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Note

Unsaturated ketonucleosides: keto derivatives of benzoylated disaccharide nucleosides

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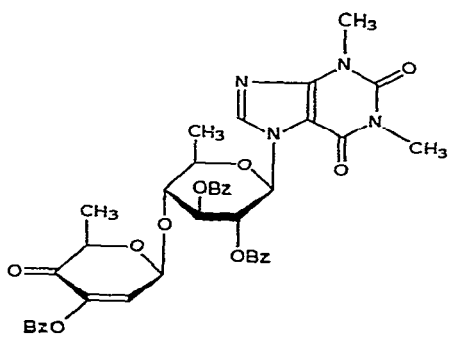
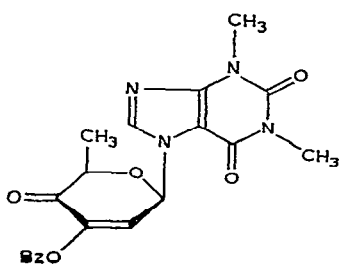
As a part of our continuing effort to develop tumor-inhibitory drugs, unsaturated ketonucleosides have been prepared and their biological activity investigated[1]. In extending these studies, we sought to introduce a glucose residue between the heterocyclic base and the unsaturated ketosugar moiety, in order to determine the effect on antileukemic activity. We now report the first synthesis of a nucleoside (**1**) containing an unsaturated, benzoylated ketodisaccharide, which is an analogue of the biologically active, unsaturated ketonucleoside **2**.



1



2

Purine disaccharide nucleosides were synthesised first by Wolfrom and co-workers[2]. Stevens and Blumbergs[3] prepared the first pyrimidine disaccharide nucleosides by condensation of an appropriately protected disaccharide with a pyrimidine base or by coupling a monosaccharide nucleoside with a second monosaccharide. More recently, Lichtenthaler and co-workers[4] synthesised 5′-*O*-glycosylribonucleosides by the latter method. In developing a synthesis of **1**, we have used the former approach which follows closely that described[1] for the synthesis of the corresponding unsaturated ketonucleoside **2**.

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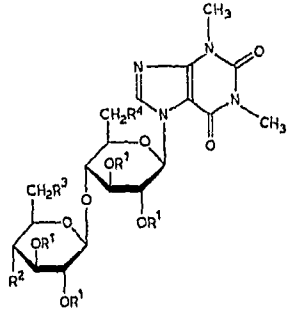

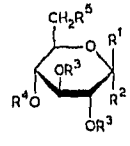

3 R^1 = Ac; R^2 = R^3 = R^4 = OAc

4 R^1 = H; R^2 = R^3 = R^4 = OH

5 R^1 = H; R^2, R^3 = PhHC(O)(O); R^4 = OH

6 R^1 = H; R^2, R^3 = PhHC(O)(O); R^4 = OTr

7 R^1 = Bz; R^2, R^3 = PhHC(O)(O); R^4 = OTr

8 R^1 = Bz; R^2 = R^3 = R^4 = OH

9 R^1 = Bz; R^2 = OH; R^3 = R^4 = Br

10 R^1 = Bz; R^2 = OH; R^3 = R^4 = H

14 R^1 = Ac; R^2 = R^3 = OAc; R^4 = H

15 R^1 = R^4 = H; R^2 = R^3 = OH

16 R^1 = R^4 = H; R^2, R^3 = PhHC(O)(O)

17 R^1 = Bz; R^2, R^3 = PhHC(O)(O); R^4 = H

18 R^1 = Bz; R^2 = R^3 = OH; R^4 = H

19 R^1 = Bz; R^2 = OH; R^3 = Br; R^4 = H

11 R^1 = theophylline; R^2 = R^4 = H; R^3 = Ac; R^5 = OH

12 R^1 = theophylline; R^2 = R^4 = H R^3 = Ac; R^5 = Br

13 R^1 = theophylline; R^2 = R^4 = R^5 = H; R^3 = Ac

The starting material, 7-(hepta-*O*-acetyl-β-cellobiosyl)theophylline (**3**) was obtained in good yield from octa-*O*-acetylcellobiose and trimethylsilyltheophylline under the conditions[5] used for the synthesis of pyrimidine disaccharide nucleosides. P.m.r. data ($J_{1',2'} = J_{2',3'} = 9$ Hz) showed that **3** had the β configuration.

