THE PREPARATION OF SOME MERCAPTO MONOSACCHARIDES[1]

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ABSTRACT

Methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside and methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside have been prepared by the reaction of sodium benzylmercaptide with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside respectively.

These two thio ethers were successfully reduced by sodium in liquid ammonia to methyl 2-deoxy-2-mercapto-α-D-altropyranoside and methyl 3-deoxy-3-mercapto-α-D-altropyranoside. An attempted replacement of the tosyl group in 1,2;5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose by benzyl mercaptan was unsuccessful.

INTRODUCTION

The preparation of monosaccharides in which an oxygen atom has been replaced by a sulphur atom has received renewed attention in recent years, primarily due to the fact that these compounds provide a route to the synthesis of deoxy sugars. A review by Raymond covering the literature on thio sugars to 1944 (1) refers to the preparation of a number of thioglycosides and ω-deoxy-ω-alkylthio-hexoses and -pentoses. The only monosaccharide mentioned which contained a free mercapto group on a carbon atom other than the anomeric carbon (2–4) was a substance described as "3-deoxy-3-mercapto-D-glucose" obtained by Freudenberg and Wolf (5) in their attempt to apply the Tschugaeff reaction (6) to the preparation of an unsaturated monosaccharide.

Since 1944, a considerable amount of work has appeared in this area, but primarily concerning the preparation of the thioglycosides and thio ethers of monosaccharides (7–12). A few reports have been made of the preparation of monosaccharides with a free mercapto group. An improved synthesis of 1-thio-D-glucose by the reaction of hydrogen sulphide with 1,2-anhydro-D-glucose and its 3,4,6-tri-O-acetate in dimethylformamide has been described (13). The reduction with lithium aluminum hydride of 5,6-dideoxy-5,6-epithio-1,2-O-isopropylidene-β-L-idose has yielded 5,6-dideoxy-5-mercapto-L-idose (14). There has also been reported the preparation of 5,6-dideoxy-1,2-O-isopropylidene-5,6-(thiocarbonyldithio)-β-L-idose, a compound which, no doubt, can be reduced readily to 5,6-dideoxy-1,2-O-isopropylidene-5,6-dimercapto-β-L-idose with lithium aluminum hydride in accordance with similar reductions carried out on the trithiocarbonates of some hexitols (14, 15).

Since a number of mercapto monosaccharides were required in this laboratory, a program for their preparation was begun. This paper presents some results obtained in this direction.

RESULTS AND DISCUSSION

The debenzylation of S-benzylcysteine has been accomplished by the use of sodium in liquid ammonia (16) and this technique has been successfully applied in this laboratory to the preparation of mercaptoindoles (17). These results suggested that mercapto monosaccharides might be prepared by the reaction of benzyl mercaptan with suitable anhydro monosaccharides followed by the reductive cleavage of the resulting benzylthio ethers with sodium in liquid ammonia. This did indeed prove to be the case.

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When methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (18, 19) was treated with sodium benzylmercaptide in methanol as solvent an almost quantitive yield of crystalline methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside was obtained. Similarly, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (19), when treated with sodium benzylmercaptide, gave crystalline methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside. The direction of opening of the anhydro ring agreed with observations recorded in the literature (7–9) and with the requirement that ring opening proceed preferentially via the more stable trans diaxial transition state according to Furst and Plattner's rule (20, 21). The position of the benzylthio group was verified by desulphurization of the benzylthio ethers with Raney nickel (9, 22) to produce the corresponding deoxy monosaccharides. These were compared with authentic specimens prepared by the reduction with lithium aluminum hydride of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (23).

When treated with sodium in liquid ammonia, methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside gave a good yield of solid methyl 2-deoxy-2-mercapto-α-D-altropyranoside which readily crystallized from alcohol. Reduction of methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside under the same conditions gave a colorless syrup which solidified on trituration with water. Attempts at purification by direct crystallization from a wide variety of solvents and solvent pairs were abortive. However, chromatography of the crude mercapto sugar on neutral alumina yielded bibenzyl in the initial fractions followed by a viscous colorless syrup which again readily solidified on trituration with water. Crystallization of this solid from ethyl propionate was slow, but large prismatic crystals were produced whose analysis agreed with the formulation of this substance as methyl 3-deoxy-3-mercapto-α-D-altropyranoside. It is thus seen that sodium in liquid ammonia removes not only the benzyl group from the sulphur atom but also provides a convenient route for the removal of the benzylidene group without affecting the glycosidic linkage. Simultaneous cleavage of the benzylidene group and desulphurization have been obtained by the use of a large excess of Raney nickel (8, 9). However, when no more than a fourfold excess of Raney nickel was employed, reductive desulphurization occurred unaccompanied by removal of the benzylidene group (9). Since 1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (24) was quite unaffected by sodium in liquid ammonia, this reductive cleavage may be specific for the benzylidene group.

