SOME OPEN-CHAIN DERIVATIVES OF GLUCOSE AND MANNOSE[1]

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ABSTRACT

The dimethyl thioacetals of D-glucose and D-mannose have been condensed with acetone. Mannose dimethyl thioacetal forms a crystalline 3,4:5,6-di-*O*-isopropylidene derivative while glucose forms a mixture of the crystalline 3,4:5,6-di-*O*-isopropylidene and syrupy 2,3:5,6-di-*O*-isopropylidene isomers. These three di-*O*-isopropylidene dimethyl thioacetals have been converted via crystalline intermediates into the corresponding di-*O*-isopropylidene dimethyl acetals. These derivatives are suitable open-chain compounds for use in Koenigs–Knorr syntheses and provide (*a*) mannose with the C_2 hydroxyl free, (*b*) glucose with the C_2 hydroxyl free, and (*c*) glucose with the C_4 hydroxyl free.

INTRODUCTION

It has already been shown (1) that in Koenigs–Knorr syntheses of disaccharides much greater yields may be obtained by the use of an open-chain hydroxyl reactant rather than the more generally used ring-form derivatives. This is presumably because there is less steric hindrance to reaction in the case of the open-chain compound. In the synthesis of lactose, however (1), the hydroxyl reactant used (syrupy 2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal) contained small amounts of other di-*O*-isopropylidene isomers due to the method of synthesis. This, of course, resulted in an impure product from the Koenigs–Knorr reaction, there being small amounts of other disaccharides present in addition to lactose. In the present work syntheses are described of open-chain derivatives of (*a*) mannose with the C_2 hydroxyl group free, (*b*) glucose with the C_2 hydroxyl group free, and (*c*) glucose with the C_4 hydroxyl group free. All of these have been made via pure crystalline intermediates and should prove very useful in Koenigs–Knorr syntheses.

Schinle (2) condensed D-glucose dibenzyl thioacetal with acetone in the presence of anhydrous copper sulphate and obtained a syrupy mixture of mono- and di-*O*-isopropylidene derivatives. There was at first some doubt as to the structure of the di-*O*-isopropylidene material but Munro and Percival (3) later showed this to be a mixture of 2,3:5,6- and 3,4:5,6-di-*O*-isopropylidene isomers of D-glucose dibenzyl thioacetal. Condensation of D-glucose diethyl thioacetal with acetone (1) gives a syrupy mixture which consists largely of the 2,3:5,6-di-*O*-isopropylidene derivative.

Pacsu and Trister (4) condensed D-mannose dibenzyl thioacetal with acetone and obtained a syrupy di-*O*-isopropylidene derivative which was shown to be mainly the 3,4:5,6 isomer. Condensation of D-mannose diethyl thioacetal with acetone yields a syrupy product which has been shown to be largely the 3,4:5,6-di-*O*-isopropylidene derivative (5).

In the present work condensation of D-mannose dimethyl thioacetal with acetone in the normal way resulted in a crystalline di-*O*-isopropylidene derivative in high yield. This compound was shown by methylation experiments to be 3,4:5,6-di-*O*-isopropylidene-D-mannose dimethyl thioacetal. The compound formed a crystalline benzoate which then was converted into 2-*O*-benzoyl-3,4:5,6-di-*O*-isopropylidene-D-mannose dimethyl acetal using a modification of the method of Wolfrom (6). Debenzoylation yielded 3,4:5,6-di-*O*-isopropylidene-D-mannose dimethyl acetal.

