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OBSERVATIONS ON THE POSSIBLE APPLICATION OF GLYCOSYL DISULPHIDES, SULPHENIC ESTERS, AND SULPHONES IN THE SYNTHESIS OF GLYCOSIDES

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ABSTRACT

Partial desulphuration of tetra-*O*-acetyl-β-D-glucopyranosyl phenyl disulphide with a phosphine derivative gave 40% of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-glucopyranoside and a similar proportion of β-D-glucopyranosyl 1-thio-α-D-glucopyranoside octa-acetate, showing that this procedure is of limited value in α-D-thioglucoside synthesis Similar treatment of allyl tetra-*O*-acetyl-β-D-glucopyranosyl sulphoxide caused abstraction of oxygen, rather than of sulphur, from the derived allyl glucosylsulphenate The phenylsulphonyl group was not readily displaced from β-D-glucopyranosyl phenyl sulphone, except intramolecularly, nor could it be displaced from the tetrabenzyl ether Elimination of benzyl alcohol from this compound afforded a new 1-(phenylsulphonyl)glycal derivative

INTRODUCTION

In the course of studies of derivatives of 1-thio sugars as glycoside precursors, we have reported on the displacement of the phenylthio group from phenyl 1-thioglycosides[1], the use of carbohydrate benzothiazolines in the synthesis of glycosylamines[2], and the reaction undergone between glycosyl *N,N*-dialkyldithiocarbamates and some organomercurials[3] We now comment on attempted monodesulphuration of glycosyl disulphides and of an allyl glycosyl sulphoxide, and on the attempted displacement of the benzenesulphonyl group from glycosyl phenyl sulphones, all of which were undertaken in efforts to develop new approaches to glycoside and 1-thioglycoside syntheses

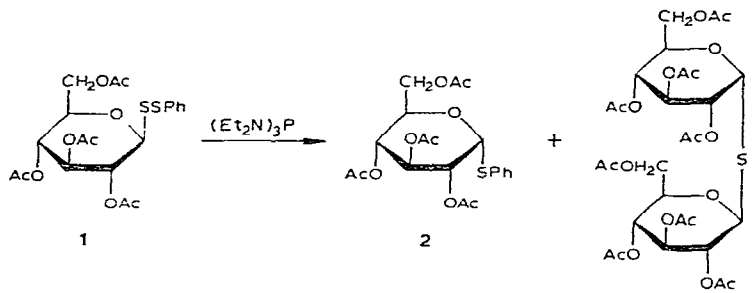
RESULTS AND DISCUSSION

1-Thioglycosides having *trans*-related substituents at C-1 and C-2 are relatively easy to obtain[4], whereas methods for preparing the *cis*-related analogues are not well developed*. Monodesulphuration of glycosyl disulphides by sulphur extrusion[5] seemed to be a possible route to the *cis*-related compounds, especially as Harpp and

*See, however, B Erbing and B Lindberg, *Acta Chem Scand Ser B*, 30 (1976) 611–612

Gleason obtained β-D-glucopyranosyl 1-thio-α-D-glucopyranoside octa-acetate from the symmetrical β,β-disulphide by such a procedure[6] By use of tris(diethylamino)-phosphine, we confirmed their finding, and isolated the main product readily and in 52% yield Tetra-*O*-acetyl-β-D-glucopyranosyl phenyl disulphide (**1**) was then prepared from 2,3,4 6-tetra-*O*-acetyl-1-thio-β-D-glucose and benzenesulphenyl chloride[7], rather than by the reverse route involving the glucosylsulphenyl bromide[8], although some bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulphide was isolated, the required compound was obtained in 60% yield Use of benzenesulphenyl bromide instead of the chloride reduced the efficiency of the reaction, presumably because the former can take part more readily in exchange processes which lead to mixed products

$$RSH + PhSX \rightleftharpoons RSX + PhSH \rightarrow RSSPh + (RS-)_2 + (PhS-)_2$$