Hydrolysis of methyl 2-deoxy-2-mercapto-α-D-altropyranoside and the 3-mercapto isomer with *N* sulphuric acid gave yellow solids which charred on heating but would not melt. Infrared spectra showed the substances to be quite impure and afforded no information as to their structures. Neither they, nor the products obtained from attempts to prepare their acetyl, benzoyl, or 3,5-dinitrobenzoyl derivatives, could be obtained in crystalline form.

Freudenberg and Brauns (25) reported that treatment of 1,2;5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose with hydrazine replaced the 3-tosyloxy group by the hydrazine moiety. The resulting compound has recently been shown unequivocally to have the allo configuration (26). Although Reichstein *et al.* (9, 27) have shown that both sodium methoxide and sodium methylmercaptide did not replace the tosyloxy group but merely caused detosylation, it was thought that the greater nucleophilic character of the benzylmercaptide might induce a reaction analogous to that obtained by Freudenberg and Brauns and thus lead to the formation of 3-deoxy-3-mercapto-D-allose. However, here again, reaction of sodium benzylmercaptide with 1,2;5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose resulted only in detosylation with retention of configuration about C_3.

EXPERIMENTAL

All melting points are uncorrected.

Methyl 4,6-O-Benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside

Sodium (2 g) was dissolved in methanol (40 ml) containing benzyl mercaptan (2.6 g, 0.022 mole) (28). Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (5 g, 0.019 mole) (18, 19) was added and the mixture then refluxed under nitrogen for 2 hours. The solution, left standing overnight at room temperature, deposited crystalline material which was removed and recrystallized from ethanol. The methanolic mother liquor was diluted with water and extracted with chloroform. The chloroform extract was washed with water until neutral and dried with sodium sulphate. Elimination of the solvent gave a further quantity of crystalline material. Total yield of methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside was 7 g (95%). M.p., 136–137° C; $[\alpha]_D^{CHCl_3}$ at 22°, +90.6° (c = 1.668). Anal. Calc. for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23; S, 8.25. Found: C, 64.97; H, 6.22; S, 8.30.

Methyl 4,6-O-Benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (19) was treated in a manner similar to that given the allo isomer with the exception that the reaction time was extended to 15 hours. Crystallization did not occur when the solution stood at room temperature overnight; therefore the reaction mixture was diluted with water and extracted with chloroform. The chloroform solution was washed until neutral and then dried with sodium sulphate. Removal of the solvent left a viscous syrup which solidified after trituration with ether. Recrystallization from methanol afforded colorless crystals. M.p., 105–106° C; yield, 88%; $[\alpha]_D^{CHCl_3}$ at 22°, −112°. (c = 1.436). Anal. Calc. for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23; S, 8.25. Found: C, 64.90; H, 6.44; S, 8.18.

Methyl 2-Deoxy-2-mercapto-α-D-altropyranoside

Finely powdered methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside (5 g) was added to liquid ammonia (150 ml) in an Erlenmeyer flask cooled in dry ice. Small pieces of sodium metal were added to the solution, constantly stirred by a magnetic stirrer, until the blue color persisted for 10 minutes. At the end of this time, ammonium chloride was added until the blue color was discharged, whereupon the ammonia was allowed to evaporate, under a blanket of nitrogen to prevent oxidation of the mercaptan. The residue was extracted with chloroform (N_2) which, upon evaporation, left a colorless solid possessing a sweetish odor. Yield of crude product, 90%; m.p., 140–145° C. Recrystallization from ethanol, in which the compound was found to be quite soluble, yielded small colorless needles, m.p., 145–146° C; $[\alpha]_D^{CHCl_3}$, +95.2° (c = 0.9352). Anal. Calc. for $C_7H_{14}O_5S$: C, 39.99; H, 6.71; S, 15.25. Found: C, 39.95; H, 6.71; S, 15.14.

Methyl 3-Deoxy-3-mercapto-α-D-altropyranoside

Finely powdered methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside was subjected to a sodium-in-liquid-ammonia reduction under the same conditions as outlined above for the 2-isomer. On removal of the solvent from the chloroform extract, a colorless viscous syrup remained which solidified on trituration with water. A solution of this material in a benzene–methanol mixture (5:1) was passed through a column of neutral alumina prepared in benzene. The initial fractions contained bibenzyl and were discarded. Subsequent fractions yielded a colorless viscous syrup which solidified when triturated with water.

Several recrystallizations from ethyl propionate gave pure methyl 3-deoxy-3-mercapto-α-D-altropyranoside as large prismatic crystals. M.p., 85–87° C; $[\alpha]_D^{H_2O}$, +68.6°

(c = 1.428). Anal. Calc. for $C_7H_{14}O_5S$: C, 39.99; H, 6.71; S, 15.25. Found: C, 40.08; H, 6.80; S, 15.44.

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