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Methyl 6-Deoxy-6-methylsulphinyl-D-glucosides

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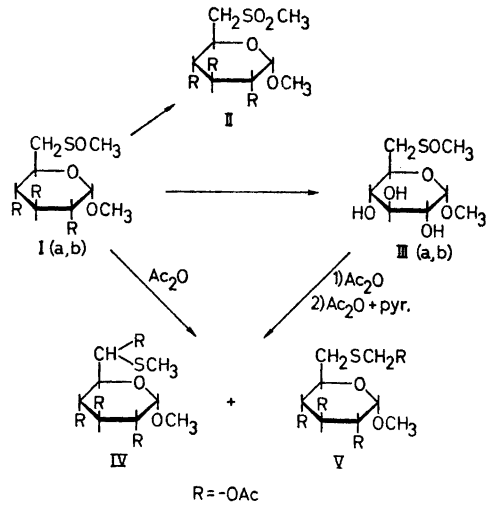
Methyl 2,3,4-tri-*O*-acetyl-6-methylsulphinyl-α- and β-D-glucoside have been prepared and the α-anomer resolved into its two diastereoisomeric forms. Attempts to achieve an intramolecular oxidation-reduction of the deacetylated sulphoxides leading to ketoglucosides were unsuccessful. On treatment with acetic anhydride, the Pummerer reaction took place, giving predominantly α-acetoxylated sulphides. With dicyclohexylcarbodiimide and pyridinium trifluoroacetate a mixture of products was obtained, indicating that largely intermolecular reactions had occurred.

There has recently been an interest in the chemistry of optically active sulphoxides, initiated by the discovery of some naturally occurring members of this group of substances.

The absolute configuration of (+)-*S*-methyl-L-cystein-*S*-oxide has been determined by X-ray crystallography.[1] The relationships between ORD and absolute configuration of methyl-n-alkylsulphoxides have been determined.[2] Different optically active sulphoxides, in which the sulphoxide group is part of a carbohydrate molecule, have also been reported recently.[3,4]

In the present paper, the synthesis and properties of some methyl D-glucopyranoside derivatives having a 6-deoxy-6-methylsulphinyl group are described.

Methyl 2,3,4-tri-*O*-acetyl-6-*S*-methyl-6-thio-α and β-D-glucoside were prepared essentially as described by Madson and coworkers [5] for the β-glucoside. Controlled peracetic acid oxidation of these yielded the corresponding sulphoxides, as diastereoisomeric mixtures; more drastic oxidation yielded the sulphones. The fully acetylated sulphides and sulphones were almost insoluble in water but the sulphoxides were soluble both in water and in polar organic solvents. The α-sulphoxide which gave only one spot on TLC could be resolved into the pure isomers by crystallisations from water. No racemisation occurred when aqueous solutions were heated at 100°. One of the isomers (Ia) gave m.p. 165—166° and $[\alpha]^{22}$ +205 (chloroform), the corresponding values for the other isomer (Ib) were 154—155°, $[\alpha]_{578}^{22}$ +148. Both isomers on oxidation with peracetic acid yielded the sulphone (II). Attempts to resolve the mixture of sulphoxides in the β-series were unsuccessful. The high optical rotation of the



crystalline product obtained, $[\alpha]_{578}^{22}$ +63 (chloroform) coupled with the low values for the corresponding sulphide and sulphone, −7° and −8°, respectively, suggest that it is the pure isomer, having the same absolute configuration in the sulphoxide part of the molecule as the corresponding, high melting α-compound (Ia). Ia and Ib could be deacetylated, clearly without racemisation, and one of the methyl 6-deoxy-6-methylsulphinyl-α-D-glucopyranosides (IIIa) from Ia, crystallised.

The ORD curves of Ia and Ib were determined (Fig. 1). That from Ia shows a positive Cotton effect. No such effect was observed for Ib, probably due to overlap of the contributions to the rotation from the sulphoxide and the carbohydrate part of the molecule. Assuming that these contributions are additive, the contribution of the sulphoxide part should be $([\alpha]_{Ia}-[\alpha]_{Ib})/2$ for Ia (Fig. 2) and $([\alpha]_{Ib}-[\alpha]_{Ia})/2$ for Ib. Methyl-n-alkylsulphoxides showing a positive Cotton effect near 200 mμ are known to have the *S*-configuration.[2]

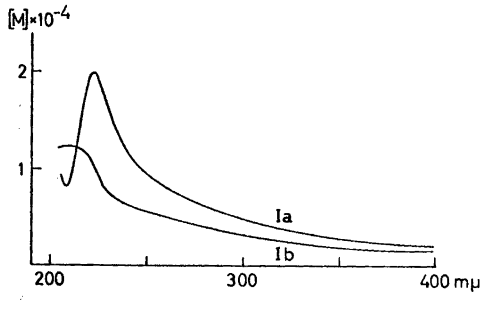


Fig. 1. ORD curves for Ia and Ib.

