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SYNTHESIS AND REACTIONS OF SUGAR CHLOROSULPHATES

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SUMMARY

Sugar chlorosulphates of furanoid and pyranoid derivatives bearing chlorosulphonyloxy groups at primary and secondary positions, were synthesized and examined mainly with a view to determine their extent of reactivity in terms of nucleophilic substitution reactions, especially with azide.

Inversion of configuration occurred at reactive chiral centres, whereas intermediate azidosulphonyloxy derivatives (azidosulphates) were formed via S-Cℓ bond fission of the chlorosulphonyloxy group at less reactive primary or secondary centres, e.g. 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-azidosulphate, 1,2-O-isopropylidene-α-D-xylofuranose 3-azidosulphate and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-azidosulphate. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose 6-azidosulphate ultimately afforded the 6-azidodeoxy derivative probably by an S_N2 mechanism.

Some S_Ni characteristics were, however, evident when substitution occurred at a reactive primary centre (e.g. methyl 2,3,4-tri-O-methyl-α-D-glucopyranoside 6-chlorosulphate), as the 6-azidodeoxy derivative obtained, appeared to be contaminated with a trace amount of the corresponding 6-chlorodeoxy sugar, which had presumably formed via an internal S_Ni mechanism, while no intermediate azidosulphonyloxy derivative was isolated.

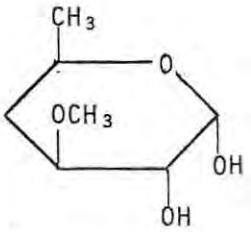
In another study, the reaction pathways for the synthesis of benzylated chlorodeoxy sugars having potential biological properties as exemplified by the multivalent drug, tribenoside, were also investigated.

1. INTRODUCTION

Biological significance and synthetic utility of chlorodeoxy sugars

Deoxyhalo sugars[1], besides being known for their potential biological and pharmacological properties, are also familiar as versatile intermediates for the synthesis of rare sugars of the aminodeoxy and and deoxy types, which form the essential components of several amino-sugar[2,3,4] and deoxy sugar[5,6,7,8] antibiotics. Stevens and coworkers[9] have further, indicated the usefulness of azido-halo sugars as intermediates for the synthesis of cardiac glycosides, antibiotics and aminosugar nucleosides containing 4-amino-4-deoxy residues. Halogeno derivatives of carbohydrates have also been claimed by Edwards and coworkers[10] as being of wide synthetic utility, since the halogeno substituents may be employed as leaving groups in nucleophilic displacement reactions to eventually yield aminosugars[11], or they may be reductively removed to afford deoxy sugars[6,12].

Chlorodeoxy sugars are readily prepared via reaction of sulphuryl chloride with carbohydrates containing free hydroxyl groups, and have been shown to be useful intermediates in the synthesis of azidodeoxy sugars[13,14,15,16] thus making the latter a valuable precursor in the preparation of aminodeoxy sugars, while reductive dechlorination[17] of chlorodeoxy pyranoid and furanoid sugars has led to the synthesis of deoxy sugars. The utility of this latter phenomenon has previously been described by Lawton and coworkers[5,6] in the synthesis of 4,6-dideoxy-3-O-methyl-D-xylo-hexose (D-chalcose) (I), a constituent of the antibiotics, chalcomycin, lankamycin and neutramycin, obtained via the chlorosulphation of methyl 3-O-methyl-α,β-D-glucopyranoside, and subsequent reduction of the resulting methyl 4,6-dichloro-4,6-dideoxy-3-O-methyl-α,β-D-galacto-pyranoside, by hydrogenation over raney nickel.



(I)

A further demonstration of the utility of chlorodeoxy sugars in the synthesis of biologically significant sugars, has been indicated[7] by the synthesis of 3,6-di-deoxy-hexoses, namely paratose (3,6-di-deoxy-D-ribo-hexose) and tyvelose (3,6-di-deoxy-D-arabino-hexose), which have been isolated from lipopolysaccharides produced by gram-negative bacteria (Salmonella and E.Coli), and are known to constitute immunodominant groups of their respective antigenic determinants.

The replacement of hydroxy groups by chlorine to form deoxyhalogeno sugars has also been cited[18,19] to yield substances having pronounced biological effects as exemplified by the observed enhanced activities due to chlorination of the carbohydrate moeities of the antibiotics lincomycin and kanamycin.

The chlorosulphation of methyl-β-maltoside was investigated by Durette and coworkers[8], with the intention of producing chlorodeoxy precursors for the synthesis of polydeoxydisaccharides that occur as the sugar moeity in the nucleoside antibiotics, amicetin, bamicetin and plicacetin. These pyrimidine nucleosides which contain a mono-amino-penta-deoxy disaccharide as the sugar residue, have also been reported[20,21] to exhibit antitumour activity.

Carbohydrate azidosulphates[22] that may be synthesized by nucleophilic displacement of chloride from chlorosulphate ester precursors, could, via a reduction sequence, lead to the formation of sulphamoyl derivatives of

potential biological significance. The sulphamoyl group is known to occur in the broad spectrum nucleoside antibiotic, nucleocidin[23,24] (4'-fluoro-5'-O-sulphamoyladenosine) (2) which is also recognized for its anti-trypanosomal activity.

(2)

Halogeno sugar nucleosides have also been considered to be of importance either as synthetic intermediates, or, similarly to nucleocidin, they may themselves possess significant biological activity.

1.1 Chlorosulphation of sugars

The selective replacement of hydroxyl groups in carbohydrates by halogen may be achieved through the use of sulphuryl chloride. The reaction of sulphuryl chloride with carbohydrates has become a recognized method for the preparation of chlorodeoxy sugars via the conversion of hydroxyl groups to chlorosulphate esters, and subsequent replacement of suitably placed chlorosulphonyloxy groups by chloride. Although several reagents [based on phosphorus compounds and N,N-dimethyl(halomethanimium) halides] have been indicated[10] for the direct replacement of a hydroxyl group in a sugar derivative by a chloro substituent, the value of the chlorosulphate residue as a leaving group was demonstrated by kinetic

studies with simple alkyl chlorosulphates[25,26].

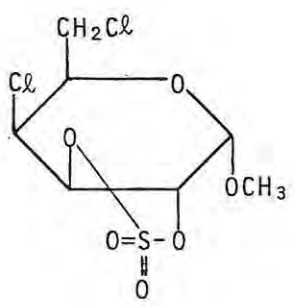
The relative reactivities of hydroxyl groups in carbohydrates and the selective halogenation of monosaccharides and disaccharides through the use of sulphuryl chloride have been reviewed by Haines[27]. Earlier reviews on deoxyhalogeno sugars by Barnett[1] and Szarek[28], and on chlorosulphates by Buncel[26] have also considered the direct replacement of hydroxyl groups through the reaction of sulphuryl chloride with carbohydrate derivatives. These reactions and the behaviour of chlorosulphate esters with particular respect to their nucleophilic displacement, is now reviewed under the following categories:

1.1.1 MONOSACCHARIDES

1.1.1.1 Glycosides

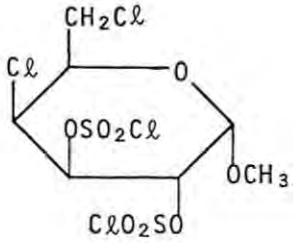
1.1.1.1.1 Pyranosides

The reaction of sulphuryl chloride (SO_2Cl_2) in pyridine-chloroform with methyl α- and β-D-glucopyranosides, to yield products in which some hydroxyl groups were replaced by chlorine atoms, whilst others formed intramolecular cyclic sulphates was first reported by Helferich and coworkers[29]. Initially, the product obtained from methyl α-D-glucopyranoside was considered to be a 5,6-dichlorodideoxy derivative, but Bragg *at al.*[30] and Jones *et al.*[31] later proved the correct structure to be that of the 2,3 cyclic sulphate, with inversion of configuration having occurred at position C-4 during introduction of the chlorosubstituent, and retention at C-2 and C-3 to yield methyl 4,6-dichloro- 4,6-dideoxy-α-D-galacto-pyranoside 2,3- cyclic sulphate (3) (see later).



