Tetrahedron Letters No.9, pp. 1033-1034, 1968. Pergamon Press. Printed in Great Britain.

STRUCTURE OF XANTHINE NUCLEOSIDES SYNTHESIZED BY THE SILYL METHOD

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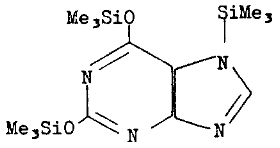
(Received in UK 20 October 1967)

Very few xanthine nucleosides have ever been synthesized, and only one nucleoside has been made directly from xanthine itself or from a simple derivative of xanthine. This is the "xanthine-3-glucoside" described by Birkofer *et al.*[1] produced by the reaction of tris-triethylsilylxanthine (I) with acetobromoglucose in nitromethane, in the presence of silver perchlorate. Formation of a 3-substituted nucleoside is unexpected, as the same paper[1] reports that methylation of I yields 7-methylxanthine, and, at higher temperature, 3,7-dimethylxanthine, observations which we have confirmed using tris-trimethylsilylxanthine (II).

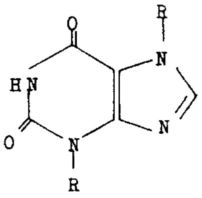
Reaction of II with acetobromoglucose in acetonitrile in the presence of silver perchlorate is supposed to give the same "xanthine-3-glucoside".[2] We have investigated this reaction, and after purification, obtained a single crystalline acetylated glucoside, m.p. 249-250°; deacetylation with methanolic ammonia yielded the free glucoside, m.p. 231-235°, $\lambda_{max.}$ 270 mμ (pH 6.0), 274 mμ (pH 10.0), 236 (shoulder) and 274 mμ (pH 14.0).

It is not possible to assign a definite structure on the basis of U.V. spectra alone, as 3- and 3,7-substituted xanthines have very similar spectra.[3] Elementary microanalyses of the acetylated and the free glucoside clearly indicated that the products were 3,7-diglucosides (III).

	Acetylated Glucoside			Free Glucoside		
	Found	Calc. for Disubst.	Calc. for Monosubst.	Found	Calc. for Disubst.	Calc. for Monosubst.
%C	48.5	48.75	47.31	41.8	42.85	42.04
%H	5.0	4.96	4.60	5.1	5.01	4.49
%N	6.7	6.89	11.61	11.3	11.76	17.83



II



III, R = β-D-glucopyranosyl

Similar reactions have been carried out with two other glycosyl halides, 2-deoxy-3,5-di-O-p-toluoylribofuranosyl chloride (IV), and 3,4,6-tri-O-acetyl-2-(2',4'-dinitroanilino)-2-deoxyglucopyranosyl bromide (V). In condensations with these halides, silver perchlorate was omitted. With IV, ultra-violet spectral evidence was obtained that, under mild conditions (non-polar solvents and/or low reaction temperature) mono-substitution of xanthine at position 7 or at positions 7 and 9 took place. However, prolonged reaction in acetonitrile at 35° or 60° again gave a 3,7-disubstituted compound as the major product.

Prolonged reaction of V, which is a less reactive glycosyl halide,[4] with I in acetonitrile gave a complex mixture of products from which two mono-substituted xanthines were isolated in crystalline form by preparative thin-layer chromatography. Product A,[5] m.p. 312°-314° dec., $[\alpha]_D^{20}$ $-145 \pm 2°$ (c, 0.5, in acetone), $\lambda_{max.}$ 266, 343 (95% EtOH), 266, 305 and 350 mµ (pH 14), on treatment with Dowex-1-OH gave an aminoglucoside with the following U.V. spectrum: $\lambda_{max.}$ 273 mµ (pH 6), 235 mµ (shoulder) and 293 mµ (pH 11), which clearly indicates 7-substitution.[3] Product B had m.p. 202-204° dec., $[\alpha]_D^{20}$ $-36 \pm 1°$ (c,0.7 in acetone), $\lambda_{max.}$ 266, 343 mµ (95% EtOH), 274 and 350 mµ (pH 14); the corresponding free aminoglucoside had $\lambda_{max.}$ 266-267 mµ (pH 4); 276 mµ (pH 10) and 280 mµ (pH 14). The shift in $\lambda_{max.}$ between pH 10 and 14 suggests that this product is a 1-substituted xanthine.[3]

REFERENCES

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4. H. G. Garg and T.L.V. Ulbricht, J. Chem. Soc., C, 51 (1967).
5. Satisfactory microanalyses were obtained.