REACTIONS OF SUGAR CHLOROSULFATES

PART V. THE SYNTHESIS OF CHLORODEOXY SUGARS[1]

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ABSTRACT

The reaction of sulfuryl chloride with reducing sugars and their methyl glycopyranosides was shown to produce fully substituted pyranose derivatives containing both chlorodeoxy and chlorosulfate ester groups. It was demonstrated that the chlorodeoxy groups were formed by nucleophilic displacement (S_N2) by chloride ion of specific reactive chlorosulfate groups in fully chlorosulfated intermediates. The degree of chloro-substitution was shown to be determined by both steric and electronic effects in the individual pyranose derivatives.

INTRODUCTION

The first direct nucleophilic substitution (S_N2) at a secondary carbon atom in a pyranose ring was achieved by Helferich (1) through the use of sulfuryl chloride. Proof of the expected change of sterochemistry at C_4 of methyl α-D-glucopyranoside when it reacts with sulfuryl chloride to give methyl 4,6-dichloro-4,6-dideoxy α-D-galactopyranoside 2,3-cyclic sulfate was given later (2). When a reduced pyridine – sulfuryl chloride ratio was employed, both D-glucose (3) and methyl α-D-glucopyranoside (4) also gave 4,6-dichloro-4,6-dideoxy-D-galactopyranoside derivatives but with positions C_2 and C_3 substituted by chlorosulfate ester groups. Most of the work recorded to date on the reaction of sulfuryl chloride with pyranose sugars (1–7) has been concerned with those in the xylo- or arabino-configuration and has indicated that position C_4 is the only secondary hydroxyl group to be converted readily to a chlorodeoxy group, with inversion of configuration. This inversion of configuration probably occurs via intermediate chlorosulfate ester groups (1–7). Positions C_2 and C_3 were found to be comparatively unreactive to chloro-substitution. This result is analogous to the substitution of the tosyl esters of methyl glucopyranosides with chloride ion (8), although the conclusion of the authors that the C_4 secondary tosyl ester group is more prone to nucleophilic substitution than the primary exocyclic C_6 tosyl ester in monosubstitution is probably incorrect. The isolation of chloro-sulfate esters under conditions which suppressed the formation of the cyclic sulfate ester derivatives (3) prompted a further study of the individual reactivities of all the chloro-sulfate esters of pyranose sugars in regard to competitive nucleophilic substitution. Besides the obvious objective of the synthesis of chlorodeoxy sugars, it was hoped to relate the high degree of selectivity found in the substitution of chlorosulfate esters in the pyranose ring structures to steric effects in each individual molecule.

DISCUSSION

Structural Determinations

In a previous communication (4) it was reported that methyl α-D-glucopyranoside when treated with sulfuryl chloride gave, at room temperature, methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulfate (III). When the above reaction was repeated, except that the product was isolated from the reaction mixture at low temperature (−70°), a crystalline tetrachlorosulfate ester derivative (I) was obtained. It was

[1]*Part IV in this series was a paper by H. J. Jennings and J. K. N. Jones. Can. J. Chem. 41, 1151 (1963).*
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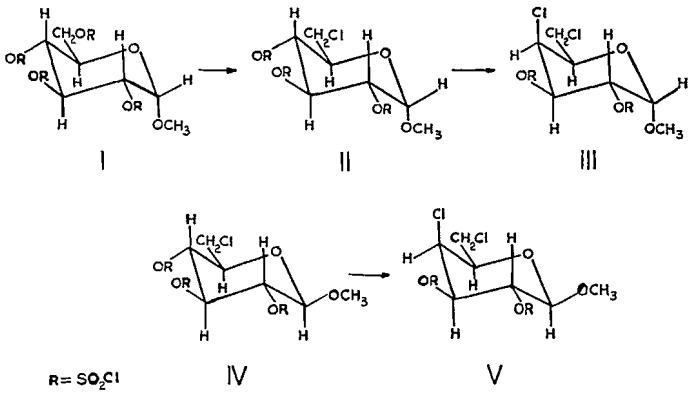
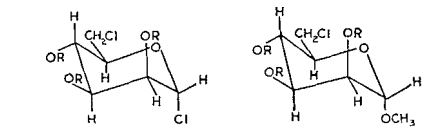
shown to be a derivative of methyl α-D-glucopyranoside because, on treatment with 1 mole of pyridine hydrochloride, it gave crystalline methyl 6-chloro-6-deoxy-α-D-glucopyranoside 2,3,4-trichlorosulfate (II). Compound II had been obtained previously from the product when the reaction of methyl α-D-glucopyranoside with sulfuryl chloride was carried out at 0°. The structure of II was ascertained by removal of the chlorosulfate ester groups (4) to give crystalline methyl 6-chloro-6-deoxy-α-D-glucopyranoside (9). Periodate oxidation of this monochloro-hexoside led to an uptake of periodate (1.99 mole) and the production of acid (1.07 mole). These figures are those expected from the oxidation of a 6-chloro-substituted derivative.

Methyl β-D-glucopyranoside, when treated with sulfuryl chloride, using the conditions which previously gave III, yielded a crystalline product which was shown to be methyl 6-chloro-6-deoxy-β-D-glucopyranoside 2,3,4-trichlorosulfate (IV), since dechlorosulfation gave crystalline methyl 6-chloro-6-deoxy-β-D-glucopyranoside (10). Periodate oxidation of this monochloro-hexoside gave results consistent only with those expected from a 6-chloro-substituted pyranose derivative. When IV was heated with pyridine hydrochloride in chloroform solution, there resulted further chloro-substitution, and the major product was shown to be V. The syrupy reaction product was dechlorosulfated and gave a non-reducing crystalline mixture from which a pure component could not be isolated. The major component of this mixture was methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (3) since its acid hydrolysis gave three reducing components (paper chromatography), the major and fastest running of which was characterized as crystalline 4,6-dichloro-4,6-dideoxy-D-galactose (2).



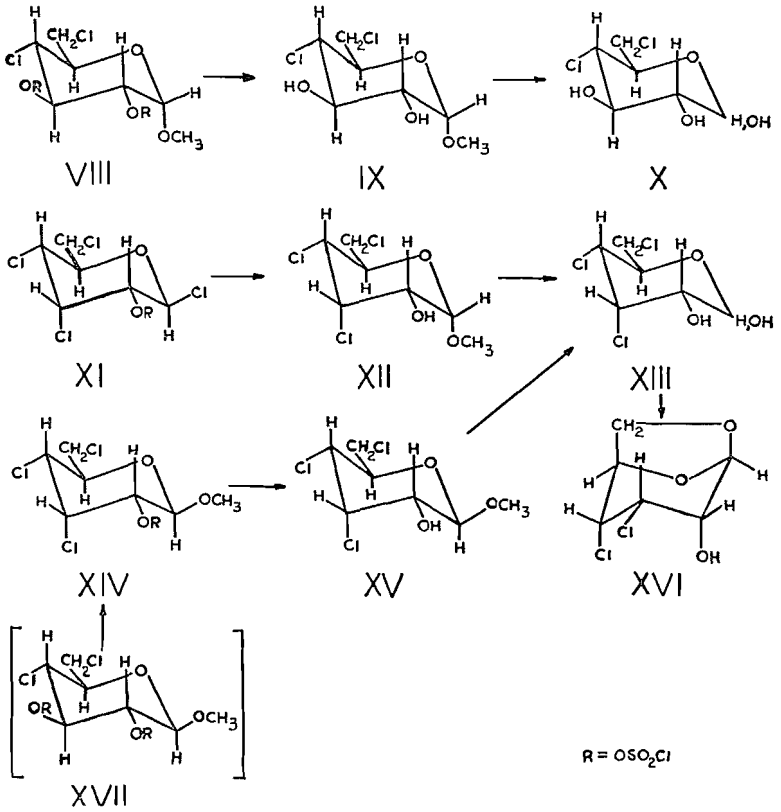
D-Mannose, when treated with sulfuryl chloride, gave a crystalline product (VI) which was shown to be 6-chloro-6-deoxy-α-D-mannosyl chloride 2,3,4-trichlorosulfate on the following evidence. The compound (VI) was considered to be the α-anomer by the similarity of its specific rotation to that of α-tetra-*O*-acetyl-D-mannopyranosyl chloride (11). Methanolysis and subsequent dechlorosulfation of VI gave a non-reducing syrupy mixture, the major component of which was shown to be methyl 6-chloro-6-deoxy-α-D-mannopyranoside. Hydrolysis of the syrupy mixture gave another syrup, which was shown to be a mixture containing three reducing components (paper chromatography), one of which (major component) was characterized as 6-chloro-6-deoxy-D-mannose in the following manner. The syrupy mixture of reducing compounds gave a crystalline 3,5-dichlorophenylhydrazone in good yield, from which a chromatographically pure monochloro-hexose was regenerated (12). The pure monochloro-hexose did not crystallize, but

