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The Oxidation of Glycosides

XV *. The Oxidation of Methyl 4-*O*-Methyl-β-D-Glucopyranoside with Chromium Trioxide

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Methyl 4-*O*-methyl-β-D-glucopyranoside has been oxidised with chromium trioxide in acetone. Three carbonyl compounds, resulting from oxidation at C-2, C-3 and C-6, were isolated: methyl 4-*O*-methyl-β-D-*arabino*-hexopyranosidulose, methyl 4-*O*-methyl-β-D-*ribo*-hexopyranosid-3-ulose and methyl 4-*O*-methyl-β-D-*gluco*-hexodialdo-1,5-pyranoside.

In a previous investigation [1] the carbonyl derivatives of methyl β-D-glucopyranoside were prepared by oxidation of this substance with chromium trioxide. The formation of these compounds has also been studied using such oxidation reagents as chlorine water and aqueous hypochlorite [2] at different pH-values, Fenton's reagent [3] and nitrogen dioxide.[4] The properties of the carbonyl glycosides, which are suitable models for oxidised cellulose, have been investigated,[5] in particular the degradation at different pH-values of the 2- and 3-keto-derivatives. Under alkaline conditions at room temperature or around the neutral point at elevated temperature they are degraded rapidly through elimination of the glycosidic methoxyl group. In oxidised cellulose, a competing elimination at C-4 can also be expected. In order to study this problem and also to obtain a model for studying the influence of an aldehyde group at C-6 in cellulose, it was thought of interest to prepare the carbonyl glycosides, methylated at C-4.

Methyl 4-*O*-methyl-β-D-glucopyranoside (I) was oxidised with chromium trioxide in acetone. A paper chromatographic and electrophoretic examination of the deionised product revealed the presence of two components with the characteristics of keto-glycosides, and one with those of an aldehydo-glycoside. The main component of the reaction mixture was unreacted glucoside. By a combination of carbon column and cellulose column chromatography the components were separated. The three possible mono-carbonyl glycosides

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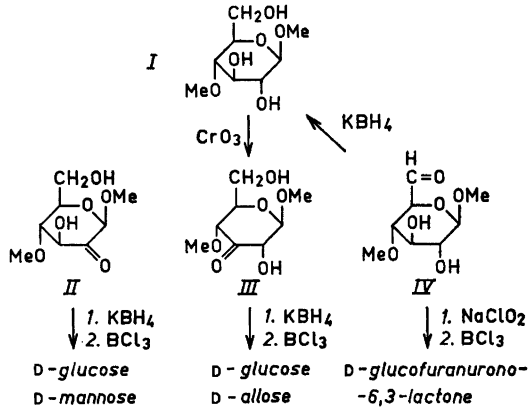
were obtained in the following yields: methyl 4-*O*-methyl-β-D-*arabino*-hexopyranosidulose (II, 0.2 %), methyl 4-*O*-methyl-β-D-*ribo*-hexopyranosid-3-ulose (III, 2,6 %) and methyl 4-*O*-methyl-β-D-*gluco*-hexodialdo-1,5-pyranoside (IV, 3.1 %).

As in the oxidation of methyl β-D-glucopyranoside the yields were reduced by secondary reactions. Considerable amounts of acids were formed.



On electrophoretograms (hydrogen sulphite as electrolyte at 50°) the carbonyl compounds appeared as single, round spots but on paper chromatograms the aldehydo compound appeared as elongated spots, being evidence of equilibrium phenomena. This behaviour is similar to that of the parent methyl dialdopyranoside and to dialdoses and aldosuloses. The reactions of the carbonyl compounds towards spray reagents were similar to the reactions of the corresponding derivatives of methyl β-D-glucopyranoside.[6]

Methyl 4-*O*-methyl-β-D-*arabino*-hexopyranosidulose (II), which was obtained in an amorphous state, was labile, and some epimerisation to the 3-keto compound occurred after storing as a syrup for a few weeks in the cold. The position of the keto-group in II was shown by the identification of glucose and mannose after borohydride reduction and demethylation with boron trichloride.[7] D-Mannose was also characterised as its phenylhydrazone.

Methyl 4-*O*-methyl-β-D-*ribo*-hexopyranosid-3-ulose (III) was obtained in a crystalline state, m.p. 152—153°, $[\alpha]_D$ +11° and $[\alpha]_{364}$ −41° (compare the previously[1] prepared methyl β-D-*ribo*-hexopyranosid-3-ulose: $[\alpha]_D$ −62° and $[\alpha]_{364}$ −272°). No mutarotation was observed at room temperature. Rotary dispersion measurements showed that both of the 3-keto compounds exhibit a negative Cotton effect. Substance III showed a strong carbonyl absorption in the IR, λ_{max}^{KBr} 5.78 μ. In the UV (in 96 % ethanol) two maxima were present at 209 mμ (ε max 980) and 285 mμ (ε max 36). The corresponding values for methyl β-D-*ribo*-hexopyranosid-3-ulose were in IR: λ_{max}^{KBr} 5.76 μ and UV: 208 mμ (ε max 1580) and 279 mμ (ε max 42).

