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Note

Unsaturated keto-nucleosides
The synthesis and properties of 7-(3-*O*-acetyl-4,6-dideoxy-β-L-*glycero*-hex-3-enopyranosylulose)theophylline

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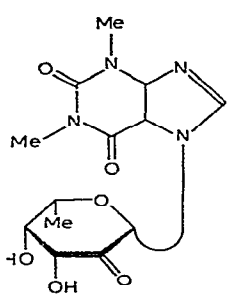
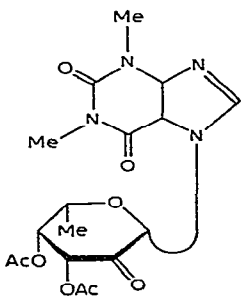
The biochemical significance of unsaturated hexosylpurines has been emphasised in recent years[1,2], and recent studies have shown that ketohexosylpurines may be used as intermediates in the synthesis of branched-chain or amino sugar nucleosides[3] Additional interest in keto-nucleosides has resulted from the recent discovery of the biological activity of 7-(6-deoxy-β-L-*lyxo*-hexopyranosylulose)theophylline[4]

We now report the first synthesis of an unsaturated keto-nucleoside, namely, the title compound (3) Unsaturated *keto-* or *aldehydo*-hexosides[5] and especially those postulated as intermediates in the formation of kojic acid from acetylated aldosulose[6] and of maltol from the streptose moiety of the antibiotic streptomycin[7], have been obtained by oxidation of partially acylated hexosides[8,9]

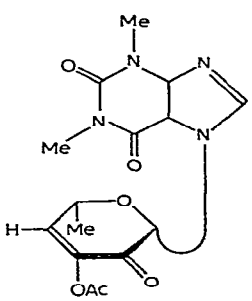
The synthesis of the unsaturated keto-nucleoside **3** was accomplished by acetylation of the recently described[3] keto-nucleoside 7-(6-deoxy-β-L-*lyxo*-hexopyranosylulose)theophylline (**1**), followed, presumably, by β-elimination of an acetyl group (**2**→**3**) Although facilitated by the carbonyl group, the elimination was not instantaneous, and 15–20% of the diacetate **2** was obtained



1



2



3

Treatment of **1** with acetic anhydride in pyridine for 1 h at room temperature gave a mixture of four compounds (t l c) After removal of the faster-moving diacetate **2** by column chromatography, crystalline **3** was readily isolated The structure of **3** was assigned on the basis of the i r band at 1440 cm^{-1} attributable to C=C,

and of a peak in the n m r spectrum at δ 2 25 characteristic of OAc The absence of a signal for H-3′ and the chemical shift (δ 4 9) of H-4′ (*cf* 6 8 in **3**, H-1′ and H-4′, superimposed) indicates that the acetyl group is at position 3′ and confirms the structural assignment

The enol acetate **3** has the same stability towards acids as the keto-nucleoside **1** In M hydrochloric acid, complete degradation was observed after 7 h, whereas no glycosidic cleavage had occurred in 0 1M acid during 20 h

Compound **3** is more stable to alkali than the keto-nucleoside **1** Thus, in 0 1M methanolic sodium hydroxide, free theophylline was detected chromatographically only after 4 h, by which time loss of the acetyl group was complete More than 18 h reaction was needed for completion of glycosidic cleavage

Compound **3** showed activity against KB cancer and F 4809 normal cells *In vitro* biological assays showed that **3** was 4–5 times more active (inhibition at 0 175 mg/ml) than the keto-nucleoside **1**, whereas 7-(β-L-fucosyl)theophylline was inactive[4] at 0 7 mg/ml

EXPERIMENTAL

General methods — Melting points are uncorrected Solutions were evaporated at 40° under diminished pressure Optical rotations were measured with a Roussel–Jouan "Quick" polarimeter U v spectra were determined with a Jobin–Yvon MVI spectrometer I r spectra were obtained for potassium bromide discs using a Perkin–Elmer 137 spectrometer N m r spectra were recorded with a Varian T-60 instrument T l c was performed on 0 25-mm layers of Merck Silica gel H F with 1-butanol saturated with water and detection by u v absorption or by spraying with a 3% solution of sulphuric acid and heating at 120° Elemental analyses were obtained from Laboratoire de Microanalyse du C N R S

*7-(3-O-Acetyl-4,6-dideoxy-β-*L*-glycero-hex-3-enopyranosylulose)theophylline* (**3**) — 7-(6-Deoxy-β-L-*lyxo*-hexopyranosylulose)theophylline[3] (**1**, 0 3 g, 0 93 mmole) was dissolved in a mixture of acetic anhydride (3 ml) and pyridine (3 ml) After 1 h at room temperature, the mixture was evaporated *in vacuo* Toluene was distilled from the syrupy residue which was then eluted from silica gel with ethyl acetate Concentration of the appropriate fractions and crystallization of the residue from methanol gave **3** (0 2 g, 62%), m p 172–174°, $[\alpha]_D^{20}$ +80° (*c* 0 1, methanol), λ_{max} 274 nm (ε 7500), R_F 0 61 N m r data δ 6 80 (*s*, H-1′ superimposed upon H-4′), 5 15 (*q* J_{gem} 9 Hz, H-5′), 2 30 (*s*, Ac), 1 58 (*d*, $J_{5\ 6'}$ 7 Hz, Me)

Anal Calc for $C_{15}H_{17}N_4O_6$ C, 51 60, H, 4 88, N, 16 02 Found C, 51 94, H, 4 46, H, 16 08

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