Deacetylation of **3** with ammonia in methanol afforded crystalline 7-β-cellobiosyltheophylline (**4**), which was treated with benzaldehyde and $ZnCl_2$ to give the 4″,6″-*O*-benzylidene derivative **5**.

When **5** was treated with 1.2 mol of trityl chloride at room temperature for 3 days, ~50% of **5** remained unchanged and three tritylated products were detected by t.l.c., indicating tritylation of secondary hydroxyl groups. The reaction mixture could be separated; laborious column chromatography yielded 45% of the 6′-*O*-trityl derivative **6** and ~30% of **5**. Longer reaction time or warming did not affect significantly the yield of **6**, but gave a higher proportion of by-products.

These results show that the HO-6′ in **5** reacts sluggishly, nevertheless its reactivity is superior to that of benzyl maltoside derivatives[6]. Apparently, the reactivity of HO-6′ is more influenced by an α-linked glucosyl substituent at C-4 of the glucose residue than by the presence of a bulky β-aglycon (*cf.* ref. 6).

Compound **6** gave the crystalline tetrabenzoate **7**, removal of the acetal and trityl groups from which with 70% acetic acid afforded the crystalline 2′,3′,2″,3″-tetrabenzoate **8** in 83% yield. Treatment[7] of **8** with *N*-bromosuccinimide–triphenylphosphine in *N*,*N*-dimethylformamide gave the 6′,6″-dibromide **9**. As anticipated, this highly selective bromination was more difficult with **8** than with monosaccharides or monosaccharide nucleosides. Prolonged warming was required to obtain **9** in 63% yield. Catalytic reduction of **9** afforded the crystalline 6′,6″-dideoxynucleoside **10**.

The p.m.r. spectrum of **10** resembled that of **9** (see Experimental), except for the presence of two methyl signals and the absence of methylene signals. The signals for H-4′,5′ and H-4″,5″ had almost identical chemical shifts, and H-4′, H-5′, and Me-5′ formed an ABX_3 system (as did H-4″, H-5″, and Me-5″), resulting[8] in broad, unresolved bands for the signals of Me-5′ and Me-5″.

The oxidation of HO-4″ in **10** was performed best with methyl sulphoxide–acetic anhydride[9]. Pyridinium chromate or pyridinium chlorochromate in the presence of a molecular sieve[10], as well as the Pfitzner–Moffatt system[11], also effected oxidation, but the simultaneous β-elimination was not complete. The desired 7-[2,3-di-*O*-benzoyl-4-*O*-(3-*O*-benzoyl-2,6-dideoxy-β-D-*glycero*-hex-2-enopyranosyl-4-ulose)-6-deoxy-β-D-glucopyranosyl]theophylline (**1**) was obtained crystalline in a yield of 70%.

The p.m.r. spectrum ($CDCl_3$) of **1** contained, *inter alia*, signals for an olefinic proton at δ 6.7, for H-1″ markedly downfield at δ 5.76, and for H-6″ as a well-resolved doublet (*J* 6.5 Hz) owing to the absence of H-4″.

