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Synthesis of Some Acetylated Alkyl 1-Thio-α-D-glucopyranosides

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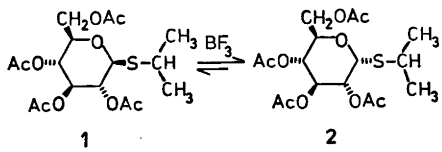
Some alkyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranosides have been prepared by anomerization of the corresponding β-D-glucopyranosides, using boron trifluoride as catalyst.

1-Thioglycosides inhibit enzymic hydrolysis of the corresponding *O*-glycosides and, when attached to a suitable matrix, may be used for the purification of glycosidases by affinity chromatography. Alkyl *trans*-1-thioglycopyranosides (generally the β-glycosides) may be prepared by reaction between a glycosyl halide and a thiol [1] or by S-alkylation of the corresponding 1-thioglycopyranose.[2] Although some alkyl *cis*-1-thioglycopyranosides have been reported, there is no general method for the synthesis of this group of substances.

Acetylated alkyl glycopyranosides are anomerized on treatment with a strong acid, such as sulfuric acid.[3] titanium tetrachloride [4] or boron trifluoride.[5] Because of the anomeric effect,[6,7] the isomer with an axial aglycone in the most stable chair form predominates, the proportion between the two anomers being approximately 9:1 at equilibrium. We have now investigated the analogous anomerization of some acetylated alkyl 1-thio-β-D-glucopyranosides.

The tetraacetates of ethyl, isopropyl and 1-heptyl 1-thio-β-D-glucopyranoside were prepared by alkylation of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside. Preliminary experiments, in which the isopropyl derivative (*1*) was treated with either sulfuric acid in acetic anhydride – acetic acid, titanium tetrachloride in chloroform or boron trifluoride in dichloromethane, demonstrated that anomerization was affected by all three reagents. The reactions with sulfuric acid and titanium tetrachloride were accompanied by discoloration and degradation. With boron trifluoride in dichloromethane at room temperature, equilibrium could be established without noticeable degradation. At equilibrium, the ratio of α- (*2*) to β-glucosides (*1*) was 7:3, and they were readily separated by chromatography on silica gel. The fully acetylated ethyl, isopropyl and 1-heptyl 1-thio-α-*D*-glucopyranosides were consequently prepared by anomerization of the corresponding β-glucosides with boron trifluoride. Separation of all 3 pairs of anomers was achieved by chromatography on silica gel and the α to β ratio was approximately 7:3.

The anomerization reaction for acetylated alkyl O-glucopyranosides [8] was slower than for the corresponding galactosides, xylosides and arabinosides. The same should most probably be valid for 1-thioglycosides, and it should consequently be possible to anomerize acetylated alkyl 1-thioglycopyranosides of all common sugars.



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EXPERIMENTAL

General methods. Concentrations were performed under reduced pressure. Precoated plates with silica gel F_{254} (Merck) and silica gel (230 – 400 mesh, Merck) were used for TLC and for column chromatography, respectively. Light petroleum refers to a fraction with b.p. 60 – 71 °C. ^{1}H NMR spectra were recorded with a Varian A-60 A instrument and optical

rotations determined in chloroform, $c = 1$, with a Perkin-Elmer 141 polarimeter. Melting points are corrected.

Alkyl 2,3,4,6-tetra-O-*acetyl-1-thio-β*-D-*glucopyranosides.* 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-thiopseudourea hydrobromide [9,10] (4 mmol) in water (25 ml) was treated with potassium carbonate (6 mmol) in water (10 ml) at room temperature for 30 min. The mixture was then extracted with chloroform (3 × 20 ml), the chloroform solution washed with water (2 × 25 ml), dried ($CaCl_2$) and concentrated to a syrup. The resulting 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose (~4 mmol) was dissolved in acetone (4 ml) and M aqueous potassium carbonate (4 ml) was added. The alkyl halide, ethyl bromide, isopropyl iodide or 1-heptyl bromide (4.4 mmol) was added and the mixture stirred, at room temterature, until all starting material had reacted (30 – 60 min, TLC, light petroleum – ethyl acetate, 3:2). The mixture was poured into ice-water (60 ml) and extracted with chloroform (3 × 25 ml). The chloroform solution was washed with water (2 × 25 ml), dried ($CaCl_2$) and concentrated to a syrup. This product was purified by chromatography on a silica gel column (4 × 30 cm), irrigated with light petroleum-ethyl acetate (3:2). The yield of crystalline 1-thio-β-D-glucopyranoside was approximately 50 %.

Ethyl 2,3,4,6-tetra-O-*acetyl-1-thio-β*-D-*glucopyranoside* crystallized from ethanol and showed m.p. 81 – 82 °C, $[\alpha]_{578}^{22}$ −27°, in good agreement with published values.[2,11]

Isopropyl 2,3,4,6-tetra-O-*acetyl-1-thio-β*-D-*glucopyranoside* crystallized from ethanol and showed m.p. 110 – 111 °C, $[\alpha]_{578}^{22}$ −22°.

1-Heptyl 2,3,4,6-tetra-O-*acetyl-1-thio-β*-D-*glucopyranoside* crystallized from hexane and showed m.p. 69 – 70 °C, $[\alpha]_{558}^{20}$ −35°.

NMR spectra of the three 1-thio-β-D-glucopyranosides were in agreement with the proposed structures and almost superimposable, except for the signals from the protons in the aglycones.

Anomerization of alkyl 2,3,4,6-tetra-O-*acetyl-1-thio-β*-D-*glucopyranosides.* A solution of the fully acetylated alkyl 1-thio-β-D-glucopyranoside (1 mmol) in dry dichloromethane (5 ml) was saturated with boron trifluoride. The solution was kept at room temperature and the reaction followed by TLC (light petroleum-ethyl acetate, 3:2). After 2 – 3 h, when equilibrium was established, the solution was washed with M sodium hydrogen carbonate (5 ml), water (2 × 5 ml) dried ($CaCl_2$) and concentrated. The product was fractionated on a silica gel column (30 × 3 cm) irrigated with light petroleum – ethyl acetate (3:2). The yield of pure α-anomer, which was eluted first, was 60 – 65 %, the recovery of the β-anomer was 20 – 25 %.

Ethyl 2,3,4,6-tetra-O-*acetyl-1-thio-α*-D-*glucopyranoside* crystallized from ethanol and showed m.p. 96 – 97 °C, $[\alpha]_{578}^{20}$ +204°, in good agreement with published values.[12]

Isopropyl 2,3,4,6-tetra-O-*acetyl-1-thio-α*-D-*glucopyranoside* crystallized from ethanol and showed m.p. 69 – 70 °C, $[\alpha]_{578}^{20}$ +204°. (Found: C 50.1; H 6.3; S 7.6. $C_{17}H_{69}O_2S$ requires: C 50.2; H 6.4; S 7.9.)

1-Heptyl 2,3,4,6-tetra-O-*acetyl-1-thio-α*-D-*glucopyranoside* crystallized from hexane and showed m.p. 40 – 41 °C, $[\alpha]_{578}^{20}$ +181°.

NMR spectra of the three 1-thio-α-D-glucopyranosides were in agreement with the proposed structures and almost superimposable, except for the signals from the protons in their aglycones.

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