THE REACTION OF CHLOROSULPHATE ESTERS OF SUGARS WITH PYRIDINE

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ABSTRACT

Hexoside and hexitol derivatives with vicinal chlorosulphate ester groups in different configurations were treated with pyridine. The corresponding cyclic sulphate esters were produced except in the case of the diaxial configuration, which gave an anyhdro derivative. The axial–equatorial configuration gave in addition a keto-deoxy compound. The structures of the cyclic sulphate esters and of other reaction products are proposed and their mode of formation is discussed.

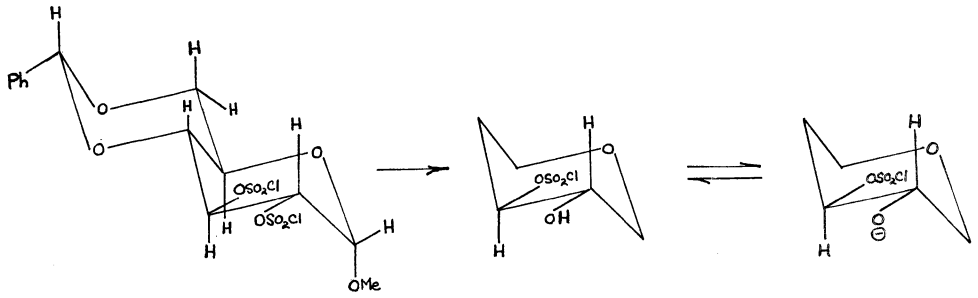
INTRODUCTION

Sulphuryl chloride is the only reagent which has been reported to yield cyclic sulphate ester derivatives of carbohydrates (1–5) and although other methods of forming diol cyclic sulphates are known they do not seem to be applicable in this field (6). Helferich and co-workers first isolated cyclic sulphate derivatives of methyl α- and methyl β-D-glucopyranoside, of mannitol, and of trehalose (1–3) and this work has been extended more recently (4, 5). The cyclic sulphate ester groups were shown to bridge adjacent hydroxyl groups on C_2 and C_3 of the glycopyranosides and possibly across C_3 and C_4 of the D-mannitol derivative (4, 5). Comparison of the reaction conditions which yielded the cyclic sulphate esters (1, 4) with more recent work which described the preparation of 2,3-dichlorosulphate ester derivatives of reducing sugars (7) showed that the ratio of pyridine to sulphuryl chloride had been approximately halved in the latter series of reactions. Therefore the effect of excess pyridine on the chlorosulphate esters of model compounds of different configurations was investigated, with particular emphasis on the 2,3-dichlorosulphate esters. This led to a new synthesis of cyclic sulphate esters in sterically favorable cases.

DISCUSSION

The reactions of pyridine on the 2,3-dichlorosulphate esters in the equatorial–equatorial configuration were carried out using derivatives of methyl α-D-glucopyranoside. Methyl α-D-glucopyranoside when treated with sulphuryl chloride gave a syrupy product which was dechlorosulphated (sodium iodide) to yield crystalline methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (4). This evidence indicated that the initial reaction product was methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate. The syrupy dichlorosulphate ester when reacted with pyridine gave methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-cyclic sulphate (4). Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside when similarly treated gave a crystalline compound which was identified as the 2,3-dichlorosulphate ester (I) by isolation of the initial reactant after dechlorosulphation with sodium iodide. Treatment of the dichlorosulphate ester with pyridine in the cold yielded crystalline methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-cyclic sulphate (4). When this reaction was carried out at 60° no cyclic sulphate derivative was formed and methyl α-D-glucopyranoside and its 4,6-*O*-benzylidene derivative were isolated.

The reaction of methanolic sodium methoxide on the 2,3-dichlorosulphate ester produced no cyclic sulphate ester and a poor yield of methyl 4,6-*O*-benzylidene-2,3-anhydro-α-D-alloside (9) was isolated. This evidence indicates that the basicity of the reagent is an important factor in the formation of the cyclic sulphate ester. The reactions probably proceed by the basic hydrolysis of the chlorosulphate ester on C_2 of I as in the case of the formation of the 2,3-anhydro derivatives from the ditosylate esters (9, 11), and the mechanism can be represented by the partial formulae (I, I*a*, and I*b*) (cf. ref. 10).