The following synthesis of **10** was superior to that described above. 7-(2,3-Di-*O*-acetyl-β-D-glucopyranosyl)theophylline (**11**) was obtained by the removal of the acetal group from 7-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)theophylline[12]. Bromination of **11** followed by catalytic reduction gave the 6′-deoxynucleoside **13**. Attempted condensation of **13** with tetra-*O*-acetyl-α-D-glucopyranosyl

bromide (**20**) in the presence of silver carbonate failed, as did stannic chloride–catalysed glycosylation[13] of **13** with penta-*O*-acetyl-β-D-glucose. However, the silver trifluoromethanesulphonate-promoted Koenigs–Knorr reaction[14] of **13** and **20** afforded mainly the desired disaccharide nucleoside **14** in 45% yield, and the β configuration of the interglycosidic bond was determined after deacetylation. The signal for H-1″ in the p.m.r. spectrum of **15** was a doublet having $J_{1,2}$ 7 Hz. The reaction sequence **16**→**19** was performed as described for compounds **5**→**9**. Catalytic hydrogenation of **19** then gave **10**.

EXPERIMENTAL

General methods. — U.v. spectra were recorded with a Varian UV-VIS M 635 spectrophotometer and n.m.r. spectra (internal Me_4Si) with a Varian T-60 instrument. Optical rotations were determined with a Roussel–Jouan Quick polarimeter, and melting points are uncorrected. T.l.c. was performed on silica gel F 1500 LS 254 (Schleicher–Schüll), silica gel 60 PF (Merck) was used for p.l.c., and silica gel 60 (Merck) for column chromatography, with ethyl acetate (*A*), and 9:1 (*B*) and 4:1 ethyl acetate–ethanol (*C*).

Benzoylation. — To a stirred solution of nucleoside in anhydrous pyridine (5 mL/mmol) at 0° was added benzoyl chloride dropwise. The reaction mixture was stored for 20 h at 4° and for 4 h at room temperature, and then poured into ice–water. The precipitate was collected and a solution in dichloromethane was washed successively with aqueous NH_4Cl, $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated to dryness.

Bromination of primary hydroxyl groups. — To a cooled solution of nucleoside and *N*-bromosuccinimide (2.5 mmol/mmol of primary HO) in *N*,*N*-dimethylformamide (10–15 mL) was slowly added triphenylphosphine (3.5 mmol/mmol of primary HO). The solution was stirred for 4–20 h at 50°, the excess of reagent was then decomposed with methanol, and the solution was concentrated *in vacuo*.

7-(Hepta-O-acetyl-β-cellobiosyl)theophylline (**3**). — A mixture of octa-*O*-acetyl-β-cellobiose (6.78 g, 10 mmol), trimethylsilyltheophylline (from 1.98 g of theophylline), and acetonitrile (100 mL) was treated with $SnCl_4$ (0.83 mL, 7 mmol) overnight at 75°. After dilution with dichloromethane, the solution was neutralised with saturated, aqueous $NaHCO_3$, filtered, washed with water, dried, and concentrated. The residue was crystallised from aqueous ethanol, to give **3** (7.4 g, 90%), m.p. 198–199°, $[\alpha]_D^{20}$ −35° (*c* 0.1, methanol), λ_{max}^{MeOH} 275 nm (ε 10000). P.m.r. data ($CDCl_3$): δ 7.83 (s, 1 H, H-8), 6.0 (d, 1 H, *J* 9 Hz, H-1′), 5.76 (t, 1 H, *J* 8.5 Hz, H-2′), 3.63 and 3.45 (2 s, 6 H, MeN-1,3), and 2.2–1.92 (7 s, 21 H, 7 OAc).

Anal. Calc. for $C_{33}H_{42}N_4O_{19} \cdot H_2O$: C, 48.53; H, 5.39; N, 6.86. Found: C, 48.78; H, 5.36; N, 7.18.

7-β-Cellobiosyltheophylline (**4**). — Compound **3** (4.2 g) was treated overnight at room temperature with methanolic ammonia saturated at 0°. The solution was concentrated, and the residue was crystallised from methanol and recrystallised from

aqueous methanol, to yield **4** (2.2 g, 85%), m.p. 237–240° (dec.), $[\alpha]_D^{20}$ −12.5° (*c* 0.1, water), $\lambda_{max}^{H_2O}$ 275 nm (ε 9700). P.m.r. data (Me_2SO-d_6): δ 8.5 (s, 1 H, H-8), 5.82 (d, 1 H, *J* 9 Hz, H-1′), 4.45 (d, 1 H, *J* 7 Hz, H-1″), 3.53 and 3.32 (2 s, 6 H, NMe-1,3).