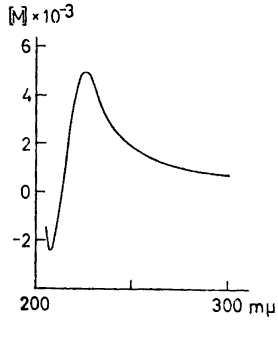


Fig. 2. ORD curve, calculated for the sulphoxide part of Ia.

The Cotton effect sometimes observed near 230 mμ is of the opposite sign.[6] These results, however, do not allow with complete certainty the assigning of absolute configurations to the present substances.

Dimethylsulphoxide together with acetic anhydride [7] or dicyclohexylcarbodiimide [8] has recently become an important reagent for the oxidation of alcohols to ketones under mild conditions. The methyl 6-deoxy-6-methylsulphinyl-D-glucosides seemed to offer possibilities for similar, intramolecular oxidations of certain hydroxyl groups in the glucose residue. Such hydroxyl groups are at C-4 in the normal and that at C-3 in the alternate conformation of this molecule. Sulphoxide IIIa was therefore treated with acetic anhydride at 40°. After consumption of the starting material, TLC indicated the presence of two reaction products. Treatment of this product with Raney-nickel in aqueous ethanol followed by acid hydrolysis, yielded a mixture of glucose and 6-deoxy-glucose. If a ketoglucoside had been obtained by an intramolecular reaction, 6-deoxy-D-galactose and/or 6-deoxy-D-allose should also have been formed by this treatment, but neither of these sugars was detected. Acetylation of the reaction product after treatment of IIIa with acetic anhydride gave a product showing two spots on TLC. The product obtained when the fully acetylated sulphoxide (Ia) was treated with acetic anhydride also gave two spots on TLC indistinguishable from those above. The latter product was separated into two fractions on a silicic acid column. The first fraction, after treatment with Raney-nickel, gave crystalline methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside, indicating that this fraction consisted of one of the isomeric methyl 2,3,4,6-tetra-*O*-acetyl-6-thiomethyl-α-D-glucosides (IV). The second fraction, after treatment with Raney-nickel, deacetylation, and hydrolysis gave a mixture of glucose and 6-deoxyglucose. This fraction is therefore most probably a mixture of the other isomer of IV and methyl 2,3,4-tri-*O*-acetyl-6-*S*-methylacetoxy-6-thio-α-D-glucoside (V), which have not been separated. The configuration at C-6 of the crystalline isomer of IV has not been investigated. IV and V are the expected products from the Pummerer reaction,[9] by which α-acyloxylated sulphides are formed on treatment of sulphoxides with anhydrides of carboxylic acids. This reaction obviously predominates to such an extent in the treatment of III with acetic anhydride that no oxidation of hydroxyl groups can be observed.

Treatment of III with dicyclohexylcarbodiimide and pyridinium trifluoroacetate in dimethylformamide at 20° yielded, in a sluggish reaction, a complicated mixture of products. As, judged from the behaviour on TLC, some contained both carbonyl groups and sulphoxide groups and others neither of these groups. It seems therefore probable that the products are formed by intermolecular reactions. None of the reaction products were formed in good yields and a closer study of the reaction was therefore not attempted.

EXPERIMENTAL

General methods. Melting points are corrected. Paper chromatograms were run on Whatman No. 1 papers, using ethyl acetate-pyridine-water, 8:2:1. TLC was performed on silicic acid using as irrigant: (*a*) toluene-ethyl ether, 1:2, (*b*) ethyl acetate-methanol, 4:1. ORD measurements were kindly carried out by Professor Klyne, London, and were

later reproduced by us, using a "fica" Spectropol 1 instrument. GLC analysis was performed on a Perkin-Elmer Model 881 instrument, with a column packing of 3 % (w/w) ECNSS—M on Gas chrom Q at 220°.

