Synthesis and *X*-Ray Crystal Structure of the First Example of an Anhydro-nucleoside with Two Oxygen Bridges between the Base and the Sugar

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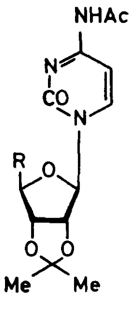
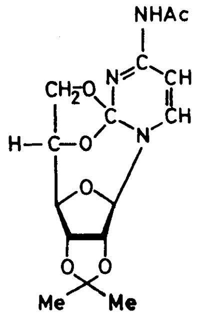
Summary The isomerization with boron trifluoride–ether of 4-*N*-acetyl-1-(2,3-*O*-isopropylidene-5,6-anhydro-β-D-allo- and -α-L-talo-furanosyl)cytosine (**4**) and (**5**), an epoxide mixture obtained in two steps from protected cytidine, gave 4-acetamido-1-(2,5′:2,6′-dianhydro-2′,3′-*O*-isopropylidene-α-L-talofuranosyl)-1,2-dihydropyrimidine (**7**), the constitution of which was confirmed by *X*-ray crystallography.

THE first synthesis of an anhydro-nucleoside, a cytidine derivative,[1] was reported in 1951, and was followed by the description of many analogues with one oxygen bridge between the base and the sugar.[2] We report here the synthesis and solid-state constitution of a novel type of anhydro-nucleoside with two oxygen bridges between the base and the sugar, arising from the acetalation of the C(2) carbonyl by the 5′,6′-diol system in a hexofuranosylcytosine derivative.

The aldehyde (**2**),† m.p. 200 °C, [imidazolidide (**3**),† m.p. 185 °C (from methanol)], prepared in 78% yield from the protected cytidine (**1**) as for the 4-*N*-benzoyl analogue,[3] was condensed with dimethyloxosulphonium methylide,[4] to give an unresolvable mixture of the epoxides (**4**) and (**5**),† (38%), m.p. 192—194 °C (from benzene–acetonitrile).



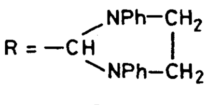


(**7**)

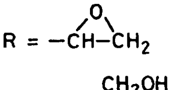
(**1**) R = CH_2OH

(**2**) R = CHO

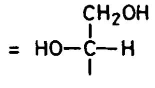
(**3**) R =



(**4**),(**5**) R =



(**6**) R =



$$\text{HO}-\overset{\displaystyle CH_2OH}{\underset{|}{\overset{|}{C}}}-\text{H}$$

The anhydro-nucleoside (**7**)† was obtained in 65% yield after 5 min at room temperature by treatment with boron trifluoride–ether of a solution of a mixture of the epoxides (**4**) and (**5**) in oxolan (THF). The partially protected β-D-allofuranosylcytosine (**6**) was also produced in lower yield (28%) and was readily removed as the more polar component by silica gel column chromatography (chloroform–methanol, 9:1).

Slow evaporation of a solution of (**7**) in acetone–acetonitrile gave crystals suitable for *X*-ray structure analysis. The compound crystallizes in the orthorhombic space group

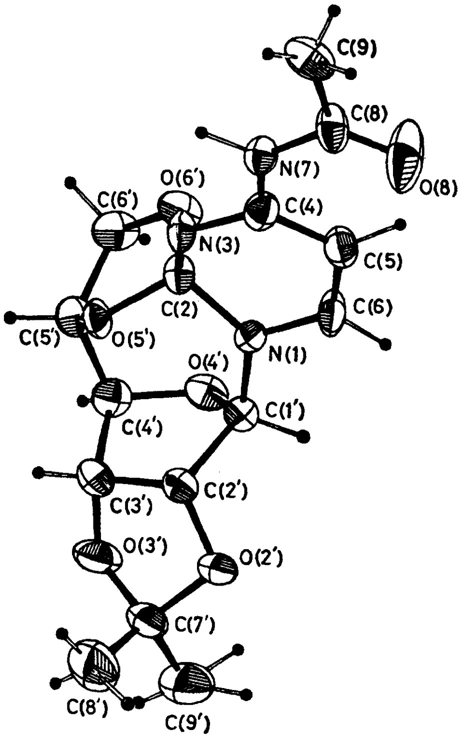


FIGURE. A perspective view of the configuration of one molecule of compound (**7**). Selected bond angles: N(1)–C(2)–N(3) 113·3 (4), O(5′)–C(2)–O(6′) 105·4 (4), C(6)–N(1)–C(2) 116·9 (4), C(2)–N(3)–C(4) 115·3 (4), N(3)–C(4)–C(5) 123·6 (5), C(4)–C(5)–C(6) 116·5 (5), C(5)–C(6)–N(1) 121·0 (5), C(2)–O(5′)–C(5′) 107·0 (4), O(5′)–C(5′)–C(6′) 103·4 (4), C(5′)–C(6′)–O(6′) 103·9 (4), C(6′)–O(6′)–C(2) 110·5 (4), N(1)–C(1′)–O(4′) 112·2 (4), N(1)–C(1′)–C(2′) 114·4 (4)°.

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† Satisfactory elemental analyses were obtained.

$P2_12_12_1$ with two independent molecules and two molecules of acetonitrile, one probably non-stocheiometric, in the asymmetric unit.

Crystal data: $C_{15}H_{19}N_3O_6.n$MeCN: $a = 10{\cdot}620(3)$, $b = 15{\cdot}815(4)$, $c = 21{\cdot}470(4)$ Å. Intensities were measured on a 4-circle diffractometer using the ω–2θ scan technique (up to $2\theta = 136°$) with graphite-monochromated Cu-K_α radiation. The structure was solved by MULTAN[5] and refined by full-matrix least-squares using 2317 observed $[I \geqslant 3\sigma(I)]$ reflections. All hydrogen atoms were located in Fourier-difference syntheses except those of the acetonitrile methyl groups. The final R-factor is 0·053.‡

As shown by the perspective view of one molecule of (**7**) (Figure), the crystal structure determination confirms the chemical results. There are no significant differences in the geometry of the independent molecules, even concerning the conformation of the *N*-acetyl groups. On the whole, bond angles and lengths are close to normal. Bond angles at the spiro carbon atom C(2) are tetrahedral, except those in the Figure caption. Within the pyrimidine ring, the angle at C(5) seems small for sp^2 hybridization. There is a slight tilting of the anomeric bond away from the C(1′)–C(2′)–O(4′) plane.

The anhydro-nucleoside (**7**), m.p. 151—153 °C (from acetone), $[\alpha]_D^{20} + 31°$ (*c* 0·6, dichloromethane), exhibited a characteristic u.v. spectrum with two almost equal maxima at 239 and 306 nm. The ^{13}C n.m.r. resonances were within the expected range for pyrimidine- or anhydro-nucleosides, except that of C(2) which was shifted to higher fields by *ca.* 38 p.p.m., an indication of a change of hybridization from sp^2 to sp^3. The pyrimidine 3-H (imino-form), 5-H, and 6-H ^{1}H n.m.r. resonances were shifted upfield as a consequence of decreased aromaticity. Compound (**7**), which may be prepared by this method in three steps in 18% overall yield from the easily available protected cytidine (**1**), is the first example of an anhydro-nucleoside with two oxygen bridges. Also, acetalation of urea-type carbonyl groups by epoxides has not been described hitherto,[6] and this is the first reported one-step procedure.

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‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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