Anal. Calc. for $C_{19}H_{28}N_4O_{12} \cdot 0.5\ H_2O$: C, 44.44; H, 5.65; N, 10.92. Found: C, 44.74; H, 5.64; N, 10.90.

7-[4-O-(4,6-O-Benzylidene-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**5**). — A mixture of **4** (2 g), benzaldehyde (15 mL), and anhydrous zinc chloride (2 g) was stirred overnight. After the addition of ether (150 mL), the precipitate was collected, stirred again with ether, and then crystallised from aqueous methanol, to yield **5** (1.45 g, 61%), m.p. 237–240°, $[\alpha]_D^{20}$ −30° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 9870).

Anal. Calc. for $C_{26}H_{32}N_4O_{12} \cdot 1.5\ H_2O$: C, 50.40; H, 5.65; N, 9.05. Found: C, 50.43; H, 5.68; N, 8.95.

7-[4-O-(4,6-O-Benzylidene-β-D-glucopyranosyl)-6-O-triphenylmethyl-β-D-glucopyranosyl]theophylline (**6**). — (*a*) To a stirred solution of dry **5** (0.97 mmol) in pyridine (5 mL) was added trityl chloride (335 mg, 1.2 mmol), and the mixture was kept for 3 days at room temperature and then poured into ice–water. The mixture was extracted with dichloromethane, and the organic layer was washed with water and dried. T.l.c. (solvent *A*) revealed components having R_F 0.95 (traces of triphenylmethanol), 0.62, 0.26, 0.10 (**6**), and 0.02 (**5**). Column chromatography (elution with solvent *A*) gave triphenylmethanol. Elution with solvent *B* followed by solvent *C*, with crystallisation of the fraction having R_F 0.10 from ethanol, gave **6** (375 mg, 43%), m.p. 178–180° (dec.), $[\alpha]_D^{20}$ −20° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 9067).

Anal. Calc. for $C_{45}H_{46}N_4O_{12} \cdot C_2H_5OH$: C, 64.09; H, 5.91; N, 6.36. Found: C, 63.43; H, 5.93; N, 6.34.

(*b*) When **5** (2.36 mmol) was treated with trityl chloride (0.792 g, 2.84 mmol) in pyridine (12 mL) at 70° for 18 h, t.l.c. revealed a greater proportion of products having R_F 0.62 and 0.26, and, in addition, the presence of a new tritylated product having R_F 0.86. Work-up as described above gave **6** (1.17 g, 56%).

7-[2,3-Di-O-benzoyl-4-O-(2,3-di-O-benzoyl-4,6-O-benzylidene-β-D-glucopyranosyl)-6-O-triphenylmethyl-β-D-glucopyranosyl]theophylline (**7**). — Treatment of **6** (1.06 g, 1.21 mmol) with benzoyl chloride (0.85 mL, 7.26 mmol), as described above, gave **7** (1.33 g, 85%), m.p. 179–180° (from ethyl acetate–ethanol), $[\alpha]_D^{20}$ +18° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 275 nm (ε 12560).

Anal. Calc. for $C_{73}H_{62}N_4O_{16} \cdot C_2H_5OH$: C, 69.44; H, 5.25; N, 4.32. Found: C, 69.57; H, 5.29; N, 4.35.

7-[2,3-Di-O-benzoyl-4-O-(2,3-di-O-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**8**). — A suspension of **7** (1.25 g, 0.96 mmol) in 70% acetic acid (60 mL) was heated for 1 h at 100°. Stirring was then continued for 1 h at 0°, triphenylmethanol was removed, the filtrate was concentrated, and the residue was triturated with ether. The resulting solid was collected, and crystallised from ethyl acetate–

diisopropyl ether, to give **8** (760 mg, 83%), m.p. 275–276°, $[\alpha]_D^{20}$ +10° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 277 nm (ε 12700).