The position of the keto group was proved by the identification after borohydride-reduction and demethylation of glucose and allose, the latter being isolated in crystalline form. The ratio of allose to glucose was 59:41, compared with that of 49:51 for the corresponding unmethylated 3-keto-glycoside.[8]

Methyl 4-*O*-methyl-β-D-*gluco*-hexodialdo-1,5-pyranoside (IV) was obtained amorphous, $[\alpha]_D$ −15° and $[\alpha]_{364}$ −50° (compare the previously[1] prepared amorphous methyl-β-D-*gluco*-hexodialdo-1,5-pyranoside: $[\alpha]_D$ −38° and $[\alpha]_{364}$ −109°. It could be stored at low temperature for a long time without detectable decomposition. The structure was shown by the isolation of methyl 4-*O*-methyl-β-D-glucopyranoside (I) after borohydride reduction and of α-D--glucofuranurono-6,3-lactone after oxidation with chlorite and demethylation. After chlorite oxidation and acid hydrolysis of IV 4-*O*-methyl-D-glucuronic acid was identified in the product by paper chromatography and electrophoresis.

As mentioned above the introduction of a methoxyl group into the 4-position of methyl β-D-*ribo*-hexopyranosid-3-ulose has some influence on the UV-absorption. This substitution also diminishes the reactivity of the carbonyl group at C-3 towards hydrogen sulphite, as revealed by the lower mobility of substance III in electrophoresis in hydrogen sulphite [9] (Table 1), but has only a negligible influence on the carbonyl group at C-2 and C-6.

Table 1. $M_{Vanillin}$-values of carbonyl derivatives of methyl β-D-glucopyranoside and its 4-*O*-methylether in hydrogen sulphite (pH 4.7, 0.1 M at 50°).

Compound	M_V
Methyl β-D-*arabino*-hexopyranosidulose	0.79
-4-*O*-methyl-	0.76
Methyl β-D-*ribo*-hexopyranosid-3-ulose	0.56
-4-*O*-methyl-	0.38
Methyl β-D-*gluco*-hexodialdo-1,5-pyranoside	1.25
-4-*O*-methyl-	1.22

EXPERIMENTAL

Concentrations were carried out under reduced pressure below 40° or by lyophilisation. Melting points are corrected. The optical rotations were measured in a Perkin-Elmer polarimeter 141.

Butan-1-ol-ethanol-water, 10:3:5 (solvent A) and ethyl acetate-acetic acid-water, 3:1:1 (solvent B) were used for paper chromatography and 0.1 M hydrogen sulphite, pH 4.7 (used at 50°) for electrophoresis (on Whatman No. 1 paper). The spray reagents used were: silver nitrate-sodium hydroxide, anisidine hydrogen chloride, resorcinol-hydrochloric acid and periodate-benzidine. Methyl 4-*O*-methyl-β-D-glucopyranoside was detectable with the latter reagent, and also with the anisidine-spray, if the paper was heated somewhat stronger then usual and then observed in UV-light when a fluorescent spot was observed.

Oxidation of methyl 4-O-methyl-β-D-glucopyranoside (I). Methyl 4-*O*-methyl-β-D-glucopyranoside was prepared either as previously reported [10] or by methylation of methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside [11] with methyl iodide and silver oxide in dimethylformamide [12] followed by deacetylation.

In a typical oxidation experiment a solution of I (15.00 g, m.p. 102−103°) in acetone (300 ml), at 5°, was poured in a slow stream into an agitated solution of chromium trioxide

(10.00 g) in acetone (1000 ml). The procedure took *ca.* 10 min and the temperature was kept below 15°. The acetone used had been purified by refluxing in the presence of potassium permanganate and distilled. During the preparation of the chromium trioxide solution, the oxidant was carefully added in small portions, to the cooled acetone with stirring.

The oxidation mixture was boiled under reflux for 30 min and was then cooled. The brown precipitate which formed was collected by filtration and washed with acetone. It was then heated under reflux with acetone (4 × 200 ml) for 10 min with intermediate filtrations. The combined filtrates were kept at 0° for 24 h and the solution then separated from the brown and sticky precipitate by decantation. The solution was concentrated to a small volume and was then diluted with water (250 ml). After extraction with chloroform (4 × 100 ml), the solution was deionised, Dowex 50 (H^+) and Dowex 3 (free base) and concentrated to a syrup (8.95 g). This product was then fractionated on a carbon-Celite column (6.5 × 52 cm) using aqueous ethanol as elutant (16 l, 0–25 % and then 4 l, 50 %); the main parts of I and III were thus obtained pure in the crystalline state. Subfractionations were then carried out on cellulose columns using butan-1-ol, saturated with water, as solvent and on thick filter papers (Whatman 3 MM) using solvents A and B. Similar separations have been described in previous communications.[1,6] The following substances were thus obtained, chromatographically and electrophoretically pure: I, 4.72 g; II, 0.03 g; III, 0.39 g and IV, 0.47 g.

