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Preliminary communication

Utilization of unsaturated amino sugars in the synthesis of nucleosides*

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Since the first report[1] on the direct utilization of unsaturated sugars in the synthesis of nucleosides, much attention has been paid to the preparation of unsaturated nucleosides[2—23], because of the biochemical significance of such compounds[24—26]. The method most frequently employed for the preparation of unsaturated nucleosides is the acid-catalyzed, fusion procedure which produces a complex mixture of reaction products. From these reactions[1—3,6—13,16—19], products of two general types were isolated: (*i*) 2′,3′-unsaturated nucleosides with the base linked at C-1′, and (*ii*) 1′,2′-unsaturated isomers having the base attached at C-3′.

We now report the first application of an unsaturated *amino* sugar (2-acetamido-2-deoxy-D-glucal derivative) in the synthesis of nucleosides, as well as the isolation and characterization of the first unsaturated nucleoside having the base linked to C-4′ of the carbohydrate moiety.

Earlier reports from our laboratory showed that the acetylated, unsaturated amino sugars are reactive in the formation of glycosidic bonds of various types[27,28]. As this class of compounds is now readily accessible from 2-acetamido-2-deoxy-D-glucose[29], the utilization of unsaturated amino sugars in the formation of C–N linkages was examined.

2-Acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**), obtained by selective *N*-deacetylation[30] from the corresponding 2-(*N*-acetylacetamido) derivative[29], was used as the starting material. A mixture of **1** (2 mmoles) and theophylline (1 mmole) in the presence of a catalytic amount of boron trifluoride etherate was fused for 4 h at 85–95°. (It should be noted that special care was given to the choice of the catalyst, because degradation of **1** in the presence of various catalysts was observed.) Several

*A part of this work (X-ray structure determination) was presented by B. K.-P. at the American Crystallographic Association Meeting, Evanston, Illinois, August 1976.
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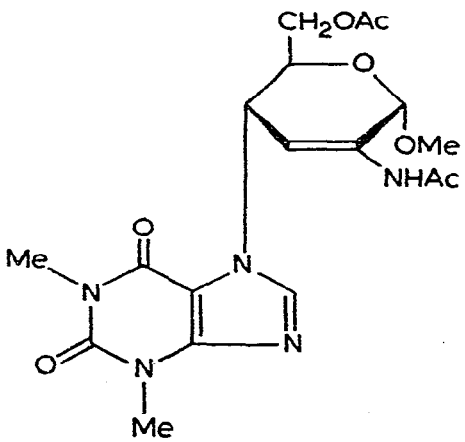
products of nucleosidic character, obtained in this reaction, were separated by repeated chromatography on columns of silica gel.

The major product **2** (~20%) was obtained, after recrystallization from methanol, in the form of large prisms, m.p. 222–224°, $[\alpha]_D$ +52.2° (*c* 1.1, chloroform); λ_{max}^{MeOH} 230 and 274 nm (ϵ_{mM} 23.70 and 9.10); ν_{max}^{KBr} 3350 (NH), 1730 (OAc), 1710 (C=O), 1605 (C=C), 1660 and 1550 (Amide I and II), 1240 (OAc), and 1115 cm^{-1} (C–O–C). The elemental composition corresponded to that calculated for $C_{18}H_{23}N_5O_7$. The n.m.r. spectrum of **2** revealed the presence of 23 protons, showed signals characteristic of a theophylline moiety, and clearly showed the existence of only two acetyl groups. However, the n.m.r. data were insufficient for structure elucidation, as the presence of an unexpected, three-proton singlet at τ 6.53 was incompatible with any of the structures proposed. Therefore, an X-ray crystal-structure determination was performed. On the basis of this study, compound **2** is designated as 7-(methyl 2-acetamido-6-*O*-acetyl-2,3,4-trideoxy-α-D-*erythro*-hex-2-eno-pyranosid-4-yl)theophylline.



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The n.m.r. and mass spectra are in full accord with this structure; n.m.r. data at 60 MHz (in $CDCl_3$): τ 2.35 (s, H-8), 3.03 (bs, removed by D_2O exchange, NH), 3.31 (d, $J_{3',4'}$ 6.4 Hz, H-3′), 4.24 (d of d, $J_{3',4'}$ 6.4 Hz, $J_{4',5'}$ 3.1 Hz, H-4′), 4.93 (s, H-1′), 5.4–5.7 (m, H-5′), 6.0–6.3 (unresolved, 2 H-6′), 6.44 and 6.64 (2 NCH_3), 6.53 (OCH_3), 7.92 and 8.04 (OAc and NAc); m.s.: *m/e* 421 (M^+), 390 (M – OCH_3), 210 (390 – base), 168 (210 – CH_2CO), 150 (210 – AcOH), 138 (168 – HCHO), 126 (168 – CH_2CO), 108 (150 – CH_2CO), and 96 (138 – CH_2CO). The pathway which starts by the loss of the base gives: *m/e* 242 [M – (base – 1)], 182 (242 – AcOH), 140 (182 – CH_2CO), and 80 (140 – AcOH).

Although unsaturated nucleosides with theophylline as the base attached to the sugar moiety at C-1′ (refs. 1, 5, 7, 9, and 12), or at C-3′ (refs. 9 and 12), have been synthesized, the crystal structure has not as yet been determined for any of these compounds.