Anal. Calc. for $C_{47}H_{44}N_4O_6$: C, 61.30; H, 4.78; N, 6.08. Found: C, 60.99; H, 4.88; N, 6.06.

7-[2,3-Di-O-benzoyl-6-bromo-6-deoxy-4-O-(2,3-di-O-benzoyl-6-bromo-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**9**). — The syrupy residue obtained by bromination (20 h) of **8** (510 mg, 0.56 mmol) was dissolved in dichloromethane. The solution was washed with water, the organic layer was dried (Na_2SO_4) and concentrated, and the residue was triturated with ether and then crystallised from acetone–ethanol, to yield **9** (364 mg, 63%), m.p. 271–272°, $[\alpha]_D^{20}$ +50° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 277 nm (ε 12300).

Anal. Calc. for $C_{47}H_{42}Br_2N_4O_{14}$: C, 53.93; H, 4.02; Br, 15.28; N, 5.35. Found: C, 53.30; H, 4.14; Br, 15.51; N, 5.17.

7-[2,3-Di-O-benzoyl-6-deoxy-4-O-(2,3-di-O-benzoyl-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**10**). — A solution of **9** (260 mg, 0.248 mmol) in ethyl acetate (12 mL), ethanol (10 mL), and triethylamine (0.14 mL, 0.992 mmol) was hydrogenated over 10% Pd/C. The catalyst was removed and the filtrate was concentrated. A solution of the residue in dichloromethane was washed with water, dried, and concentrated. The residue was crystallised from acetone–ethanol, to give **10** (122 mg, 55%), m.p. 306–307° (dec.), $[\alpha]_D^{20}$ +63° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 276 nm (ε 10760). P.m.r. data ($CDCl_3$): δ 8.2–7.1 (m, 21 H, H-8 and Ar), 6.4–5.7 (m, 3 H, H-1′,2′,3′), 5.65–5.15 (m, 2 H, H-2″,3″), 4.86 (d, 1 H, *J* 7.5 Hz, H-1″), 4.16–3.7 (m, 2 H, H-4′,5′), 3.48 and 3.3 (2 s, 6 H, NMe-1,3), ~3.48–3.0 (obscured m, 3 H, H-4″,5″ and HO-4″) 1.27 (b, 3 H, Me-5′), and 0.82 (b, 3 H, Me-5″).

Anal. Calc. for $C_{47}H_{44}N_4O_{14}$: C, 63.51; H, 4.95; N, 6.31. Found: C, 63.27; H, 5.0; N, 6.27.

7-[2,3-Di-O-benzoyl-4-O-(3-O-benzoyl-2,6-dideoxy-β-D-glycero-hex-2-enopyranosyl-4-ulose)-6-deoxy-β-D-glucopyranosyl]theophylline (**1**). — To a solution of **10** (100 mg, 0.11 mmol) in methyl sulphoxide (0.4 mL) was added acetic anhydride (0.25 mL). The mixture was kept for 2 days at room temperature and then poured into ice–water. The product was collected, and recrystallised from ethyl acetate–diisopropyl ether, to yield **1** (60 mg, 70%), m.p. 146–148° (dec.), $[\alpha]_D^{20}$ +45° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 277 nm (ε 10490). P.m.r. data ($CDCl_3$): δ 8.2–7.18 (m, 16 H, H-8 and Ar), 6.71 (d, 1 H, *J* 1.5 Hz, H-2″), 6.55–5.83 (m, 3 H, H-1′,2′,3′), 5.75 (d, 1 H, H-1″), 4.3–3.83 (m, 3 H, H-4′,5′,5″), 3.55 and 3.37 (2 s, 6 H, NMe–1,3), 1.53 (b, 3 H, Me-5′), and 1.0 (d, 3 H, *J* 6.5 Hz, Me-5″).

Anal. Calc. for $C_{40}H_{36}N_4O_{12}$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.18; H, 4.68; N, 7.12.

