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A POTENTIALLY VERSATILE SYNTHESIS OF GLYCOSIDES

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ABSTRACT

Phenyl 1-thio-D-glucopyranosides in the presence of mercury(II) salts are readily solvolysed to give alkyl D-glucopyranosides with inverted anomeric configuration. Methanolyses of the β and α anomers afford the methyl α- and β-glycosides which were isolated in yields of 74 and 87%, respectively; n.m.r. examinations indicated that, whereas the β-glycoside was produced stereospecifically, the α-glycoside was formed together with $\sim$6% of its β isomer. The approach can be extended to the synthesis of complex glycosides (the α anomers of which are of special interest) as was illustrated by the preparation of cholestanyl and 1-naphthyl α-D-glucopyranoside and a disaccharide derivative.

INTRODUCTION

Although a wide range of reactions has been applied to the synthesis of glycosides[1], there remains a need for appreciable developments before systems are found which can be utilised readily and efficiently in the specific preparation of any required compound. Ideally, readily available and stable glycosylating agents are required which can be made to react efficiently under mild conditions with equimolar proportions of the compounds to be glycosylated to give, specifically, products with desired ring-size and anomeric configuration.

The great majority of the reactions which have been applied utilise the principle of nucleophilic displacement of leaving groups from the anomeric centre of the glycosylating agent, and, most frequently, these leaving groups are either halide ions or co-ordinated (usually protonated) oxygen functions. Substituted glycosyl halides have been applied with great success (most notably in the Koenigs–Knorr reaction) but these compounds are normally less stable on storage than is desirable, and are limited in their use because many isomeric forms are not readily available and also because of their mode of action. In particular, their use is normally confined to the preparation of 1,2-*trans*-related products. On the other hand, the acidic conditions required for the second type of reaction are specifically those which are likely to preclude the specific production of one glycoside.

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In an attempt to develop a synthetic method free from deficiencies of these types, we have been attracted to the use of the readily available and stable 1-thioglycosides and their possible activation as glycosylating agents by utilisation of the well-known, high affinity which mercury(II) has for sulphide sulphur, the former being a "soft" acid and the latter a "soft" base[2]. Although, to our knowledge, this approach has not been adopted systematically before, several reports in the literature suggest its feasibility. Thus, for example, 1-thioaldofuranosides undergo hydrolysis in aqueous solution in the presence of mercury(II) salts[3], and acetylated aldose diethyl dithioacetals are converted into dimethyl analogues in methanol under similar conditions[4]. Furthermore, ethyl 1-thio-α- and -β-D-glucopyranoside, on treatment with bromine and silver carbonate in methanol, are reported to give methyl β- and α-D-glucopyranoside, respectively, in high yield apparently by way of bromosulphonium ion intermediates[5]. More specifically, 1-thioglycosides undergo reaction with mercury(II) carboxylates to give the corresponding glycosyl carboxylates[6], and dialkyl dithioacetals (and apparently 1-thioglycosides) have been condensed with a mercury(II) derivative of a purine to afford nucleosides[7].

Literature evidence on the adaptability of this approach to glycoside synthesis is not altogether encouraging. An attempt to methanolyse ethyl tetra-*O*-acetyl-1-thio-β-D-mannopyranoside, using mercury(II) chloride and cadmium carbonate (used to remove any hydrogen chloride produced), met with no success although forcing conditions were employed[8]. However, the 2-acetamido-2-deoxy-D-*gluco* analogue, under similar conditions, did yield the methyl β-glycoside[9]. 1-Thiofuranosides, by analogy with the relative ease of acid-catalysed hydrolysis of furanosides, might be expected to be more reactive, and there is evidence that alcoholysis of thiofuranosides in the presence of mercury(II) salts can give alkyl glycofuranosides[10], but it has been pointed out[11] that this reaction cannot be facile since alkyl 1-thioaldofuranosides are frequently obtained as the products of solvolysis of aldose dialkyl dithioacetals carried out with mercury(II) salts. However, such alcoholyses can give alkyl glycofuranosides as main products, and these may have arisen by way of alkyl 1-thiofuranosides. Most evidence would appear to favour mixed monothioacetals rather than alkylthiofuranosides as intermediates in this process[11], but work in this Department[12] suggests, at least for diphenyl dithioacetals, that alkyl furanosides can indeed be obtained from dithioacetals by way of 1-thiofuranosides.