(3)

At low temperatures, namely -70°C and 0°C, the reaction of methyl α-D-glucopyranoside with sulphuryl chloride afforded the tetrachlorosulphate and 6-chloro-6-deoxy-trichlorosulphate esters respectively, whereas at room temperature (25°C), the 4,6-dichloro-4,6-dideoxy galactoside 2,3-dichlorosulphate (4) was isolated[32]



(4)

At higher temperatures the reactive chlorosulphate groups on C-6 and C-4 of the tetrachlorosulphate derivative are replaced by chloride ion (pyridinium chloride) produced during the esterification of the hydroxyl groups.

When treated with 1.0 mole of pyridinium chloride the tetrachlorosulphate ester was observed to form the 6-chloro-6-deoxy trichlorosulphate ester, whilst treatment with an excess of pyridinium chloride resulted in 4 being formed. The latter, however, failed to undergo further chlorosubstitution even after additional treatment by prolonged heating with pyridinium chloride.

From the evidence submitted by Jennings and Jones[32] it may be seen that the chlorodeoxy derivatives formed from secondary pyranose ring hydroxyl groups, are formed with inversion of configuration. The reaction has thus, on a stereochemical basis, been categorized as a bimolecular nucleophilic substitution (S_N2). That further substitution does not occur

at C-3 is probably the result of steric factors where formation of the optimum transition state[26,32] would create considerable skew interactions between the C(4)-Cℓ and C(3)-$OSO_2Cℓ$ groups (Fig. I), thus causing the transition state to become energetically unfavourable.

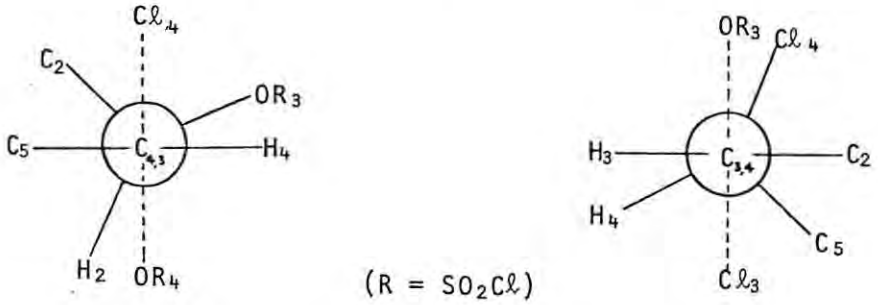


Fig. I (End on representation along the C_4–C_3 and C_3–C_4 bonds)

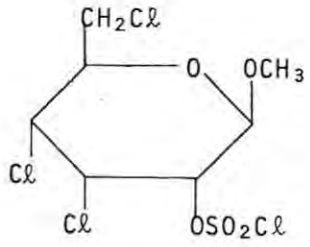
Although the facile replacement of the 4-chlorosulphonyloxy group by a chlorine atom occurred with inversion in both anomers of methyl-D-glucopyranoside and methyl-D-galactopyranoside[32] on treatment with sulphuryl chloride, this did not occur with methyl α-D-mannopyranoside[32], nor with methyl α-L-rhamnopyranoside[33], which formed only the 6-chloro-6-deoxy trichlorosulphate (5) and 6-deoxy trichlorosulphate (6) derivatives respectively.

(5) (6)

(R = $SO_2Cℓ$)

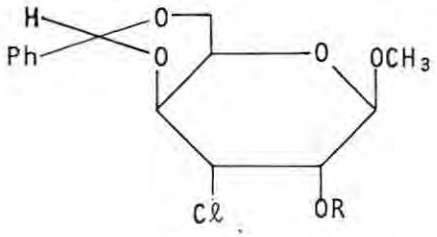
Attempts to obtain further chlorosubstitution of these trichlorosulphate esters with pyridinium chloride, were found to be unsuccessful. Although a chlorodeoxy group might perhaps be introduced into methyl α-L-rhamnopyranoside at C-2 since it is axially orientated, (with cyclohexyl derivatives axial substituents are displaced at a faster rate than corresponding equatorial substituents) the axial methoxyl group at C-1 would further hinder substitution at C-2. (The latter effect has been verified by Cottrell and coworkers[33] in the reaction of L-rhamnose with sulphuryl chloride; see later). Richardson[34] has ascribed the lack of substitution at C-2, to an unfavourable alignment of dipoles in the transition state of the reaction. Jennings and Jones[32] have attributed the lack of reactivity towards bimolecular nucleophilic substitution at C-4 in α-D-mannopyranoside to steric interactions of the 1,3 diaxial type, which occur between a chloride ion approaching C-4 and the axial chlorosulphonyloxy substituent on C-2, whereas the non-reactivity of the α-L-rhamnopyranoside trichlorosulphate ester has been discussed by Cottrell and coworkers[33] in terms of steric interactions in the transition state for substitution. Richardson[34], however, has stated that the development of an S_N2 transition state at C-3 and C-4 is affected by steric and mainly polar factors in the transition state, emanating from the effects of (non-anomeric) β-trans-axial, and vicinal axial substituents respectively.

The influence of the anomeric configuration on chlorosubstitution was demonstrated[32] when methyl-β-D-galactopyranoside was treated with sulphuryl chloride. It was found to undergo chlorination at C-3, C-4 and C-6 to afford the trichlorotrideoxy allopyranoside derivative (7). However, when the α-anomer, methyl 4,6-dichloro-4,6-dideoxy-α-D-galacto-pyranoside 2,3-dichlorosulphate was treated with pyridinium chloride in an attempt to obtain further chlorosubstitution as previously mentioned, it



(7)

was found to be unsuccessful. This phenomenom may also be attributed to steric and perhaps polar factors manifested in the β-trans-axial effect proposed by Richardson[34]. Further examples of the dependance of the reactivity at C-3 on the configuration at C-1, were cited by the chlorosulphation of methyl 4,6-O-benzylidene-β-D-glucopyranoside to the corresponding 3-chloro-3-deoxy-allopyranoside[32] derivative, (8), and of methyl 4,6-O-benzylidene-α-D-glucopyranoside under similar conditions to the 2,3-dichlorosulphate ester[35] (9).