7-(2,3-Di-O-acetyl-β-D-glucopyranosyl)theophylline (**11**). — A solution of 7-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)theophylline (2.9 g, 5.6 mmol) in ethyl acetate (150 mL) and ethanol (150 mL) was hydrogenated over 10% Pd/C, filtered, and concentrated. The residue was crystallised from ethyl acetate and

recrystallised from 96% ethanol–diisopropyl ether, to give **11** (2.3 g, 96%), m.p. 154–156°, $[\alpha]_D^{20}$ −35° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 8530).

Anal. Calc. for $C_{17}H_{22}N_4O_9$: C, 47.88; H, 5.16; N, 13.14. Found: C, 47.53; H, 5.29; N, 12.89.

7-(2,3-Di-O-acetyl-6-bromo-6-deoxy-β-D-glucopyranosyl)theophylline (**12**). — The syrupy residue obtained by bromination (4 h) of **11** (13.54 g, 31.8 mmol) was triturated with pentane. A solution of the resulting solid in dichloromethane was washed with water, dried, and concentrated, and the residue was dissolved in ethyl acetate. Triphenylphosphine oxide was precipitated by addition of pentane. Filtration, concentration of the solution, and crystallisation of the residue from ethanol–diisopropyl ether gave **12** (12.3 g, 78%), m.p. 198° (dec.), $[\alpha]_D^{20}$ −29° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 7970).

Anal. Calc. for $C_{17}H_{21}BrN_4O_8$: C, 41.73; H, 4.29; Br, 16.34; N, 11.45. Found: C, 41.74; H, 4.29; Br, 16.43; N, 11.39.

7-(2,3-Di-O-acetyl-6-deoxy-β-D-glucopyranosyl)theophylline (**13**). — A solution of **12** (10.73 g, 21.97 mmol) in ethanol (360 mL), ethyl acetate (360 mL), and triethylamine (6.21 mL, 44 mmol) was hydrogenated over Pd/C and worked-up as described for **10**. Recrystallisation of the product from ethanol yielded **13** (5.85 g, 65%), m.p. 193–194°, $[\alpha]_D^{20}$ −50° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 8026).

Anal. Calc. for $C_{17}H_{22}N_4O_8$: C, 49.76; H, 5.36; N, 13.66. Found: C, 49.63; H, 5.42; N, 13.68.

7-[2,3-Di-O-acetyl-6-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**14**). — To a stirred solution of **13** (3.93 g, 9.6 mmol) and tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.67 g, 11.3 mmol) in dichloromethane (55 mL) was added silver trifluoromethanesulphonate (2.9 g, 11.3 mmol). After 6 h at room temperature, the mixture was diluted with dichloromethane, filtered, washed successively with aqueous $NaHCO_3$ and water, dried, and concentrated. Compound **14** (40%) crystallised from ethyl acetate–diisopropyl ether. P.l.c. of the mother liquor (9:1 benzene–methanol) gave 7–9% of **14** and ~5% of the α-linked disaccharide nucleoside. Recrystallisation from methanol yielded **14** (3.20 g, 45%), m.p. 255–257°, $[\alpha]_D^{20}$ −53° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 276 nm (ε 8935).

Anal. Calc. for $C_{31}H_{40}N_4O_{17}$: C, 50.27; H, 5.41; N, 7.57. Found: C, 49.78; H, 5.60; N, 7.69.

7-(6-Deoxy-4-O-β-D-glucopyranosyl-β-D-glucopyranosyl)theophylline (**15**). — Deacetylation of **14** (2.7 g) with methanolic ammonia and recrystallisation of the product from aqueous methanol gave **15** (1.76 g, 98%), m.p. 237–238°, $[\alpha]_D^{20}$ −30° (*c* 0.1, water), $\lambda_{max}^{H_2O}$ 275 nm (ε 9900). P.m.r. data (Me_2SO-d_6): δ 8.45 (s, 1 H, H-8), 5.75 (d, 1 H, *J* 9 Hz, H-1′), 4.42 (d, 1 H, *J* 7.5 Hz, H-1″), 3.53 and 3.33 (2 s, 6 H, NMe-1,3), and 1.35 (d, 3 H, *J* 6 Hz, H-6′).

