ACTA CHEMICA SCANDINAVICA 17 (1963) 930–932

Catalytic Oxidation of the Anomeric Methyl 4,6-*O*-Ethylidene-D-Mannopyranosides

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The anomeric methyl D-*arabino*-hexopyranosiduloses (methyl 2-keto-D-manno(gluco)pyranosides) were prepared by platinum catalysed oxidation of the corresponding methyl 4,6-*O*-ethylidene-D-mannopyranosides.

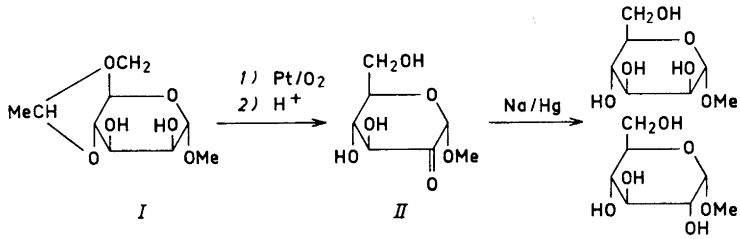
The isolation in low yields of the anomeric methyl D-*arabino*-hexopyranosiduloses was reported by Theander [1] from chromium trioxide oxidation of methyl α- and β-D-glucopyranoside. The 2-keto-glycosides are potential starting materials for the preparation of 3-keto-glycosides, to which they can be transformed, in high yield, by epimerisation [2]. The difficulty hitherto encountered in preparing keto-glycosides prompted investigations into other methods which might make these compounds more readily available. Treatment of D-glucosone with methanolic hydrogen chloride, for example gave, *inter alia*, only traces of methyl 2-keto-glycosides [3].

Pentopyranosides containing an axial hydroxyl group are selectively oxidised at this position with oxygen in the presence of a platinum catalyst. This reaction has been used by Brimacombe *et al.*[4] and Heyns and Lenz [5] to give keto-glycosides in yields of *ca.* 15 %. Application of this method to the hexopyranosides necessitates protection of the primary hydroxyl group at C-6 which is more readily oxidised under these conditions. The 4,6-*O*-ethylidene derivatives of the anomeric methyl D-mannopyranosides in the sterically favoured C-1 conformation have axial hydroxyl groups at C-2.

Methyl 4,6-*O*-ethylidene-α-D-mannopyranoside (I) was oxidised at 45° and pH 4 for 18 h with oxygen in the presence of platinum. After removal of the ethylidene group with mild acid, the neutralised hydrolysate of the pro-

duct mixture revealed a component which resembled a keto-glycoside in its chromatographic and electrophoretic behaviour. This component was isolated by cellulose column chromatography together with methyl α-D-mannopyranoside, α-mannose and unidentified products.

The keto-glycoside (II), which was chromatographically and electrophoretically indistinguishable from methyl α-D-*arabino*-hexopyranosidulose,[1] was obtained as an amorphous powder ($[\alpha]_D$ + 95° in H_2O) in yields of 8—11 %. Its structure was established by reduction with sodium amalgam at pH 6 to yield a mixture of methyl α-D-mannopyranoside and methyl α-D-glucopyranoside in the ratio 1:4, respectively. It is noteworthy that under similar conditions methyl β-D-*arabino*-hexopyranosidulose yielded almost equal amounts of the epimers [6]. If pH 6—7 was maintained during the oxidation compounds resembling 3-keto-glycosides were also obtained signifying that epimerisation had occurred after formation of the 2-keto-glycoside. The formation of acidic products was also greater under these conditions.



I *II*

Methyl 4,6-*O*-ethylidene-β-D-mannopyranoside (mp. 180—181°, $[\alpha]_D$ −128° in chloroform) together with methyl 2,3:4,6-di-*O*-ethylidene-β-D-mannopyranoside (m.p. 124—125°, $[\alpha]_D$ −176° in chloroform) were prepared by condensation of methyl β-D-mannopyranoside with paraldehyde. The mono-ethylidene derivative was oxidised in the presence of a platinum catalyst to yield a single keto-glycoside, which after removal of the ethylidene group, was chromatographically and electrophoretically indistinguishable from an authentic sample of methyl β-D-*arabino*-hexopyranosidulose [1].

Preliminary experiments [7] with methyl α-L-rhamnoside have again indicated that the axial hydroxyl group at C-2 is selectively oxidised.