I Ia Ib

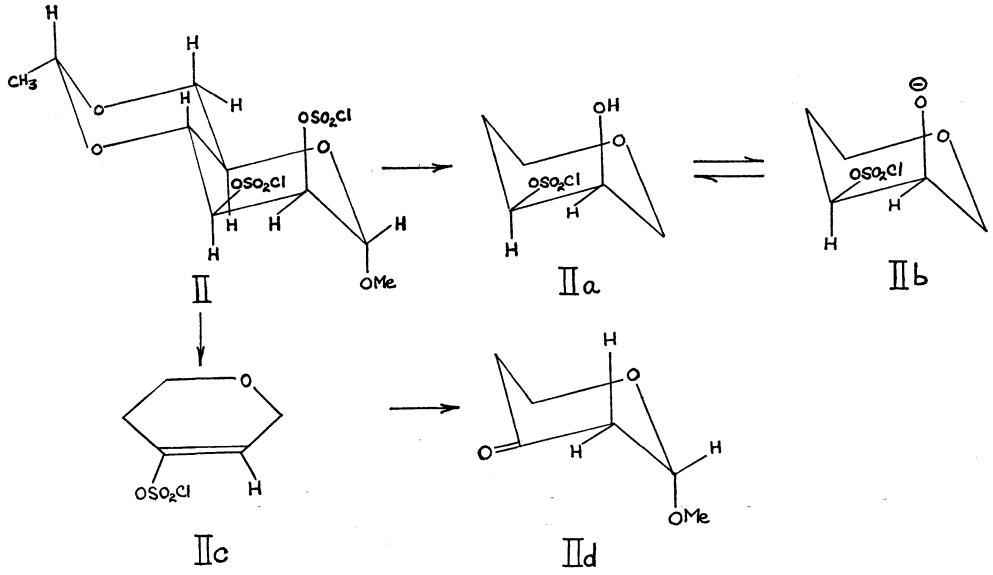
Sodium methoxide produced the 2,3-anhydro derivative due to the large concentration of oxide ion (I*b*), whereas in the less basic reagent (pyridine) the concentration of I*b* would be much smaller, enabling the formation of the cyclic sulphate from I*a* to take place.

The reaction of pyridine on the 2,3-dichlorosulphate ester in the axial–equatorial configuration was carried out using the 2,3-dichlorosulphate derivative of methyl 4,6-*O*-ethylidene-α-D-mannopyranoside (II), the structure of which was proved by the isolation and identification of the following reaction products. The dichlorosulphate ester was treated with pyridine to give two crystalline products identified as methyl 4,6-*O*-ethylidene-α-D-mannopyranoside 2,3-cyclic sulphate, and methyl 4,6-*O*-ethylidene-2-deoxy-3-keto-α-D-*erythro*-hexoside. The structure of the cyclic sulphate derivative was indicated by its analysis and desulphation followed by hydrolysis (4) to give syrupy D-mannose (identified as the crystalline phenylhydrazone).

The structure of the 2-deoxy-3-keto compound was confirmed by sodium borohydride reduction of the 3-keto group and hydrolysis of the reduced product to give 2-deoxy-D-*ribo*-hexose (13). This reduction appears to be stereospecific in absolute ethanol and practically so in ethanol–water (1:1). Although 2-deoxy-D-glucose was detected when ethanol–water (1:1) was used it seems that solvent effects of the type reported by Eliel (14) are insignificant and that the main factor is steric hindrance of the reducing species. Models of the 2-deoxy-3-keto compound (II*d*) indicate possible interaction between the axial glycosidic group on C_1 of the molecule and the axial approach of the borohydride complex (14) needed for reduction of the keto group on C_3 to form an equatorial hydroxyl group. The bulky group would therefore be expected to approach from the less hindered equatorial side of the molecule, producing a hydroxyl group in the axial configuration (15).

The reaction of the axial–equatorial vicinal chlorosulphate ester groups with pyridine to give the cyclic sulphate and 2-deoxy-3-keto derivatives can be explained by the same mechanism as proposed previously and is represented by the partial formulae II, II*a*, and

II*b*. The formation of the 2-deoxy-3-keto compound using pyridine indicates that hydrolysis of the chlorosulphate ester group on C_2 of II must take place slowly for diaxial

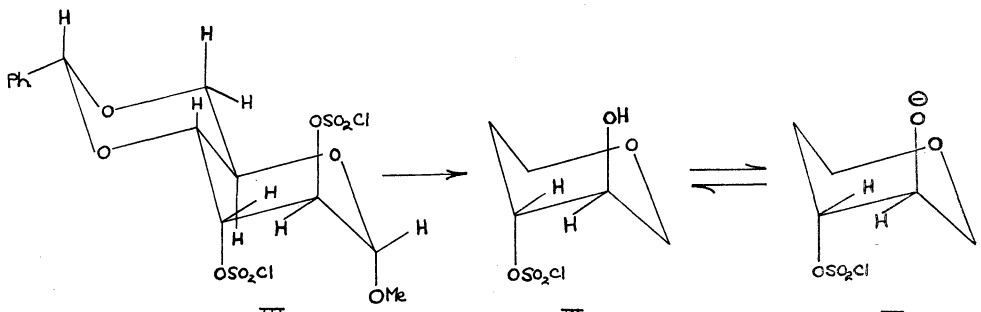


elimination (16), with the subsequent formation of the transient compound (II*c*). This compound (II*c*) in the basic medium would be rapidly converted to the 2-deoxy-3-keto compound (II*d*) via an intermediate enolate. Sodium methoxide produced no keto-deoxy compound because the hydrolysis of II to II*a* was rapid. The formation of the cyclic sulphate derivative probably takes place via II*a* using pyridine and II*b* using sodium methoxide, as the formation of a 2,3-anhydro compound from II*b* is sterically unfavorable.