Condensation of D-glucose dimethyl thioacetal with acetone resulted in a syrupy product which partially crystallized on standing. The crystalline portion (19% yield)

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was shown by methylation experiments to be 3,4:5,6-di-*O*-isopropylidene-D-glucose dimethyl thioacetal, while methylation of the syrupy portion (76% yield) showed this to be mainly the 2,3:5,6-di-*O*-isopropylidene isomer. Both isomers formed benzoates. 2-*O*-Benzoyl-3,4:5,6-di-*O*-isopropylidene-D-glucose dimethyl thioacetal was converted into the dimethyl acetal, which on debenzoylation yielded 3,4:5,6-di-*O*-iso-propylidene-D-glucose dimethyl acetal. By a similar route, 2,3:5,6-di-*O*-isopropylidene-D-glucose dimethyl acetal was also formed. 3,4:5,6-Di-*O*-isopropylidene-D-glucose dimethyl acetal formed a crystalline toluene-*p*-sulphonyl derivative.

EXPERIMENTAL

Optical rotations were measured in water at 21°±2° C unless otherwise stated. Solutions were concentrated under reduced pressure at 40° C. The following solvent systems (v/v) were used to separate sugars on paper chromatograms: (A) ethyl acetate:acetic acid:water, 9:2:2; (B) *n*-butanol:ethanol:water, 3:1:1. Sugars were detected using the *p*-anisidine hydrochloride spray (7). Infrared absorptions were measured as solutions in chloroform or as a powder suspended in a potassium bromide pellet on a Perkin–Elmer Model 21 spectrophotometer.

Preparation of Di-O-isopropylidene-D-mannose Dimethyl Thioacetal

Mannose dimethyl thioacetal (22 g) was added to a mixture of dry acetone (400 ml), anhydrous copper sulphate (12 g), and concentrated sulphuric acid (2 ml), and the resulting mixture was shaken at room temperature for 24 hours. The solution was neutralized with concentrated ammonium hydroxide solution and filtered. The precipitate was washed with acetone and filtrate and washings were evaporated to a colorless syrup. This was diluted with chloroform (200 ml) and extracted once with water. The chloroform solution was dried ($MgSO_4$), filtered, and evaporated to a syrup (23 g) which crystallized completely on standing. After recrystallization from light petroleum the material weighed 21.8 g (76% yield) and had a melting point of 58–59° C and $[\alpha]_D$ +5.0° (*c*, 7.6, chloroform). Anal. Calc. for $C_{14}H_{26}O_5S_2$: C, 49.70; H, 7.69; S, 18.94. Found: C, 49.87; H, 7.78; S, 18.99.

Methylation of Di-O-isopropylidene-D-mannose Dimethyl Thioacetal

Di-*O*-isopropylidene-D-mannose dimethyl thioacetal (2 g) was dissolved in methyl iodide (20 ml). Silver oxide (3.6 g) plus Drierite (2 g) were added to the solution which was then shaken in the dark at room temperature for 24 hours. Filtration and subsequent evaporation yielded a brown syrup (1.5 g). Isopropylidene and thioacetal groupings were removed by refluxing for 5 hours with aqueous ethanol (20%) containing hydrochloric acid (5%). The solution was neutralized by passage through a column of Duolite A-4 resin (OH form) and concentrated to a syrup (0.9 g). Chromatographic examination of this (solvent A) showed mainly a spot at R_{mannose} 2.15, with smaller spots corresponding to mannose and arabinose. Part of this syrup (200 mg) was separated by chromatography on sheets of Whatman No. 1 filter paper using solvent B as eluent. Guide strips were cut and sprayed and the fraction R_{mannose} 2.15 was cut out and eluted with acetone. The acetone solution was evaporated to dryness. The residue was diluted with a little ethanol, warmed with charcoal, and filtered. Evaporation of the filtrate yielded a syrup (77 mg) which crystallized on dilution with a little ethanol.

After recrystallization from methanol/ether the material had a melting point of 134–136° C and $[\alpha]_D$ +5.2° (constant) (*c*, 1.2). It formed a phenylhydrazone which had a melting point of 161–163° C and $[\alpha]$ −60.5° (constant) (*c*, 0.38, pyridine). Authentic

2-*O*-methyl-α-D-mannose has a melting point of 136–137° C and $[\alpha]_D$ $+7.0° \rightarrow +4.5°$ (constant) and forms a phenylhydrazone with a melting point of 163° C and $[\alpha]_D$ $-49.1° \rightarrow -60.7°$ (pyridine, constant) (4).

