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THE OXIDATION OF METHYL α-D-GLUCOPYRANOSIDE WITH METHYL SULPHOXIDE AND ACETIC ANHYDRIDE*

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ABSTRACT

The relative proportions of carbonyl, *O*-acetyl, and *O*-(methylthio)methyl sugars resulting from the partial oxidation of methyl α-D-glucopyranoside with methyl sulphoxide and acetic anhydride have been investigated. The preparation of the 2- and 6-(methylthio)methyl ethers of methyl α-D-glucopyranoside is described.

INTRODUCTION

Mixtures of methyl sulphoxide and acetic anhydride have proved effective for the introduction of carbonyl groups into suitably protected sugars[1–3]. However, side-reactions leading to *O*-(methylthio)methyl and *O*-acetyl derivatives may sometimes predominate[4–7]. In connexion with our use of this reagent for introducing carbonyl groups into polysaccharides for the purpose of coupling to biologically active molecules, it was deemed of interest to study this oxidation by means of a model compound, methyl α-D-glucopyranoside, and thereby to decrease the undesirable side-reactions. It was, however, first necessary to identify the main components of the oxidation mixture.

RESULTS AND DISCUSSION

Since the extent of oxidation of methyl α-D-glucopyranoside was low, we have confined our attention in the first instance to the mono-substituted derivatives, *i.e.*, the mono-acetates, mono-(methylthio)methyl ethers, and the mono-carbonyl derivatives. Of the mono-carbonyl derivatives, all but methyl α-D-*xylo*-hexopyranosid-4-ulose had been described prior to the start of this work. We did not attempt to synthesise the 4-ulose, but its preparation has recently been reported[8].

Of the four possible monoacetates, the 6-*O*-acetyl derivative is known[9], and methyl 2-*O*-acetyl- and 3-*O*-acetyl-α-D-glucopyranoside were prepared by treating the corresponding 4,6-*O*-benzylidene derivatives with 90% trifluoroacetic acid. Methyl

*Dedicated to the memory of Professor Edward J. Bourne.

4-*O*-acetyl-α-D-glucopyranoside was prepared by partial acetylation of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside, fractionation of the 4- and 6-isomers, and thereafter debenzylation of the crystalline 4-*O*-acetyl derivative. The monoacetates were later described by Borén *et al.*[10,11].

Finally, two of the four possible mono-(methylthio)methyl ethers were synthesised as reference compounds. The 2-ether was obtained by treating methyl 4,6-*O*-benzylidene-3-*O*-(tetrahydropyran-2-yl)-α-D-glucopyranoside[12] with chloromethyl methyl sulphide and subsequent removal of the blocking groups. The 6-isomer was synthesised likewise by alkylation of methyl 2,3,4-tri-*O*-allyl-α-D-glucopyranoside. The isomerisation of the allyl to the prop-1-enyl ethers prior to acid hydrolysis could not be effected with sodium methylsulphinylmethanide, but treatment with an excess of potassium *tert*-butoxide worked well.

As expected, the (methylthio)methyl ethers are more resistant to acid hydrolysis than the corresponding methoxymethyl ethers. However, (methylthio)methyl substituents may be removed by treatment with M hydrochloric acid at 50° for 1–2 h. The 3- and 4-derivatives were not synthesised individually, but were identified by inspection of gas chromatograms of the mixtures formed on partial (methylthio)-methylation of methyl α-D-glucopyranoside and its 4,6-*O*-benzylidene derivative.

The silyl ethers of the various derivatives are for the most part well-separated on g.l.c. Their relative retention and detector-response factors relative to methyl α-D-glucopyranoside are listed in Table I. Silylation of the 6-aldehydo derivative gave a complex trace containing one dominant peak, which also coincided with the traces for the 3- and 4-acetates. The 2-keto derivative had a surprisingly low response factor (0.35), for which we have no explanation. It is evident from the g.l.c. traces (see Fig. 1)

TABLE I

G.L.C. RETENTION TIMES AND RESPONSE FACTORS

Substance	*Relative retention*[a]	*Response factor*[a]
1 Methyl α-D-glucopyranoside	1.00	—
2 Methyl α-D-*arabino*-hexopyranosid-2-ulose	1.06	0.35
3 Methyl α-D-*xylo*-hexopyranosid-4-ulose	1.13	—
4 Methyl α-D-*ribo*-hexopyranosid-3-ulose	1.21	0.75
5 Methyl 2-*O*-acetyl-α-D-glucopyranoside	1.40	0.70
6 Methyl 3-*O*-acetyl-α-D-glucopyranoside	1.53	0.70
7 Methyl 4-*O*-acetyl-α-D-glucopyranoside	1.51	0.70
8 Methyl α-D-*gluco*-hexodialdo-1,5-pyranoside	1.53	—
9 Methyl 3-*O*-(methylthio)methyl-α-D-glucopyranoside	1.62	—
10 Methyl 4-*O*-(methylthio)methyl-α-D-glucopyranoside	1.69	—
11 Methyl 2-*O*-(methylthio)methyl-α-D-glucopyranoside	1.72	—
12 Methyl 6-*O*-acetyl-α-D-glucopyranoside	1.75	0.70
13 Methyl 6-*O*-(methylthio)methyl-α-D-glucopyranoside	1.95	—
14–17 Not identified		