DISCUSSION

The work here reported has been carried out with phenyl 1-thioglycosides which, according to preliminary studies, solvolyse faster than do the corresponding ethyl compounds because, it is speculated, the aryl-group electrons can participate in the stabilisation of the transition states involved in the reaction step in which C-1–S bond fission occurs. While this reactivity order is consistent with that observed for the acid-catalysed hydrolysis of alkyl and aryl glycosides, it is at variance with the order found for the corresponding thioglycosides[13]. Methanolysis of phenyl 1-thio-α- and

-β-D-glucopyranoside, separately in dry methanol containing 20% of tetrahydrofuran, occurred smoothly in the presence of mercury(II) acetate, and the respective $t_{0.75}$ values were ~2 and ~6 min. For comparison, the $t_{0.75}$ values for ethyl 1-thio-β-D-glucopyranoside, phenyl 1-thio-α-D-glucofuranoside, and ethyl 1-thio-α-D-glucofuranoside under the same conditions were ~45, ~1, and ~8 min, respectively. In keeping, therefore, with expectations based on findings obtained during studies of the acid-catalysed hydrolysis of glycosides[14], the furanosides reacted faster than the corresponding pyranosides, and phenyl 1-thio-α-D-glucopyranoside was more reactive than the β anomer.

Preparative methanolyses of phenyl 1-thio-α- and -β-D-glucopyranoside occurred smoothly at room temperature in the presence of mercury(II) acetate, and it was found (n.m.r.; methoxyl resonances) that the α-thioglycoside had reacted to give methyl β-D-glucopyranoside specifically (87% isolated), whereas the β compound gave methyl α-D-glucopyranoside (74% isolated) together with ~6% of the β anomer. This is in interesting agreement with observations made during studies of the ethanolysis of the anomeric ethyl D-xylopyranosides[15] and of the methanolysis of the phenyl D-glucopyranosides[16]; in both these cases, stereochemical inversions were more prevalent during reactions of the α anomers.

Since β-D-glucopyranosides (and other 1,2-*trans*-related glycosides) are comparatively accessible by application of the Koenigs–Knorr and the related ortho-ester reactions[17], and because of the continuing challenge presented by α-D-glucoside synthesis (despite the sophisticated procedures developed by Lemieux and his coworkers[18]), the present approach was further assessed as a means of obtaining α-D-glucopyranosides specifically. Ethyl α-D-glucopyranoside and isopropyl α-D-glucopyranoside were obtained by solvolytic processes in yields of 67 and 55% (isolated as acetate), respectively, establishing the procedure as comparable in efficiency with the "nitrosyl chloride method"[18].

For the synthesis of α-D-glucosides of more-complex alcohols, it was necessary to use *O*-substituted phenyl 1-thio-β-D-glucopyranoside, and after the trimethylsilyl ether and the acetate ester had been found unsatisfactory [the former since it gave rise to many products; the latter because the esters inhibited the condensation (*cf.* inhibition of the methanolysis of methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-6-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside by the acetyl groups)[19]], the tetrabenzyl ether was employed. Condensation of phenyl tetra-*O*-benzyl-1-thio-β-D-glucopyranoside with cholesterol (1.1 mol.) in dry refluxing tetrahydrofuran, in the presence of mercury(II) sulphate (the acetate appeared to give the glycosyl acetate), gave the crystalline cholesteryl α-D-glucopyranoside derivative in 55% yield. Hydrogenolysis over palladium black then gave in high yield the known cholestanyl α-D-glucopyranoside, the molecular rotation of which was consistent (according to the Klyne generalisation[20]) with its having the assigned anomeric configuration:

$$M_{\text{glycoside}}(+400°) \simeq M_{\text{cholestanol}}(106°) + M_{\text{methyl α-D-glucopyranoside}}(+308°)$$

In the n.m.r. spectrum of the compound in pyridine, a one-proton doublet was

observed at δ 5.42 with a splitting of 3.3 Hz, consistent with its being the resonance of an anomeric proton of an α-D-glucopyranoside.