*2-O-Benzoyl-di-O-isopropylidene-*D*-mannose Dimethyl Thioacetal*

Di-*O*-isopropylidene-D-mannose dimethyl thioacetal (17.2 g) was dissolved in dry pyridine (180 ml). The solution was stirred mechanically and cooled externally. The temperature was kept at −5° C while a solution of benzoyl chloride (18 g) in pyridine (30 ml) was added dropwise. Cooling was continued at −5° C (30 minutes) and then at 0° C (7 hours), and the solution was finally stored at room temperature (14 hours). The product was precipitated by slowly pouring the solution into ice plus water (700 ml). After 30 minutes at room temperature, the crude crystalline material was filtered and washed with water. It was recrystallized from methanol and weighed 19.3 g (86% yield). It had a melting point of 83–84° C and $[\alpha]_D$ +7.8° (*c*, 1.0, methanol). Anal. Calc. for $C_{21}H_{30}O_6S_2$: S, 14.48. Found: S, 14.68.

*2-O-Benzoyl-di-O-isopropylidene-*D*-mannose Dimethyl Acetal* (ref. 6)

2-*O*-Benzoyl-di-*O*-isopropylidene-D-mannose dimethyl thioacetal (10 g) was dissolved in dry methanol (300 ml). Cadmium carbonate (87 g) was added to the solution and a solution of mercuric chloride (87 g) in methanol (100 ml) was then added portionwise with vigorous stirring at room temperature. After completion of the addition (5 hours), stirring was continued for a further 15 hours at room temperature, and the solution was then boiled under reflux for 15 minutes. The cooled solution was filtered through a Celite pad and the precipitate was washed with methanol. Filtrate and washings were concentrated to ca. 150 ml and this solution was poured into 200 ml each of chloroform and water. The chloroform layer was extracted with water until chloride-free, dried ($MgSO_4$), filtered, and evaporated to a syrup (7.5 g) which crystallized on standing overnight. Recrystallization from methanol yielded 6.5 g of product (70%). After further recrystallizations from methanol and from light petroleum the material had a melting point of 73.5–74° C and $[\alpha]_D$ −1.6° (*c*, 3.5, chloroform). Anal. Calc. for $C_{21}H_{30}O_8$: C, 61.43; H, 7.37. Found: C, 61.35; H, 7.53.

*3,4:5,6-Di-O-isopropylidene-*D*-mannose Dimethyl Acetal*

2-*O*-Benzoyl-di-*O*-isopropylidene-D-mannose dimethyl acetal (0.67 g) was dissolved in 50% aqueous ethanol (30 ml) containing potassium hydroxide (0.12 g) and the solution was warmed at 70° C (4 hours). The solution was concentrated to a small volume to remove ethanol and then extracted with chloroform. The chloroform solution was extracted three times with water, dried ($MgSO_4$), filtered, and evaporated to a syrup (0.49 g, 98%). Infrared analysis showed no absorption for carbonyl group (1700–1750 cm^{-1}). The material had $[\alpha]_D$ −1.3° (*c*, 1.6, methanol).

*Preparation of a Mixture of Di-O-isopropylidene-*D*-glucose Dimethyl Thioacetals*