The reaction of pyridine on the 2,3-dichlorosulphate esters in the axial–axial configuration was carried out using the 4,6-*O*-benzylidene derivative of methyl α-D-altroside. Methyl 4,6-*O*-benzylidene-α-D-altropyranoside was treated with sulphuryl chloride to give a crystalline dichlorosulphate ester derivative (III), which decomposed rapidly and could not be analyzed. When a chloroform solution of the compound was allowed to evaporate to dryness another crystalline derivative was obtained which had lost the benzylidene group and which was indicated by analysis to be methyl α-D-altropyranoside 2,3-dichlorosulphate. The removal of the benzylidene group was probably facilitated by the presence of traces of acid caused by the partial decomposition of the chlorosulphate ester groups. The 4,6-*O*-benzylidene dichlorosulphate ester was treated immediately with pyridine to give crystalline methyl 4,6-*O*-benzylidene 2,3-anhydro-α-D-mannopyranoside (11).

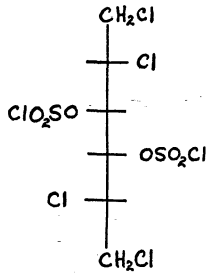
The formation of the 2,3-anhydro derivative from III using pyridine indicates that the small concentration of III*b* is in a sterically more favorable position to react than III*a*. Models show that the distance between the groups on C_2 and C_3 of III*a* is much greater than for the equatorial–equatorial and axial–equatorial configurations, which gave cyclic sulphate derivatives with ease. Also the trans–axial configuration of III*b* is the most preferred configuration for nucleophilic attack of the oxide ion on C_3 to give the 2,3-anhydro derivative.

The reactions of pyridine on vicinal dichlorosulphate esters in the open chain form were carried out on derivatives of D-mannitol. D-Mannitol when treated with sulphuryl



III IIIa IIIb

chloride gave a crystalline tetrachlorotetradeoxy dichlorosulphate ester (IV). The ester (IV) when treated with pyridine gave a crystalline derivative which was shown by analysis to be a tetrachlorotetradeoxy cyclic sulphate ester (2, 4). This evidence indicates that the chlorosulphate groups in the original compound (IV) must have been vicinal. There is also some evidence that they are situated on C_3 and on C_4, as 1,2:5,6-di-*O*-isopropylidene mannitol gave an unstable dichlorosulphate ester which with pyridine yielded a crystalline cyclic sulphate derivative.



IV

Because of the free rotation of the bond between C_3 and C_4 of IV it is possible for the two chlorosulphate groups to approach each other closer than is possible for structures I, II, and III. It might therefore be expected that the reaction of pyridine on the vicinal dichlorosulphate ester would form the cyclic sulphate derivative with ease. The fact that sodium iodide also produced the cyclic sulphate derivative is unusual as the same treatment of the 2,3-dichlorosulphate esters in the equatorial–equatorial configuration (7) has so far resulted in dechlorosulphation to give the 2,3-dihydroxy compound. A possible explanation for this could be that the proximity of the two groups is favorable for cyclic sulphate formation in this case.

1,2:5,6-Di-*O*-isopropylidene-D-glucose when treated with sulphuryl chloride gave a crystalline monochlorosulphate ester as shown by analysis and dechlorosulphation (sodium iodide) to form the starting product. The monochlorosulphate ester when treated with pyridine also gave 1,2:5,6-di-*O*-isopropylidene-D-glucose, which indicates that pyridine can hydrolyze the chlorosulphate ester.