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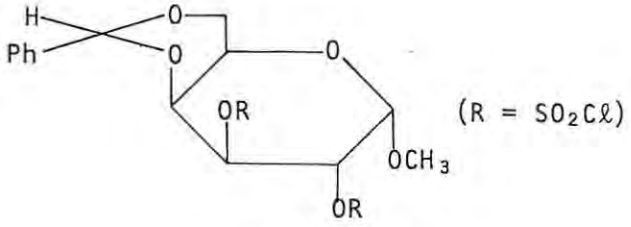
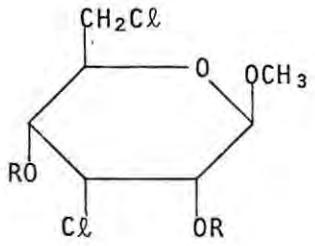


(9)

The orientation of substituents at C-4 may also exert an influence on the reactivity at C-3 of the pyranose ring; e.g. methyl β-D-galacto-pyranoside was observed by Jennings and Jones[32] to readily undergo chlorination at C-3, C-4 and C-6, to form the trichloro-trideoxy alloside 2-mono-chlorosulphate (7), but the β-D-glucopyranoside gave methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside 2,3-dichlorosulphate (4),

whilst formation of the trichloro-trideoxy derivative did not occur. However, the feasibility of nucleophilic displacement at C-3 in the β-glucopyranoside series was reported by Dean and coworkers[36] after they had re-investigated the reaction of methyl-β-D-glucopyranoside with sulphuryl chloride. They reported the isolation of methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside 2,4-dichlorosulphate (10) in addition to methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside 2,3-dichlorosulphate (4).



(R = $SO_2C\ell$)

(10)

The earlier work by Jennings and Jones[32] however, did not explicitly establish the formation of a 3,6-dichloro-3,6-dideoxy alloside dichlorosulphate ester. Edwards and coworkers[37] also reported the isolation of methyl 3,6-dichloro-3,6-dideoxy-β-D-allo-pyranoside after reacting methyl-β-glucopyranoside with the dimethylformamide-methanesulphonyl chloride reagent. It was thus upon this basis and Dean's[36] re-investigation, as well as the fact that the β-methoxyl group at C-1 is equatorially orientated, that the feasibility of nucleophilic displacement at C-3 in the β-glucopyranoside series had been indicated by Dean and coworkers[36]. The absence of trichlorination of the β-glucopyranosides may be accounted for by the fact[33] that an axial chlorodeoxy group in a pyranose ring, deactivates a neighbouring (vicinal) equatorial chlorosulphate group, and thus prevents further chlorodeoxy groups from being introduced into

such positions, since formation of the S_N2 transition state would create considerable skew interactions[33,39] between the respective chlorodeoxy and chlorosulphate groups, thus creating an increase in steric interaction in the transition state of the reaction. Ali and Richardson[39] have preferred to regard this as mainly a polar effect[34].

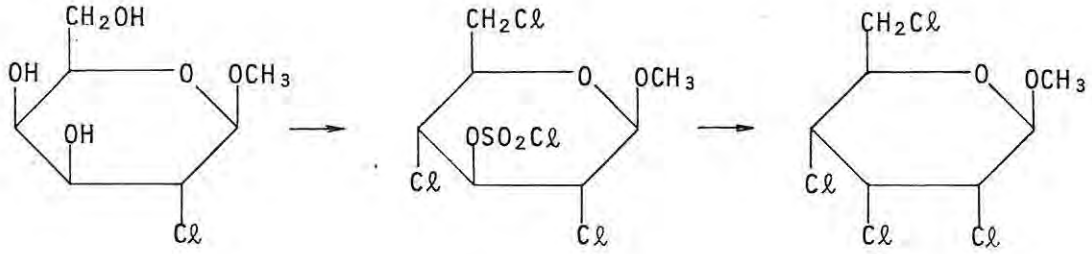
A common feature in the glycoside series is the relative inertness of the C-2 chlorosulphate group to nucleophilic substitution by chloride ion. The proximity of the C-2 group to the ring oxygen atom and to the anomeric group, results in an inductive effect at C-2, and has been accounted for by Jennings and Jones[32] as being responsible for the deactivation of the 2-chlorosulphate group to further chlorosubstitution. In addition, substitution at C-2 in methyl 4,6-dichloro-4,6-di-deoxy-β-D-galactopyranoside 2,3-dichlorosulphate[39] is not favoured. The latter phenomenom has been attributed by Cottrell and coworkers[39] to a 1,3 diaxial type interaction between the axially positioned C-4 - Cl group and the incoming chloride ion at C-2. However, Richardson[34] later ascribed this to an unfavourable alignment of dipoles in the transition state of the reaction, and maybe visualized by viewing projections along the C-2 - C-1 bond of both α-D and β-D anomers (Fig.11).

α-D-anomer β-D-anomer

Fig. 11

From the above illustrations it may be seen that in the β-D anomer, the

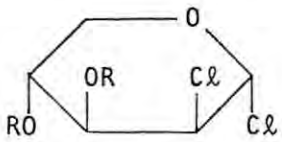
C-1 - O-1 bond is perpendicular to the polar bonds of the transition state, and therefore the dipolar interaction should be at a minimum. Considerable dipolar repulsion would, however, still be expected as the uppermost polar bond of the transition state is inclined at about 30° to the C-1 - O-5 bond. Richardson[34] has thus implied that comparitively less hindrance would be experienced with the β-D-anomer than with the α-D-anomer; hence if displacement is to be achieved in the 2-position, use of the β-D anomer may prove more successful. The possibility of synthesizing a fully chlorinated hexoside presented an interesting challenge to Cottrell and coworkers[39], who successfully synthesized methyl 2,3,4,6-tetrachloro-2,3,4,6-tetradeoxy-β-D-allopyranoside via the chlorosulphation of methyl 2-chloro-2-deoxy-β-D-galactopyranoside, and subsequent treatment of the intermediate, methyl 2,4,6-trichloro-2,4,6-trideoxy-β-D-glucopyranoside 3-chlorosulphate with excess pyridinium chloride. (Scheme I)



(Scheme I)

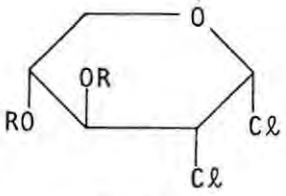
However, a useful procedure for the synthesis of 2-chloro-2-deoxy pentoses was devised during a study[40] of the anomerization of chlorosulphated glycosyl chlorides. Treatment of β-D-xylopyranosyl chloride 2,3,4 tri-chlorosulphate with aluminium chloride was found by Jennings[40] to result in specific chloro-displacement of the C-2 chlorosulphate group via a mechanism involving anomeric chlorine migration, to yield 2-chloro-2-deoxy-α-D-lyxopyranosyl chloride 3,4-di-chlorosulphate (11). Similarly α-D-lyxopyranosyl chloride 2,3,4-tri-chlorosulphate was found to yield 2-chloro-

2-deoxy-α-D-xylopyranosyl chloride 3,4-dichlorosulphate (12). In both instances removal of the 3,4-dichlorosulphate groups afforded the 2-chloro-2-deoxy pentoses.



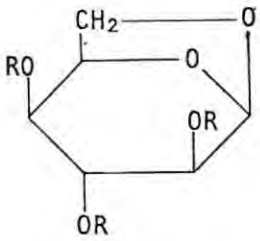
(11)

(R = $SO_2Cℓ$)



(12)

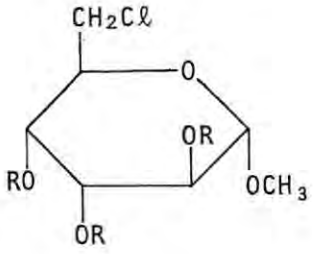
Cottrell and coworkers[33] also investigated the chlorosulphation of several 1,6-anhydrohexopyranoside derivatives. The product obtained in each case was a tri-chlorosulphate ester (e.g.13) which failed to undergo further substitution with chloride ion. They concluded that steric interactions and the rigidity of the bicyclic system may have resulted in this failure.