*Methyl 4-O-methyl-β-*D*-arabino-hexopyranosidulose* (II) wax obtained as an amorphous powder, $R_{Glucose}$-values 2.02 (A) and 1.92 (B). A small amount (20 mg) was reduced with an excess of potassium borohydride in aqueous solution at pH 9.5. After deionisation (by cation-exchange resin (Dowex-50 (H^+)) and removal of boric acid as methyl ester and evaporation, the product demethylated with boron trichloride in dichloromethane.[6] It was shown by paper chromatography that the sugars formed were glucose and mannose. This mixture was separated on thick filter paper (Whatman 3 MM) using solvent B. The small amount of mannose recovered from the paper was characterised as the crystalline D-mannose phenylhydrazone, m.p. and mixed m.p. 194–195°.

*Methyl 4-O-methyl-β-*D*-ribo-hexopyranosid-3-ulose* (III), m.p.152–153° (recrystallised from propanol); $[\alpha]_D^{23}$ +10.7 and $[\alpha]_{364}^{23}$ −40.8 (*c* 0.5, water) and $R_{Glucose}$-values 2.73 (A) and 2.37 (B) [as comparison I has 2.50 (A) and 2.13 (B)]. IR-and UV-data are given in the text. (Found: C 46.8; H 6.57; O 47.0; OCH_3 29.7. $C_8H_{14}O_6$ requires: C 46.6; H 6.83; O 46.6; OCH_3 30.0).

A sample of III (40 mg) was reduced and demethylated as described for compound II, and the sugars obtained were identified as glucose and allose. The ratio of these was estimated as 41:59 after chromatography in solvent B, using the procedure of Saeman *et al.*[13] After separation on a thick filter paper (Solvent B) D-allose was isolated. After crystallisation from ethanol 5 mg was obtained having m.p. and mixed m.p. 126–127°.

*Methyl 4-O-methyl-β-*D*-gluco-hexodialdo-1,5-pyranoside* (IV) was obtained as an amorphous powder $[\alpha]_D^{23}$ −15° and $[\alpha]_{364}^{23}$ −50° (*c*, 0.5 water) and IR λ_{max}^{KBr} 5.78 (carbonyl, medium). $R_{Glucose}$-values (elongated spots) 3.1 (A) and 1.5 (B). The pellet for IR was prepared from a dry lyophilizate of an equilibrium solution of IV to which the desired amount of potassium bromide had been added.

A sample (40 mg) was reduced with an excess of borohydride in aqueous solution at pH 9.5. Deionisation, evaporation and recrystallisation (ethyl acetate) yielded methyl 4-*O*-methyl-β-D-glucopyranoside (15 mg), m.p. and mixed m.p. 102–103°.

Another sample of IV (100 mg) was oxidised with 1.2 times the stoichiometric amount of sodium chlorite (pH 3.5) and the product worked up as previuosly[2] described. The main part (80 %) of the product was demethylated[6] to yield mainly glucuronic acid and its 6,3-lactone, as shown by paper chromatography and electrophoresis. After purification by chromatography on a thick filter paper (solvent B) the D-glucofuranurono-6,3-lactone was obtained crystalline (*ca.* 10 mg from aqueuos ethanol), m.p. and mixed m.p. 173–175°.

The other part of the oxidised product was treated with 2 N sulphuric acid on a boiling water bath for 3 h. After cooling, neutralisation with barium carbonate and treatment with cation exchange resin, Dower-50 (H^+), 4-*O*-methyl-D-glucuronic acid was identified as the main product by paper chromatography and electrophoresis.

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REFERENCES

1. Assarsson, A. and Theander, O. *Acta Chem. Scand.* **12** (1958) 1507.
2. Theander, O. *Svensk Papperstid.* **18** (1958) 581.
3. de Belder, A. N., Lindberg, B. and Theander, O. *Acta Chem. Scand.* **17** (1963) 1012
4. Assarsson, A. and Theander, O. *Acta Chem. Scand.* **18** (1964) 553.
5. Theander, O. *Advan. Carbohydrate Chem.* **17** (1962)223.
6. Theander, O. *Acta Chem. Scand.* **11** (1957) 1557.
7. Bonner, T. G., Bourne, E. J. and McNally, S. *J. Chem. Soc.* **1960** 2929.
8. Theander, O. *Acta Chem. Scand.* **12** (1958) 1883.
9. Theander, O. *Acta Chem. Scand.* **11** (1957) 717.
10. Bouveng, H. O., Lindberg, B. and Theander, O. *Acta Chem. Scand.* **11** (1957) 1788.
11. Levene, P. A. and Raymond, A. L. *J. Biol. Chem.* **97** (1932) 763.
12. Kuhn, R., Trischmann, H. and Löw, I *Angew. Chem.* **67** (1955) 32.
13. Saeman, J. F., Moore, W. E., Mithell, R. L. and Millett, M. A. *Tappi* **37** (1954) 336.

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