Glucose dimethyl thioacetal (20 g) was added to a mixture of dry acetone (400 ml), anhydrous copper sulphate (12 g), and concentrated sulphuric acid (2 ml) and the resulting solution was shaken at room temperature for 24 hours. The solution was neutralized with concentrated ammonium hydroxide solution, filtered, and the precipitate was washed with acetone. Filtrate and washings were evaporated to a syrup which was diluted with chloroform (150 ml) and extracted once with water. The chloroform solution was dried ($MgSO_4$), filtered, and evaporated to a syrup (26 g). This partially crystallized on standing. The mixture of crystals and syrup was diluted with light petroleum and refrigerated. Subsequent filtration yielded 3.1 g crystalline material. Concentration of the filtrate followed by seeding produced a further 2.0 g crystals; total yield of crystalline product 5.1 g (19%). This was recrystallized from light petroleum and had a melting point of 92–94° C and $[\alpha]_D$ $-1.0°$ (*c*, 9.8, chloroform). Anal. Calc. for $C_{14}H_{26}O_5S_2$: C, 49.70; H, 7.69; S, 18.94. Found: C, 49.64; H, 7.52; S, 18.86.

When all the above crystalline material had been removed from the reaction product there remained 20.6 g (76%) syrup which could not be crystallized. It had $[\alpha]_D$ $-92.4°$ (*c*, 1.2, chloroform). Anal. Calc. for $C_{14}H_{26}O_5S_2$: S, 18.94. Found: S, 18.72, 18.64.

*Methylation of Crystalline Di-O-isopropylidene-*D*-glucose Dimethyl Thioacetal*

Crystalline di-*O*-isopropylidene-D-glucose dimethyl thioacetal (0.93 g) was dissolved in dry tetrahydrofuran (20 ml). Small pieces of clean sodium were then added to the solution until no further reaction took place. Methyl iodide (0.5 ml) was added to the solution which was stored in a darkened, stoppered flask at room temperature for 24 hours, further small quantities of sodium and methyl iodide being added at intervals. The solution was filtered and the precipitate was washed with tetrahydrofuran. Filtrate and washings were evaporated to dryness and the residue was dissolved in chloroform and washed with water until free from iodide. The solution was dried (Na_2SO_4), filtered, and evaporated to a syrup (0.91 g). Infrared examination of this indicated only a very small amount of free hydroxyl group present. Thioacetal groupings were removed by the method of Wolfrom (8), using mercuric chloride in the presence of cadmium carbonate in aqueous ethanol and isopropylidene groupings were subsequently hydrolyzed by warming the product in sulphuric acid (0.5 *N*) solution. The solution was deionized by passage through a column of Amberlite IR-120 (H form) and Duolite A-4 (OH form) resins in series and the neutral eluate was concentrated to a syrup (0.50 g). Chromatography of this (solvent A) showed mainly a spot at R_{glucose} 2.61, with much smaller spots at R_{glucose} 1.01, 3.92, and 7.30, these latter two being presumably due to unhydrolyzed isopropylidene derivatives.

The syrup was stored in a stoppered flask at room temperature and after 6 weeks it was found that a crystal nucleus had developed. When this was mixed with the syrup the mass crystallized. Part of the crude material (200 mg) was transferred to a porous tile and the crystals were cleaned by rapidly washing them with methanol. This material (110 mg) was recrystallized from methanol/ether. Chromatography in solvent A showed a single spot at R_{glucose} 2.61. It had a melting point of 156–158° C and $[\alpha]_D$ $+26.3° \rightarrow +67.8°$ (constant) (*c*, 2.3). It formed a tetrabenzoate which had a melting point of 167°–168° C and $[\alpha]_D$ $-8.4°$ (*c*, 0.6, chloroform). 2-*O*-Methyl-β-D-glucose has a melting point of 157–159° C and $[\alpha]_D$ $+12.0 \rightarrow +66.0$ (constant) (9) and forms a tetrabenzoate with a melting point of 169°–170° C and $[\alpha]_D$ $-6.2°$ (10). Under drastic conditions the material formed an osazone whose infrared spectrum was identical with that of authentic D-glucosazone.