(R = $SO_2Cℓ$)

(13)

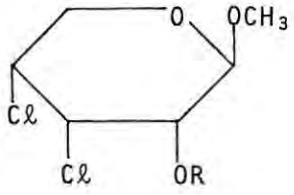
The above workers[33] also reported the synthesis of methyl 6-chloro-6-deoxy-α-D-altropyranoside 2,3,4-trichlorosulphate (14) which was obtained via the chlorosulphation of methyl α-D-altropyranoside.



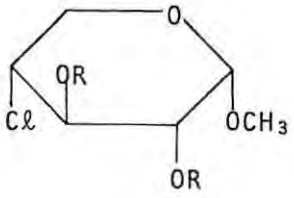
(R = $SO_2Cℓ$)

(14)

Several pentopyranosides have also been subjected to selective chlorination with sulphuryl chloride. Methyl α- and β-L-arabinopyranosides[41] were found to yield methyl 3,4-dichloro-3,4-dideoxy-β-D-ribopyranoside 2-chlorosulphate, (15) and methyl 4-chloro-4-deoxy-α-D-xylopyranoside 2,3-dichlorosulphate (16) respectively. No further chlorosubstitution was obtained when the latter was treated with pyridinium chloride.

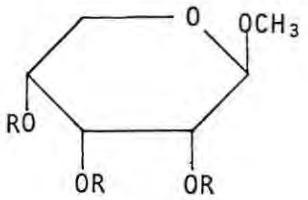


(R = $SO_2Cℓ$)

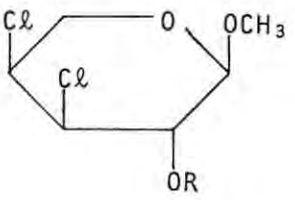


(15) (16)

The reaction of methyl-β-D-ribopyranoside with sulphuryl chloride was described by Ali and coworkers[42] who found that the glycoside could readily be converted into methyl β-D-ribopyranoside 2,3,4-trichlorosulphate (17). Treatment of the latter with pyridinium chloride afforded methyl 3,4-dichloro-3,4-dideoxy-α-L-arabinopyranoside 2-chlorosulphate (18).



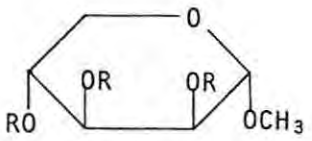
(R = $SO_2Cℓ$)



(17) (18)

During the latter reaction with chloride ion, no monochlorodeoxy compound was isolated, but their consideration of the conformational aspects of the substitution process suggested that the 3-chlorosulphate group was first displaced with chloride and substitution then occurred at C-4. They supported this conclusion by means of a reaction series in which 3-chloro-3-deoxy-β-D-xylopyranoside was synthesized and converted to the dichloro-dideoxy arabinopyranoside 2-chlorosulphate ester.

The chlorosulphation of methyl-α-D-lyxopyranoside was undertaken by Cottrell and coworkers[33] who found that the resultant methyl α-D-lyxopyranoside 2,3,4-trichlorosulphate (19) failed to undergo further chlorosubstitution when treated with pyridinium chloride. A similar observation was made by them with the chlorosulphation of methyl-α-L-



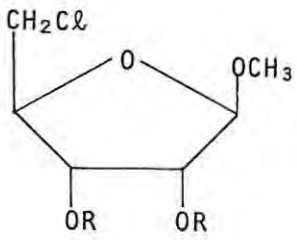
(R = SO_2Cl)

(19)

rhamnopyranoside[33], which also has the anomeric methoxyl group on C-1 and the hydroxyl group on C-2 axially oriented, and an analogous situation was reported for methyl-α-D-mannopyranoside[32], the trichlorosulphate ester of which could not undergo further substitution with chloride ion.

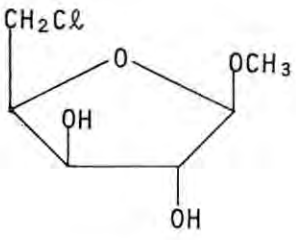
1.1.1.1.2 Furanosides and other Furanoid Sugars

A study of the reaction of various pentofuranosides such as methyl α- and β-D-ribo- and -D-xylo-furanosides with sulphuryl chloride, was undertaken by Achmatowicz and coworkers[43]. In the case of the α-anomers of the ribo- and xylo-furanosides, the reactions produced mixtures of 5-chloro-5-deoxy 2,3-dichlorosulphate pentofuranoside esters and the 2,3,5-trichlorosulphate esters in both instances, whereas reaction with the β-anomer of methyl D-ribofuranoside afforded only the 5-chloro-5-deoxy 2,3-dichlorosulphate pentafuranoside ester (20).



(20)

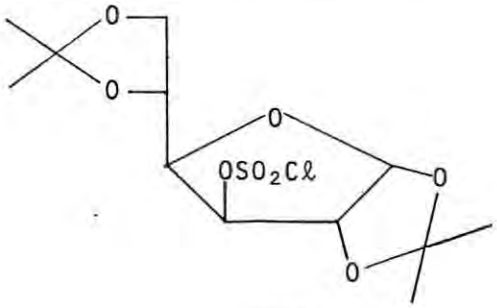
(R = SO_2Cl)



(21)

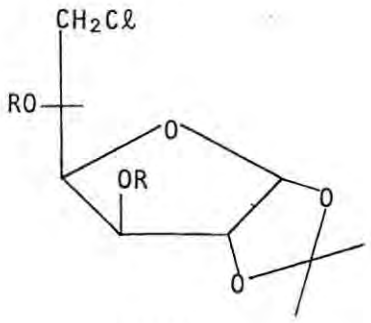
In the case of methyl β-D-xylofuranoside, the mixture of chlorosulphation products was not resolved, but after dechlorosulphation methyl 5-chloro-5-deoxy-β-D-xylofuranoside (21) was obtained. Under the conditions employed, formation of the dichlorodideoxy compounds was not observed.

Earlier studies of sulphuryl chloride with hexofuranoid derivatives were those involving the D-fructofuranosyl moeity of sucrose[30,44], and 1,2;5,6-di-O-isopropylidene α-D-glucofuranose; the latter was reported by Jennings and Jones[35] of having reacted to form the 3-chlorosulphate ester (22).



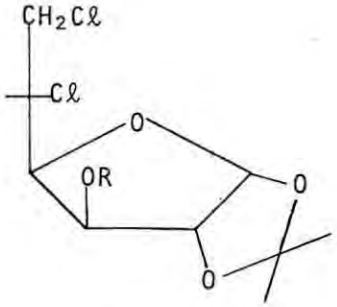
(22)

The reaction of 1,2-O-isopropylidene-α-D-glucofuranose with sulphuryl chloride was reoorted by Parolis[45], and found to yield 6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose 3,5-dichlorosulphate (23) at room temperature, but when the reaction mixture was heated to 50°C, the inversion product 5,6-dichloro-5,6-dideoxy-1,2-O-isopropylidene-β-L-idofuranose 3-chlorosulphate (24) was observed to have formed.