[a]Relative to that for methyl α-D-glucopyranoside; conditions for g.l.c. as detailed in the Experimental Section.

that the (methylthio)methyl ethers comprise a considerable proportion of the oxidation mixture even at low extents of oxidation. The 3-ether is preponderant, and this accords with the results of Defaye and Gadelle[13] who isolated a 29% yield of methyl 4,6-*O*-benzylidene-3-*O*-(methylthio)methyl-α-D-glucopyranoside from the mixture obtained by oxidation of methyl 4,6-*O*-benzylidene-α-D-glucoside. The amounts of 2-keto- and 3-keto-glucosides were similar and corresponded to the amounts of the corresponding (methylthio)methyl ethers. Only small proportions of the monoacetates were present.

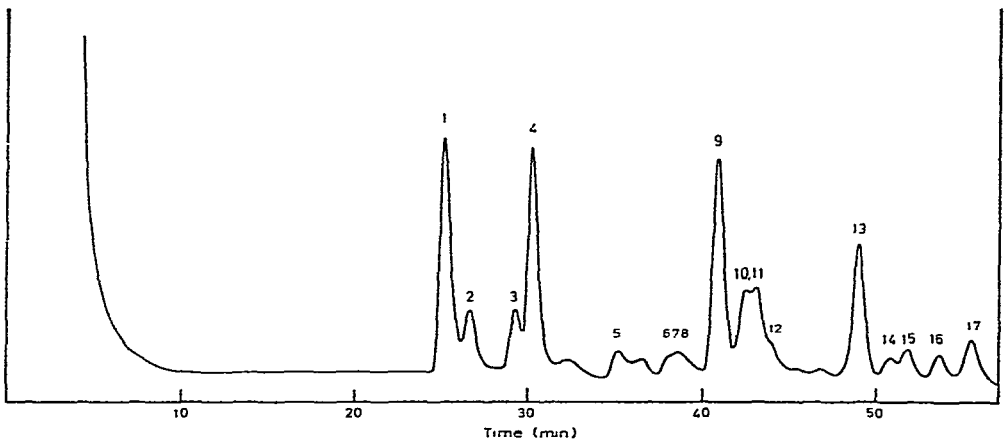

Fig. 1. G.l.c. trace of oxidised methyl α-D-glucopyranoside. For identification of peaks 1–13, see Table I; peaks 14–17 were not identified. Conditions are given in the Experimental Section.

Indirect evidence that peak 3 in Fig. 1 corresponds to the 4-keto derivative was the observation that peaks 2, 3, and 4 disappeared on borohydride reduction, with the appearance of peaks corresponding to methyl α-D-allopyranoside, -galactopyranoside, and -mannopyranoside.

At higher extents of oxidation, although many of the peaks 1–13 were still evident, a large number of other peaks appeared with longer retention times. Presumably, these are di (and tri) substituted derivatives, in many cases containing different substituents[13]. Wide variations in the proportion of acetic anhydride, time, and temperature did not improve the proportion of the uloses in comparison to the (methylthio)methyl ethers and other by-products.

EXPERIMENTAL

For g.l.c., a Hewlett–Packard 5750 instrument fitted with a flame-ionisation detector was used. Separations were performed on a glass column (8 ft × 0.25 in.) containing 5% of BDS on Chromosorb W (80–100 mesh). Initial temperature, 100°; temperature programme, 2°/min; injection port, 205°; detector, 260°; carrier gas, N_2

at 40 ml/min. Column chromatography was performed on silicic acid (100–200 mesh). Optical rotations were recorded with a Perkin–Elmer 141 instrument, using a 10-cm micro-cell.

Methyl α-D-*arabino*-hexopyranosid-2-ulose, prepared as described earlier[12], had m.p. 152°, $[\alpha]_{578}^{22}$ +75° (*c* 2.0, water); lit.[12] m.p. 151–153°, $[\alpha]_{578}^{20}$ +141° (*c* 0.5, water).