Application of the procedure to the preparation of 1-naphthyl α-D-glucopyranoside was less successful, but by preparative t.l.c. the required product was isolated in 10% yield. The n.m.r. spectrum ($CDCl_3$) of the tetrabenzyl ether of the glycoside showed a doublet at δ 5.65 (J 3.3 Hz) indicative of an α-D-glucosidic bond. Debenzylation gave a product which, although it melted sharply, was difficult to purify; acetylation afforded a tetra-acetate which could be readily handled.

Condensation of phenyl tetra-*O*-benzyl-1-thio-β-D-glucopyranoside with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose then gave, after preparative chromatography, a syrupy product in good yield which was shown by n.m.r. and mass spectrometry to be a tetra-*O*-benzyldi-*O*-isopropylidene disaccharide derivative. In particular, condensation was established to have occurred by the presence of a strong ion [$m/e = 575$ (M − 15, base peak)] in the mass spectrum of the derived tetra-*O*-acetyldi-*O*-isopropylidene compound. The anomeric configuration was not determined by n.m.r. methods, but the specific rotation (+60°) of the glucosyldi-*O*-isopropylidenegalactose, produced by debenzylation of the first product, suggested that, as expected, it was α-D-linked (calculated from the rotations of methyl α-D-glucopyranoside and di-*O*-isopropylidene-D-galactose, +39°: for the β-D-linked disaccharide derivative, a value of *ca.* −50° would be expected).

EXPERIMENTAL

All reactions were followed to completion by thin-layer chromatography.

Materials. — Phenyl 1-thio-α-D-glucopyranoside {m.p. 155–156°, $[\alpha]_D$ +258° (*c* 2, pyridine)} was prepared from the diphenyl dithioacetal according to the method of Ziss *et al.*[21], and the β anomer {m.p. 132–133°, $[\alpha]_D$ −76.5° (*c* 1, ethanol)} from tetra-*O*-acetyl-α-D-glucopyranosyl bromide[22], using sodium hydride to prepare the thiolate. The other 1-thioglycosides had m.p. and $[\alpha]_D$ values consistent with literature data.

Methanolysis of 1-thioglycosides. — Phenyl 1-thio-α- and -β-D-glucopyranoside, phenyl 1-thio-α-D-glucofuranoside, ethyl 1-thio-β-D-glucopyranoside, and ethyl 1-thio-α-D-glucofuranoside (1.84×10^{-4} mole) were separately dissolved in dry methanol–tetrahydrofuran (4:1, 10 ml) containing mercury(II) acetate (3.1×10^{-4} mole), and the changes in optical rotation of the solutions were followed. The $t_{0.75}$ values recorded in the Discussion represent the times taken for the solution rotations to alter by 0.75 of the difference between the rotations of the thioglycosides in methanol and the final figures.

Methyl α-D-glucopyranoside. — Phenyl 1-thio-β-D-glucopyranoside (0.5 g) in dry methanol (5 ml) was stirred with dry mercury(II) acetate (60 mg, 1.0 mol.) at room temperature for 30 min, during which time a precipitate was formed together with a soluble carbohydrate product. Removal of the solid and solvent gave a residue which was dissolved in water and treated with hydrogen sulphide; filtration and

evaporation to dryness gave a syrupy residue. The n.m.r. spectrum (pyridine) showed two methyl resonances (94 and 6%) at δ 3.42 and 3.57; methyl α- and β-D-glucopyranosides give[23] corresponding methyl resonances at δ 3.43 and 3.59. Crystallisation of the product from ethanol gave methyl α-D-glucopyranoside (0.26 g, 74%), m.p. and mixed m.p. 166°, $[\alpha]_D$ +158° (*c* 1, water); lit.[24] m.p. 167–168°, $[\alpha]_D$ +157° (water).