(23)

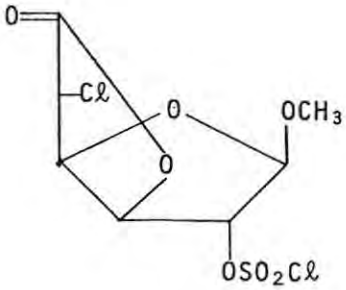
(R = $SO_2C\ell$)



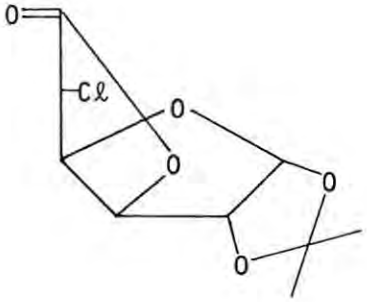
(24)

The lactone derivatives[45], methyl-β-D-glucofuranosidurono-6,3 lactone and

1,2-O-isopropylidene-α-D-glucofuranurono-6,3 lactone, appeared to be more reactive at their chiral centres, as the inversion products, namely, methyl 5-chloro-5-deoxy-α-L-idofuranosidurono-6,3 lactone 2 chlorosulphate (25) and 5-chloro-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono-6,3 lactone (26) respectively, were isolated at room temperature.

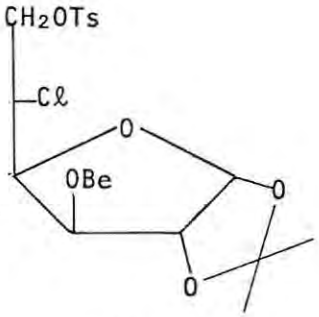


(25)



(26)

Treatment of 3-O-benzyl-1,2-O-isopropylidene-6-O-p-tolylsulphonyl α-D-glucofuranose[46] with sulphuryl chloride, also resulted in inversion of configuration at C-5, to form 3-O-benzyl-5-chloro-5-deoxy-1,2-O-isopropylidene-6-O-p-tolysulphonyl-β-L-idofuranose, (27) which was isolated at room temperature.



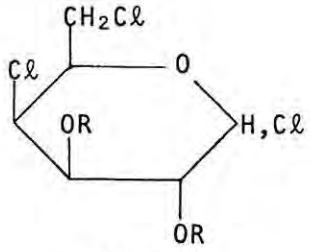
(27)

1.1.1.2 FREE SUGARS

Pyranoses

Reaction of these sugars with sulphuryl chloride yields glycosyl chloride derivatives containing both chlorodeoxy and chlorosulphate groups. The reactivities of the secondary hydroxyl group towards sulphuryl chloride are often similar to those of the corresponding alkyl glycosides[27].

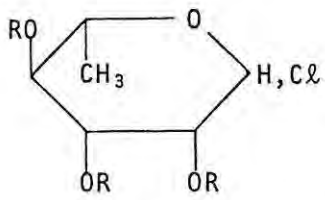
Sulphuryl chloride reacted with D-glucose[47] to yield what was presumed to be 4,6-dichloro-4,6-dideoxy-α-, β-D-galactosyl chloride 2,3-dichlorosulphate (28). Further substitution at C-3 did not occur due to the deactivation of the equatorial chlorosulphate group at C-3 by the vicinal axial chloro substituent at C-4[32].



(R = $SO_2Cℓ$)

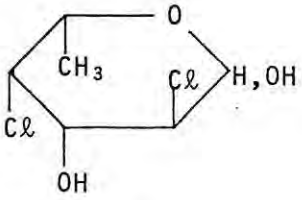
(28)

L-Rhamnose was found by Cottrell and coworkers[33] to form a crystalline compound L-rhamnosyl chloride 2,3,4-trichlorosulphate (29) which on treatment with pyridinium chloride gave a syrup, which after dechlorosulphation afforded a dichloro-tri-deoxy compound assumed to be 2,4-dichloro 2,4,6-trideoxy-L-galactose (30)



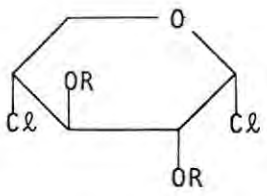
(29)

(R = $SO_2Cℓ$)



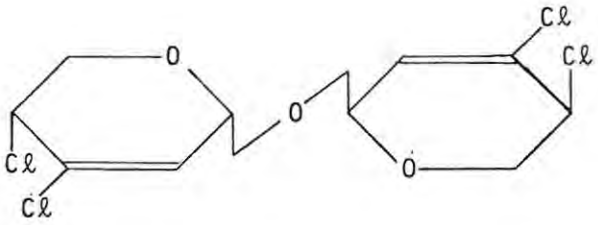
(30)

A unique property of L-arabinose[41] when compared to other reducing sugars and their reactions with sulphuryl chloride, is its formation in addition to the usual chloroform soluble product, of a crystalline, water-insoluble, non-reducing, trehalo type, unsaturated dimer; when treated with sulphuryl chloride for 4 hours at room temperature, L-arabinose was found to form 4-chloro-4-deoxy-α-D-xylosyl chloride 2,3-dichlorosulphate (31), together with the tetrachloro-tetradeoxy dimer, 3,4-dichloro-4-deoxy-α-D-glycero-pent-2-enopyranosyl-3',4'-dichloro-4'-deoxy-α-D-glycero-pent-2'-enopyranoside (32), which crystallized out from the acid wash of the reaction mixture.



(31)

(R = SO_2Cl)

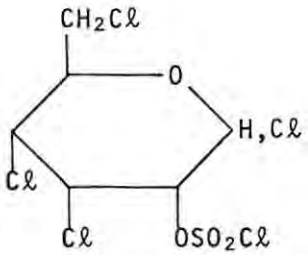


(32)

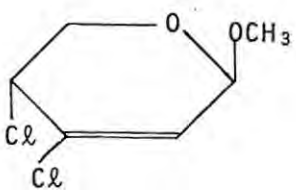
The structure and mode of formation of these compounds have been discussed by Jennings and Jones[41], and although they did not fully understand the mechanism of the aqueous dimerization process, they postulated that the mixture resulting from the reaction contained the D-ribopyranosyl chloride (D-arabinose was found to yield the L-enantiomer of the dimer), and that this was a precursor of the dimer. This was confirmed by Coxon and coworkers[48] as a result of the isolation of 3,4-dichloro-3,4-dideoxy-β-D-ribopyranosyl chloride 2-monochlorosulphate, as a major component, together with the dichlorosulphate - xylosyl chloride, after reaction of L-arabinose with sulphuryl chloride for 24 hours, and from the observation that, treatment of the ribopyranosyl ester with pyridine in chloroform, followed by partitioning of the product between chloroform and an aqueous acidic solution, led to the separation of the β-dimer from the latter solution.

