Ring Contraction and Epimerization During a Displacement Reaction of a Hexose Sulphonate

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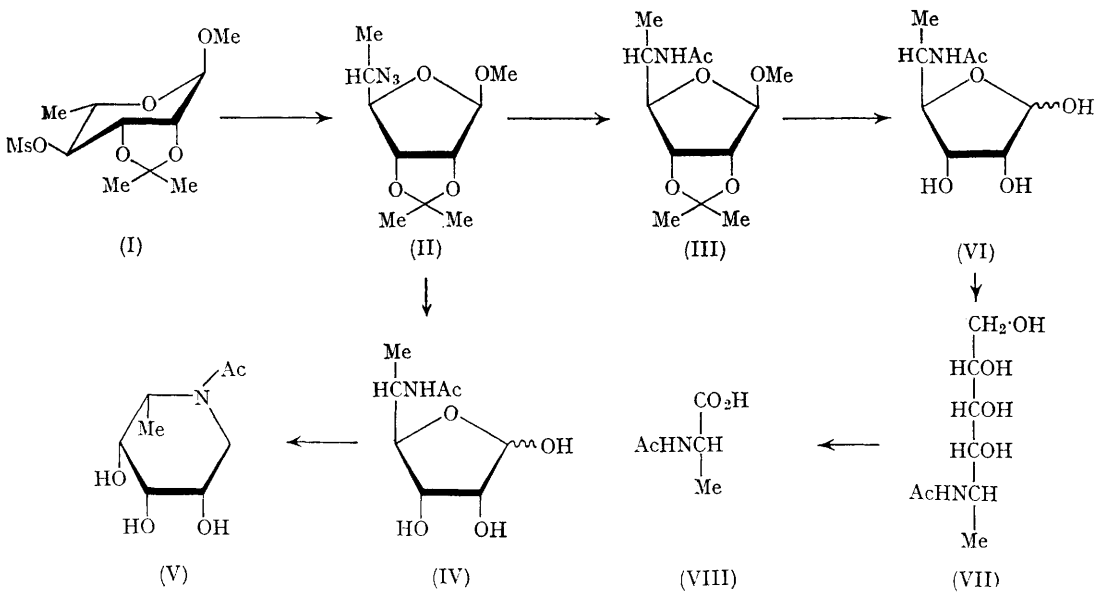
NUCLEOPHILIC displacement reactions of methyl pyranoside 4-*O*-sulphonates are considered to occur with relative ease compared to other secondary ring sulphonates.[1] The unassisted displacement of a 4-*O*-sulphonate by azide ion should theoretically afford the epimeric 4-azido-derivative by an S_N2 process, and subsequently a 4-amino-sugar[2] after reduction. Members of the latter type are of interest[3] primarily because of their occurrence in several antibiotics[4] and the possibility of forming furanose derivatives containing nitrogen in the ring.[5]

An unusual rearrangement reaction occurs during the attempted displacement of methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulphonyl-α-L-mannopyranoside (I), m.p. 128—129°, with azide ion. Reaction of (I) with an excess of sodium azide in refluxing *NN*-dimethylformamide for 18 hr. afforded after processing, a crude syrup in approximately 59% yield. The major component in this mixture was found to be the rearranged product (II), which was purified by preparative thin-layer chromatography[6] (benzene–2,2,4-trimethylpentane–methanol, 100 : 30 : 1) and obtained as a pure liquid[7] in 56·5% yield [34% overall from (I)]; $[\alpha]_D^{25}$ −21° [*c*, 0·84 (MeOH)]. Examination of the n.m.r. spectrum of (II) and comparison of it with that of (I) clearly indicated a change in ring form and suggested a furanoside structure; τ 4·88 (J_{12} = 0 c./sec., C-1 proton), 5·33 (C-2 and C-3 protons), 5·92 (J = 10 c./sec., C-4 proton), 6·33 (J = 7 c./sec., apparent triplet, C-5 proton), 6·52 (OCH_3 protons). Furanoside formation was also suspected because of the extreme acid lability of (II). Cleavage of acetal and glycoside bonds could be effected even with 30% aqueous acetic acid at 100° for 1 hr. Catalytic reduction of (II), followed by *N*-acetylation gave the 5-acetamido derivative (III) as a liquid, $[\alpha]_D^{25}$ −84° [*c*, 5·08 (MeOH)]; τ 4·89 (J_{12} = 0 c./sec., C-1 proton), 6·53 (OCH_3 protons), 8·06 (*N*-acetyl protons). The structure of this product [and consequently that of (II)] was unequivocally established from its mass spectrum;[8,9] *m/e* 244 $M^{\cdot+}$ −15), *m/e* 212 $M^{\cdot+}$ −15—MeOH), *m/e* 86 [$(MeCH{\cdot}NHAc)^+$], *m/e* 44 [$(MeCHNH_2)^+$]. The latter two fragments are indicative of the side chain in (III). Further evidence in favour of the furanoside structure (II) was obtained by its transformation into compound (V).[10] Thus, acid hydrolysis of (II) gave (IV) as a homogeneous syrup, which was reductively rearranged[3,11] to *N*-acetyl-3,4,5-trihydroxy-6-methylpiperidine (V). The structure of (V) was confirmed by infrared, n.m.r., and mass-spectral[8] studies.

