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THE FORMATION OF BOTH NUCLEOSIDE ANOMERS IN THE REACTION OF A CRYSTALLINE 1,2-<u>CIS</u>-GLYCOSYL HALIDE WITH A HEAVY METAL SALT OF A PURINE

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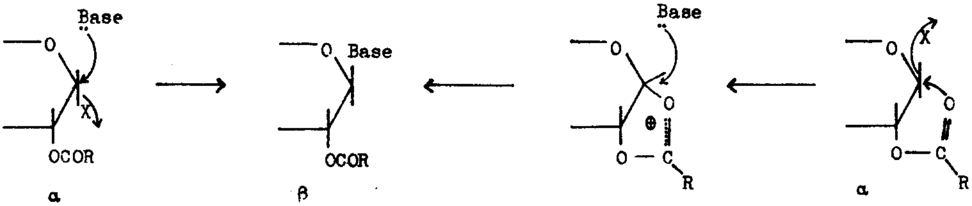
Rules regarding the anomeric configuration of the nucleosides produced by the reaction of glycosyl halides with the heavy metal salts of purine bases were originally formulated by Baker.[1] In the case of sugar derivatives with a participating group (such as -OCOR) at position 2, both 1,2-*cis* and *trans*-glycosyl halides give a 1,2-*trans* nucleoside as product, by single and double S_N2 reactions respectively, as shown below for ribose or glucose[2] (for which 1,2-*cis* = α, 1,2-*trans* = β).



In reactions which constituted an apparent exception to the above rule, either a syrupy glycosyl halide (probably a mixture of α and β forms) was used, or the reaction was carried out in the presence of a Lewis acid which could anomerise the glycosyl halide. The formation of some α-nucleoside in these cases was attributed to the presence of some of the β-glycosyl halide, a portion of which underwent a single S_N2 displacement.[3] No case appears to have been recorded in which a crystalline 1,2-*cis*-glycosyl halide with a participating group in position 2 has given rise to both anomers in the reaction with a heavy metal salt, and we now report the first example.

In continuation of our studies of the nucleosides formed by the reaction of glycosyl halides with derivatives of tautomeric bases,[4] we investigated the products obtained from the silver salt of hypoxanthine.[5] Condensation with crystalline α-acetobromoglucose in refluxing xylene yielded a complex mixture of products, which was analysed by chromatography on Dowex-1-formate, after deacetylation with alcoholic ammonia. In this paper we are concerned with

Fraction III, eluted at pH 6.5 (0.01M ammonium formate buffer). This fraction gave a single spot in various solvent systems, but its U.V. spectrum suggested that it was a mixture. It was found that paper chromatography in the system BuOH:EtOH:H_2O (9:1:2, ammonia atmosphere) resolved the material into four components, A, B, C, D, in order of increasing R_F.[6] The U.V. spectra of A and B were identical, $\lambda_{max.}$ 248 mμ (pH 1); 249 mμ (pH 5); 254 mμ (pH 11), and these compounds are obviously 9-substituted hypoxanthines.[7,8] C and D had identical U.V. spectra quite distinct from the above, $\lambda_{max.}$ 252 mμ (pH 1); 254 mμ (pH 5); 264 mμ (pH 11), and these products are clearly 7-substituted hypoxanthines.[7,9,10]

After preparative paper chromatography, all four products were obtained crystalline. Microanalyses confirmed that all were monoglucosylhypoxanthines, and the anomeric configuration was established by ^1H n.m.r. spectroscopy[11] (see Table). The structure of the products is therefore as follows: A, m.p. 286-287°d (lit.[12] m.p. 275-276°), 9-β-D-glucopyranosylhypoxanthine; B, m.p. 180-185°, 9-α-D-glucopyranosylhypoxanthine; C, m.p. 230°D (lit.[12] m.p. 203-204°), 7-β-D-glucopyranosylhypoxanthine; and D, m.p. 180°d, 7-α-D-glucopyranosylhypoxanthine. B and D appear to be new compounds. The product ratios were: 7:9 = 2:1, β:α = 3:1.

TABLE

^1H n.m.r. spectra of Hypoxanthine Glucosides measured at 60 Mc/sec.

Product	Structure	$H_{1'}$ (τ)	$J_{1',2'}$ (c/sec.)	Solvent
A	9-β	4.59	9.0	DMSO-d_6
B	9-α	3.57	5.0	D_2O + Bu^tOH
C	7-β	4.2	9.0	D_2O + Bu^tOH
D	7-α	3.33	5.1	D_2O + Bu^tOH

A similar experiment with triacetylribofuranosyl chloride has also yielded 7- and 9-glycosides of hypoxanthine, but it has not yet proved possible to separate the anomers.

One possible mode of formation of the α-nucleosides is from β-acetobromoglucose, produced by silver bromide-catalysed anomerisation. The extent to which this may occur in such condensation reactions would depend on the temperature and time necessary to effect conversion of reactants to products. In the present instance, a poor yield is obtained in toluene (b.p. 111°) and it is necessary to use xylene (b.p. 140°) as the medium for the condensation reaction, whereas with silver salts of cytosine, rapid reaction takes place in refluxing toluene.[13]

It is possible that small amounts of α-anomers are formed in other nucleoside syntheses of this type, but have not previously been detected. However, not even traces of α-anomer were found in the recently reinvestigated condensation of the silver salt of a hydroxypyridine with acetobromoglucose.[14] It is curious that no α-anomers were detected in the products obtained from the bromomercuri derivative of hypoxanthine and acetobromoglucose;[12] the melting-points recorded for 7- and 9-β-glucopyranosylhypoxanthine by these workers are significantly lower than ours.

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