EXPERIMENTAL

Optical rotations were measured at 21±3°. Melting points were determined on a Kofler hot stage and were uncorrected. All solutions were concentrated under reduced pressure below 50°. Paper chromatography

was carried out by the descending method on Whatman No. 1 filter paper using the following solvent systems (v/v): (*a*) butan-1-ol, ethanol, water (3:1:1), (*b*) ethyl acetate, acetic acid, formic acid, water (18:3:1:4), and (*c*) 2-butanone, acetic acid, saturated aqueous boric acid (9:1:1). Reducing sugars were located on chromatograms by *p*-anisidine hydrochloride (17) or alkaline silver nitrate (18) spray reagents and keto-sugars by orcinol – trichloracetic acid spray reagent (19); the rates of movement are quoted relative to that of D-xylose (R_x). Paper electrophoresis was performed using Whatman 3MM filter paper impregnated with 0.05 *M* borate buffer and the sugars were detected on the electrophoretograms by *p*-anisidine hydrochloride spray reagent (17). The rates of movement of compounds on paper electrophoretograms are given relative to that of D-glucose (M_g). Infrared spectra were measured in chloroform solution (unless otherwise stated) using a Perkin–Elmer Model 21 spectrophotometer.

The reactions with sulphuryl chloride and the isolation of the chlorosulphate esters were carried out by the method described in a previous communication ("general method") (7), except that in most cases the reaction mixture was homogeneous.

Methyl 4,6-Dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-Dichlorosulphate

Methyl-α-D-glucoside (10 g) was treated with sulphuryl chloride (26 ml) and pyridine (40 ml) in chloroform solution (7). Concentration of the chloroform extracts gave a yellow syrup (12 g, 55%) which had $[\alpha]_D$ +115° (*c*, 1.2 in chloroform) and gave a positive test with aniline–pyridine (7). The syrup showed strong absorption frequencies in the infrared spectrum at 1427 cm^{-1} and 1195 cm^{-1}.

Dechlorosulphation of Methyl 4,6-Dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-Dichlorosulphate

The above syrup (10 g) was dissolved in methanol (150 ml), and a solution of sodium iodide (8 g dissolved in 20 ml of methanol–water (1:1)) was added, producing an immediate formation of iodine and the evolution of sulphur dioxide. The solution was neutralized with barium carbonate, filtered, and concentrated to a semicrystalline mass, which was dissolved in water. Following the addition of a few crystals of sodium thiosulphate to remove traces of iodine, the aqueous solution was continuously extracted with chloroform. Concentration of the chloroform solution gave a crystalline mass which was recrystallized from chloroform – light petroleum (b.p. 40–60°) to give colorless needle-shaped crystals (4.5 g, 82%) of $[\alpha]_D$ +179° (*c*, 2.0 in water) and m.p. 158°, undepressed on admixture with authentic methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (4).

Methyl 4,6-Dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-Cyclic Sulphate

The syrupy 2,3-dichlorosulphate (9.7 g) was dissolved in redistilled pyridine (40 ml) and the solution was kept at 60° for 8 hours. The resultant dark brown solution, which still gave a positive test with aniline–pyridine (7), was poured into water and extracted (×2) with chloroform. The chloroform solution was washed with dilute sulphuric acid (5%), saturated sodium bicarbonate solution, and distilled water before being dried over anhydrous sodium sulphate. The chloroform solution was treated with charcoal, filtered, and concentrated to a pale yellow syrup (5 g, 76%). The syrup crystallized on standing, and the crude crystals gave a negative test with aniline–pyridine (7) and showed absorption frequency in the infrared spectrum at 1412 cm^{-1}. No strong absorption was detected in the 1200 cm^{-1} region as with the chlorosulphate esters (7). Recrystallization from ether – light petroleum (b.p. 40–60°) gave large needles (3 g, 46%) of $[\alpha]_D$ +139° (*c*, 1.75 in methanol) and m.p. 103–104°, undepressed on admixture with authentic methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-sulphate (4).

Methyl 4,6-O-Benzylidene-α-D-glucopyranoside 2,3-Dichlorosulphate

Methyl 4,6-*O*-benzylidene-α-D-glucoside (8) (5 g) was treated with sulphuryl chloride (13 ml) and pyridine (20 ml) in chloroform solution (7). Concentration of the chloroform extracts gave a syrup (8 g, 94%) which crystallized immediately. Recrystallization from chloroform – light petroleum (b.p. 60–80°) gave large colorless crystals of m.p. 133–136° (decomp.) and $[\alpha]_D$ +41.5° (*c*, 1.5 in chloroform). The crystals gave a positive test with aniline–pyridine (7) and showed strong absorption frequencies in the infrared spectrum at 1415 cm^{-1} and 1190 cm^{-1}. Analysis: Calc. for $C_{14}H_{16}O_{10}Cl_2S_2$: C, 35.1; H, 3.3; Cl, 14.8; S, 13.4. Found: C, 35.0; H, 3.3; Cl, 14.5; S, 13.2.