gave a crystalline phenylhydrazone, which, on further heating with phenylhydrazine, gave a crystalline phenylosazone identical with the phenylosazone of authentic 6-chloro-6-deoxy-D-glucose (3). Dechlorosulfation of the crystalline derivative (VII) obtained from the reaction of sulfuryl chloride with methyl α-D-mannopyranoside gave a syrupy non-reducing mixture which had the same specific rotation as the mixture of glycosides obtained previously by the methanolysis and dechlorosulfation of VI. The syrupy mixture obtained from VII was converted to crystalline methyl 3,6-anhydro-α-D-mannopyranoside (13) by base, while hydrolysis of the mixture gave 6-chloro-6-deoxy-D-mannose as the major product (characterized as its crystalline phenylhydrazone).



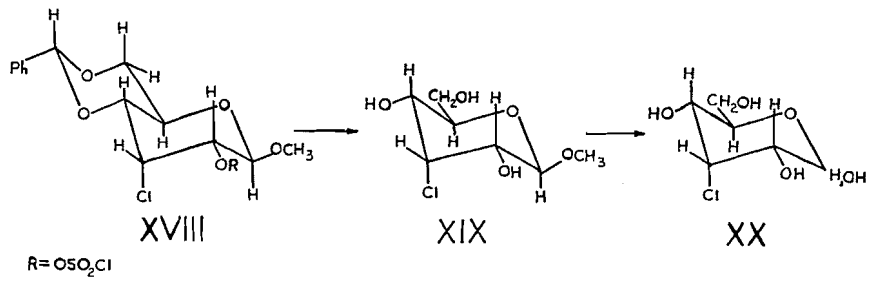
Methyl α-D-galactopyranoside, when treated with sulfuryl chloride, gave methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside 2,3-dichlorosulfate (VIII), the structure of which was proved by dechlorosulfation of VIII to give crystalline methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (IX) (2). Hydrolysis of IX, which required vigorous conditions, gave crystalline 4,6-dichloro-4,6-dideoxy-D-glucose (X). D-Galactose, when treated with sulfuryl chloride, gave a syrupy product which was shown to contain 3,4,6-trichloro-3,4,6-trideoxy-D-allopyranosyl chloride 2-chlorosulfate (XI). Methanolysis and subsequent dechlorosulfation of XI gave a crystalline derivative (XII) which was shown to have the structure methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside on the basis of the following evidence. Elemental analysis of XII and of its crystalline tosyl ester and methyl ether derivatives proved it to be a trichloro-substituted compound. Hydrolysis of XII gave a crystalline trichlorohexose (XIII), which was also obtained directly from the syrupy mixture containing XI, by treatment of an aqueous acetone solution of the syrupy mixture with sodium iodide. The trichlorohexose (XIII) gave a crystalline *p*-nitrophenylhydrazone also containing three chlorine atoms. The same crystalline trichlorohexose was also formed in the hydrolysis of XV, which was obtained by dechlorosulfation of the reaction product (XIV) of methyl β-D-galactopyranoside with sulfuryl chloride. This implied that XV was the β-anomer of XII. That chloro-groups were present on C_6 and C_4 of XII, the one at C_4 having been introduced with inversion of configuration, was ascertained by the fact that further reaction of 4,6-dichloro-D-glucose (X) with sulfuryl chloride gave a syrupy product, which, on methanolysis and subsequent dechlorosulfation, gave XV as the major product of a mixture of methyl glycosides (thin-layer chromatography). Hydrolysis of the mixture of methyl glycosides also gave crystalline XIII as the major component of the hydrolysate. Evidence that XII was a 3,4,6-trichloro-trideoxy-D-allose derivative was obtained, although some preliminary experiments had suggested that the third chloro-group was in fact situated at C_2 of XIII. These later experiments included (*a*) the inability to reform the methyl glycoside of XIII using methanolic hydrogen chloride; (*b*) the failure to obtain a phenylosazone or a 1;2-*O*-isopropylidene derivative of XIII; (*c*) the failure to form a trichlorotrideoxy hexitol by reduction under acidic conditions of XIII; (*d*) the unusually slow uptake of periodate by XIII (14); and (*e*) a negative tetrazolium red test (15) on XIII. A probable explanation for some of these anomalous reactions can be attributed to an axial chloro-group on C_3 of XIII which is in close proximity to C_1, and could hinder reactions at this site. That the third chloro-group was,

in fact, at C_3 of XII was established by paper electrophoresis of XIII in borate buffer, where XIII had a comparable electrophoretic mobility to 3,4,6-tri-*O*-methyl-D-glucose, whereas 2,4,6-tri-*O*-methyl-D-glucose is known not to move under these conditions (16). Evidence for chloro-substitution having occurred with inversion of configuration on C_3 of XII (allo-configuration) is the fact that elimination of chloride ion did not take place under basic conditions and this is consistent with the chloro-group at C_3 of XII being cis to the hydroxyl group at C_2 (2). Also the trichlorohexose (XIII) obtained from XII was immediately converted to a crystalline non-reducing derivative (XVI) by 1 mole of sodium hydroxide. The elemental analysis of XVI was consistent with the structure 1,6-anhydro-3,4-dichloro-3,4-dideoxy-β-D-allopyranose, and as the formation of the 1,6-anhydro derivative (XVI) requires the trichlorohexose (XIII) to change to the Cl conformation, it is likely that the axial chloro-group on C_3 of XIII facilitated this change.