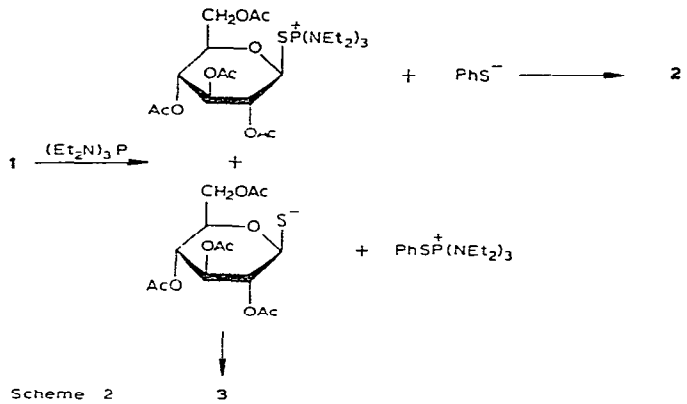


1 2 3

Scheme 1

Treatment of the disulphide **1** in boiling benzene with tris(diethylamino)-phosphine gave 40% of the desired α-thioglycoside **2** (n m r determination), 11% of which was obtained in pure state after preparative t l c An improved isolation procedure would make the method comparable with the only previously reported synthesis, which involves partial hydrolysis of D-glucose diphenyl dithioacetal[9] A second product of the reaction, which was formed together with **2** in similar amount and could be isolated by direct crystallisation in 29% yield, was β-D-glucopyranosyl 1-thio-α-D-glucopyranoside octa-acetate (**3**) (Scheme 1) Conceivably, the interchange of groups occurs followed the generation of two thiolate anions, each of which attacks C-1 of the glycosylthiophosphonium salt (Scheme 2) It is noteworthy that α-linked products preponderate, which suggests that the initially formed phenyl-thiolate and glycosylthiophosphonium ions remain paired so as to preclude participation in the displacement from C-1 by the acetoxyl group at C-2, but loosely paired so that anion exchange can occur Others[10] have found that benzene favours α-glycoside formation in displacements from glycosyl halides lacking participating groups at C-2 This exchange process must be overcome before such mixed disulphides as **1** can be used for the efficient synthesis of α-thioglycosides

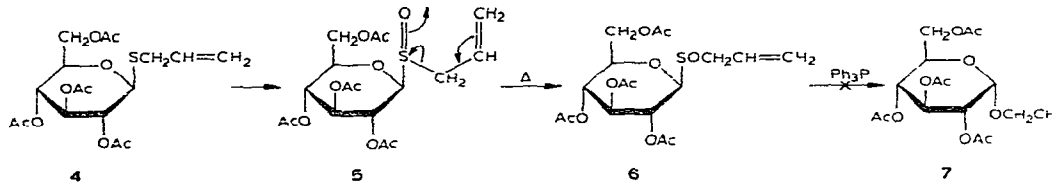
As it has been reported[11] that sulphenic esters can be desulphurised to give ethers, and in particular that *O*-methyl *tert*-butylsulphenate affords *tert*-butyl methyl ether, it seemed probable that *S*-glycosylsulphenic esters would, on treatment with



Scheme 2

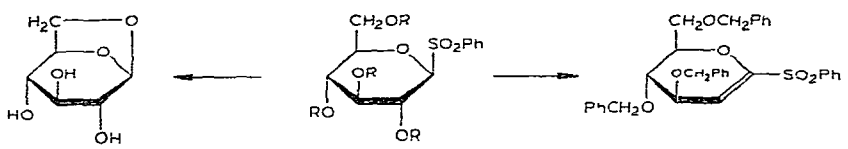
trivalent phosphorus compounds, offer access to *O*-glycosides With the precedent of the above disulphide desulphuration, it was anticipated that *β*-sulphenates would afford *α*-glycosides, the synthesis of which remains a primary goal in carbohydrate chemistry[10] As there are difficulties associated with the direct synthesis of sulphenates[11], an allyl glycosylsulphenate was selected for study because allyl esters become available by thermal [2,3]sigmatropic rearrangement of allyl sulphoxides[12] It was anticipated, therefore, that heating an allyl *β*-glycosyl sulphoxide in the presence of a trivalent phosphorus compound might afford a route to an allyl *α*-glycoside (Scheme 3), and sulphoxide **5** was chosen Oxidation of the known allyl thioglycoside **4** with hydrogen peroxide afforded crystalline samples of the sulphone and the mixed diastereoisomeric sulphoxides (**5**) Oxidation with 3-chloroperoxybenzoic acid[13] was more selective, and the sulphoxides were obtained directly with this reagent, their different physical constants from those of the first sample being attributed to their presence in a different ratio However, the two samples had identical t l c characteristics and gave identical n m r spectra, and their isomeric composition was considered irrelevant, as the chirality of the sulphur would be lost during the thermal formation of the sulphenate **6** Heating the sulphoxide **5** in benzene caused a substantial change in optical rotation, which suggests that the ester **6** was being formed (probably reversibly), but no further change occurred on addition of tris-(diethylamino)phosphine to the refluxing benzene When refluxing toluene was used as solvent, addition of this phosphine caused substantial degradation, and so the thiophile triphenylphosphine was used in refluxing toluene in an attempt to abstract the sulphur Under these conditions, compound **5** was converted into a chromatographically more-mobile product, which was catalytically deacetylated, and the unfractionated mixture was partitioned between water and chloroform From the organic phase, a high yield of triphenylphosphine oxide and sulphide (95 5) was obtained, and the aqueous phase afforded a syrup with $[\alpha]_D$ −25° This suggests that the process caused preferential extrusion of oxygen rather than sulphur (whether from the sulphoxides or sulphenate is not known) and gave rise to the initial thioglycoside **4**, the value for the optical rotation indicates that the procedure is not