*Methyl 2,3,4-tri-*O*-acetyl-6-*S*-methyl-6-thio-α-*D*-glucoside.* A solution of sodium propylate (from 5 g sodium) in propanol (350 ml) was saturated with methanethiol, methyl 6-*O*-tosyl-α-D-glucopyranoside (70 g) was added and the solution was refluxed under nitrogen for 3.5 h. The sodium tosylate precipitate was removed by filtration of the cooled solution which was then saturated with carbon dioxide. The precipitate thus formed was removed by centrifugation and the solution concentrated to a syrup under reduced pressure. The syrup was dissolved in a mixture of pyridine (100 ml) and acetic anhydride (80 ml), kept at room temperature for 48 h, poured into ice-water (1 l) and the mixture obtained extracted with chloroform. The chloroform solution was washed first with 0.5 M sulphuric acid, then with saturated sodium hydrogen carbonate solution and finally with water, and after drying over sodium sulphate the solution was concentrated under reduced pressure. The remaining syrup was crystallised from ethanol-water, 1:3, to yield the title compound (30 g), m.p. 117—118°, $[\alpha]_{578}^{20}$ +157° (*c* 0.9 chloroform). (Found: C 48.0; H 6.36; S 9.17. $C_{14}H_{22}O_8S$ requires: C 48.0; H 6.34; S 9.15).

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-methylsulphinyl-α-D-glucoside (Ia, Ib).* An equimolar quantity of hydrogen peroxide (about 4.5 ml 34 % hydrogen peroxide) in acetic acid (100 ml), was added over a period of 4 h, to a solution of methyl 2,3,4-tri-*O*-acetyl-6-*S*-methyl-6-thio-α-D-glucoside (15 g) in acetic acid (75 ml). When all the peroxide had been consumed (negative reaction with starch-iodide) the solution was concentrated to a thick syrup, water was added and the mixture kept at 5° overnight. The crystals formed were collected and the mother liquor further worked up to give a total yield of 14.6 g. This product was subjected to fractional crystallisation from water. The m.p. and optical rotation of each fraction were determined, suitable fractions were combined and recrystallised until fractions were obtained, for which these values did not change upon further recrystallisations. The less soluble isomer (Ia, 2.0 g) gave m.p. 165—166° and $[\alpha]_{578}^{22}$ +205° (*c* 0.5 chloroform). (Found: C 45.9; H 6.06; S 8.75. $C_{14}H_{22}O_8S$ requires: C 45.9; H 5.99; S 8.85). The more soluble isomer (Ib 1.5 g) gave m.p. 154—155° and $[\alpha]_{578}^{22}$ +148° (*c* 0.7 chloroform). (Found: C 45.9; H 5.98; S 8.76).

*Methyl 2,3,4-tri-*O*-acetyl-6-methylsulphonyl-α-D-glucoside (II).* A solution of methyl 2,3,4-tri-*O*-acetyl-6-*S*-methyl-6-thio-α-D-glucoside (0.56 g) and 34 % hydrogen peroxide (0.32 ml) in acetic acid (35 ml) was heated at 100° for 30 min and then diluted with water (35 ml). The mixture was cooled and the crystals (0.36 g) which formed were collected and recrystallised from methanol to give pure II, m.p. 216—217°, $[\alpha]_{578}^{22}$ +141° (*c* 0.3 chloroform). (Found: C 44.0; H 5.79; S 8.42. $C_{14}H_{22}O_{10}S$ requires: C 44.0; H 5.78; S 8.39).

Similar oxidation of either Ia or Ib yielded the same product.

Methyl 6-deoxy-6-methylsulphinyl-α-D-glucopyranoside (III). A solution of Ia (0.40 g) and sodium methoxide (from 10 mg sodium) in anhydrous methanol (10 ml), was kept at room temperature for 20 min, treated with Dowex 50 (H^+), concentrated, and recrystallised twice from acetone to yield pure IIIa (0.18 g), m.p. 151—152°, $[\alpha]_{578}^{22}$ 271° (*c* 0.5 water). (Found: C 40.1; H 6.67; S 13.3. $C_8H_{16}PO_6S$ requires: C 40.0; H 6.72; S 13.3). Similar deacetylation of Ib yielded an amorphous product $[\alpha]_{578}^{22}$ +174° (*c* 0.8 water).