Although the structure of XII has been fairly well established, a further experiment was performed to avoid the complication of three-chloro-groups being attached to the product. A configurational analogue of X methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (17) was treated with sulfuryl chloride on the assumption that chloro-substitution with inversion of configuration would take place at C_3 of the 4,6-*O*-benzylidene derivative. The product of the reaction was a syrup, which on dechlorosulfation gave a mixture of two components, the minor component of which was characterized as the crystalline starting compound. The major component was characterized as syrupy methyl 3-chloro-3-deoxy-4,6-*O*-benzylidene-β-D-allopyranoside (XVIII) on the following evidence. Mild hydrolysis of

XVIII gave a syrupy derivative (XIX) which had lost the benzylidene group and was shown to be pure by gas–liquid chromatographic analysis of its triacetate derivative. The triacetate derivative of XIX did not crystallize but analyzed as a monochloro-triacetate methyl glycoside. That the chloro-group of XIX was on C_3 was indicated by the fact that XIX remained resistant to periodate oxidation and also that hydrolysis of XIX gave a syrupy monochlorohexose (XX), the electrophoretic mobility of which in borate buffer was comparable to that of 3-*O*-methyl-D-glucose and not to that of 2-*O*-methyl-D-glucose (16). Finally, XIX was assigned the allo-configuration as treatment of XIX with base gave no elimination of chloride ion; it is known that 3-chloro-3-deoxy-α-D-glucopyranoside as its 4,6-*O*-benzylidene derivative eliminates chloride ion under basic conditions (18). It might be supposed, however, that XIX might eliminate chloride ion under more drastic conditions to give methyl 3,6-anhydro-β-D-glucopyranoside. To check this possibility, XIX was heated in sodium hydroxide solution but was recovered unchanged. The triacetate derivative of the product had the same retention time as the triacetate derivative of XIX (gas–liquid partition chromatography). Also, hydrolysis of the recovered product gave a compound which had the same electrophoretic mobility as XX in borate buffer and a different mobility from that of 3,6-anhydro-D-glucose (13) in molybdate buffer.



Mechanism of the Substitution Reaction

In all the cases studied so far (2–4) and in the evidence submitted in this publication, the chlorodeoxy products formed from secondary pyranose ring hydroxyl groups have been shown to be formed with inversion of configuration. Thus the reaction seems to fall into the category of a bimolecular nucleophilic substitution reaction (S_N2) on stereochemical grounds. That the chlorosulfate ester group is the precursor of the chlorodeoxy groups is well established. Low temperature isolations of the products of the reaction of methyl α-D-glucopyranoside with sulfuryl chloride in the presence of pyridine gave the tetrachlorosulfate (I) and the 6-chloro-trichlorosulfate (II) intermediates (isolated at −70° and 0° respectively), whereas the usual reaction conditions (3) gave the 4,6-dichloro-dichlorosulfate derivative (III). It is probable therefore that at higher temperatures the reactive chlorosulfate groups on C_6 and C_4 of I are replaced by chloride ion (pyridine hydrochloride), which is itself formed in the esterification of the hydroxyl groups. Both the intermediates (I and II) were converted smoothly to the 4,6-dichloroderivative (III) by excess pyridine hydrochloride in chloroform solution and also the tetrachlorosulfate derivative (I) was converted to the 6-chloro derivative (II) by 1 mole of pyridine hydrochloride using similar conditions. The latter experiment eliminates the possibility of the regeneration of pyridine hydrochloride in the substitution reaction (catalytic effect) and also the thermal decomposition of the chlorosulfate ester group under the conditions used.

It is interesting to note that treatment of the chlorosulfate ester derivatives with iodide ion (sodium iodide) in 6% aqueous methanol solution did not give the corresponding iododeoxy compounds. For example, the 6-chloro-trichlorosulfate derivative (II) gave only methyl 6-chloro-6-deoxy-α-D-glucopyranoside (9) on treatment with sodium iodide. This removal of chlorosulfate ester groups to give the corresponding hydroxyl groups with retention of configuration was found to be of wide application and constitutes an efficient and fast method of dechlorosulfation. Only one exception to this general reaction pattern has been recorded (4) where vicinal chlorosulfate ester groups in the open-chain hexitol series gave a cyclic-sulfate ester derivative when treated with sodium iodide.

Steric Effects

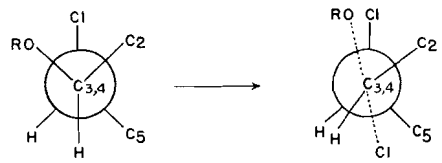
In all the experiments carried out on the reaction of sulfuryl chloride with hexopyranoses and hexopyranosides, chloro-substitution on the primary C_6 position (via the intermediate 6-chlorosulfate ester) was facile. That the C_6 chlorosulfate ester was also the most reactive one was demonstrated by the fact that methyl α-D-glucopyranoside tetrachlorosulfate (I) gave only the 6-chloro-substituted derivative (II) when treated with 1 mole of pyridine hydrochloride. These results were expected on the basis of previous work (19) and a probable explanation is that the approach of the chloride ion to the exocyclic C_6 position is not sterically hindered by other large groups in the pyranose ring.

Only the derivatives in the D-manno-configuration failed to give chloro-substitution at position C_4 under the normal conditions of the reaction (3). This result could be interpreted as due to 1;3-diaxial interaction between the approaching chloride ion at C_4 and the large axial chloro-sulfate group at C_2 in VI and VII. This is supported by the fact that II, which differed from VII only in the configuration of the C_2 chlorosulfate group, gave good yields of the methyl 4,6-dichloro-D-galactoside derivative (III) under similar experimental conditions. Further evidence of these 1;3-diaxial interactions was found in the D-galacto-series. Both D-galactose and methyl β-D-galactopyranoside gave 3,4,6-trichloro-D-allose derivatives (XI and XIV respectively) whereas methyl α-D-galactopyranoside under similar reaction conditions gave only a 4,6-dichloro-D-glucose derivative (VIII), which was shown to be resistant to further chloro-substitution even when heated at 50° with pyridine hydrochloride in chloroform solution. Crystalline VIII was recovered from the reaction mixture and examination (g.l.p.c.) of the dechlorosulfated residual syrupy product indicated a preponderance of the 4,6-trichloro-derivative (IX) and only a very minor quantity of the 3,4,6-trichloro-derivative (XII). This evidence indicated an effect that was due to the anomeric substituent of VIII, which could be interpreted as 1;3-diaxial interaction to the approach of the chloride ion to C_3 by the axial methyl-glycosidic group of VIII. This effect is not present in XIV (methyl β-glycoside) and there is some evidence that is not present in XI since it is probable that XI is the β-chloro anomer ($[\alpha_D] = -30°$). In any event, even if XI were the α-chloro anomer, it is likely that anomerization could occur under the reaction conditions used. Another example of the 1;3-diaxial interaction effect, concerning the methyl glycosidic group, is found in the reaction of sulphuryl chloride with the 4,6-*O*-benzylidene derivatives of methyl α- and β-D-glucopyranosides. The α-anomer has been shown to give a 2,3-dichlorosulfate derivative (4), whereas under similar reaction conditions the β-anomer gave mainly a 3-chloro-substituted D-alloside derivative (XVIII).

Although nucleophilic substitution by chloride ion at position C_3 is controlled by the configuration of the anomeric substituent, other factors have to be considered. Both methyl α- and β-D-glucopyranoside gave only 4,6-dichloro-substituted derivatives (III

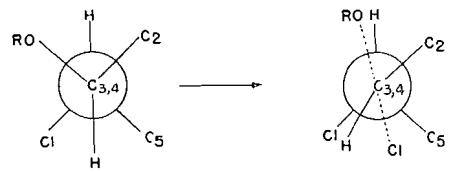
and V respectively), whereas it might have been expected that the methyl β-glycoside would have given a 3,4,6-trichloro-D-gulose derivative. The fact that no substitution by chloride ion occurred on C_3 of V indicated a deactivating effect by the axial chloro-group at C_4 of V. This deactivating effect by an axial substituent at C_4 was also observed in the reaction of sulfuryl chloride with D-glucose and 4,6-*O*-ethylidene-D-galactose: the former gave a 4,6-dichloro-D-galactose derivative (3) and the latter only a 2,3-dichloro-sulfate derivative. In contrast, compounds which had a configuration identical with that of V except for an equatorial substituent at C_4 (methyl 4,6-*O*-benzylidene-β-D-glucopyranoside and 4,6-dichloro-4,6-dideoxy-D-glucose (X)) gave facile chloro-substitution at C_3. In view of this evidence it is also probable that XVII was the unidentified intermediate in the formation of XIV.