viable as an α-glycoside synthesis In concurrence with this observation, Barton and his colleagues have now reported their inability to repeat the desulphuration of *O*-methyl *tert*-butylsulphenate, with tri-n-butylphosphine, they found that this compound gives the phosphine oxide and methyl *tert*-butyl sulphide[14]



Scheme 3

Since solvolytic displacement of the phenylthio group from phenyl 1-thioglycosides occurs readily in the presence of mercury(II) ions[1], it was of interest to determine under what conditions the phenylsulphonyl group might be removed from the derived sulphones Treatment of β-D-glucopyranosyl phenyl sulphone (**8**) in refluxing methanol with mercury(II) acetate caused no reaction, so that, not surprisingly, the metal no longer acted as a specific "soft" Lewis acid for "soft" sulphur Nor did added calcium acetate nor magnesium acetate give rise to hydrolysis when the sulphone was heated in water, and therefore the anticipated "harder" calcium–oxygen and magnesium–oxygen interactions were also inefficient in leading to cleavage of the glycosyl–sulphur bond When the sulphone was heated in methanol with sodium methoxide, reaction did occur, but did not give methyl glycosides, instead, 1,6-anhydro-β-D-glucopyranose (**10**) was formed, presumably by way of an intermediate 1,2-epoxide[15], in keeping with the finding of Clingman and Richtmyer[16] who treated a *p*-tolylsulphone with base



This establishes that the phenylsulphonyl group can be displaced but that if glycoside synthesis is to be achieved the hydroxyl groups in the compound must be inactivated Consequently, the benzyl ether **9** was prepared by oxidation of the benzylated thioglycoside, but when treated with alkoxides or thiolates, it did not undergo the desired displacement reaction The only compound which could be isolated from the reaction products was the sulphonylglycal derivative **11** formed by

base catalysed β-elimination of benzyl alcohol With sodium thiophenate in methyl sulphoxide, compound **11** was obtained in 18% yield, the best yield of 24% was achieved by using barium oxide in ethanol Compound **11** absorbed in the infrared at 1640 cm^{-1} consistent with the presence of a vinyl system, and in the ultraviolet at 243 nm (log ε 3 9) Phenyl vinyl sulphone absorbs at 225 nm[17] (log ε 4 1), and small bathochromic shifts are to be expected for the substitution of oxygen- and carbon-bonded groups The n m r spectrum showed resonances for 20 aromatic protons, an 8-proton envelope for the benzylic protons and H-6,6′, an envelope for H-3,4,5, and an isolated vinylic doublet at δ 6 15 which is assigned to H-2 Splitting of 3 Hz is consistent with the 3 2-Hz value reported for $J_{2,3}$ of tri-*O*-acetyl-D-glucal[18]

EXPERIMENTAL

Optical rotations were measured in chloroform and within the concentration range 0 5–2% unless otherwise stated

Bis(tetra-O-acetyl-β-D-glucopyranosyl) disulphide — The diglycosyl disulphide was prepared by the method of Černý *et al* [19], and had m p 141–143°, $[\alpha]_D$ −153°, lit [19] m p 142–143°, $[\alpha]_D$ −156°

Tetra-O-acetyl-β-D-glucopyranosyl phenyl disulphide (**1**) — Benzenesulphenyl chloride[7], prepared from thiophenol (1 6 ml), was added to 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose (5 0 g, 0 88 mol equiv), and a main carbohydrate product was detected in 5 min The crude solid, after two recrystallisations from ethanol, gave **1** (3 92 g, 60%), m p 117–126°, $[\alpha]_D$ −223°, lit [8 20] m p 123–124°, $[\alpha]_D$ −241°, 117–118°, $[\alpha]_D$ −228°