Dechlorosulphation of Methyl 4,6-O-Benzylidene-α-D-glucopyranoside 2,3-Dichlorosulphate

The crystals (3 g) were dechlorosulphated by the method described previously in the dechlorosulphation of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactoside 2,3-dichlorosulphate except that barium carbonate (8 g) was stirred into the methanol solution before the addition of the sodium iodide (3 g). This kept the solution neutral and prevented the removal of the benzylidene group. The solution was filtered, concentrated to small volume, and, on the addition of water, the reaction product was precipitated. The precipitate was filtered from the solution and recrystallized from acetone–water to give crystals of m.p. 165°, undepressed on admixture with authentic methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (8).

Methyl 4,6-O-Benzylidene-α-D-glucopyranoside 2,3-Cyclic Sulphate

The crystals of the dichlorosulphate ester above (5 g) were dissolved in pyridine and kept at 0° for 8 hours, after which time the solution still gave a positive test with aniline–pyridine (7). The product was isolated as described previously for the 4,6-dichlorodideoxy cyclic sulphate derivative to yield a syrup which

crystallized on standing and gave a negative test with aniline–pyridine (7). Recrystallization from chloroform – *n*-hexane gave needles (2 g, 72%) which had m.p. 103–106° (decomp.) and $[\alpha]_D$ +69° (*c*, 2.28 in chloroform). The crystals showed a strong absorption frequency in the infrared spectrum at 1405 cm^{-1} and a weak absorption frequency at 1203 cm^{-1}. Analysis: Calc. for $C_{14}H_{16}O_8S$: C, 48.8; H, 4.7; S, 9.3. Found: C, 48.8; H, 4.7; S, 9.4. This compound was isolated previously by Bragg *et al.* (4).

When the above reaction was carried out at 60° as with the 4,6-dichlorodideoxy derivative, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and methyl α-D-glucoside were isolated and characterized as the only products.

Methyl 4,6-O-Benzylidene-2,3-anhydro-α-D-alloside

Methyl 4,6-*O*-benzylidene-α-D-glucoside 2,3-dichlorosulphate (0.25 g) was treated with 4.8 moles of sodium methoxide (1 ml of 2.5 *N* solution in methanol) by the method of Richtmyer and Hudson (20). It was observed that the chloroform solution gave a negative test with aniline–pyridine (7) immediately after the addition of the sodium methoxide. Therefore the chloroform solution was washed with distilled water, dried (anhydrous $NaSO_4$), and concentrated to a crystalline solid (0.032 g, 23.2%). Recrystallization from methanol gave needles of m.p. 200–201°, undepressed on admixture with authentic methyl 4,6-*O*-benzylidene-2,3-anhydro-α-D-alloside (9).

Methyl 4,6-O-Ethylidene-α-D-mannopyranoside 2,3-Dichlorosulphate

Methyl 4,6-*O*-ethylidene-α-D-mannoside (12) (4.2 g) was treated with sulphuryl chloride (10 ml) and redistilled pyridine (16 ml) in chloroform solution (7). Concentration of the chloroform extracts gave a brown syrup which was redissolved in chloroform and treated with charcoal. Filtration and concentration of the solution gave a yellow syrup which slowly crystallized (7.2 g, 90%). Recrystallization from light petroleum (b.p. 60–80°) gave colorless crystals (5 g, 63%) of m.p. 94–96° and $[\alpha]_D$ −10° (*c*, 1.8 in chloroform). The crystals gave a positive test with aniline–pyridine (7) and showed strong absorption frequencies in the infrared spectrum at 1417 cm^{-1} and 1200 cm^{-1}. Analysis: Calc. $C_9H_{14}O_{10}Cl_2S_2$: C, 25.9; H, 3.4; Cl, 17.0; S, 15.4. Found: C, 25.7; H, 3.3; Cl, 17.0; S, 15.2.

Methyl 4,6-O-Ethylidene-α-D-mannopyranoside 2,3-Cyclic Sulphate

The crystals above (4 g) were treated with redistilled pyridine (40 ml) by the same method as used previously with methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate. After treatment with charcoal the chloroform solution was filtered and concentrated to a light yellow syrup (1.5 g) which partially crystallized and gave a negative test with aniline–pyridine (7). The strong absorption frequencies shown by the product in the infrared spectrum at 1740 cm^{-1} and 1405 cm^{-1} indicated that it was a mixture containing a keto compound and a cyclic sulphate derivative. The presence of the keto compound was further substantiated by chromatographic analysis of the mixture in solvents (*a*) and (*b*), which showed the presence of one component at R_x 4.0 with *p*-anisidine hydrochloride (brown) and orcinol – trichloracetic acid (green) sprays. The cyclic sulphate ester was obtained by repeated crystallizations from methanol as colorless plates (0.35 g, 12%) of m.p. 163–164° (slow decomp.) and $[\alpha]_D$ −23° (*c*, 1.2 in chloroform). Analysis: Calc. for $C_9H_{14}O_8S$: C, 38.3; H, 5.0; S, 11.4. Found: C, 38.4; H, 5.5; S, 11.3.