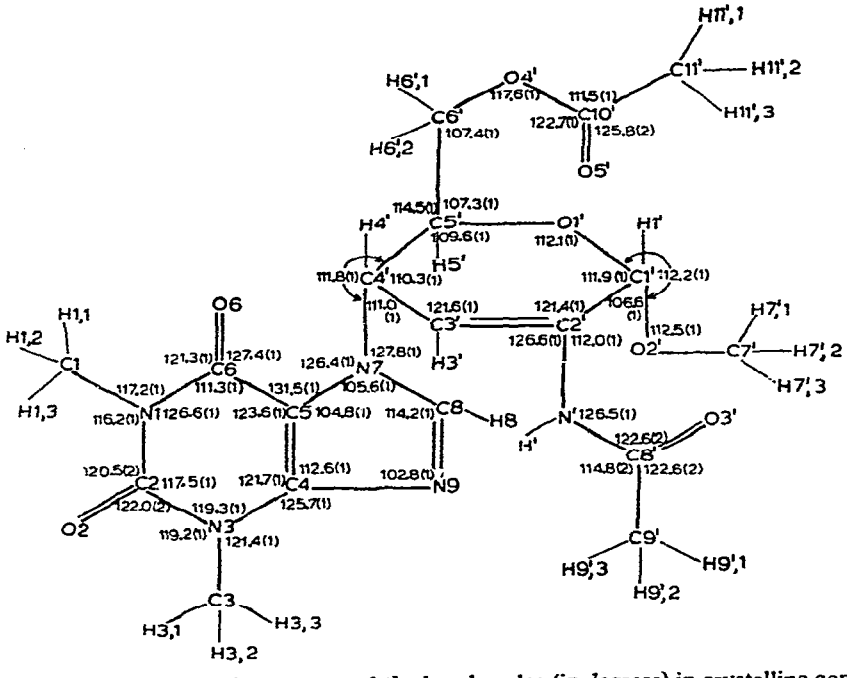

Fig. 1. Numbering of the atoms, and the bond angles (in degrees) in crystalline compound **2**.

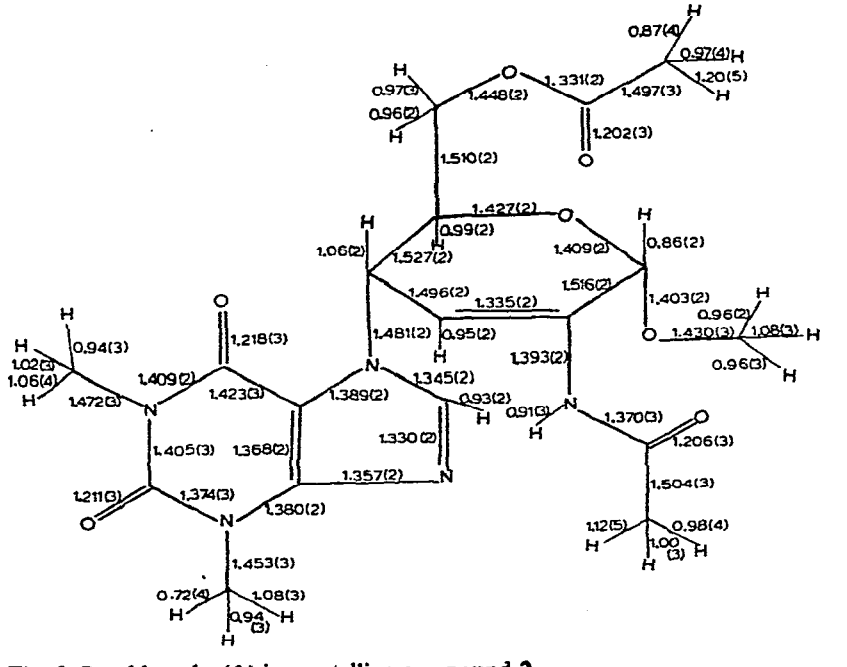

Fig. 2. Bond lengths (Å) in crystalline compound **2**.

The crystals of compound **2** crystallize in the orthorhombic space-group $P2_12_12_1$; $Z = 4$; with $a = 13.1444$ (4), $b = 14.9593$ (4), and $c = 10.5007$ (3) Å. The intensities for 2405 reflexions with $\theta < 75°$ were measured on an Enraf–Nonius CAD-4 diffractometer using Cu$K\alpha$ radiation. The structure was solved by MULTAN[31], and refined to an R of 0.037.

The orientation of the base relative to the sugar ring, described in terms of rotation about the C-4′–N-7 glycosyl bond for the sequence of C-5′–C-4′–N-7–C-8, is 80.6°, and the molecule is *anti*. The base conformation can be described by means of the mean torsion-angles of 1.8 and 0.0° for six- and five-membered rings, respectively. The sugar moiety has the $^0H_5$ conformation. The ring substituents are attached at C-1′ in *quasi*-axial, at C-4′ in *quasi*-equatorial, and at C-5′ in equatorial positions[32]. Bond angles (see Fig. 1) and bond lengths (see Fig. 2) in the sugar part are comparable to the values found in some peracetylated 2,3-dideoxyaldopyranoses[33]. Molecules are connected by N′-H···O-5′ hydrogen bonds [2.917 (3) Å] between sugar moieties. There is no base stacking.

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