyltheophylline[1] (**1**, 2.0 g) was added, and stirring was continued for 4 days. The clear reaction mixture was poured into a vigorously stirred mixture of light petroleum and water, and the precipitated syrup was isolated by decantation and washed with light petroleum to remove benzaldehyde. A solution of the syrup in dichloromethane was then washed with water to remove any remaining zinc chloride, dried ($MgSO_4$), and evaporated. The syrup crystallised from acetone, giving **2** (0.62 g, 20%), m.p. 224–234°, $[\alpha]_D$ +77° (*c* 1, chloroform). (Found: C, 62.7; H, 5.0; N, 11.0. $C_{27}H_{26}N_4O_7$ calc.: C, 62.6; H, 5.0; N, 10.8%). The mother liquor contained a mixture of dibenzylidene derivatives (^{1}H-n.m.r. evidence), which could not be readily separated.

7-(4,6-O-Benzylidene-β-D-galactopyranosyl)theophylline (**4**) *and its 2′,3′-dimethanesulphonate* (**5**). — A mixture of 7-β-D-galactopyranosyltheophylline[1] (**3**), zinc chloride (2 g), and benzaldehyde (20 ml) was stirred for 5 h. The clear, yellow reaction mixture was poured into ether (200 ml), with stirring, and the white precipitate was filtered off, washed with ether until free of benzaldehyde, and then dried in air to give **4** (0.9 g, 72%), m.p. 248–254°, $[\alpha]_D$ −59° (*c* 1, pyridine) (Found: C, 55.5; H, 5.0; N, 12.7. $C_{20}H_{22}N_4O_7$ calc.: C, 55.8; H, 5.2; N, 13.0%).

The acetal **4** (0.5 g) was dissolved in pyridine (3.5 ml), mesyl chloride (0.3 g, *ca.* 3 mol.) was added, and the mixture was kept at room temperature overnight. It was then treated with a few drops of cold water and poured slowly into ice–water (50 ml). The white precipitate was filtered off and dissolved in dichloromethane. After drying ($MgSO_4$), the solution was diluted with ethanol (50 ml), and the dichloromethane was evaporated. Upon cooling of the residual solution, **5** (0.32, 48%) crystallised out, m.p. 233–239°, $[\alpha]_D$ +24° (*c* 1, chloroform) (Found: C, 45.1; H, 4.5; N, 9.5. $C_{22}H_{26}N_4O_{11}S_2$ calc.: C, 45.0; H, 4.5; N, 9.6%).

7-(4,6-O-Benzylidene-β-D-glucopyranosyl)theophylline (**8**) *and its 2′,3′-diacetate* (**9**) *and 2′,3′-dimethanesulphonate* (**10**). — Zinc chloride (40 g) was dissolved in benzaldehyde (200 ml), and 7-β-D-glucopyranosyltheophylline[1] was then added. The mixture was stirred for 3 days, after which the homogeneous mixture was shaken vigorously with water and light petroleum, which resulted in precipitation of the product. Filtration, followed by washing with water and light petroleum, gave the acetal **8** (19.3 g, 77%). Successive recrystallizations from 2-methoxyethanol–methanol and then acetone gave **8**, m.p. 275–279° with a transition at ~220°, $[\alpha]_D$ −59° (*c* 1.4, pyridine); lit.[5] m.p. 272–273°. However, a satisfactory elemental analysis could not be obtained.

A solution of the acetal **8** (1.65 g) in a mixture of pyridine (10 ml) and acetic anhydride (5 ml) was kept at 0° for 2 days, and then poured on to crushed ice with stirring. The white precipitate was filtered off and recrystallised from 2-methoxyethanol–methanol to give the 2',3'-diacetate **9** (1.44 g, 73%), m.p. 267–268°, $[\alpha]_D$ −76° (*c* 1, chloroform) (Found: C, 56.0; H, 5.0; N, 10.9. $C_{24}H_{26}N_4O_9$ calc.: C, 55.9; H, 5.1; N, 10.9%).