Anal. Calc. for $C_{19}H_{28}N_4O_{11} \cdot 0.5\ H_2O$: C, 45.87; H, 5.84; N, 11.26. Found: C, 45.64; H, 5.84; N, 11.22.

7-[4-O-(4,6-O-Benzylidene-β-D-glucopyranosyl)-6-deoxy-β-D-glucopyranosyl]-theophylline (**16**). — Benzylidenation of **15** (1.63 g), as described for the preparation

of **5**, and crystallisation of the product from methanol afforded **16** (1.08 g). P.l.c. of the mother liquor yielded more (0.57 g) **16** (total yield, 1.65 g, 87%), m.p. 214–215°, $[\alpha]_D^{20}$ −34° (*c* 0.1, methanol), λ_{max}^{MeOH} 274 nm (ε 7460).

Anal. Calc. for $C_{26}H_{32}N_4O_{11}$: C, 54.17; H, 5.55; N, 9.72. Found: C, 54.10; H, 5.68; N, 9.82.

7-[2,3-Di-O-benzoyl-6-deoxy-4-O-(2,3-di-O-benzoyl-4,6-O-benzylidene-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**17**). — The crude product (1.82 g, 98%) obtained by benzoylation of **16** (1.08 g, 1.87 mmol) was sufficiently pure for the next step. A sample crystallised from ethyl acetate–methanol had m.p. 297–298°, $[\alpha]_D^{20}$ +40° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 276 nm (ε 14000).

Anal. Calc. for $C_{54}H_{48}N_4O_{15}$: C, 65.32; H, 4.84; N, 5.65. Found: C, 65.10; H, 4.93; N, 5.59.

7-[2,3-Di-O-benzoyl-6-deoxy-4-O-(2,3-di-O-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**18**). — Hydrogenolysis of **17** over Pd/C, as described above, and crystallisation of the product from ethanol gave **18** (1.25 g, 81%), m.p. 275–277°, $[\alpha]_D^{20}$ +47° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 276 nm (ε 11700).

Anal. Calc. for $C_{47}H_{44}N_4O_{15}$: C, 62.38; H, 4.87; N, 6.19. Found: C, 61.99; H, 4.91; N, 6.26.

7-[2,3-Di-O-benzoyl-6-deoxy-4-O-(2,3-di-O-benzoyl-6-bromo-6-deoxy-β-D-glucopyranosyl)-β-D-glucopyranosyl]theophylline (**19**). — The syrupy residue obtained by bromination (20 h) of **18** (1.21 g, 1.3 mmol) was triturated with methanol. A solution of the resulting solid in dichloromethane was washed with water, and then worked-up as usual. The crude product was crystallised from acetone–ethanol, to give **19** (886 mg, 69%), m.p. 284–285° (dec.), $[\alpha]_D^{20}$ +44° (*c* 0.1, chloroform), $\lambda_{max}^{CHCl_3}$ 276 nm (ε 10400). P.m.r. data ($CDCl_3$): δ 8.27–7.03 (m, 21 H, H-8 and Ar), 6.37–5.73 (m, 3 H, H-1',2',3'), 5.58–5.18 (m, 2 H, H-2",3"), 4.95 (d, 1 H, *J* 7.5 Hz, H-1"), 3.45 and 3.25 (2 s, 6 H, NMe-1,3), and 1.33 (b, 3 H, H-6').

Anal. Calc. for $C_{47}H_{43}BrN_4O_{14}$: C, 58.33; H, 4.45; Br, 8.26; N, 5.79. Found: C, 58.14; H, 4.79; Br, 8.40; N, 5.78.

Catalytic hydrogenation of **19** (836 mg, 0.86 mmol) afforded **10** (574 mg, 75%), which was identical with the product described above.

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