Note

Preparation of rare-sugar nucleosides from keto-nucleosides: the synthesis of theophylline derivatives of 6-deoxy-β-L-talopyranose and 3-*O*-methyl-β-D-mannopyranose

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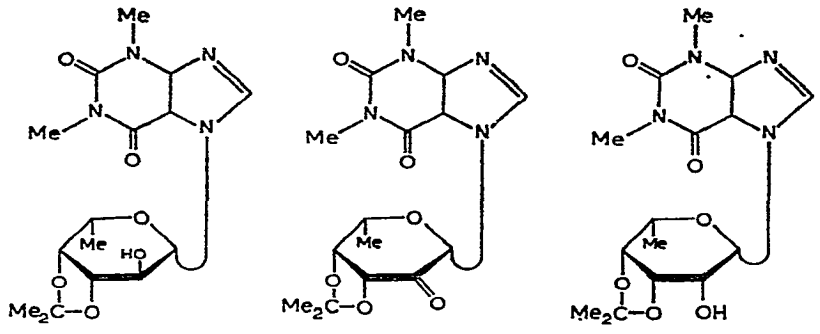
(Received April 17th, 1972; accepted for publication, June 22nd, 1972)

In recent papers[1,2], we reported the first synthesis of ketohexosyl- and deoxyketohexosyl-purines, and examined their possible utilisation as synthetic intermediates. Further studies[3] showed that 7-(6′-deoxy-β-L-*lyxo*-hexopyranosylulose)-theophylline (**4**) exhibits biological activity. In order to convert L-fucosyl- and 3-*O*-methyl-D-glucosyl-purines into nucleosides of the naturally occurring, rare sugars 6-deoxy-L-talose[4] and 3-*O*-methyl-D-mannose, which are constituents of bacterial polysaccharides, we have now studied inversion at C-2 by stereospecific reduction of 7-(6′-deoxy-3′,4′-*O*-isopropylidene-β-L-*lyxo*-hexopyranosylulose)theophylline (**2**) and 7-(4′,6′-*O*-benzylidene-3′-*O*-methyl-β-D-*arabino*-hexopyranosylulose)-theophylline (**7**) recently synthesised in this laboratory[1,2].

Reduction of **2** and **7** with sodium borohydride in ethanol afforded the expected theophylline derivatives **3** and **8** of 6-deoxy-3,4-*O*-isopropylidene-β-L-talose and 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannose, respectively, which were readily isolated in high yield (>90%) by direct crystallisation from the reaction mixtures. These reductions appeared to be essentially stereospecific, since no trace of the isomers **1** and **6** were detected by chromatography. The stereospecificity of the reduction of **2** and **7** from the less-hindered, equatorial side of the carbonyl group parallels previous observations[5] with several hexopyranosulose derivatives. Attempted, similar reduction of the unprotected keto-nucleoside **4**, obtained by selective, acid hydrolysis of the isopropylidene group in **2**, gave 7-(6′-deoxy-L-talopyranosyl)theophylline in 70% yield, together with a small proportion of the isomeric L-fucosyl nucleoside.

The structures of **3** and **8** were established by the disappearance of the C=O band in the infrared spectra and by the appearance of an H-2′ signal in the n.m.r. spectra of both compounds. The n.m.r. spectra also clearly showed the conversions **1**→**3** and **6**→**8**. Whereas for **1** and **6**, H-1′ exhibited a large coupling with H-2′ ($J_{1',2'}$ ~9 Hz) suggesting a *trans*-diaxial relationship, the corresponding coupling in the nucleosides **3** and **8** was smaller ($J_{1',2'}$ ~2 Hz) indicative of an axial–equatorial relationship. Additional evidence for the structures of **3** and **8** was obtained by total, acid hydrolysis, which gave 6-deoxy-L-talose and 3-*O*-methyl-D-mannose (identified chromatographically).



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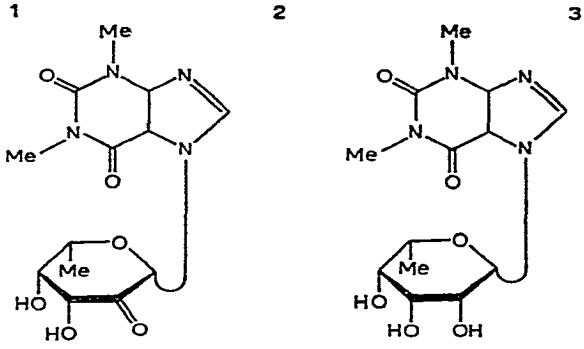

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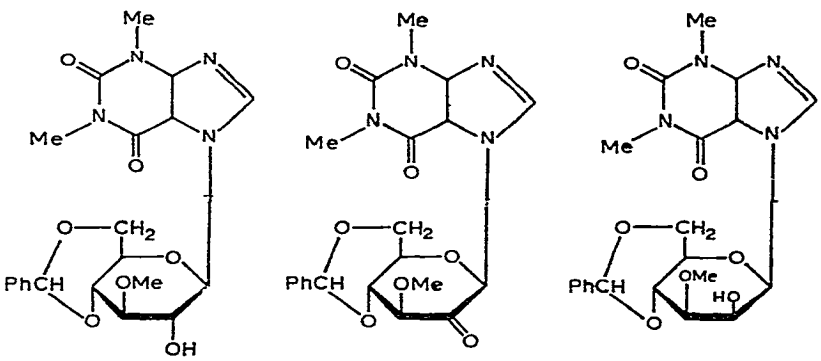

6 7 8

It is of interest to note that the u.v.-absorption maximum of the theophylline nucleoside **3** (λ_{max} 275 nm, ε 9700) was, as expected, identical with that of 7-(L-rhamnosyl)theophylline[6], indicating 7-substitution. In a similar way, the site of glycosidation in the nucleoside **8** was confirmed by a comparison with 7-(D-glycosyl)-theophyllines[1,6].