The deactivation of an equatorial chlorosulfate ester group by a vicinal axial substituent cannot be explained by steric affects because of the approach of the chloride ion at C_3 of V, as an examination of a model of V indicates that there are no large groups in proximity to this approach. However, a possible explanation can be found by consideration of the transition state in the substitution reaction. Reaction of V with Cl^- would involve the formation of a transition state possessing considerable skew interactions due to the near-eclipsed conformation of the large substituents on C_3 and C_4. This is illustrated in XXI



XXI XXII

and XXII, representing the end-on views (20) of the C_3—C_4 bond of V and of the transition state respectively. This could raise the energy requirements of the transition state (XXII) considerably. When the chloro-group on C_4 is equatorial as in X and in the intermediate XVII, similar skew interactions would be avoided, giving a transition state (XXIV) of lower energy than XXII. This is indicated by the end-on representations of the C_3—C_4 bond of XVI in the ground state (XXIII) and in the transition state (XXIV). Similar skew interactions have been postulated to explain the large differences in the rates of nucleophilic substitution of highly substituted erythro- and threo-bromobenzenesulfonate derivatives (21).



XXIII XXIV

$R = SO_2Cl$

All of the derivatives discussed so far have, as a common feature, the relative inertness of the C_2 chlorosulfate ester group to nucleophilic substitution by chloride ion. This observation cannot be justified on the basis of steric interactions as it might be expected that the chlorosulfate ester groups on C_2 and C_4 of IV would be equally active as they are

both in a similar conformational environment. However, compound IV gave mainly a 4,6-dichloro-D-galactoside derivative (V), when heated with pyridine hydrochloride in chloroform solution. This might be explained by the fact that the ester groups on C_2 and C_4 of IV are in different electronic environments. Thus position C_2 of IV is in the proximity of two β-oxygen atoms (ring oxygen and anomeric group) whereas C_4 is only in the proximity of one (ring oxygen). This explanation has some credence as it is known that β-methoxyl substituents do retard considerably the rate of nucleophilic substitution (22). However, it is possible that C_2 chloro-substitution may have occurred in D-mannose as discussed below. The 6-chloro-substituted derivative (VI), obtained from the reaction of D-mannose with sulfuryl chloride, gave a tetrachloro-substituted derivative on further heating with pyridine hydrochloride in chloroform solution, whereas VII was resistant to further chloro-substitution. It could be argued that to obtain further substitution of VI the deactivating influence of the axial C_2 chlorosulfate ester group would have to be removed. This could be achieved by chloro-substitution at C_2 of VI to produce an equatorial chlorodeoxy group at this position. This would then allow the normally reactive C_4 ester group VI to be substituted and thus one might postulate a 1,2,4,6-tetrachloro-D-galacto-configuration for the product. Further structural studies on this tetrachloro-substituted product are being carried out.

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°. Aqueous solutions were deionized by passage through Amberlite I.R. 120 (H form) and Duolite A.4 (OH form) ion exchange resins. 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). The rates of movement of the sugars are quoted relative to that of D-xylose (R_x). Paper electrophoresis was performed using Whatman 3 MM filter paper impregnated with buffer solutions: (i) 0.05 *M* borate solution (23) and (ii) 2% aqueous solution of sodium molybdate (24). The rates of movement of sugars in (i) are given relative to that of D-glucose (M_g) and in (ii) relative to that of sorbitol (M_s). Sugars were detected on paper chromatograms and electrophoretograms by *p*-anisidine hydrochloride (25) and (or) alkaline silver nitrate (26) spray reagents. Thin-layer chromatographic analysis (t.l.c.) was carried out on prepared silica gel G plates.

Analytical gas–liquid chromatographic analysis (a.g.l.c.) was carried out using a Pye Argon gas chromatograph with the following column packings: (A) 1:1:2 intimate mixture of 20% w/w butanediol–succinate polyester on 60–80 mesh Chromosorb W, 20% w/w Apiezon M grease on 60–80 mesh silver-coated Chromosorb W, 0.3% w/w Apiezon M grease on 60 plus mesh silver-coated glass beads, at 175° with a flow rate of 145 ml per min; (B) 10.7% of LAC-4R-886 on 100–120 mesh Chromosorb W at 207° with a flow rate of 160 ml per min.

Anhydrous pyridine hydrochloride was made by passing dry gaseous hydrogen chloride into a petrol solution of anhydrous pyridine. The precipitated pyridine hydrochloride was collected by filtration, quickly washed with petrol, and stored in a desiccator over phosphoric oxide.

Periodate oxidations were carried out in the dark at 25°, using a small sample (20 mg) of the compounds in distilled water (25 ml) containing 0.3 *M* sodium metaperiodate (1 ml). Aliquots (1 ml) were removed at intervals and the consumption of periodate (27) and the production of acid (28) were measured.

Methyl α-D-Glucopyranoside 2,3,4,6-Tetrachlorosulfate (I)

Methyl α-D-glucopyranoside (10 g) was treated with sulfuryl chloride (26 ml) and pyridine (40 ml) in chloroform solution as described in a previous communication (3), except that the reaction mixture, while still at the temperature of the acetone – solid carbon dioxide bath (ca. −70°), was quickly poured into a vigorously stirred solution of ice-cold 10% sulfuric acid (1 000 ml). The product (8.7 g, 29%) was recrystallized from chloroform–petrol (b.p. 50–60°) and gave colorless needles (7 g, 23%) of m.p. 118° and $[\alpha]_D$ +92° (*c*, 0.8 in chloroform).

Anal. Found: C, 14.6; H, 1.7; Cl, 24.6; S, 22.5. Calcd. for $C_7H_{10}Cl_4O_{14}S_4$: C, 14.6; H, 1.7; Cl, 24.2; S, 21.8.

Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside 2,3,4-Trichlorosulfate (II)

The above reaction was repeated using methyl α-D-glucopyranoside (10 g), except that the reaction mixture was allowed to warm up slowly to 0° and then was poured, at this temperature, into a vigorously stirred

solution of ice-cold 10% sulfuric acid (1 000 ml). The crystalline chloroform-soluble product was recrystallized twice from chloroform–petrol (b.p. 35–60°) and gave large colorless prisms (15.5 g, 59%) of m.p. 90–91° and $[\alpha]_D$ +115° (*c*, 0.9 in chloroform).

Anal. Found: C, 16.3; H, 1.9; Cl, 28.2; S, 19.0. Calcd. for $C_7H_{10}Cl_4O_{11}S_3$: C, 16.5; H, 2.0; Cl, 27.9; S, 18.9.

Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside

The compound II (5 g) was dissolved in methanol and dechlorosulfated as described previously (4). The product (2.5 g, 60%) was recrystallized from benzene–methanol to give colorless plates (1.5 g, 36%) of m.p. 110–111° and $[\alpha]_D$ +187° (*c*, 1.25 in water). The physical constants are consistent with those reported for methyl 6-chloro-6-deoxy-α-D-glucopyranoside (9).

Periodate Oxidation of Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside

The moles of periodate consumed and the moles of formic acid produced were respectively as follows: 0.57, 0.26 (1 h); 1.60, 0.71 (7 h); 1.91, 1.05 (21 h); 1.99, 1.07 (46 h).

Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside 2,3,4-Trichlorosulfate (II)

Methyl α-D-glucopyranoside 2,3,4,6-tetrachlorosulfate (8 g) was dissolved in chloroform (70 ml) and anhydrous pyridine hydrochloride (1.6 g, 1 mole) was added, and the solution was heated at 40–50° for 2 h. The chloroform solution was then washed with sodium bicarbonate solution and distilled water and dried over anhydrous sodium sulfate. Concentration of the chloroform solution gave a syrup which crystallized. Recrystallization from chloroform–petrol (b.p. 40–60°) gave large colorless plates (4.5 g, 65%) of m.p. 90–91°, undepressed on admixture with previously prepared methyl 6-chloro-6-deoxy-α-D-glucopyranoside 2,3,4-trichlorosulfate.

Methyl 4,6-Dichloro-4,6-dideoxy-α-D-galactopyranoside (III)

Compound I (1.1 g) was dissolved in chloroform (20 ml) and after the addition of anhydrous pyridine hydrochloride (1 g, 4.4 mole) the solution was heated at 40–50° for 8 h. The product isolated as described above was dechlorosulfated (4) and the resulting solid was recrystallized from chloroform–petrol (b.p. 40–60°) to give needles (0.42 g, 84%) of m.p. 158°, undepressed on admixture with authentic methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (2).

Methyl 6-Chloro-6-deoxy-β-D-glucopyranoside 2,3,4-Trichlorosulfate (IV)

Methyl β-D-glucopyranoside (4.5 g), prepared from acetobromglucose (29), was treated with sulfuryl chloride (12 ml) and pyridine (18 ml) in chloroform solution (3). Removal of the solvent gave a product (6 g, 54%) which was recrystallized from chloroform–petrol (b.p. 40–60°) to give colorless needles (1.1 g, 10%)* of m.p. 134–135° and $[\alpha]_D$ +1.7° (*c*, 1.2 in chloroform).

Anal. Found: C, 16.7; H, 2.0; Cl, 27.5; S, 18.9. Calcd. for $C_7H_{10}Cl_4O_{11}S_3$: C, 16.5; H, 2.0; Cl, 27.9; S, 18.9.

Methyl 6-Chloro-6-deoxy-β-D-glucopyranoside

The crystals of IV (0.5 g) were dechlorosulfated as described previously (4) and the product (0.2 g, 95%) was recrystallized from benzene–methanol to give large colorless crystals of m.p. 157–159° and $[\alpha]_D$ −50° (*c*, 1.0 in water) (10).

Periodate Oxidation of Methyl 6-Chloro-6-deoxy-β-D-glucopyranoside

The moles of periodate consumed and the moles of formic acid produced per mole of sugar were respectively as follows: 0.60, 0.28 (1 h); 1.65, 0.75 (7 h); 1.90, 0.98 (21 h); 1.98, 1.00 (46 h).

Methyl 4,6-Dichloro-4,6-dideoxy-β-D-galactopyranoside (V)

The crystals of methyl 6-chloro-6-deoxy-β-D-glucopyranoside 2,3,4-trichlorosulfate (4 g) were dissolved in chloroform and anhydrous pyridine hydrochloride (4 g) was added to the solution. The chloroform solution was heated at 50° for 14 h and the syrupy product (3 g) isolated in the usual way had $[\alpha]_D$ −5.5° (*c*, 0.9 in chloroform). Dechlorosulfation (4), followed by continuous extraction with chloroform, gave a crystalline residue of m.p. 142°. Recrystallization from chloroform–petrol (b.p. 35–60°) gave colorless needles (1.2 g, 75%) of m.p. 144–146° and $[\alpha]_D$ −16° (*c*, 1.2 in water). Successive recrystallizations from ether did not raise the melting point to that of authentic methyl 4,6-dichloro-4,6-dideoxy-β-D-galactoside (m.p. 154°) (3).

4,6-Dichloro-4,6-dideoxy-D-galactose

A solution of the above impure preparation of V (0.4 g) was refluxed in *N* sulfuric acid (50 ml) for 16 h. The acidic solution was neutralized ($BaCO_3$) and filtered. Concentration of the aqueous solution gave colorless, syrupy crystals (0.3 g), paper chromatographic analysis in solvent *a* indicated the presence of three reducing components at R_x 1.4 (slight), R_x 2.2 (slight), and R_x 2.9 (intense). The component at R_x 2.9 was found to be chromatographically indistinguishable from 4,6-dichloro-4,6-dideoxy-D-galactose (5). Recrystallization of the syrupy crystals from methanol–water gave colorless crystals (0.1 g, 27%) of m.p. 184–186°, undepressed in admixture with authentic 4,6-dichloro-4,6-dideoxy-D-galactose (5).

**A repetition of this experiment, by Mr. A. Cottrell, showed (t.l.c.) that the non-crystalline material was mainly the 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside derivative.*

6-Chloro-6-deoxy-α-D-mannosyl Chloride 2,3,4-Trichlorosulfate (VI)

D-Mannose (25 g) was treated with sulfuryl chloride (63 ml) and pyridine (100 ml) in chloroform solution (3), and the reaction mixture was allowed to stand at room temperature for 7 h before isolation of the product as described above. Concentration of the chloroform extracts and recrystallization of the residue (31 g,) 44% from chloroform–petrol (b.p. 40–60°) gave large colorless crystals (15 g, 21%) of m.p. 156° and $[\alpha]_D$ +52° (*c*, 1.2 in chloroform).

Anal. Found: C, 14.3; H, 1.2; Cl, 34.5; S, 18.5. Calcd. for $C_6H_7Cl_5O_{10}S_3$: C, 14.1; H, 1.3; Cl, 34.6; S, 18.6.

Methyl 6-Chloro-6-deoxy-α-D-mannopyranoside

A solution of VI (10 g) in anhydrous methanol (100 ml) was refluxed for 8 h. The resulting glycoside(s) were dechlorosulfated (4) and the product, a colorless syrup (4.0 g, 96%) had $[\alpha]_D$ +60° (*c*, 1.0 in water). Paper chromatograms developed in solvent *a* and sprayed with periodic acid – *p*-anisidine hydrochloride (30) indicated that the syrup contained three components at R_x 2.1 (trace), R_x 2.5 (slight), and R_x 3.0 (intense). All of the components were non-reducing (negative test with *p*-anisidine hydrochloride).

6-Chloro-6-deoxy-D-mannose

The above syrup (3.0 g) was dissolved in *N* sulfuric acid and the solution was boiled for 7 h. The solution was neutralized with barium carbonate and filtered. Concentration of the aqueous solution gave a syrup (2.5 g). Paper chromatographic analysis in solvent *a* indicated three reducing components at R_x 0.7 (trace), R_x 1.6 (slight), and R_x 2.1 (intense). The syrup (0.8 g) gave a crystalline 3,5-dichloro phenylhydrazone which was recrystallized from chloroform–ethyl acetate to give yellow plates (0.9 g, 62%) of m.p. 149° (decomp.).

Anal. Found: C, 39.9; H, 4.1; Cl, 29.6; N, 8.0. Calcd. for $C_{12}H_{15}Cl_3N_2O_4$: C, 40.2; H, 4.2; Cl, 29.8; N, 7.8.

The 3,5-dichlorophenylhydrazone (0.8 g) was converted to the reducing sugar by the procedure of Sowden and Fischer (12). Concentration of the water-soluble fraction gave a colorless syrup (0.35 g, 79%) $[\alpha]_D$ +18° (*c*, 1.0 in water) which was shown to be chromatographically pure in solvents *a* and *b*. The syrup with phenylhydrazine in the cold gave a crystalline phenylhydrazone, m.p. 141–142° (decomp.).

Anal. Found: C, 50.1; H, 6.1; Cl, 12.3; N, 9.7. Calcd. for $C_{12}H_{17}ClN_2O_4$: C, 49.9; H, 5.9; Cl, 12.3; N, 9.7.

