A General Method for the Synthesis of Hex-3-uloses

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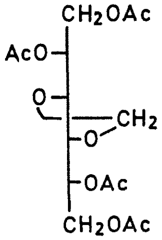
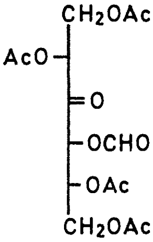
Summary Fully acetylated 2,4- or 3,4-*O*-methylene and -benzylidene derivatives of hexitols are oxidized by chromium trioxide in acetic acid to acetylated monoformates and monobenzoates, respectively, of hex-3-uloses.

WHILE hex-2-uloses occur in Nature and are well-known, there is very little information about hex-3-uloses. L-*threo*-L-*glycero*-Hex-3-ulose[1] and its racemate[2] have been synthesized and the *keto*-penta-acetate of the D-*erythro*-D-*glycero*-isomer has been described.[3] A method for the synthesis of derivatives of hex-3-uloses had recently been published[1] but this method gives only two of the diastereoisomers and of these only one was isolated. We describe here a general method for the synthesis of hex-3-uloses.


(I)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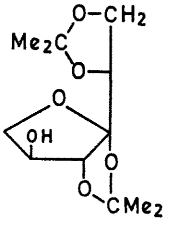
(III)

It was found that an excess of chromium trioxide in acetic acid oxidizes cyclic acetals of aldehydes at room temperature to esters in which one of the alkoxy-groups forming the acetal has been retained as the alkoxy-group of the ester. The other one has been removed and usually appears as a ketone or a carboxylic acid. Acetylated glycosides are oxidized in this way to esters of ketoglyconic acids.[4] Hydroxy-groups, if present, have to be protected by acylation.

Acetylated cyclic methylene and benzylidene acetals of alditols are oxidized by chromium trioxide in acetic acid to acetylated monoformyl and monobenzoyl derivatives of alduloses, respectively. For example, 1,3,5-tri-*O*-acetyl-2,4-*O*-benzylidenexylitol[5] is oxidized to 1,3,5-tri-*O*-acetyl-4-*O*-benzoyl-DL-*threo*-pentulose, m.p. 67—68°, in 84% yield.

For the synthesis of hex-3-uloses, 3,4-acetals of hexitols are the best starting materials. Thus 1,2,5,6-tetra-*O*-acetyl-3,4-*O*-methylene-D-mannitol (I) (obtained by acetylation of 3,4-*O*-methylene-D-mannitol,[6] itself prepared from 1,2,5,6-tetra-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol by treatment with paraformaldehyde and concentrated sulphuric acid, followed by debenzoylation with sodium methoxide in methanol) was oxidized in nearly quantitative yield to syrupy 1,2,5,6-tetra-*O*-acetyl-4-*O*-formyl-D-*erythro*-L-*glycero*-hex-3-ulose (II), $[\alpha]_D^{24}$ − 18·5° (*c* 4, $CHCl_3$). The n.m.r. spectrum showed a formate proton at δ 8·15, and the absence of a dioxymethylene group. A similar oxidation of 2,4,5,6-tetra-*O*-acetyl-1,3-*O*-methylene-D-mannitol[6] gives 2,4,5,6-tetra-*O*-acetyl-1-*O*-formyl-D-*erythro*-L-*glycero*-hex-3-ulose, $[\alpha]_D^{24}$ −13·3° (*c* 1·5, $CHCl_3$), in 50% yield.

3,4-*O*-Methylene-D-glucitol, m.p. 113—115°, $[\alpha]_D^{22}$ +46° (*c* 1, DMF) (prepared in poor yield by a method analogous to that used for the mannitol derivative) was acetylated and the tetra-acetate was oxidized with chromium trioxide in acetic acid. Two products were obtained of which the main one appeared to be 1,2,5,6-tetra-*O*-acetyl-4-*O*-formyl-D-*erythro*-D-*glycero*-hex-3-ulose; the other product, the L-*threo*-L-*glycero* derivative, can more readily be prepared from 1,3,5,6-tetra-*O*-acetyl-2,4-*O*-benzylidene-D-glucitol.[7] Oxidation of this compound gives, as the major product, 1,3,5,6-tetra-*O*-acetyl-4-*O*-benzoyl-D-fructose, m.p. 83°, $[\alpha]_D^{23}$ +35·5° (*c* 1·8, $CHCl_3$). The material remaining in the mother-liquors was first treated with sodium methoxide in methanol and then with acetone and concentrated sulphuric acid: a di-*O*-isopropylidene derivative (presumably 1,2 : 3,4; III) of L-*threo*-L-*glycero*-hex-3-ulose, m.p. 99—100°, $[\alpha]_D^{23}$ −15·4° (*c* 1·2, $CHCl_3$), was obtained.

All the new compounds gave n.m.r. spectra, and all the crystalline compounds gave elemental analyses, in accordance with the structures assigned.

The tetra-acetate of 3,4-*O*-methylene-L-iditol should give a derivative of L-*threo*-D-*glycero*-hex-3-ulose. This synthesis is now in progress. When it is completed, one enantiomer of each of the four diastereomeric hex-3-uloses will be known.

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