EXPERIMENTAL

Melting points are corrected. All distillations were carried out under reduced pressure (bath temperature < 40°) or by freezedrying. Paper chromatography was carried out on Whatman No. 1 paper by downward irrigation using the organic phase of the solvent system butan-1-ol:ethanol:water (10:3:5), and electrophoresis on Whatman No. 1 paper in 0.1 M hydrogen sulphite buffer (pH 4.7) at 50° [8].

Oxidation of methyl 4,6-O-ethylidene-α-D-mannopyranoside (I). The optimal conditions for the oxidation were determined in small-scale experiments. Prolongation of the oxidation did not substantially increase the yield of keto-glycoside and resulted in the formation of secondary products.

A rapid stream of oxygen was passed for two periods of 9 h through a stirred solution of methyl 4,6-*O*-ethylidene-α-D-mannopyranoside [9] (10.00 g) in water (170 ml) containing the catalyst [4] (7.00 g) at 45°. The solution was maintained at pH 4 throughout by the addition of sodium hydrogen carbonate. The filtered solution was deionised through

Dowex-50 (H^+) and Dowex-3 (free base), and concentrated to a syrup which was hydrolysed with 0.1 N sulphuric acid at 96° for 1 h. The neutralised ($BaCO_3$) hydrolysate was fractionated on a cellulose column (55 × 4.5 cm) eluted with butan-1-ol saturated with water. The following fractions (average of two experiments) were obtained: ethylidene derivatives (0.04 g), methyl α-D-mannopyranoside (3.47 g), methyl α-D-*arabino*-hexopyranosidulose (0.76 g), D-mannose (0.88 g) and a mixture of unidentified components (1.79 g) with low R_F-values. Acids (1.75 g) were recovered from the anion-exchange resin.

Methyl α-D-arabino-*hexopyranosidulose* (II), $[\alpha]_D^{22}$ + 95° (*c*, 0.4 in water) was obtained as an amorphous powder. A sample of II (112 mg) in 0.2 M phosphate buffer (pH 6, 5 ml) was reduced with 2 % sodium amalgam for 4 h, at room temperature. The deionised product mixture was fractionated on Whatman No. 3 MM filter papers to yield methyl α-D-mannopyranoside (13 mg) and methyl α-D-glucopyranoside (49 mg) which, after recrystallisation from ethanol, had melting points 190—191° and 165—166°, respectively, alone or admixed with authentic samples.

Preparation and oxidation of methyl 4,6-O-ethylidene-β-α-mannopyranoside. This compound was prepared in an analogous manner to that of the corresponding α-anomer [9].

Methyl β-D-mannopyranoside isopropylate [10] (15.00 g) was shaken with paraldehyde (90 ml), containing two drops of concentrated sulphuric acid, at room temperature for 5 min. The solution was decanted, neutralised with sodium hydrogen carbonate, filtered and concentrated to a syrup. The unreacted material was subjected to six further treatments with paraldehyde. The combined products were suspended in water (120 ml), the crystals of methyl 2,3:4,6-di-*O*-ethylidene-β-D-mannopyranoside filtered off, washed with acetone (5 ml) and the combined filtrates and washings were shaken with ethyl ether (3 × 25 ml). The aqueous layer was concentrated, dried and the residue crystallised from benzene to yield methyl 4,6-*O*-ethylidene-β-D-mannopyranoside (1.20 g). Concentration of the ether layer afforded more of the di-*O*-ethylidene derivative, the combined of crops which were recrystallised from aqueous methanol to give 3.80 g of material. These yields are considerably lower than those obtained with the corresponding α-anomers.

Methyl 4,6-O-ethylidene-β-D-mannopyranoside, m.p. 180—181°, $[\alpha]_D^{22}$ −128° (*c*, 0.2 in chloroform) (Found: C 49.2; H 7.33. $C_9H_{18}O_6$ requires C 49.1; H 7.32). The substance consumed 1 mole of lead tetraacetate in agreement with the proposed structure.

Methyl 2,3:4,6-di-O-ethylidene-β-D-mannopyranoside, m.p. 124—125°, $[\alpha]_D^{22}$ −176° (*c*, 0.6 in chloroform) (Found: C 54.0; H 7.63. $C_{11}H_{18}O_6$ requires C 53.7; H 7.37).

Methyl 4,6-*O*-ethylidene-β-D-mannopyranoside (1.00 g) was oxidised and the product isolated as described above for the α-anomer. Methyl β-D-*arabino*-hexopyranosidulose (82 mg) thus obtained was chromatographically and electrophoretically indistinguishable from an authentic sample.

One of us (M.C.C.) thanks the *Department of Scientific and Industrial Research*, England, for the award of a scholarship.

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Received November 22, 1962.