EXPERIMENTAL

General methods. — Melting points are uncorrected. Solutions were evaporated at 40° under diminished pressure. Infrared spectra were obtained for potassium

bromide discs. Ascending paper chromatography was carried out on Whatman No. 1 paper with butyl alcohol saturated with water. Thin-layer chromatography (t.l.c.) was performed on 0.25-mm layers of Merck Silica gel H.F. with (*A*) ethyl acetate–pentane (3:1) or (*B*) chloroform–acetone (1:1); the products were detected by u.v. absorption, or by spraying with a 3% solution of sulphuric acid and heating at 120°.

7-(6′-Deoxy-3′,4′-O-isopropylidene-β-L-talopyranosyl)theophylline (**3**). — Sodium borohydride (210 mg, 6.3 mmoles) was added to a stirred solution of 7-(6′-deoxy-3′,4′-*O*-isopropylidene-β-L-*lyxo*-hexopyranosylulose)theophylline (**2**) (300 mg, 0.9 mmole) in ethanol (30 ml). After 1.5 h at 5°, the mixture was concentrated *in vacuo*, diluted with water (20 ml), and extracted with chloroform (3 × 40 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. Two recrystallisations of the residue from ethanol gave **3** (280 mg, 92%), m.p. 197–198° [depressed on admixture with a sample of 7-(6′-deoxy-3′,4′-*O*-isopropylidene-β-L-galactopyranosyl)theophylline)], $[\alpha]_D^{20}$ −110° (*c* 0.1, methanol), $\lambda_{max}^{H_2O}$ 274 nm (ε 7000), R_F 0.26 (t.l.c., solvent *A*). N.m.r. data: δ 6.18 (1-proton doublet, $J_{1',2'}$ 1.5 Hz, H-1′).

Anal. Calc. for $C_{16}H_{22}N_4O_6$: C, 52.48; H, 6.02; N, 15.32. Found: C, 52.25; H, 6.10; N, 15.36.

7-(6′-Deoxy-β-L-talopyranosyl)theophylline (**5**). — (*a*) *By acid hydrolysis of* **3** *with 0.1M hydrochloric acid.* Compound **3** (0.3 g, 0.9 mmole) was dissolved in methanol (3 ml). 0.1M Hydrochloric acid (10 ml) was added and the mixture was kept for 5 h at room temperature. The solution was neutralised with Amberlite IR-45(HO^-) resin, and the filtered solution was evaporated *in vacuo*. The residue was crystallised from methanol to give **5** (0.20 g, 61%), m.p. 249–250°, $[\alpha]_D^{20}$ −120° (*c* 0.1, methanol), $\lambda_{max}^{H_2O}$ 275 nm (ε 7580), R_F 0.11 (t.l.c., solvent *A*). N.m.r. data: δ 6.1 (1-proton doublet, $J_{1',2'}$ 1.5 Hz, H-1′).

Anal. Calc. for $C_{13}H_{18}N_4O_6$: C, 47.95; H, 5.52; N, 17.18. Found: C, 47.84; H, 5.71; N, 16.90.

Compound **3** (0.3 g, 0.9 mmole) was dissolved in methanol (2 ml) and M hydrochloric acid (10 ml) was added. The mixture was stirred for 10 h at room temperature, and the filtered solution was then evaporated *in vacuo*. T.l.c. (solvent *A*) revealed L-talose (R_F 0.15, R_{Fuc} 0.80).

(*b*) *By reduction of* **4** *with sodium borohydride.* Application to **4** of the procedure described for compound **2** gave the *talo*-nucleoside **5** as the main product (60% yield); 10% of 7-(β-L-fucopyranosyl)theophylline[2], m.p. 272°, $[\alpha]_D^{20}$ −1° (*c* 0.1, water), was also isolated from the reaction mixture.

7-(4′,6′-O-Benzylidene-3′-O-methyl-β-D-mannopyranosyl)theophylline (**8**). — A solution of compound **7**[1] (500 mg, 1.13 mmoles) in dry methanol (50 ml) was stirred with sodium borohydride (300 mg, 7.9 mmoles) for 1.5 h at room temperature. The solvent was evaporated and the residual oil was partitioned between chloroform (100 ml) and water (50 ml). The organic phase was dried (Na_2SO_4) and evaporated, and the residue was crystallised from methanol to give **8** (480 mg, 94%), m.p. 224–225°, $[\alpha]_D^{20}$ +49.3° (*c* 0.12, methanol), λ_{max}^{MeOH} 274 nm (ε 8000), R_F 0.71 (t.l.c., solvent *B*). N.m.r. data: δ 6.36 (1-proton doublet, $J_{1',2'}$ 1.5 Hz, H-1′).

Anal. Calc. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.41; N, 12.61. Found: C, 56.82; H, 5.25; N, 12.87.

Compound **8** was treated for 18 h at room temperature with M hydrochloric acid. The solution was neutralised with Amberlite IR-45(HO^-) resin, and the filtered solution was then concentrated *in vacuo*. T.l.c. (ethyl acetate–propan-2-ol–water, 65:24:11) revealed 3-*O*-methyl-mannose (R_F 0.375, $R_{3\text{-MeGlc}}$ 0.88).

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