*Methylation of Syrupy Di-O-isopropylidene-*D*-glucose Dimethyl Thioacetal*

Syrupy di-*O*-isopropylidene-D-glucose dimethyl thioacetal (5 g) was methylated using silver oxide and methyl iodide in the same way as described for di-*O*-isopropylidene-D-mannose dimethyl thioacetal. After removal of thioacetal and isopropylidene groupings and deionization, a clear syrup (1.9 g) was obtained. Chromatography of this (solvent A) showed spots at R_{glucose} 1.00 and 2.56 with much smaller spots at 2.65, 3.40, and 4.45. The spot at R_{glucose} 2.65 was presumably due to 2-*O*-methyl-D-glucose, formed from traces of the 3,4:5,6-di-*O*-isopropylidene isomer not removed by crystallization.

The spots at 3.40 and 4.45 were due either to unhydrolyzed isopropylidene residues or to methylation of mono-isopropylidene materials. Part of the syrup (1.4 g) was separated by chromatography on a column of powdered cellulose using solvent A as eluent. A fraction (0.73 g) was collected which showed a single spot at R_{glucose} 2.56 in solvent A. The material had $[\alpha]_D$ $+52.1°$ (*c*, 2.4). It did not crystallize. Authentic 4-*O*-methyl-D-glucose has $[\alpha]_D$ $+53°$ (3). It formed an osazone which had a melting point of 157–159° C and $[\alpha]_D$ $-17.4°$ (constant) (*c*, 0.6, pyridine). Anal. Calc. for $C_{19}H_{24}O_4N_4$: OMe, 8.35. Found: OMe, 8.15. 4-*O*-Methyl-D-glucose phenylosazone has a melting point of 158–160° C and $[\alpha]_D$ $-32.6° \rightarrow -15.5°$ (constant) (3).

Part of the syrup was converted into 4-*O*-methyl-D-glucose methyl glucoside by refluxing it for 3 hours with hydrochloric acid in methanol (2%). The solution was neutralized (Ag_2CO_3) and filtered, and the filtrate was evaporated to a clear syrup. This crystallized after it was diluted with a drop of ethyl acetate and nucleated with authentic 4-*O*-methyl-D-glucose methyl-α-D-glucoside. The material was washed on a porous tile with ethyl acetate and dried. It showed an infrared spectrum identical with that of 4-*O*-methyl-D-glucose methyl-α-D-glucoside.

*2-O-Benzoyl-di-O-isopropylidene-*D*-glucose Dimethyl Thioacetal*

3,4:5,6-Di-*O*-isopropylidene-D-glucose dimethyl thioacetal (3.1 g) was dissolved in dry pyridine (30 ml). The solution was stirred mechanically and cooled to −5° C while a solution of benzoyl chloride (2 g) in pyridine (10 ml) was added dropwise, after which the temperature was kept at −5° C (30 minutes) and then at 0° C (4 hours). The solution was finally stored at room temperature (20 hours). It was poured slowly into ice plus water (200 ml) when the product separated as an oil which did not crystallize on standing. The solution was extracted with chloroform (4×40 ml) and the combined extracts were washed successively with solutions of dilute sulphuric acid, sodium bicarbonate, and water. The solution was dried ($MgSO_4$), filtered, and evaporated to a syrup (3.9 g). This proved difficult to crystallize. However, seed crystals were obtained by dissolving part of the syrup in methanol and cooling this in an acetone/Dry Ice bath, and at the same time scratching the side of the vessel with a glass rod. The syrup crystallized completely on subsequent seeding. Recrystallization from methanol yielded 3.8 g (93%). The material had a melting point of 85–86° C and $[\alpha]_D$ $-15.5°$ (*c*, 1.0, methanol). Anal. Calc. for $C_{21}H_{30}O_6S_2$: S, 14.48. Found: S, 14.66.