The mother liquor yielded bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulphide (0 28 g, 6%) Recrystallised from methanol, it had m p 142–143°, $[\alpha]_D$ −151°

Treatment of bis(tetra-O-acetyl-β-D-glucopyranosyl) disulphide with tris(diethylamino)phosphine[21] — The disulphide (2 0 g) and the phosphine (1 0 g, 1 5 mol equiv) were heated in benzene (50 ml) under reflux in an atmosphere of nitrogen for 1 5 h The solution was washed with dilute hydrochloric acid and then water, and dried prior to removal of the solvent Crystallisation from ethanol gave β-D-glucopyranosyl 1-thio-α-D-glucopyranoside octa-acetate (**3**, 1 0 g, 52%) Recrystallised from ethanol, **3** had m p 168–169°, $[\alpha]_D$ +109°, δ 5 93 (1 H, d, $J_{1,2}$ 5 Hz, H-1e), lit [6 22] m p 170°, $[\alpha]_D$ +115°, δ 6 0 (d, *J* 5 Hz)

Treatment of tetra-O-acetyl-β-D-glucopyranosyl phenyl disulphide (**1**) *with tris(diethylamino)phosphine* — The mixed disulphide **1** (2 5 g) and the phosphine (2 1 g, 1 6 mol equiv) were heated in benzene (25 ml) under reflux in an atmosphere of nitrogen for 0 75 h, and the solution was processed as above to give a syrup that contained (t l c) two main carbohydrate products The less-mobile product, β-D-glucopyranosyl 1-thio-α-D-glucopyranoside octa-acetate (**3**, 0 54 g, 29%), crystallised from the mixture with methanol as solvent Recrystallised from ethanol (×2), **3** had m p 169–170°, $[\alpha]_D$ +110°, and gave an n m r spectrum identical with that of authentic material The mother liquors were taken to dryness, and purified by preparative

t l c to give a syrup (1 4 g) which appeared, from its n m r spectrum, to be a mixture of phenyl tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (**2**) and tris(diethylamino)-phosphine sulphide in the ratio 3 2 From this mixture, the glycoside **2** (0 47 g) was obtained by crystallisation from methanol A pure sample (0 25 g, 11%) was isolated by recrystallisation from the same solvent, m p 86–88°, $[\alpha]_D$ +225°, lit [9] m p 90–91°, $[\alpha]_D$ +230°

*Allyl tetra-*O*-acetyl-β-*D*-glucopyranosyl sulphoxides* (**5**) *and sulphone* — (*a*) Allyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[23] (**4**, m p 53–56°, $[\alpha]_D$ +2 6°, lit [23] m p 53°, $[\alpha]_D$ −0 5°) (5 8 g) in acetone (70 ml) was treated with hydrogen peroxide (0 49 g, 1 0 mol equiv) in water (70 ml), no reaction was detectable by t l c after 4 days When the solvent had been removed under vacuum and at ~50°, two products were detected (R_F 0 24 and 0 1, starting material, 0 5, methanol–chloroform 1 100), and the residue crystallised spontaneously Fractionation of the mixture (0 5 g) by preparative t l c gave the sulphone (0 19 g, R_F 0 24) and the sulphoxides (**5**, 0 22 g, R_F 0 1) Recrystallised from ethanol, the sulphone had m p 160–162°, $[\alpha]_D$ +13°

Anal Calc for $C_{17}H_{24}O_{11}S$ C, 46 8, H, 5 5, S, 7 3 Found C, 46 9, H, 5 4, S, 7 5

The sulphoxide mixture, on recrystallisation from ethanol, had m p 150–152°, $[\alpha]_D$ −90°, and was resolvable into its isomeric components by high-resolution t l c

Anal Calc for $C_{17}H_{24}O_{10}S$ C, 48 6, H, 5 7, S, 7 6 Found C, 48 6, H, 5 6, S, 7 9

(*b*) The glycoside (12 3 g) in chloroform (200 ml) was treated with 3-chloroperoxybenzoic acid (4 47 g, 0 85 mol equiv) in chloroform (200 ml) at −20° for 1 h, and the solution was then washed with aqueous sodium hydrogen carbonate and water, and dried Removal of the solvent gave an oil which was mainly the sulphoxides (t l c) Crystallisation from 1-propanol gave a product (7 3 g, 57%) which contained small proportions of starting material and sulphone, these were removed by crystallisation from methanol (×3) The sulphoxides (**5**) were obtained chromatographically free from starting material and sulphone in 22% yield by this method and had m p 160–162°, $[\alpha]_D$ −27° The sulphoxide mixture was indistinguishable from the analysed sample by t l c , and by n m r and infrared spectroscopy