Methyl 4,6-O-Ethylidene-2-deoxy-3-keto-α-D-erythro-hexoside

The mother liquors from the reaction above were concentrated to a syrup and dissolved in a small quantity of ether from which solution crystallization occurred. The crystals were recrystallized from ether – *n*-hexane, giving colorless needles (0.25 g, 14.5%) of m.p. 103–104° and $[\alpha]_D$ +155° (*c*, 1.23 in methanol). Analysis: Calc. for $C_9H_{14}O_5$: C, 53.4; H, 6.9. Found: C, 53.0; H, 6.6.

Reaction of Methyl 4,6-O-Ethylidene-α-D-mannopyranoside 2,3-Dichlorosulphate with Sodium Methoxide

The crystals of the 2,3-dichlorosulphate ester (2 g) were dissolved in methanol (25 ml) and treated with 3.8 moles of sodium methoxide (64 ml of 0.2 *N* solution in methanol). Both the solutions were previously cooled in an ice bath before mixing and the reaction mixture was kept at 0° for 16 hours. Excess sodium methoxide was decomposed by the addition of solid carbon dioxide and the methanol solution was concentrated to a syrup, which was dissolved in chloroform. The chloroform solution was washed with dilute sulphuric acid (10%) in order to disperse a gel formation and then with saturated sodium bicarbonate solution and distilled water. The chloroform solution was dried (anhydrous Na_2SO_4) and concentrated to a syrup (0.9 g) which gave a negative test with orcinol – trichloracetic acid (19) and showed the absence of carbonyl absorption in the infrared spectrum. Crystallization of the syrup occurred from ether – light petroleum (b.p. 40–60°) and two recrystallizations from methanol gave colorless plates (0.05 g) of m.p. 162–163° (decomp.) and $[\alpha]_D$ −26.5° (*c*, 1.25 in chloroform). Mixed melting point with the cyclic sulphate derivative obtained previously by the reaction of pyridine on the dichlorosulphate ester of methyl 4,6-*O*-ethylidene-α-D-mannoside was 159–164° (decomp.). The two cyclic sulphate esters also gave identical infrared spectrums (0.8% in potassium bromide).

Desulphation of Methyl 4,6-O-Ethylidene-α-D-mannopyranoside 2,3-Cyclic Sulphate

The crystals of the cyclic sulphate ester (0.35 g) were desulphated by the method of Bragg *et al.* (4) using methanolic ammonia and sulphuric acid to yield a syrup (0.15 g). Chromatographic examination of the

syrup in solvents (*a*) and (*b*) indicated that it was a reducing sugar which co-chromatographed with D-mannose. The phenylhydrazone derivative of the syrup had m.p. 186–187° (decomp.), undepressed on admixture with authentic D-mannose phenylhydrazone.

*Reduction of Methyl 4,6-O-Ethylidene-2-deoxy-3-keto-α-*D-erythro-*hexoside with Sodium Borohydride*

The crystals of the 2-deoxy-3-keto compound (0.35 g) were dissolved in ice-cold absolute ethanol (20 ml). Sodium borohydride (0.35 g) was added at 0° and the solution was stirred continuously until it gave a negative test with orcinol – trichloracetic acid (19) (40 hours). Acetone was then added to the solution to destroy the excess sodium borohydride. The solution was deionized (Amberlite IR.120 (H form) ion exchange resin) and the eluate was concentrated to a syrup, which was co-distilled with methanol to constant weight in order to remove boric acid. The resultant pale yellow syrup (0.33 g), which could not be obtained crystalline, was dissolved in 0.2 *N* sulphuric acid and the solution was heated at 60° for 14 hours. The solution was neutralized with barium carbonate, filtered, and passed through Amberlite IR.120 (H form) and Duolite A.4 (OH form) ion exchange resins and concentrated to a syrup (0.27 g, 88%) which crystallized on standing. Chromatographic analysis of the crystals in solvent (*c*) indicated one component at R_x 1.7 which chromatographed with 2-deoxy-D-allose (2-deoxy-D-*ribo*-hexose). Electrophoresis showed one component at M_g 0.64 which ran at the same speed as 2-deoxy-D-allose and a faint unidentified spot at M_g 0.77. Recrystallization from ethanol–ether gave colorless needles of $[\alpha]_D$ +57° (*c*, 0.76 in water) and m.p. 138°, undepressed on admixture with authentic 2-deoxy-D-allose (13).