*2-O-Benzoyl-di-O-isopropylidene-*D*-glucose Dimethyl Acetal*

2-*O*-Benzoyl-di-*O*-isopropylidene-D-glucose dimethyl thioacetal (3 g) was converted to the acetal using the method described above for the preparation of 2-*O*-benzoyl-di-*O*-isopropylidene-D-mannose dimethyl acetal. A syrup (2.7 g) was obtained which crystallized on standing. Recrystallization from aqueous methanol yielded 2.5 g material (90%). After further recrystallizations from methanol and from light petroleum it had a melting point of 71–72.5° C and $[\alpha]_D$ $-40.8°$ (*c*, 2.0, chloroform). Anal. Calc. for $C_{21}H_{30}O_8$: C, 61.43; H, 7.37. Found: C, 61.39; H, 7.34.

*3,4:5,6-Di-O-isopropylidene-*D*-glucose Dimethyl Acetal*

2-*O*-Benzoyl-di-*O*-isopropylidene-D-glucose dimethyl acetal (1.11 g) was dissolved in 50% aqueous ethanol (40 ml) containing potassium hydroxide (0.17 g) and the solution was warmed at 70° C (5 hours). The product was worked up as described above for the corresponding mannose derivative. A syrup (0.77 g, 93%) was obtained which crystallized on standing in a vacuum desiccator. After recrystallization from light petroleum it had a melting point of 88–89° C and $[\alpha]_D$ $-9.0°$ (*c*, 4.2, methanol). Infrared analysis showed no absorption for the carbonyl group (1700–1750 cm^{-1}).

*2-O-Tosyl-di-O-isopropylidene-*D*-glucose Dimethyl Acetal*

3,4:5,6-Di-*O*-isopropylidene-D-glucose dimethyl acetal (0.113 g) was dissolved in dry pyridine (1 ml) and toluene *p*-sulphonyl chloride (0.098 g) was added to the solution. Moisture was excluded from the solution, which was kept at room temperature (18 hours) and then warmed to 70° C on a water bath (30 minutes). The product was isolated in the usual way, a syrup (0.116 g, 68%) being obtained which crystallized immediately. After recrystallization from light petroleum the material had a melting point of 109–111° C and $[\alpha]_D$ $+10.4°$ (*c*, 2.5, chloroform). Anal. Calc. for $C_{21}H_{32}O_9S$: S, 6.96. Found: S, 6.82.

*Benzoylation of Syrupy Di-O-isopropylidene-*D*-glucose Dimethyl Thioacetal*

Syrupy di-*O*-isopropylidene-D-glucose dimethyl thioacetal (14.3 g) was benzoylated as described above. A clear syrup (21 g) was obtained which showed no absorption for hydroxyl group (3500–3600 cm^{-1}) on infrared analysis. It had $[\alpha]_D$ $+34.0°$ (*c*, 1.05, methanol).

*4-O-Benzoyl-di-O-isopropylidene-*D*-glucose Dimethyl Acetal*

Syrupy 4-*O*-benzoyl-di-*O*-isopropylidene-D-glucose dimethyl thioacetal (9.3 g) was converted to the dimethyl acetal in the usual way. A syrup (7.7 g) was obtained which crystallized on standing. Recrystallization from methanol yielded 4.9 g (56%). After further recrystallization from light petroleum the material had a melting point of 101.5–102° C and $[\alpha]_D$ $-5.8°$ (*c*, 1.85, chloroform). Anal. Calc. for $C_{21}H_{30}O_8$: C, 61.43; H, 7.35. Found: C, 61.47; H, 7.38.

*2,3:5,6-Di-O-isopropylidene-*D*-glucose Dimethyl Acetal*

4-*O*-Benzoyl-di-*O*-isopropylidene-D-glucose dimethyl acetal (2.73 g) was dissolved in 50% aqueous methanol (100 ml) containing sodium hydroxide (0.27 g) and the solution was warmed at 70° C (4 hours). Following the usual method of isolation a syrup (1.92 g, 95%) was obtained. This had $[\alpha]_D$ $-15.9°$ (*c*, 3.5, methanol). Infrared analysis showed no absorption for carbonyl peak.

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