Methyl β-D-glucopyranoside. — Phenyl 1-thio-α-D-glucopyranoside (0.30 g) was treated as above with methanol (10 ml) and mercury(II) acetate (0.34 g, 1.0 mol.) for 1 h at room temperature. The purified, syrupy product showed only a methyl resonance (δ 3.57) for methyl β-D-glucopyranoside; crystallisation from ethanol gave methyl β-D-glucopyranoside (0.185 g, 87%), m.p. 109–110°, $[\alpha]_D$ −30° (*c* 1, water); lit.[25] m.p. 108–110°, $[\alpha]_D$ −32° (water).

Ethyl α-D-glucopyranoside. — Phenyl 1-thio-β-D-glucopyranoside (0.5 g) in dry ethanol (15 ml) was stirred with mercury(II) chloride (0.5 g) and mercury(II) oxide (0.4 g) for 48 h. After filtration, pyridine (5 ml) was added and the solution was cooled to precipitate mercury salts, which were removed by filtration. From the filtrate, after removal of the solvent, a syrup was obtained which, on trituration with ethanol, gave ethyl α-D-glucopyranoside (0.25 g, 67%), m.p. 113–114°, $[\alpha]_D$ +150° (*c* 1, methanol); lit.[26] m.p. 113°, $[\alpha]_D$ +152°.

Isopropyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside. — Phenyl 1-thio-β-D-glucopyranoside (0.5 g) was stirred in dry propan-2-ol (15 ml) with mercury(II) chloride (0.5 g) and mercury(II) oxide (0.4 g) for 96 h. After removal of the mercury salts and the solvent, a syrup was obtained which was acetylated by using acetic anhydride (1 ml) in pyridine (5 ml). Addition of ice caused the precipitation of a solid which, on recrystallisation from aqueous ethanol, afforded isopropyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (0.4 g, 55%), m.p. 89–90°, $[\alpha]_D$ +140° (*c* 1, chloroform); lit.[27] m.p. 86–88°, $[\alpha]_D$ +145° (chloroform).

Phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside. — Phenyl 1-thio-β-D-glucopyranoside (1 g) was dissolved in dry *N,N*-dimethylformamide (10 ml) and stirred with sodium hydride (0.35 g) for 15 min. Benzyl bromide (2.2 ml) was added and the mixture was heated for 2 h at 120°. The mixture was then poured on to ice (30 g), ethanol (20 ml) was added, and on stirring a solid separated which, on recrystallisation from ethanol, gave the title compound (1.85 g, 80%), m.p. 84–85°, $[\alpha]_D$ −10° (*c* 1, chloroform)*.

Anal. Calc. for $C_{40}H_{40}O_5S$: C, 76.0; H, 6.4; S, 5.1. Found: C, 76.0; H, 6.6; S, 5.1.

The n.m.r. spectrum ($CDCl_3$) was consistent with the assigned structure:

**Note added in proof* (Received March 15th, 1973). Since this paper was submitted P. J. Pfäffli, S. H. Hixson, and L. Anderson[29] have reported this compound with m.p. 93.5–94.5°, $[\alpha]_D$ +0.65° ($CHCl_3$). R. H. Furneaux in this laboratory finds that the benzylation of phenyl 1-thio-β-D-glucopyranoside as described above proceeds exothermally and completely without heating, and has obtained a product with m.p. 92–93°, $[\alpha]_D$ +1° ($CHCl_3$) from ethanol. The n.m.r. data are consistent with those reported here and by Pfäffli and coworkers.

25 phenyl protons, δ 7.0–7.7; 8 benzylic protons and H-1, δ 4.4–4.9; H-2,3,4,5,6,6', δ 3.4–3.8).

*Cholesteryl 2,3,4,6-tetra-*O*-benzyl-α-*D*-glucopyranoside.* — The benzylated thioglycoside (1.0 g) and cholesterol (0.68 g, 1.1 mol.) were stirred in dry, refluxing tetrahydrofuran with mercury(II) sulphate (0.3 g) for 3 h. Removal of the solids and the solvent gave a solid residue which, on recrystallisation from ethanol, afforded the title compound (0.70 g, 50%), m.p. 127–128°, $[\alpha]_D$ +40° (*c* 1, chloroform).

Anal. Calc. for $C_{61}H_{80}O_6$: C, 80.6; H, 8.8. Found: C, 80.8; H, 9.0.