The phenylhydrazone, on further heating with phenylhydrazine acetate, gave a crystalline phenylosazone. Two recrystallizations from ethanol–water gave yellow needles of m.p. 165–168° (decomp.), undepressed on admixture with 6-chloro-6-deoxy-D-glucose phenylosazone (3). The infrared spectra of the two phenylosazones were also identical (0.8% in potassium bromide).

Further Chloro-substitution of 6-Chloro-6-deoxy-α-D-mannosyl Chloride 2,3,4-Trichlorosulfate (VII)

The crystals of the 6-chloro-6-deoxy-D-mannosyl chloride derivative (8 g) were dissolved in chloroform (150 ml) and anhydrous pyridine hydrochloride (6 g) was added to the solution. The chloroform solution was heated at 50° for 20 h the product isolated in the usual way, was recrystallized from chloroform–petrol (b.p. 40–60°) yielding large prisms (1.5 g, 27%) of m.p. 147° (decomp.) and $[\alpha]_D$ +65° (*c*, 1.2 in chloroform).

Anal. Found: C, 20.5; H, 2.1; Cl, 50.5; S, 9.4. Calcd. for a tetrachloro-monochlorosulfate derivative $C_6H_7Cl_5O_4S$: C, 20.4; H, 2.0; Cl, 50.0; S, 9.1.

Methyl Trichloro-trideoxy-α-D-hexoside

A solution of VII (2.5 g) in anhydrous methanol (200 ml) was boiled under reflux. The resultant glycoside was dechlorosulfated (4) and the product was crystallized from chloroform–petrol (b.p. 40–60°) to give colorless needles (0.4 g, 33%) of m.p. 122–123° and $[\alpha]_D$ +81° (*c*, 0.9 in chloroform), and +122° (*c*, 0.9 in methanol).

Anal. Found: C, 33.5; H, 4.1; Cl, 43.1. Calcd. for $C_7H_{11}Cl_3O_3$: C, 33.6;H, 4.4; Cl, 42.6.

Hydrolysis of the Methyl Trichloro-trideoxy-α-D-hexoside

The above glycoside was unaffected by boiling *N* sulfuric acid during 16 h. Hydrolysis in 25% sulfuric acid for 5 h yielded a complex mixture of reducing components as was indicated by thin-layer chromatographic analysis. All attempts to obtain a crystalline derivative of the hydrolysis product have so far failed.

Methyl 6-Chloro-6-deoxy-α-D-mannopyranoside 2,3,4-Trichlorosulfate (VII)

Methyl α-D-mannopyranoside (20 g) was treated with sulfuryl chloride (52 ml) and pyridine (80 ml) in chloroform solution (3). The chloroform extracts were concentrated to give a syrup which rapidly crystallized. Recrystallization from chloroform–petrol (b.p. 40–60°) (×2) gave large colorless prisms (15 g, 29%) of m.p. 134° and $[\alpha]_D$ +19° (*c*, 1.2 in chloroform).

Anal. Found: C, 16.7; H, 2.0; Cl, 27.8; S, 18.9. Calcd. for $C_7H_{10}Cl_4O_{11}S_3$: C, 16.5; H, 2.0; Cl, 27.9; S, 18.9.

Methyl 6-Chloro-6-deoxy-α-D-mannopyranoside

Compound VII (10 g) was dechlorosulfated and the syrupy product (4 g, 100%) which was isolated in the usual way had $[\alpha]_D$ +59° (*c*, 1.1 in water). Paper chromatograms developed in solvent *a* and sprayed with periodic acid – *p*-anisidine hydrochloride (30) indicated that the syrup contained two components at R_x 2.5 (slight) and R_x 3.0 (intense). Hydrolysis of the syrup (*N* sulfuric acid, 7 h at 100°) gave a reducing syrupy product, which yielded a crystalline phenylhydrazone derivative of m.p. 140° (decomp.), undepressed on admixture with an authentic sample.

Methyl 3,6-Anhydro-α-D-mannopyranoside

The syrupy methyl 6-chloro-6-deoxy-D-mannoside (0.5 g) (above) was dissolved in *N* sodium hydroxide (5 ml), and the solution was allowed to stand at room temperature for 10 h. The solution was deionized and concentrated to a syrup (0.4 g, 100%) which crystallized when seeded with authentic methyl 3,6-anhydro-α-D-mannopyranoside. Recrystallization from benzene gave colorless crystals (0.15 g, 36%) of m.p. 129°, undepressed on admixture with the authentic compound (13).

Attempt to Obtain Further Chloro-substitution of Methyl 6-Chloro-6-deoxy-α-D-mannopyranoside 2,3,4-Trichlorosulfate (VII)

The crystals of the methyl glycoside (6 g) (VII) were dissolved in chloroform (40 ml) and anhydrous pyridine hydrochloride (4 g) was added to the solution. After the solution had been heated at 50° for 12 h the product was recrystallized from chloroform–petrol (b.p. 40–60°) to yield colorless prisms (4.5 g, 75%) of m.p. 134°, undepressed on admixture with the starting material.

Methyl 4,6-Dichloro-4,6-dideoxy-α-D-glucopyranoside 2,3-Dichlorosulfate (VIII)

Methyl α-D-galactopyranoside (31) (10 g) was treated with sulfuryl chloride (26 ml) and pyridine (40 ml) in chloroform solution (3). The reaction mixture was allowed to stand at room temperature for 12 h before the chloroform-soluble product was isolated. It was recrystallized from chloroform–petrol (b.p. 40–60°) to give large colorless prisms (6 g, 27%) of m.p. 122–124° and $[\alpha]_D$ +68° (*c*, 2.66 in chloroform).

Anal. Found: C, 19.6; H, 2.2; Cl, 32.9; S, 14.6. Calcd. for $C_7H_{10}Cl_4O_8S_2$: C, 19.6; H, 2.3; Cl, 33.2; S, 15.0.

Methyl 4,6-Dichloro-4,6-dideoxy-α-D-glucopyranoside

Compound VIII (6 g) was dechlorosulfated (4) and the product isolated in the usual way. It (3 g, 93%) was recrystallized from chloroform–petrol (b.p. 40–60°) and had m.p. 119–121°, undepressed on admixture with authentic methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (2).

4,6-Dichloro-4,6-dideoxy-α-D-glucose

The crystalline methyl glycoside was unaffected by hot *N* sulfuric acid. Therefore, more drastic conditions were tried.

The glycoside (3 g) was dissolved in 3 *N* sulfuric acid and the solution was refluxed for 24 h. The solution was neutralized ($BaCO_3$) and filtered and the filtrate was concentrated to a solid. Recrystallization from chloroform gave colorless needles of m.p. 136–137° and $[\alpha]_D$ +49° (10 minutes) → +25° (24 h, equilibrium) (*c*, 1.1 in water). The crystals reduced Fehlings' solution and gave a positive tetrazolium red test (15).

Anal. Found: C, 33.0; H, 4.6; Cl, 32.9. Calcd. for $C_6H_{10}Cl_2O_4$: C, 33.2; H, 4.6; Cl, 32.8.

The crystals formed a crystalline phenylosazone which, when recrystallized from ethanol–water, had m.p. 129–131° (decomp.).

Anal. Found: C, 54.4; H, 4.8; Cl, 18.0; N, 14.4. Calcd. for $C_{18}H_{20}Cl_2N_4O_2$: C, 54.6; H, 5.1; Cl, 18.0; N, 14.2.