The reduction was repeated using ethanol–water (1:1) as the solvent and crystalline 2-deoxy-D-allose was again isolated as the main product. In this case chromatographic analysis in solvent (*c*) did indicate a faint spot at R_x 1.5 which was found to chromatograph with authentic 2-deoxy-D-glucose, and this was confirmed by electrophoresis as it showed a trace of material at M_g 0.33 which ran at the same speed as 2-deoxy-D-glucose. However, 2-deoxy-D-glucose was not present in sufficient quantities to allow its isolation.

*Reaction of Methyl 4,6-O-Ethylidene-α-*D-*mannopyranoside 2,3-Cyclic Sulphate with Pyridine*

The crystals of the cyclic sulphate were treated with redistilled pyridine at 60° by the same method previously used with the dichlorosulphate ester of methyl 4,6-*O*-ethylidene-α-D-mannopyranoside (12). The pyridine solution gave a negative test with orcinol – trichloracetic acid spray (19) and the chloroform-soluble crystalline product was recrystallized from methanol and gave colorless plates of m.p. 163°, undepressed on admixture with the starting material.

*Methyl 4,6-O-Benzylidene-α-*D-*altropyranoside 2,3-Dichlorosulphate*

Methyl 4,6-*O*-benzylidene-α-D-altroside (20) (1.2 g) was treated with sulphuryl chloride (3.2 ml) and redistilled pyridine (5 ml) in chloroform solution (7). Concentration of the chloroform gave a syrup which rapidly crystallized. Recrystallization from chloroform – light petroleum (b.p. 30–60°) gave colorless needles (1.65 g, 82%) of m.p. 105–108° (slow decomp.) and $[\alpha]_D$ +25.5° (*c*, 1.2 in chloroform). The crystals gave a positive test with aniline–pyridine (7) and showed strong absorption frequencies in the infrared spectrum at 1410 cm^{-1}, 1192 cm^{-1} (chlorosulphate ester), 3010 cm^{-1}, and 1605 cm^{-1} (aromatic) and no hydroxyl absorption. The substance began to decompose rapidly and it was therefore quickly dissolved in chloroform. A fraction (A) of the chloroform solution was kept and the remainder was concentrated to a crystalline solid (B) and was treated with pyridine.

*Methyl α-*D-*Altroside 2,3-Dichlorosulphate*

The chloroform was allowed to evaporate slowly from fraction A, leaving a comparatively stable crystalline compound. Recrystallization from chloroform–ether gave colorless needles of the 2,3-dichlorosulphate of m.p. 120–122° (decomp.) and $[\alpha]_D$ +44° (*c*, 1.09 in dioxane). The crystals showed strong absorption frequencies at 3550 cm^{-1}, 3315 cm^{-1} (hydroxyl), 1410 cm^{-1}, and 1192 cm^{-1} (chlorosulphate ester) and no aromatic absorption in the infrared spectrum. Analysis: Calc. for $C_7H_{12}O_{10}Cl_2S_2$: C, 21.5; H, 3.0; Cl, 18.2; S, 16.4. Found: C, 21.3; H. 3.0; Cl, 18.5; S, 16.2.

*Reaction of Methyl 4,6-O-Benzylidene-α-*D-*altropyranoside 2,3-Dichlorosulphate with Pyridine*

The crystalline mass (B) from above (1 g) was dissolved in pyridine and left at 0° for 16 hours. The chloroform-soluble component was isolated as described in previous reactions with pyridine, and gave a negative test with aniline–pyridine (7). The solution was concentrated to a crystalline mass which was recrystallized from methanol–water to give needles (0.33 g, 60%) of m.p. 146° and $[\alpha]_D$ 107° (*c*, 0.98 in chloroform). Analysis: Calc. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1. Found: C, 63.5; H, 5.9. The physical constants and the analysis are consistent with those of methyl 4,6-*O*-benzylidene-2,3-anhydro-α-D-mannopyranoside (11). Chromatographic analysis of the methanol–water mother liquors in solvents (*a*) and (*b*) showed the presence of a component R_x 3.7 which gave a faint green color with orcinol – trichloracetic acid (19). The infrared spectrum of the residue from the mother liquors also showed a weak absorption frequency at 1700 cm^{-1} indicating the presence of a ketonic compound. However, it was not present in sufficient quantities for isolation.

Tetrachlorotetradeoxyhexitol Dichlorosulphate

D-Mannitol (10 g) was treated with sulphuryl chloride (26 ml) and pyridine (40 ml) in chloroform solution

(7). The chloroform extract was treated with charcoal, filtered, and concentrated to a yellow syrup, which slowly crystallized (16.7 g, 67%). Recrystallization from chloroform – light petroleum (b.p. 40–60°) gave colorless crystals of the dichlorosulphate derivative of m.p. 134° and $[\alpha]_D$ +41° (*c*, 1.07 in chloroform). Analysis: Calc. for $C_6H_8O_6Cl_6S_2$: C, 15.9; H, 1.8; Cl, 47.0; S, 14.1. Found: C, 15.9; H, 1.8; Cl, 47.8; S, 14.2.