Methyl α-D-*ribo*-hexopyranosid-3-ulose was prepared by partial oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and fractionation[14] of the products on Dowex 1 (HSO_3^-) resin. The 3-ulose had m.p. 92.5–93.0°, $[\alpha]_{578}^{21}$ +149° (*c* 1.0, water); lit.[14] m.p. 91–92°, $[\alpha]_D^{25}$ +155° (*c* 2.6, water).

Methyl α-D-*gluco*-hexodialdo-1,5-pyranoside was kindly donated by Professor O. Theander (Royal Agricultural College, Ultuna).

Methyl 2-*O*-acetyl- and 3-*O*-acetyl-α-D-glucopyranoside were prepared by treating the corresponding 4,6-*O*-benzylidene derivatives[12,15] with 90% trifluoroacetic acid. The 2-acetate had m.p. 110–111°, $[\alpha]_{578}^{22}$ +156° (*c* 1.0, water); lit.[11] $[\alpha]_D$ +149° (*c* 0.9, acetone). The 3-acetate had m.p. 150–151°, $[\alpha]_{578}^{23}$ +164° (*c* 1.0, water); lit.[11] m.p. 134–136°, $[\alpha]_D^{22}$ +179° (*c* 0.9, acetone).

Methyl 6-*O*-acetyl-α-D-glucopyranoside was prepared according to Hurst and McInnes[9]; it had $[\alpha]_{578}^{22}$ +141° (*c* 1.2, ethanol); lit.[9] $[\alpha]_D^{21}$ +150.1° (*c* 1.12, acetone).

Methyl 4-O-acetyl-α-D-glucopyranoside. — Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside[16] (3.5 g) was treated with 90% trifluoroacetic acid (25 ml) for 15 min at room temperature. After work-up, ethanol (20 ml) was twice evaporated from the residue which was then partially acetylated with pyridine (20 ml) and acetic anhydride (1.3 g) dissolved in a little chloroform. After 5 h, the product was poured into ice. After 1 h, the solution was evaporated, the residue was taken up in ethanol–benzene, and the solution evaporated. The residual syrup was dissolved in a small volume of benzene–methanol (96:4) and applied to a column (700 mm × 400 mm) of silicic acid which was eluted with benzene–methanol, increasing the concentration of methanol in stages from 4 to 10%; 25-ml fractions were collected. Fractions 49–68 were combined and evaporated, yielding methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-α-D-glucopyranoside (0.18 g, after recrystallisation from hexane), m.p. 104°, $[\alpha]_{578}^{22}$ +51° (*c* 1.3, ethanol).

Anal. Calc. for $C_{23}H_{28}O_7$: C, 66.3; H, 6.73. Found: C, 66.7; H, 6.75. N.m.r. data (60 MHz, chloroform-*d*): τ, 8.05 (3 H, CH_3CO), 6.6 (3 H, CH_3O), and 2.70 (10 H, 2 $C_6H_5CH_2$).

The di-*O*-benzyl derivative was debenzylated using hydrogen and a palladium-on-charcoal catalyst to give the 4-acetate, m.p. 127–129°, $[\alpha]_{578}^{22}$ +166° (*c* 0.4, water); lit.[10] $[\alpha]_D^{22}$ +119° (water).

Methyl 2-O-(methylthio)methyl-α-D-glucopyranoside. — A solution (5 ml) of sodium methylsulphinylmethanide in methyl sulphoxide (prepared from 50 ml of methyl sulphoxide and 4 g of sodium hydride as a 50% oil dispersion) was transferred (syringe) to a sealed serum bottle containing methyl 4,6-*O*-benzylidene-3-*O*-(tetrahydropyran-2-yl)-α-D-glucopyranoside[12] (1 g). After 10 min, chloromethyl methyl

sulphide (0.5 ml) was added, and the reaction was allowed to proceed for 30 min at room temperature. Water (40 ml) was then added, the product was extracted with chloroform (3 × 15 ml), and the combined extracts were filtered and evaporated. A solution of the residue in water (10 ml) was evaporated, and chloroform–ethanol was distilled from the residue. The protecting groups were then hydrolysed with ethanolic HCl (6 ml of conc. HCl in 60 ml of ethanol). After neutralisation, the mixture was evaporated, and a solution of the residue in chloroform–ethanol (3:1) was applied to a column (400 mm × 25 mm) of silicic acid which was eluted with the above solvent. The fractions containing the main component were combined and evaporated to yield the syrupy 2-*O*-(methylthio)methyl derivative (0.3 g), $[\alpha]_{578}^{22}$ +11° (*c* 1.1, ethanol). N.m.r. data (60 MHz, chloroform-*d*): τ 7.8 (3 H, CH_3S), 6.6 (3 H, CH_3O).

Anal. Calc. for $C_9H_{18}O_6S$: C, 42.5; H, 7.01; S, 12.6. Found: C, 42.8; H, 7.10; S, 12.2.