D-Galactose[32] when treated with sulphuryl chloride was found to give a syrupy mixture containing 3-4,6-trichloro-3,4,6-trideoxy-D-allosylchloride 2-chlorosulphate (33), without the formation of a dimeric product, as was found to occur with its configurational analogue, L-arabinose[41]. This has been attributed to the larger $-CH_2Cl$ group at C-5 which does not favour formation of the 2,3 unsaturated dimer percursor. Treatment of the allosyl chloride monochlorosulphate ester with pyridine afforded only the hydrolysis product of the 2-chlorosulphate ester, whereas the analogous compound, methyl 3,4-dichloro-3,4-dideoxy-β-D-ribopyranoside 2-monochlorosulphate[41], gave the 2,3 trans elimination product, methyl 4-deoxy-3,4-

dichloro-β-D-glycero-pent-2-enopyranoside (34).

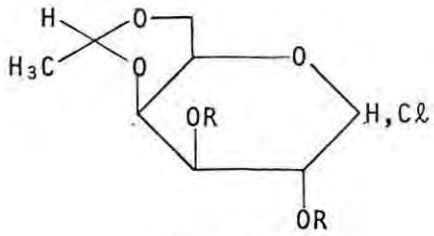


(33)



(34)

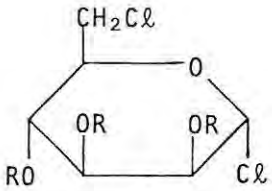
Reaction of 4,6-O-ethylidene-D-galactopyranose[32] with sulphuryl chloride gave a 2,3-dichlorosulphate derivative (35) which reformed the starting material, as well as D-galactose after dechlorosulphation. (Formation of a 3-chloro-deoxy derivative during chlorosulphation did not occur due to the deactivation of the equatorial 3-chlorosulphate ester group, by the vicinal axial group at C-4).



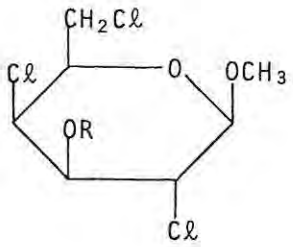
(R = SO_2Cl)

(35)

D-Mannose[32], upon chlorosulphation yielded a crystalline product which was shown to be 6-chloro-6-deoxy-α-D-mannosyl chloride 2,3,4-trichlorosulphate (36), and the latter was observed to undergo further chlorosubstitution with pyridinium chloride to form a trichloro-trideoxy glycosyl chloride of undefined structure, but whose methyl glycoside was assigned the structure, methyl 2,4,6-trichloro-2,4,6-trideoxy-β-D-galactopyranoside 3-monochlorosulphate[33] (37). As previously mentioned, chlorosubstitution to this extent was not observed with the corresponding α-D-mannopyranoside.



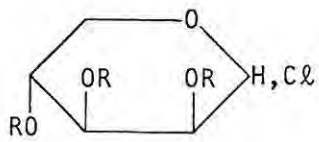
(R = $SO_2C\ell$)



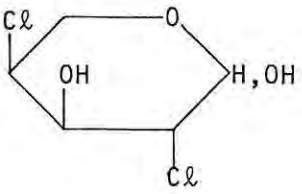
(36)

(37)

In order to extend the analogy with the manno conformation, Cottrell and coworkers[33] examined the reaction of D-lyxose with sulphuryl chloride, and found it to give a chloro-trichlorosulphated derivative, D-lyxosyl-chloride 2,3,4-trichlorosulphate (38). Treatment with pyridinium chloride and subsequent dechlorosulphation yielded a dichloro-dideoxy sugar which was presumed to be 2,4-dichloro-2,4-dideoxy-L-arabinose (39).



(R = $SO_2C\ell$)



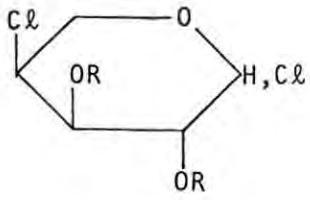
(38)

(39)

The other possible structure considered for the latter compound, was 2,3-dichloro-2,3-dideoxy-D-ribose, but since the D-ribose configuration is known to undergo further substitution at C-4, this seemed unlikely. According to Cottrell and coworkers[33], this was indicative of the fact that D-lyxopyranose and D-mannopyranose react mainly in the Cl conformation. If it were in the 1C conformation, there would be an axial chlorosulphate group at both C-3 and C-4, and an equatorial group at C-2, which would be unlikely to lead to further chlorosubstitution.

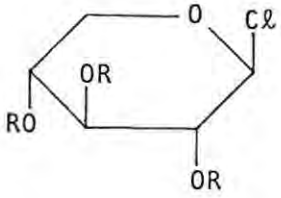
Reaction of D-xylose[47] with sulphuryl chloride was assumed to have formed 4-chloro-4-deoxy-L-arabinopyranosyl chloride 2,3-dichlorosulphate (40)

when isolated at room temperature. Low temperature isolation afforded the crystalline β-D-xylopyranosyl chloride 2,3,4-trichlorosulphate derivative[49] (41).



(40)

(R = $SO_2Cℓ$)

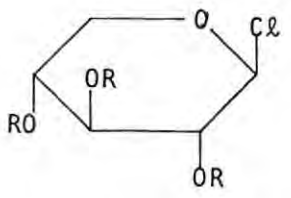


(41)

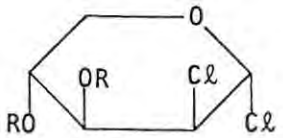
An improved yield of the trichlorosulphate ester was reported by Jennings[50] who isolated the compound from the reaction mixture at -10°C instead of at -20°C as reported in the earlier communication[49]. The increased yield was attributed to the fact that chlorosubstitution of an intermediate 1-chlorosulphate ester takes place at this stage of the reaction by an S_N2 process, with overall inversion of configuration at the anomeric centre, thus attaining a controlled synthesis of single anomers of glycosyl chlorides. N.m.r. studies[51] have also augmented these proposals. (Improved yields at optimum low temperature isolation were also observed when the crystalline β-D-lyxopyranose[51] was treated with sulphuryl chloride to form α-D-lyxopyranosyl chloride 2,3,4-trichlorosulphate). Methanolysis gave a crystalline methyl glycoside which still had the three chlorosulphate groups intact, and both α- and β-D-xylopyranosyl chloride trichlorosulphates gave good yields of their inversion products after methyl glycosidation[50], thus demonstrating the non-participating properties of the chlorosulphate group in these displacements.

Attempts[51] to anomerize β-D-xylopyranosyl chloride 2,3,4-trichlorosulphate (42) with aluminium chloride, had resulted in poor yields of the α-D-anomer, and were found to be unreliable. N.m.r. studies[40] indicated

that the poor yield was due to both incomplete anomerization and to simultaneous formation of an anomerized C-2 inversion product to which the structure of 2-chloro-2-deoxy-α-D-lyxopyranosyl chloride 3,4-dichlorosulphate, (43) was assigned.



(R = $SO_2Cℓ$)

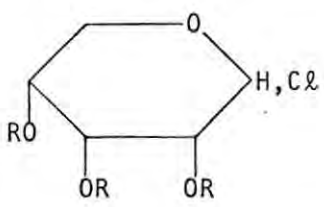


(42)

(43)

It was previously suggested that the efficiency of the reaction could be improved through the use of titanium tetrachloride[51], instead of aluminium chloride. However, Jennings[40] later indicated that when the molar concentration of aluminium chloride was increased, the 2-chloro-deoxy-pyranosyl dichlorosulphate ester became the exclusive product in the reaction. Anomerization and inversion of the α-isomer was also observed to occur when treated similarly with aluminium chloride. In these reactions, specific chloro-displacement of the C-2 chlorosulphate group was said to have occurred via a mechanism involving anomeric chlorine migration.