Tetrachlorotetradeoxyhexitol Cyclic Sulphate

The crystalline hexitol derivative (3 g) was dissolved in pyridine (26 ml) and allowed to stand at ambient temperature for 24 hours. The chloroform-soluble product was isolated from the reaction mixture as described in previous reactions with pyridine. The chloroform extract was concentrated to a syrup (1.7 g, 80%) which crystallized on standing. Two recrystallizations from chloroform – light petroleum (b.p. 40–60°) gave yellow plates (0.5 g, 23%) of the cyclic sulphate derivative of m.p. 105° and $[\alpha]_D$ +104° (*c*, 1.0 in methanol). Analysis: Calc. for $C_6H_8O_4Cl_4S$: C, 22.6; H, 2.5; Cl, 44.7. Found: C, 22.6; H, 2.4; Cl, 44.8. The infrared spectrum of the compound showed a strong absorption frequency at 1410 cm^{-1} and a weak one at 1197 cm^{-1} (cyclic sulphate ester), and the physical constants and analysis indicate that it is identical with the compound isolated by Helferich *et al.* (2).

An attempt was made to dechlorosulphate the tetrachlorotetradeoxyhexitol dichlorosulphate (12 g) with sodium iodide (5 g) by the method used previously in the dechlorosulphation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-dichlorosulphate. The resultant chloroform solution was treated with charcoal, filtered, and concentrated to a syrup (4.2 g, 50%) which crystallized on standing. Recrystallization from ether – light petroleum (b.p. 40–60°) gave pale yellow plates of $[\alpha]_D$ +103° (*c*, 1.06 in methanol) and m.p. 105°, undepressed on admixture with the tetrachloro cyclic sulphate ester derivative obtained above.

1,2:5,6-Di-O-isopropylidene-D-mannitol 3,4-Cyclic Sulphate

1,2:5,6-Di-*O*-isopropylidene-D-mannitol (21) (6.5 g) was treated with sulphuryl chloride (13 ml) and pyridine (26 ml) in chloroform solution (7). The chloroform extract was concentrated to a syrup (10 g, 82%) which gave a positive test with aniline–pyridine (7) and which began to decompose rapidly. The syrup was dissolved in pyridine (40 ml) and left at ambient temperature for 8 hours and the chloroform-soluble product was isolated as described in previous reactions with pyridine. The resultant chloroform solution was concentrated to a syrup (3.5 g, 48%) which crystallized on standing. Successive recrystallizations from ether, methanol, and light petroleum (b.p. 30–60°) gave long colorless needles of m.p. 114–118° and $[\alpha]_D$ +41° (*c*, 0.6 in chloroform). Analysis: Calc. for $C_{12}H_{20}O_8S$: C, 44.4; H, 6.2; S, 9.9. Found: C, 44.6; H, 6.1; S, 9.8.

1,2:5,6 Di-O-isopropylidene-D-glucose 3-Chlorosulphate

Diacetone glucose (10 g) (22) was treated with sulphuryl chloride (26 ml) and pyridine (40 ml) in chloroform solution (7). Concentration of the chloroform extract gave a syrup which crystallized immediately and recrystallization from light petroleum (b.p. 60–80°) gave colorless needles (10 g, 72%) which had m.p. 92° and $[\alpha]_D$ −40° (*c*, 1.36 in chloroform). Analysis: Calc. for $C_{12}H_{29}O_8ClS$: C, 40.2; H, 5.3; Cl, 9.9; S, 8.9. Found: C, 40.2; H, 5.7; Cl, 9.9; S, 8.9. It was found to decompose rapidly in the atmosphere but could be kept for a longer period of time under vacuum over phosphoric oxide.

Dechlorosulphation of 1,2:5,6-Di-O-isopropylidene-D-glucose 3-Chlorosulphate

The crystals above (2 g) were dechlorosulphated using sodium iodide (2 g) as described previously for the dechlorosulphation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-dichlorosulphate. The barium carbonate was filtered from the methanol solution and the filtrate was concentrated to a syrup, which was dissolved in water and extracted with ether. Concentration of the ethereal extract gave a crystalline mass, which was recrystallized from light petroleum (b.p. 40–60°) to give needles (0.6 g, 41%) of m.p. 107–108°, undepressed on admixture with authentic 1,2:5,6 di-*O*-isopropylidene-D-glucose (22).

When the monochlorosulphate ester of di-*O*-isopropylidene-D-glucose was dissolved in pyridine and the solution was kept at 0° for 8 hours, di-*O*-isopropylidene-D-glucose was isolated in good yield (melting point undepressed on admixture with an authentic sample).

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