Hydrolysis of the foregoing compound (M HCl for 2 h at 50°) afforded methyl α-D-glucopyranoside, and treatment with methyl sulphoxide–sodium methylsulphinylmethanide–methyl iodide[17] followed by acid hydrolysis and conversion of the product into the alditol acetate gave a product which was identical (g.l.c.–m.s.[18]) with the alditol acetate of 3,4,6-tri-*O*-methylglucose.

Methyl 6-O-(methylthio)methyl-α-D-glucopyranoside. — To methyl 6-*O*-trityl-α-D-glucopyranoside (10 g) in *N*,*N*-dimethylformamide (100 ml) was added finely divided sodium hydroxide (20 g). Allyl bromide (20 ml) was added dropwise to the mixture during 20 min, keeping the temperature below 40°. After 2 h, water (500 ml) was added and the solution extracted with chloroform (3 × 100 ml). The combined extract was washed with water (100 ml) and then evaporated. The syrupy residue was treated with 90% trifluoroacetic acid at 50° for 1 h, and the hydrolysate was then evaporated. Since much starting material remained, hydrolysis of the trityl groups was repeated in chloroform (100 ml) saturated with hydrogen chloride. After 1 h, the solution was shaken with aqueous sodium hydrogen carbonate, filtered, and evaporated. The residue was taken up in light petroleum (100 ml), insoluble trityl alcohol was filtered off, and the solution was evaporated. The residue was fractionated on a column (30 mm × 500 mm) of silicic acid, using benzene–methanol (97.5:2.5). The main fraction (1.8 g) was methyl 2,3,4-tri-*O*-allyl-α-D-glucopyranoside, $[\alpha]_{578}^{22}$ +37° (*c* 1.1, ethanol). N.m.r. data (60 MHz, chloroform-*d*): τ 3.7–4.4 (3 H, $-CH_2-CH=CH_2$), 4.5–5.0 (6 H, $-CH_2-CH=CH_2$), 5.25 (d, 1 H, H-1), 6.6 (s, 3 H, OCH_3).

Methylation, removal of the allyl groups, reduction, and acetylation gave a product which was identical with the alditol acetate of 6-*O*-methyl-D-glucose by g.l.c.–m.s.[18].

The triallyl ether (2.0 g) was treated with potassium *tert*-butoxide (5.0 g) in methyl sulphoxide (30 ml) for 2 h under nitrogen on a steam bath. Thereafter, sodium methylsulphinylmethanide in methyl sulphoxide (30 ml, prepared as described above) was added followed by chloromethyl methyl sulphide (1.0 ml). After 1 h, the mixture was diluted with water (30 ml) and extracted with chloroform (3 × 20 ml). The

combined extracts were washed with water (20 ml), filtered, and evaporated. A solution of the residue in ethanol (20 ml) containing conc. HCl (3 ml) was kept for 10 min at room temperature, and the solution was neutralised with sodium hydrogen carbonate, filtered, and evaporated. The crude product was fractionated on a column of silicic acid with chloroform–ethanol (3:1). The main component, the 6-(methylthio) methyl ether, was obtained as a syrup (0.7 g, which failed to crystallise), $[\alpha]_{578}^{22}$ +127° (*c* 0.9, ethanol). N.m.r. data (60 MHz, chloroform-*d*): τ 7.8 (3 H, SCH_3), 6.55 (3 H, OCH_3), 5.25 (3 H, H-1 and OCH_2S).

Anal. Calc. for $C_9H_{18}O_6S$: C, 42.5; H, 7.01; S, 12.6. Found: C, 42.4; H, 6.9; S, 12.7.

Hydrolysis of the foregoing ether (M HCl for 1 h at 50°) afforded methyl α-D-glucopyranoside. Methylation (as described for the 3-ether) and conversion into the alditol acetate gave a product which was identical with the alditol acetate of 2,3,4-tri-*O*-methyl-D-glucose by g.l.c.–m.s.[18].

Partial (methylthio)methylation of methyl α-D-glucopyranoside and its 4,6-O-benzylidene derivative. — The glucosides were treated with chloromethyl methyl sulphide in *N*,*N*-dimethylformamide in the presence of silver oxide overnight at 40°. After work-up, and hydrolysis in the case of the benzylidene compound, the residues were examined by g.l.c.

Oxidation of methyl α-D-glucopyranoside. — The glucoside (5 g) was dissolved in methyl sulphoxide (50 ml), and acetic anhydride (25 ml) was then added. The mixture was stirred at 60° for various times (1–5 h). The reagents were then removed by vacuum distillation, and the products were silylated and examined by g.l.c. In other experiments, the volumes of acetic anhydride were varied from 10 to 50 ml.

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