Chlorosulphation of D-ribose[42] yielded a crystalline D-ribopyranosyl-chloride 2,3,4-trichlorosulphate (44), for which the n.m.r. spectroscopic profile was discussed, whilst treatment of L-fucose[52] with sulphuryl chloride at low temperature, afforded mainly β-L-fucopyranosyl chloride 2,3,4-trichlorosulphate (45), and a small proportion of the α-anomer.



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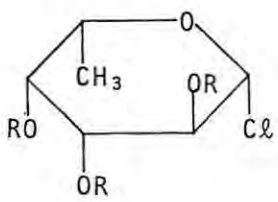
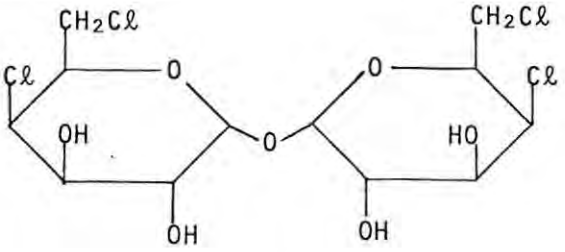


(44)

(45)

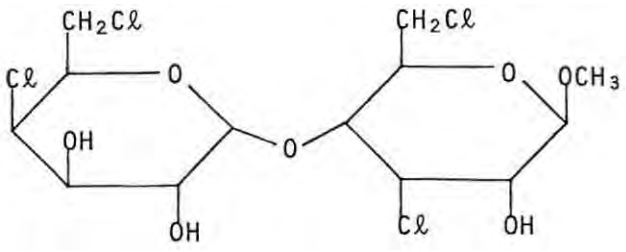
1.1.2 DISACCHARIDES

Early investigations of the reactions of sulphuryl chloride with disaccharides were conducted by Helferich and coworkers[53], on trehalose, which was described as having undergone similar reactions to that of the glycosides reported in an earlier communication[29]. The reaction of α,α-trehalose was found later by Birch and coworkers[54] to give 4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galacto-pyranoside (46).



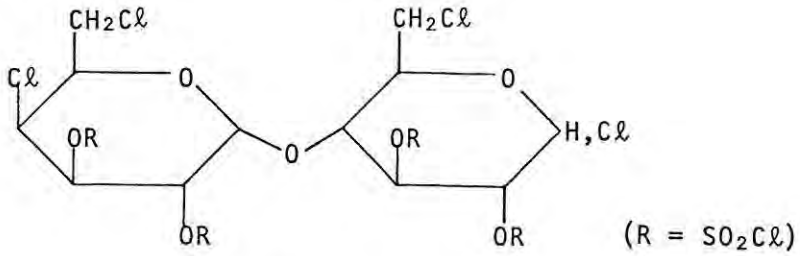
(46)

Durette and coworkers[55] investigated the chlorosulphation of methyl β-maltoside, with a view to synthesizing disaccharide nucleosides having potential antibiotic activity. The reaction coupled with subsequent dechlorosulphation, was found to yield a 3,6,4',6'-tetra-chloro-disaccharide in which the chloro groups at the secondary positions were introduced with inversion of configuration to yield methyl 3,6-dichloro-4-O-(4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl)-3,6-dideoxy-β-D-allopyranoside (47).



(47)

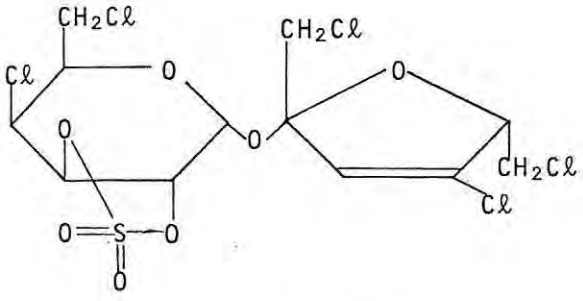
Maltose[47] was found to yield 4-O-α-4,6-dichloro-4,6-dideoxy-D-galacto-pyranosyl-6-chloro-6-deoxy-D-glucopyranosyl chloride 2,3,2',3'-tetra-chlorosulphate (48).



(48)

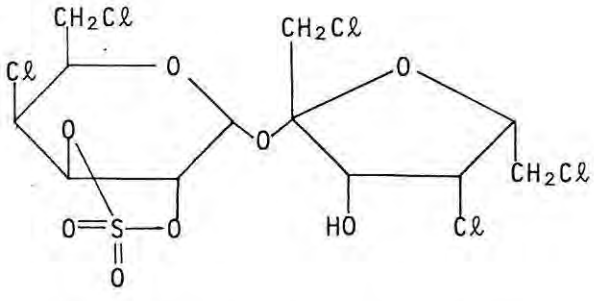
The reaction of sucrose with sulphuryl chloride was first studied by Bragg and coworkers[30], who isolated a mixture of di- and tri-chloro-deoxy sucrose di-cyclic sulphates, the structures of which were not elucidated. They suggested that the glucopyranosyl group of sucrose had been converted mainly into the 4,6-dichloro-4,6-dideoxy-2,3-di-O-sulpho-α-D-galactopyranosyl system, as predicted from their results on methyl-α-D-glucopyranoside.

Ballard and coworkers[56] re-investigated this reaction, and at 50°C found it to yield two pentachloro (49 and 50) and one tetrachloro derivative (51).



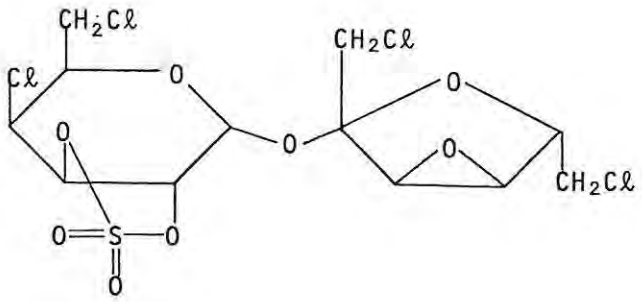
4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 1',4',6'-trichloro-1',3',4',6'-tetradeoxy-β-D-glycero-hex-3'-eno-furanuloside 2,3-sulphate.

(49)



4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 1',4',6'-trichloro-1',4',6'-trideoxy-β-D-allofuranose.

(50)

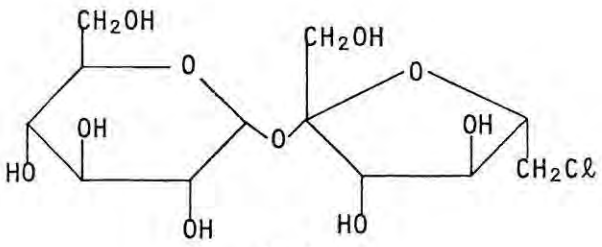


4,6-dichloro-4,6-dideoxy-α-D-galacto-pyranosyl 3',4'-anhydro-1',6'-dichloro-1',6'-dideoxy-β-D-ribofuranuloside 2,3-sulphate

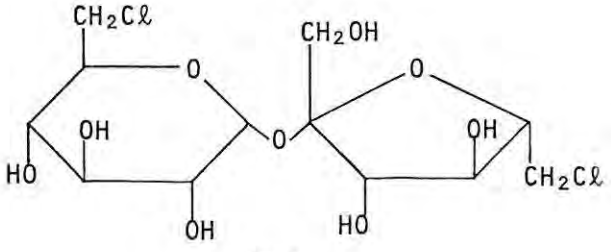
(51)

The pyranoid moeity with the galacto configuration (confirmed by n.m.r. spectroscopy) was found to have chloro substituents at C-4 and C-6, whilst the furanoid moeity carried chloro substituents at the primary centres (C-1' and C-6'), and also at C-4' in the two pentachloro-pentadeoxy compounds. Proposals for the formation of these compounds via chloro-sulphate intermediates have also been discussed by these workers.