Attempt to Obtain Further Chloro-substitution of Methyl 4,6-Dichloro-4,6-dideoxy-α-D-glucopyranoside 2,3-Dichlorosulfate

The crystals of the 2,3-dichlorosulfate (4.5 g) were dissolved in chloroform (25 ml) and anhydrous pyridine hydrochloride (4 g) was added to the chloroform solution. The solution was heated at 50° for 18 h, and the products were then isolated in the usual way. Recrystallization from methanol–water gave large crystals (1.5 g, 33%) of m.p. 124°, undepressed on admixture with the starting compound. The mother liquors were concentrated to a syrup (2.5 g) which was dechlorosulfated (4). The dechlorosulfated products were examined by gas–liquid chromatographic analysis using a column (A) and the results are shown in Table I.

TABLE I

Gas–liquid chromatographic analysis of the dechlorosulfated products from VIII

Compound or mixture	Components	Retention time relative to compound 1	Estimated % of individual compounds in mixture
(1) Methyl 4,6-dichloro 4,6-dideoxy-α-D-glucopyranoside	1	1.000	—
(2) Methyl 3,4,6-trichloro 3,4,6-trideoxy-α-D-allopyranoside	1	0.545	—
(3) Syrup from experiment above	1	0.246	3–4
	2	0.324	3–4
	3	0.545	1
	4	1.000	90

3,4,6-Trichloro-3,4,6-trideoxy-D-allosyl Chloride 2-Monochlorosulfate (XI)

D-Galactose (10 g) was treated with sulfuryl chloride (26 ml) and pyridine (40 ml) in chloroform solution (3). Concentration of the chloroform extracts gave a syrup (9.5 g) which had $[\alpha]_D$ −7° (*c*, 5.0 in chloroform).

Paper chromatograms developed in solvent *a* and sprayed with aniline-pyridine reagent (3) indicated that the syrup was a mixture of two components.

Methyl 3,4,6-Trichloro-3,4,6-trideoxy-β-D-allopyranoside (XII)

The above syrup (XI) (9 g) was dissolved in anhydrous methanol and the solution was refluxed to form the methyl glycoside(s). The methyl glycoside(s) was dechlorosulfated (4) and the product was crystallized from water to give colorless needles (1.5 g, 11%) of m.p. 116° and $[\alpha]_D$ +159° (*c*, 1.8 in methanol).

Anal. Found: C, 33.6; H, 4.4; Cl, 42.3. Calcd. for $C_7H_{11}Cl_3O_3$: C, 33.6; H, 4.4; Cl, 42.6.

The overall yield of this product could be increased to 36% by first dissolving the original syrup, obtained from the reaction of sulfuryl chloride with D-galactose, in chloroform, and heating the resultant solution with anhydrous pyridine hydrochloride at 50° for 16 h, followed by the methanolysis and dechlorosulfation of the product. Methylation of the methyl trichlorotrideoxy glycoside by the method of Purdie (32) gave a crystalline monomethyl derivative which, when recrystallized from *n*-hexane, gave colorless needles of m.p. 68–69° and $[\alpha]_D$ +116° (*c*, 1.12 in methanol).

Anal. Found: C, 36.7; H, 4.8; Cl, 39.7. Calcd. for $C_8H_{13}Cl_3O_3$: C, 36.5; H, 4.9; Cl, 40.0.

The methyl trichloro-trideoxy glycoside also gave a crystalline monotosylate which, when recrystallized from ethanol, had m.p. 120–121°.

Anal. Found: C, 41.9; H, 4.2; Cl, 26.6; S, 8.1. Calcd. for $C_{14}H_{17}Cl_3O_5S$: C, 41.6; H, 4.2; Cl, 26.4, S, 7.9.

Attempted Reaction of Methyl 3,4,6-Trichloro-3,4,6-trideoxy-α-D-allopyranoside (XII) with Sodium Hydroxide

The crystals of the methyl glycoside (0.05 g) were dissolved in methanol (5 ml) and 0.1 *N* sodium hydroxide (5 ml) was added to the solution. The reaction mixture was left at room temperature for 8 h, and then was deionized. The solution was concentrated to a solid which was recrystallized from water. It had m.p. 116°, which was undepressed on admixture with the starting compound.

3,4,6-Trichloro-3,4,6-trideoxy-D-allose (XIII)

The original syrup obtained from the reaction of sulfuryl chloride with D-galactose (10 g) was dissolved in acetone (200 ml) and barium carbonate (30 g) was added and the heterogeneous mixture was stirred. Sodium iodide solution (5 g in 20 ml water) was added drop by drop until the formation of iodine had ceased. The solution was filtered and the filtrate was concentrated. The residue was dissolved in water and the aqueous solution was continuously extracted with chloroform for 10 h. Concentration of the chloroform solution and recrystallization from chloroform gave colorless crystals (1.9 g, 29%) of m.p. 170–171°. The crystals reduced Fehling's solution and gave a negative tetrazolium red test (15). The same crystalline compound was also obtained by the hydrolysis of methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-alloside with *N* sulfuric acid under reflux for 10 h.

The crystals failed to give a phenylosazone or a *p*-nitrophenylosazone but gave a crystalline *p*-nitrophenylhydrazone, which, when recrystallized from methanol–water, had m.p. 105° (decomp.) and $[\alpha]_D$ −58° (*c*, 0.75 in methanol).

Anal. Found: Cl, 28.5; N, 11.4. Calcd. for $C_{12}H_{13}Cl_3N_3O_4$: Cl, 28.8; N, 11.3.

Paper electrophoresis of the crystalline trichlorohexose in buffer solution i gave the results shown in Table II.

TABLE II

Paper electrophoresis of 3,4,6-trichloro-3,4,6-trideoxy-D-allose (XIII)

Compound	Electrophoretic mobility, mg × 10^2
3,4,6-Trichloro-3,4,6-trideoxy-D-allose	23
3,4,6-Tri-*O*-methyl-D-glucose	29
2,4,6-Tri-*O*-methyl-D-glucose	0

The crystalline trichlorohexose failed (*a*) to form an 1,2,-*O*-isopropylidene derivative, (*b*) to re-form the methyl glycoside by refluxing the sugar in a 2% (w/w) anhydrous solution of hydrochloric acid in methanol, and (*c*) to be reduced to the trichloro-trideoxy-hexitol (33). In each case the crystalline starting material was obtained.

1,6-Anhydro-3,4-dichloro-3,4-dideoxy-D-allose (XVI)

The crystals of the trichlorohexose (0.5 g) were dissolved in water and treated with 0.1 *N* sodium hydroxide (21 ml, 1 mole). The alkali reacted rapidly and the neutral solution was then continuously extracted with chloroform. The chloroform extracts were concentrated to a solid which, on recrystallization from benzene–petrol (b.p. 60–80°), gave colorless crystals (0.3 g, 77%) of m.p. 94° and $[\alpha]_D$ −96° (*c*, 1.1 in methanol). The crystals did not reduce Fehling's solution and did not appear as reducing spots when paper chromatograms developed in solvent *a* were sprayed with *p*-anisidine hydrochloride, or with the alkaline silver nitrate spray.

Anal. Found: C, 36.3; H, 4.0; Cl, 35.4. Calcd. for $C_6H_8Cl_2O_3$: C, 36.2; H, 4.0; Cl, 35.7.

Methyl 3,4,6-Trichloro-3,4,6-trideoxy-β-D-allopyranoside 2-Monochlorosulfate (XIV)

Methyl β-D-galactopyranoside (5 g) was treated with sulfuryl chloride (13 ml) and pyridine (20 ml) in chloroform solution (3). The reaction mixture was allowed to stand at room temperature for 12 h. The chloroform extracts on concentration gave a dark-colored syrup which was decolorized (5 g, 56%).

