

The Stereochemistry of a 2-S-Ethyl-2-thioaldohexose: Ready Epimerization of a 2-Thioaldose

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Summary The acid-catalysed replacement of the C-2 hydroxy-group in 3,4,5,6-tetra-*O*-benzoyl-*D*-glucose diethyl dithioacetal (1) by an ethylthio-group proceeds with inversion of configuration, probably through an episulphonium-ion intermediate, to give the diethyl dithioacetal (2) of 2-*S*-ethyl-2-thio-*D*-mannose (9), the free sugar (9) being exceptionally readily epimerized, at pH 8, to give the *gluco*-analogue (8).

TREATMENT of 3,4,5,6-tetra-*O*-benzoyl-*D*-glucose diethyl dithioacetal (1) with ethanethiol and hydrogen chloride (or zinc chloride) leads to replacement of the hydroxy-group at C-2 by an ethylthio-group.¹ The product (m.p. 82–83°) is 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-*D*-mannose diethyl dithioacetal (2).

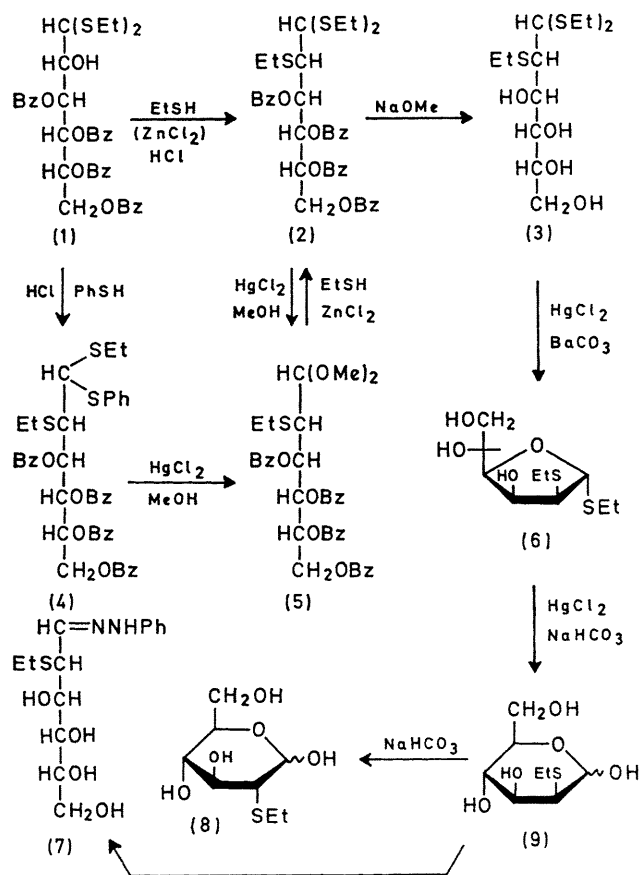
Saponification of (2) gives 2-*S*-ethyl-2-thio-*D*-mannose diethyl dithioacetal (3), m.p. 100–101°, whose stereochemistry at C-2 was previously^{1,2} not established. Treatment of (3) with aqueous mercuric chloride (1.1 moles) and

whose structure has been established by chemical and X-ray crystallographic methods. When the desulphurization reaction was performed at room temperature with 2.0 moles of mercuric chloride for 30 min in the presence of 2.0 moles of sodium hydrogen carbonate, the yield of (6) decreased almost to zero and 2-*S*-ethyl-2-thio-*D*-mannopyranose^{2,3} (9) was obtained in 92% yield as a chromatographically homogeneous syrup containing the α - and β -anomers in 3:2 proportion. The product (9) was characterized by conversion into its phenylhydrazone (7) (yield 75%), m.p. 159–160°, $[\alpha]_D^{25} + 102^\circ$ (*c* 1, pyridine) and by acetylation to give 1,3,4,6-tetra-*O*-acetyl-2-*S*-ethyl-2-thio- α -*D*-mannopyranose; yield 60%, m.p. 116°, $[\alpha]_D^{25} + 40^\circ$ (*c* 1, chloroform), identical with a sample prepared³ by a different route.

Since extended treatment of (3) with hot, aqueous mercuric chloride in the presence of barium carbonate gives² not only (9) but some of the 2-epimer, 2-*S*-ethyl-2-thio-*D*-glucose^{2,4} (8), the possibility of epimerization of (9) at C-2 was investigated. A solution of (9) (200 mg) in water containing sodium hydrogen carbonate (40 mg) was kept for 1 hr at 25°, evaporated at 35°, and the residue kept 18 hr at 25°. An aqueous solution of the product was deionized (Amberlite MB-3 resin), evaporated, and crystallized (ethanol) to give the *D*-*gluco*-derivative⁴ (8), m.p. 161–162° in 68% yield. The mother-liquor contained *ca.* 20% of unchanged *D*-*manno*-derivative (9), characterized as the phenylhydrazone (7) m.p. 158–159°.

The ready epimerization of (9) at pH *ca.* 8, due presumably to the ease of stabilization of a C-2 carbanion on account of the sulphur atom, explains why desulphurization of (3) under vigorous conditions² leads to a mixture of (8) and (9). The stepwise sequence (3) \rightarrow (6) \rightarrow (9) clearly establishes that the derivatives (2) and (3) have the *D*-*manno*-stereochemistry, and the conversion (3) \rightarrow (6) provides a convenient route to (6) (a useful precursor for synthesis of furanosyl nucleoside analogues) in a sequence of high-yielding steps from *D*-glucose.

The mechanism of conversion of (1) into (2) was investigated by treating (1) with benzenethiol and hydrogen chloride in chloroform. The product, obtained crystalline in 71% yield, was identified as 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-*D*-mannose ethyl phenyl dithioacetal (4), m.p. 99–101°, $[\alpha]_D^{25} + 37^\circ$ (*c* 1, chloroform), by elemental analysis, n.m.r. spectroscopy, and by the fact that demercaptation with mercuric chloride in methanol gave 90% of crystalline 3,4,5,6-tetra-*O*-benzoyl-2-*S*-ethyl-2-thio-*D*-mannose dimethyl acetal¹ (5), m.p. 94–95°, $[\alpha]_D^{25} + 58^\circ$ (*c* 1, chloroform), identical with a sample prepared from (2) by treatment with ethanethiol and zinc chloride regenerated (2). These observations indicate that the introduction of the third ethylthio-group in the conversion of (1) into (2) does not proceed by an S_N2 type of displacement but probably passes through an intermediate, 1,2-episulphonium ion formed with inversion at C-2, which subsequently is attacked at the less-hindered C-1 position by a thiol molecule. Similar considerations probably apply in the



barium carbonate (2 moles) for 45 min at 40° gave 60–70% of crystalline ethyl 2-*S*-ethyl-1,2-dithio- α -*D*-mannofuranoside (6), m.p. 90–91°, identical with an authentic sample²

corresponding conversions of the xylose analogue⁵ of (1) and preliminary experimental work and the National Institutes of Health for financial support.⁶

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