*Treatment of allyl tetra-*O*-acetyl-β-*D*-glucopyranosyl sulphoxides* (**5**) *with triphenylphosphine* — The sulphoxides (**5**, 0 91 g) and triphenylphosphine (0 58 g, 1 04 mol equiv) were heated in refluxing toluene (50 ml) and under nitrogen for 2 h The solvent was removed, and the residue was deacetylated with catalytic amounts of sodium methoxide in methanol and then shaken with chloroform (50 ml) and water (50 ml) The phases were separated and each was washed with the other solvent Drying of the chloroform layer and removal of the solvent gave a solid residue (0 64 g) which, by infrared comparison with synthetic mixtures, was shown to be triphenylphosphine oxide [95%, ν_{max} 1200 cm^{-1} (P = O)] and triphenylphosphine sulphide [5%, 670 cm^{-1} (P = S)] The aqueous phase was not examined further after the syrupy residue obtained therefrom was found to have $[\alpha]_D$ −25° (water)

Reactions of β-D-glucopyranosyl phenyl sulphone (**8**) — The sulphone was prepared by deacetylation (barium methoxide) of its tetra-acetate, and had m p 91–92°, $[\alpha]_D$ −13° (*c* 0 9, water), lit [24] m p 92–93°, $[\alpha]_D$ −15° (water) Samples (0 1 g) were separately dissolved in methanol (10 ml) containing mercury(II) acetate (0 5 g, 5 0 mol equiv), water (10 ml) containing calcium acetate (0 24 g, 5 0 mol equiv), and water (10 ml) containing magnesium acetate (0 22 g, 5 0 mol equiv) The solutions were boiled under reflux for 1 h, no rotational changes were observed nor were any products detectable by t l c

Reaction did occur when the sulphone (1 0 g) was heated under reflux for 1 h with sodium methoxide (1 25 g, 8 mol equiv) in methanol (100 ml) The base was removed with cationic resin, and the solvent by distillation, to give an oil which was acetylated with acetic anhydride (5 ml) and pyridine (5 ml) Normal processing gave 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucose (0 1 g, 10%), m p 109–110°, $[\alpha]_D$ −48° (*c* 0 6, ethanol), lit [25] m p 109°, $[\alpha]_D$ −46° (ethanol) The n m r spectrum was consistent with the assigned structure, and the non-crystalline portion of the product gave an identical spectrum

Tetra-O-benzyl-β-D-glucopyranosyl phenyl sulphone (**9**) — Phenyl tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (10 g) was treated with 3-chloroperoxybenzoic acid (7 8 g, 2 5 mol equiv) in chloroform (300 ml) for 18 h, after which the solution was washed with aqueous sodium hydrogen carbonate and then water, and dried Removal of the solvent gave the sulphone (10 2 g, 97%) which, when recrystallised from ethanol, had m p 136–137°, $[\alpha]_D$ +19°

Anal Calc for $C_{40}H_{40}O_7S$ C, 72 3, H, 6 1, S, 4 8 Found C, 72 1, H, 6 1, S, 4 8

The compound was also obtained, but much less efficiently, by treatment of β-D-glucopyranosyl phenyl sulphone with sodium hydride followed by benzyl bromide in *N,N*-dimethylformamide

3,4,6-Tri-O-benzyl-2-deoxy-D-arabino-hex-1-enopyranosyl phenyl sulphone (**11**) — The tetra-*O*-benzyl sulphone **9** (0 65 g) in methyl sulphoxide (35 ml) was heated at 95° with sodium thiophenate (3 0 g) for 4 h The solution was then diluted with chloroform (40 ml), washed with water (3 × 600 ml), dried, and taken to dryness to give a yellow syrup, which crystallised on trituration with light petroleum Recrystallisation from ethanol gave the unsaturated sulphone **11** (0 1 g, 18%), m p 85–86°, $[\alpha]_D$ −58°.

Anal Calc for $C_{33}H_{32}O_5S$ C, 71 2, H, 5 8, S, 5 8 Found C, 71 4, H, 5 6 S, 5 9

A similar reaction with barium oxide in ethanol gave **11** in 24% yield after 1 h under reflux

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