Methyl 3,4,6-Trichloro-3,4,6-trideoxy-β-D-allopyranoside (XV)

The above syrup (XIV) (5 g) was dechlorosulfated (4) and the syrupy product (2.5 g, 71%) of $[\alpha]_D$ −12.8° (*c*, 1.18 in methanol) was isolated in the usual way.

Anal. Found: C, 34.4; H, 4.3; Cl, 41.7. Calcd. for $C_7H_{11}Cl_3O_3$: C, 33.6; H, 4.4; Cl, 42.6.

The syrup appeared homogeneous by thin-layer chromatographic analysis, also hydrolysis of the syrupy glycoside in 2 *N* sulfuric acid gave a crystalline trichlorohexose of m.p. 170°, undepressed on admixture with the previously isolated 3,4,6-trichloro-3,4,6-trideoxy-D-allose.

Formation of 3,4,6-Trichloro-3,4,6-trideoxy-D-allose from 4,6-Dichloro-4,6-dideoxy-D-glucose

Crystalline 4,6-dichloro-4,6-dideoxy-D-glucose (0.15 g) was treated with sulfuryl chloride (0.4 ml) and pyridine (0.6 ml) in chloroform solution (3). The chloroform soluble product was redissolved in chloroform and heated at 50° for 8 hours with anhydrous pyridine hydrochloride (0.2 g). The syrupy product (0.2 g), isolated from the reaction mixture in the usual way, on methanolysis and dechlorosulfation (4) gave a syrup (0.1 g) which was shown by thin-layer chromatography to be chromatographically indistinguishable from methyl 3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranoside. Hydrolysis of the syrupy glycoside in *N* sulfuric acid gave a crystalline trichlorohexose of m.p. 171°–172°, undepressed on admixture with 3,4,6-trichloro-3,4,6-trideoxy-D-allose.

Reaction of Sulfuryl Chloride with 4,6-O-Ethylidene-D-galactopyranose

4,6-*O*-Ethylidene-D-galactose (10 g) (34) was treated with sulfuryl chloride (21 ml) and pyridine (40 ml) in chloroform solution (3). Concentration of the chloroform extracts gave a solid which was recrystallized from chloroform–petrol (b.p. 40–60°) to give large colorless prisms (6 g, 30%) of m.p. 133–135° and $[\alpha]_D$ +207° (*c*, 1.12 in chloroform).

Anal. Found: C, 22.7; H, 2.5; Cl, 25.4; S, 15.1. Calcd. for $C_8H_{11}Cl_3O_9S_2$: C, 22.8; H, 2.6; Cl, 25.3; S, 15.2.

A small quantity of the crystals were dechlorosulfated (4), and paper chromatographic analysis of the resultant methanol solution in solvents *a* and *b* indicated two reducing components which were chromatographically indistinguishable from D-galactose and 4,6-*O*-ethylidene-D-galactose (34).

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-β-D-allopyranoside (XVIII)

Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (4 g) (17) was treated with sulfuryl chloride (10.4 ml) and pyridine (16 ml) in chloroform solution (3). The chloroform extracts were concentrated to a syrup (6 g) (XVIII). The substance was dechlorosulfated (4) in the presence of barium carbonate to prevent the removal of the benzylidene group. The resulting syrupy product (4 g) was extracted with a solution of benzene–petrol (b.p. 40–60°) (1:2) leaving a crystalline residue (0.2 g). Recrystallization of the residue from acetone gave needles of m.p. 199°, undepressed on admixture with authentic methyl 4,6-*O*-benzylidene-β-D-glucoside (7). The benzene–petrol extract was concentrated to a syrup (2.8 g) which had $[\alpha]_D$ −30° (*c*, 1.05 in methanol) and was shown to be homogeneous by thin-layer chromatographic analysis (XVIII, R = H).

Methyl 3-Chloro-3-deoxy-β-D-allopyranoside (XIX)

The above syrup (XVIII) (2.8 g) was dissolved in methanol (15 ml) and 0.1 *N* sulfuric acid (15 ml) was added to the solution. The solution was heated at 50° for 2 h, neutralized ($BaCO_3$) and filtered, and the filtrate was extracted with ether to remove the liberated benzaldehyde. The aqueous solution was deionized and concentrated to a syrup (1.5 g, 75%) of $[\alpha]_D$ −49° (*c*, 1.0 in water) which was shown to be homogeneous by thin-layer chromatographic analysis. Periodate oxidation of the syrup resulted in no consumption of periodate up to a reaction time of 60 h.

The syrup gave a syrupy triacetate derivative which had $[\alpha]_D$ −21° (*c*, 1.15 in methanol).

Anal. Found: C, 46.1; H, 6.0; Cl, 10.4. Calcd. for $C_{13}H_{19}ClO_8$; C, 46.1; H, 5.6; Cl, 10.5.

Gas liquid chromatographic analysis of the triacetate using column (B) gave one sharp peak which had a retention time of 12.3 min.

3-Chloro-3-decxy-D-allose (XX)

The syrupy monochloro methyl glycoside (XIX) (0.3 g) was refluxed in 2 *N* sulfuric acid for 16 h. The solution was neutralized and concentrated to a syrup (0.25 g, 89%), which had $[\alpha]_D$ +5.4° (*c*, 0.92 in water). Attempts to form phenylosazone, *p*-nitrophenylosazone, and *p*-nitrophenylhydrazone derivatives were unsuccessful. Paper chromatographic analysis of the syrup in solvent *a* indicated one reducing component at R_x 1.5. The syrup also gave a negative tetrazolium red test (15). Paper electrophoresis of the syrup in buffer solutions i and ii gave the following results shown in Tables III and IV respectively.

Effect of Sodium Hydroxide on Methyl 3-Chloro-3-deoxy-β-D-allopyranoside

The syrupy monochloro methyl glycoside (0.25 g) was dissolved in *N* sodium hydroxide (5 ml) and the solution was allowed to stand for 16 h at room temperature. It was deionized, and concentrated to a syrup (0.2 g) which had $[\alpha]_D$ +28° (*c*, 1.0 in methanol). It was hydrolyzed by the same method used in the previous

TABLE III

Paper electrophoresis of 3-chloro-3-deoxy-D-allose in buffer solution i

Compound	Electrophoretic mobility, mg × 10^2
Hydrolysis product (above)	84.5
2-*O*-Methyl-D-glucose	23
3-*O*-Methyl-D-glucose	80
3,6-Anhydro-D-glucose	82

TABLE IV

Paper electrophoresis of 3-chloro-3-deoxy-D-allose in buffer solution ii

Compound	Electrophoretic mobility, mg × 10^2
Hydrolysis product (above)	0
3,6-Anhydro-D-glucose	29

experiment and gave another syrup. Paper chromatography in solvent *a* and paper electrophoresis in buffer solutions i and ii of the syrup, all indicated one component indistinguishable from 3-chloro-3-deoxy-D-allose.

The reaction with *N* sodium hydroxide solution was repeated and the solution was heated at 50–60° for 10 h and then allowed to stand at room temperature for a further 16 h. The solution was deionized, and concentrated to a syrup (0.22 g) which had $[\alpha]_D$ −27° (*c*, 0.93 in methanol). The syrup gave an acetate derivative which did not crystallize and had $[\alpha]_D$ −22° (*c*, 1.32 in methanol). Gas–liquid chromatographic analysis of the derived acetate gave one sharp peak with a retention time (12.3 minutes) identical with that of methyl 3-chloro-3-deoxy-β-D-allopyranoside triacetate, when carried out using similar conditions.

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