*Methyl 2,3,4-tri-*O*-acetyl 6-*S*-methyl-6-thio-β-D-glucoside* was prepared by acetylation of methyl 6-*S*-methyl-6-thio-β-D-glucopyranoside [5] as described above for the α-compound. The substance after recrystallisation from ethanol-water 3:1 melted at 83—84° and gave $[\alpha]_{578}^{22}$ −7° (*c* 0.7 chloroform). (Found: C 47.9; H 6.30; S 9.12. $C_{14}H_{22}O_8S$ requires: C 48.0; H 6.34; S 9.15).

*Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-methylsulphinyl-β-D-glucoside.* Methyl 2,3,4-tri-*O*-acetyl-6-*S*-methyl-6-thio-β-D-glucoside (12 g) was oxidised with an equimolar amount of hydrogen peroxide in acetic acid as described above for the corresponding α-compound. When the reaction was completed the solution was concentrated to a syrup and dissolved in water (25ml). The crystals formed were recrystallised twice from water to give a product (3.5 g) with m.p. 176—178° and $[\alpha]_{578}^{22}$ +63° (*c* 0.8 chloroform). Further crystallisations did not change these values. (Found: C 45.8; H 5.97; S 8.47. $C_{14}H_{22}O_9S$ requires: C 45.9; H 6.06; S 8.75). The mother liquor, $[\alpha]_{578}^{20}$ −5°, did not yield any further crystalline product.

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-methylsulphonyl-β-D-glucoside. A solution of methyl 2,3,4-tri-*O*-acetyl-6-*S*-methyl-6-thio-β-D-glucoside (20 g) and 34 % hydrogen peroxide (1 ml) in acetic acid (20 ml) was heated at 100° for 2 h. Water (40 ml) was added to the solution and the acetic acid neutralised by addition of sodium hydrogen carbonate, when the sulphone precipitated. Recrystallisation from ethanol yielded the pure substance, m.p. 136—137°, $[\alpha]_{578}^{22}$ −8° (*c* 1.1 chloroform). (Found: C 44.1; H 5.80; S 8.40. $C_{14}H_{22}O_{10}S$ requires: C 44.0; H 5.79; S 8.38).

Reaction of Ia with acetic anhydride. A solution of Ia (0.17 g) in acetic anhydride (3 ml) was heated at 100° for 10 h and then concentrated to a syrup under reduced pressure. TLC (solvent system *a*) revealed that the starting material had disappeared and that two new products had been formed. These were separated on a silicic acid column (1.5 × 35 cm), using the same solvent system, to give IV (54 mg) and V (27 mg), eluted in this order. IV was crystallised from ether-light petroleum, m.p. 111—112°, $[\alpha]_{578}^{22}$ +137° (*c* 0.3 chloroform). (Found: C 46.8; H 5.92; S 7.61. $C_{14}H_{22}O_{10}S$ requires: C 46.9; H 5.88; S 7.84).

IV, on treatment with Raney-nickel in boiling 80 % aqueous ethanol for 3 h, gave methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside, m.p. 100—102°, $[\alpha]_{578}^{20}$ *ca.* 120° (*c* 0.1 chloroform, microtube). V, after Raney-nickel reduction, deacetylation, and acid hydrolysis, yielded two sugars, identified as glucose and 6-deoxy-glucose by paper chromatography and by GLC of the derived alditol acetates.

Reaction of IIIa with acetic anhydride. A solution of IIIa (26 mg) in acetic anhydride (5 ml) was heated at 40° and, at intervals, samples were withdrawn for investigation by TLC (solvent system *b*). The consumption of the starting material was observed and two new compounds were seen to be formed. Neither of the products gave a positive reaction with 2,4-dinitrophenylhydrazine, showing the absence of keto-groups.

After 20 h, when all the starting material had disappeared the solution was concentrated to a syrup under reduced pressure. Part of the product was treated with Raney-nickel as described above, and hydrolysed to give a mixture of glucose and 6-deoxy-glucose, as shown by paper chromatography. Another part of the reaction product was acetylated with pyridine-acetic anhydride. TLC of the acetylated product (solvent system *a*) revealed the presence of two components, indistinguishable from those obtained on treatment of Ia with acetic anhydride.

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