A solution of the acetal **8** (2 g) in pyridine (20 ml), cooled to 0°, was added to a solution of mesyl chloride (1.3 ml, 3.6 mol.) in pyridine (10 ml), and the mixture was kept at room temperature overnight. After pouring into ice–water (50 ml), the crude product was filtered off and dissolved in dichloromethane, and the solution was decolourized with activated charcoal, filtered through Kieselguhr, and finally diluted with ethanol (200 ml). The dichloromethane was boiled off until needles of the product started to appear. Cooling then gave **10** (2.57 g, 90%), m.p. 253–254° (dec.), $[\alpha]_D$ −47° (*c* 1.6, chloroform); lit.[5] m.p. 223–234° (dec.). A satisfactory analysis could not be obtained. The dimethanesulphonate **10** was characterized by hydrolysis to give **7**, and also by conversion into the known *allo*-2',3'-epoxide **12**.

7-(2,3-Di-O-mesyl-β-D-glucopyranosyl)theophylline (**7**). — The acetal **10** (0.5 g) was treated with boiling 1% methanolic hydrogen chloride (0.4 ml of acetyl chloride + 20 ml of methanol) for a few min, until a clear solution was obtained. The solution was then made alkaline with ammonia, filtered, and evaporated to a white solid. The product was washed with ethanol and then dichloromethane to give the diester **7** (0.37 g, 86%). Recrystallisation from methanol gave the analytical sample, m.p. 222–228°, $[\alpha]_D$ +3.5° (*c* 1, acetone) (Found: C, 35.9; H, 4.5; N, 10.8. $C_{15}H_{22}N_4O_{11}S_2$ calc.: C, 36.2; H, 4.5; N, 11.2%).

7-(2,3-Anhydro-4,6-O-benzylidene-β-D-allopyranosyl)theophylline (**12**). — The dimethanesulphonate **10** (2.0 g) was dissolved in dichloromethane (350 ml), methanolic sodium methoxide [1.4 g (3 mol.) of sodium in 25 ml of methanol] was added, and the mixture was stirred for 2 days at room temperature, after which it was filtered. The filtrate was washed with water (4 × 25 ml) until the aqueous phase was neutral. The organic phase was dried ($MgSO_4$), decolourized with activated charcoal, and evaporated to a syrup which, on trituration with acetone, gave a solid product (5.8 g, 69%). Recrystallization from acetone gave **12** as needles, m.p. 235–238° (dec.) after a transition at ~200°, $[\alpha]_D$ +82° (*c* 1.5, chloroform) (Found: C, 58.0; H, 4.9; N, 13.3. $C_{20}H_{20}N_4O_6$ calc.: C, 58.3; H, 4.9; N, 13.6%); lit.[5] m.p. 225–226°.

Reaction of 7-(2,3-Anhydro-4,6-O-benzylidene-β-D-allopyranosyl)theophylline (**12**) *with iodide anion.* — The *allo*-epoxide **12** (4.0 g) was dissolved in boiling acetone (80 ml), and anhydrous sodium acetate (0.40 g, 0.5 mol.), glacial acetic acid (11 ml, 20 mol.), and dry sodium iodide (7.4 g, 5 mol.) were added. The mixture was heated under reflux for 5 h and then evaporated to a syrup, which was taken into dichloromethane (200 ml). The solution was washed in sequence with water (50 ml), saturated, aqueous sodium hydrogen carbonate (2 × 50 ml), aqueous sodium thiosulphate (50 ml), and water, dried ($MgSO_4$), and evaporated to a syrup. Trituration with ethanol gave the crude anhydride (4.3 g, 82%), shown by t.l.c. (dichloromethane–

ethanol 20:1) to be a 2-component mixture (~4:1). Fractional crystallisation from methanol gave the major component, 7-(4,6-*O*-benzylidene-2-deoxy-2-iodo-β-D-altropyranosyl)theophyiline (**13**), m.p. 205–220° followed by resolidification to prisms melting at ~250°, $[\alpha]_D$ +8.2° (*c* 1, chloroform) (Found: C, 44.0; H, 4.0; N, 10.2. $C_{20}H_{21}IN_4O_6$ calc.: C, 44.4; H, 3.9; N, 10.4%). The minor component was not isolated.

A solution of the 2-iodide (**13**) (0.25 g) in a mixture of pyridine (2.5 ml) and acetic anhydride (0.4 ml, 9 mol.) was stored at −12° overnight, and then poured into water. The precipitate was collected, and recrystallised from ethanol to give the 3-acetate **14** (0.15 g, 55%), m.p. 225–229° (dec.) with softening from 210°, $[\alpha]_D$ −25° (*c* 1, chloroform) (Found: C, 44.5; H, 4.1; N, 9.2. $C_{22}H_{23}IN_4O_7$ calc.: C, 44.3; H, 4.0; N, 9.6%).

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