Having thus ascertained the ring structure of the rearranged product (II), it remained to establish the configuration at C-4 and C-5. From a

mechanistic viewpoint, as well as from considerations of optical rotation data, compound (II) can only have the L-*talo*- or D-*allo*-stereochemistry. Mild acid hydrolysis of (III) gave 5-acetamido-5,6-dideoxy-L-talofuranose (VI), R_f 0·592, which from its infrared spectrum appeared to exist as the furanose (or acyclic) form, rather than the pyranose structure containing nitrogen in the ring.[5] Sodium borohydride reduction, followed by sequential oxidation of the produced itol (VII) with lead tetra-acetate and bromine, afforded after processing, *N*-acetyl-L-alanine (VIII), which was identified[12] by its optical rotation and infrared spectrum. This fragment arises from C-4, C-5, and C-6 of the original compound (III) and establishes beyond doubt the L-*glycero*-configuration of C-5 in (III), attack at C-4. Any ring opening and subsequent closure of the ring to give furanoside products appears to occur in a concerted fashion, since the anomeric integrity (α-glycoside) was retained during the rearrangement.

An identical rearrangement has been recently reported by Stevens and co-workers.[13] It was stated that reaction of (I) (D-enantiomer) with lithium azide in *NN*-dimethylformamide gave complex mixtures which after reduction, afforded methyl 5-amino-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-talofuranoside as the sole basic product in 20% yield. The structure and stereochemistry of this compound was ascertained indirectly by its synthesis from the C-5 epimeric brosylate (L-*allo*) through displacement with azide ion followed by



and consequently in (II). The major product of this seemingly simple displacement reaction is therefore methyl 5-azido-5,6-dideoxy-2,3-*O*-isopropylidene-α-L-talofuranoside, rather than the expected 4-azido-derivative.

A probable mechanism for this unusual ring contraction takes into account the fact that (I) exists as the 1*C* form (τ 5·0, $J_{12} = 0$ c./sec., C-1 proton; 6·55, OCH_3 protons). In such a conformation (and not in the alternative *C*1 chair form), the C-5 ring oxygen bond is *trans*-antiparallel to the C-4 sulphonate bond; the ring oxygen is thus in favourable position for an intramolecular back-side hydrogenation. All attempted displacement reactions on sulphonates of (I) (D-enantiomer) led to rearranged furanoside products.[13] In this respect, it is noteworthy that displacement of (I) (4-toluene-*p*-sulphonate) with potassium thiolbenzoate reportedly[14] gives the inverted 4-thiolbenzoate (L-*talo*) which was converted into the free sugar, presumed to exist in the thiofuranose form. In view of the findings of Stevens *et al.* and our present experiences, the alternative rearranged 5,6-dideoxy-5-mercapto-L-talopyranose structure should be also considered.

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[6] Thin-layer chromatography was carried out on silica gel HF plates. Components were detected with acidified ammonium molybdate and alkaline silver nitrate (free sugars). Paper chromatography was done in the solvent n-butanol–ethanol–water (3 : 1 : 1).
[7] The compounds reported herein gave correct analyses. Vapour-phase chromatography was performed on columns packed with 5% SE-30.
[8] We thank Dr. D. C. DeJongh, Wayne State University, Detroit, Michigan, for recording the spectrum and assisting in its interpretation.
[9] For a study of amino-sugars by mass spectrometry, see D. C. DeJongh and S. Hanessian, *J. Amer. Chem. Soc.*, 1965, **87**, 1408, 3744.
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