Cholestanyl α-D-glucopyranoside.— The tetra-*O*-benzyl derivative (0.5 g) in ethyl acetate (25 ml) was hydrogenolysed in an atmosphere of hydrogen over palladium black freshly prepared from palladium chloride (0.3 g). Hydrogen (72 ml, 5 mol.) was absorbed in 0.5 h, after which the catalyst and the solvent were removed to leave a white, powdery residue which, on recrystallisation from ethanol, afforded cholestanyl α-D-glucopyranoside (0.24 g, 78%), m.p. 212–213°, $[\alpha]_D$ +73° (*c* 1, methanol), $[\alpha]_D$ +82° (*c* 1, pyridine); lit.[28] m.p. 253° (indefinite), $[\alpha]_D$ +94° (pyridine).

Anal. Calc. for $C_{33}H_{58}O_6$: C, 72.0; H, 10.5. Found: C, 71.2; H, 10.5.

*1-Naphthyl 2,3,4,6-tetra-*O*-benzyl-α-*D*-glucopyranoside.* — Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (2.0 g) and 1-naphthol (0.75 g, 1.6 mol.) were heated at 50° in tetrahydrofuran (15 ml) with mercury(II) sulphate for 6 h. T.l.c. indicated the formation of one fast-moving product together with minor amounts of less-mobile products. Removal of the solids and the solvent gave a syrup from which the chromatographically mobile product was obtained by preparative t.l.c. Recrystallisation from ethanol gave the title compound (0.2 g, 10%), m.p. 91°, $[\alpha]_D$ +12° (*c* 1, chloroform).

Anal. Calc. for $C_{44}H_{42}O_6$: C, 79.3; H, 6.3. Found: C, 79.5; H, 6.5.

The n.m.r. spectrum was consistent with the assigned structure: 27 aromatic protons, δ 7.0–7.7; H-1 doublet, δ 5.65 ($J_{1,2}$ 3.3 Hz); 8 benzylic protons, δ 4.4–5.3; H-2,3,4,5,6,6', δ 3.6–4.0.

1-Naphthyl α-D-glucopyranoside. — The foregoing tetrabenzyl ether (0.2 g) was debenzylated in ethanol by hydrogenolysis over a palladium black catalyst to give the title compound (90 mg, 91%), m.p. 178–179°, $[\alpha]_D$ +60° (*c* 1, ethanol), isolated as a hygroscopic, microcrystalline powder. Acetylation with acetic anhydride in pyridine gave the tetra-acetate, m.p. 148–150°, $[\alpha]_D$ +37° (*c* 1, chloroform).

Anal. Calc. for $C_{24}H_{26}O_{10}$: C, 60.8; H, 5.5. Found: C, 60.5; H, 5.7.

The n.m.r. spectrum was consistent with the allocated structure; H-1 and H-2, and H-3 and H-4 gave unresolved resonances.

*1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-glucopyranosyl)-α-*D*-galactopyranose.* — Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (1.0 g) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (0.45 g, 1.1 mol.) were stirred in refluxing tetrahydrofuran (20 ml) with mercury(II) sulphate (0.3 g) for 3 h. Removal of the solids and solvent gave a syrup which was shown by t.l.c. to contain mainly one compound. This was isolated by preparative t.l.c. as a syrup (0.67 g, 54%), $[\alpha]_D$ +30° (*c* 1, chloroform). The n.m.r. spectrum indicated the presence of four benzyl groups

and two isopropylidene groups. Debenzylation of this compound (0.6 g), as above, gave a syrupy di-*O*-isopropylidene-disaccharide (0.20 g, 62%), $[\alpha]_D$ +60° (*c* 1, methanol). Acetylation of this product with acetic anhydride in pyridine gave a syrupy tetra-acetate (0.24 g, 80%), $[\alpha]_D$ +20° (*c* 1, chloroform), which was shown by n.m.r. to contain four acetyl groups and two isopropylidene groups. The mass spectrum revealed a base peak at *m/e* 575 (M − 15), and ions at 331 (cleavage at C-1 of the glucosyl moiety) and 229 (cleavage at C-5–C-6 of the galactosyl group).

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