Synthesis and Stereochemical Correlation of Acyclic Sugar Nucleoside Analogues: X-Ray Crystal Structure of (1R)-2,3,4,5-Tetra-O-acetyl-1-S-ethyl-1-(1,6-dihydro-6-thioxopurin-9-yl)-1-thio-D-arabinitol

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Summary A crystal structure determination has been used to establish the absolute stereochemistry of a mixed acetal derivative, a nucleoside analogue (1) having purine-6-thione ('6-mercaptopurine') attached to an acyclic D-arabinose derivative.

THE attachment of acyclic sugar chains to nucleic acid bases leads to nucleoside analogues that are of interest as potential antimetabolites, antitumor agents, and as biochemical probes.^{1,2} By treating acylated aldose dialkyl dithioacetals, R¹-CH(SR²)₂, with bromine and then condensing the resultant unstable bromide, R¹-CH(SR²)Br, with an appropriate heterocyclic base derivative B, various stereochemical and structural series of the corresponding nucleoside analogues, R¹-CH(SR²)B, have been prepared.^{1,3,4} These compounds are formally derivatives of unsymmetrical aldehydrols and are frequently encountered as separable mixtures of the two diastereoisomers differing in configuration at the acetal carbon atom 4,5 Their complete structural characterization requires (a) proof of the position of attachment of the sugar chain to the heterocycle, (b) determination of the absolute stereochemistry at the acetal carbon atom, (c) establishment of the particular tautomeric form of the heterocycle, and (d) evidence for the conformational disposition of the sugar chain As the route of synthesis does not provide absolute proof of (a) the linkage position, and as optical methods do not provide secure assignment of (b) the stereochemistry at the acetal carbon atom in the absence of a suitable reference-standard, the crystal structure determination reported here was undertaken to provide a point of reference for further structural correlation of the entire series of related derivatives.

The four acetylated D-aldopentose diethyl dithioacetals were treated with bromine and the products condensed with 6-chloro-9-chloromercuripurine. The resultant derivatives, obtained as mixture of 1'-epimers in all but the arabino-series, were converted by action of thiourea into the 6-thio-analogues, which were then O-deacetylated by treatment with hot butylamine. In the D-arabino-series the O-acetylated product (1) was obtained as needles of a single epimer (n.m.r.), m.p. 206–208° (decomp), $[\alpha]_{D}^{22} + 131°$ (CHCl₃), showing a positive Cotton effect in its o.r.d. spectrum. The deacetylated product (2) had m.p. 194-195.5° (decomp.) $[\alpha]_D + 60°$ (pyridine). Crystallographic data firmly established the product (1) as (1R)-2,3,4,5-tetra-O-acetyl-1-S-ethyl-1-(1,6-dihydro-6-thioxopurin-9-yl)-1-

thio-D-arabinitol, having the sugar chain in an extended, zigzag conformation (Figure).

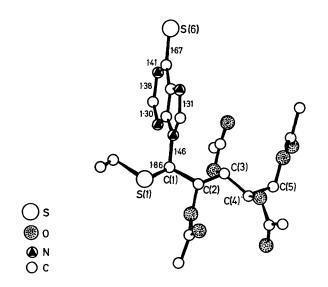
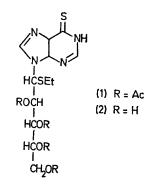


FIGURE. The structure of compound (1) as determined crystallographically (mean interatomic distances in Å).

Crystals of (1) were monoclinic, space group $P2_1$, a =13.192, b = 11.429, c = 17.232, $\beta = 94.83^{\circ}$. The intensities were collected with a Philips four-circle diffractometer,

using $\operatorname{Cu}-K_{\alpha}$ radiation with a graphite monochromator and 4380 reflections were recorded above the background. As there are two molecules per asymmetric unit, the basic structural unit contains 68 nonhydrogen atoms and the structure was solved by direct methods, by application of the phase function.⁶ Difficulties were encountered in the resolution of the structure, as the introduction of sigma-1 relationships led to false results. The structure was refined by a full-matrix, least-squares method to a final Rindex of 0.07.



The two molecules of the asymmetric unit are related by a pseudo-twofold axis located at a/4 and c/4. The bond distances and angles are in good agreement with generally observed values. The carbon chain of the sugar residue is attached to N-9 of the heterocycle. The configuration at the acetal carbon atom is established as 1-(R), from the relative stereochemistry of the substituent groups and the known absolute configuration of D-arabinose. The C-6-S bond distance establishes that the base is present as the 6-thione tautomer' and not the 6-thiol. The carbon chain of the sugar unit adopts an essentially planar, zigzag conformation, with C-2, C-3, C-4, and C-5 lying approximately coplanar and with C-1 displaced by ca. 0.5 Å from this plane. In chloroform solution the same conformation is also favoured, as indicated⁸ by the n.m.r. spin-coupling values of J1,2 9.0, J2,3 2.4, J3,4 7.5, J4,58 4.0, and J4,50 5.8 Hz.

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