In an attempt to optimize product yields, these reactions were re-examined[44] at -78°C, room temperature and 50°C. The results showed that selective chlorination of sucrose was possible when the reaction was carried out at low temperatures; reaction at -78°C gave essentially, a polychlorosulphate compound, which on dechlorosulphation, was found to yield a mixture containing 6'-chloro-6'-deoxy sucrose (52) and 6,6'-dichloro-6,6'-dideoxy sucrose (53), whilst mixtures of increasing complexity were obtained at room temperature and 50°C respectively.



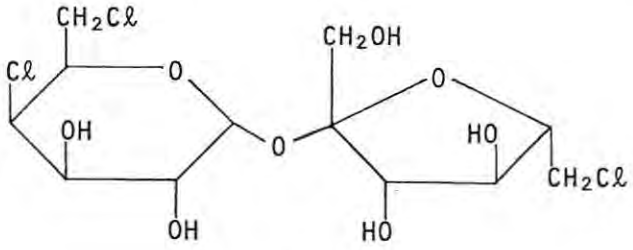
(52)



(53)

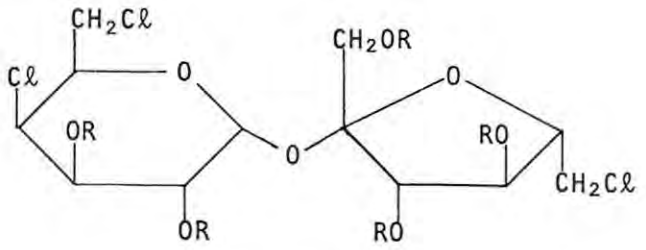
The structures of the products obtained were assigned on the basis of n.m.r. and mass spectroscopy.

The above reactions were re-investigated by Hough and coworkers[57] in order to find optimal conditions for the direct preparation of di- and trichlorinated derivatives. Thus reaction initially at -78°C and then at -30°C to -35°C for 4 days, afforded after dechlorosulphation, 6-chloro-6-deoxy-α-D-glucopyranosyl 6-chloro-6-deoxy-β-D-fructofuranoside (53). A similar reaction at -5°C to -10°C for 16 hours, with subsequent dechlorosulphation was found to yield a trichlorosucrose, the structure of which was elucidated by n.m.r. and mass spectroscopy and assigned as 4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 6-chloro-6-deoxy-β-D-fructofuranoside (54).



(54)

Parolis[58] reported on an improved chlorosulphation procedure, and the isolation of a crystalline trichlorosucrose pentachlorosulphate without recourse to column chromatography. The compound was shown by n.m.r. and mass spectroscopy to be 4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 6-chloro-6-deoxy-β-D-fructofuranoside 1',2,3,3',4'-pentachlorosulphate (55).



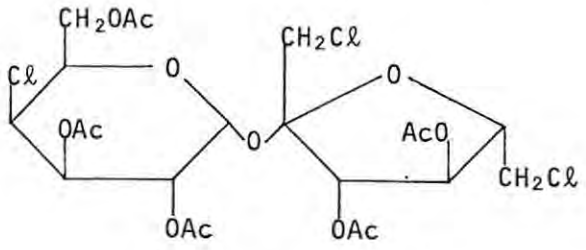
(R = $SO_2C\ell$)

(55)

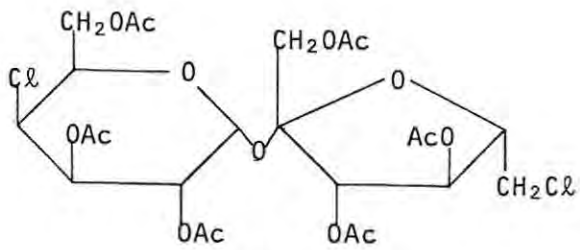
An attempt to synthesize the 1',4,6',6-tetrachloro-1',4,6',6-tetradeoxy

derivative by effecting chlorosubstitution of the 1'-chlorosulphonyloxy group, by heating at 50°C with pyridinium chloride was, however, unsuccessful.

A reaction carried out by Fairclough and coworkers[59] on 3,4-di-O-acetyl-β-D-fructofuranosyl 2,3,6-tri-O-acetyl-α-D-glucopyranoside (1',4,6'-triol) at -75°C, and then allowed to approach room temperature, was found to proceed according to the rules proposed by Richardson[34], as all three hydroxyl groups were replaced by chloride (although HO-1' should have been the least reactive because of its adjacency to the anomeric position) to form 1',4,6'-trichloro-1',4,6'-trideoxy-galacto-sucrose penta-acetate (56). Similar treatment of the 4,6'-diol, 1,3,4-tri-O-acetyl-β-D-fructofuranosyl 2,3,6-tri-O-acetyl-α-D-glucopyranoside afforded the 4,6'-dichloride, 1,3,4-tri-O-acetyl-6-chloro-6-deoxy-β-D-fructofuranosyl 2,3,6-tri-O-acetyl-4-chloro-4-deoxy-α-D-galactopyranoside (57).



(56)



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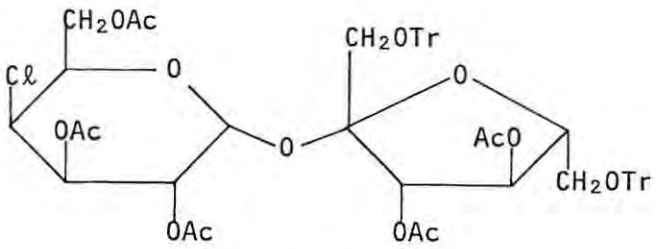
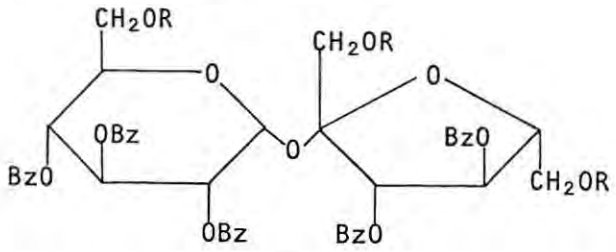


(58)

The dityrityl ether, 3,4-di-O-acetyl-1,6-di-O-trityl-β-D-fructofuranosyl 2,3,6-tri-O-acetyl-α-D-glucopyranoside, having a free hydroxyl group at C-4 was observed to lend itself to two methods of chlorination, in that

3,4-di-O-acetyl-1,6-di-O-trityl-β-D-fructofuranosyl 2,3,6-tri-O-acetyl-4-chloro-4-deoxy-α-D-galactopyranoside (58), was isolated after treatment with either sulphuryl chloride, or mesyl chloride in N,N-dimethylformamide.

Khan[60,61] has reported on nucleophilic substitution reactions of some chlorosulphate derivatives of sucrose. Sucrose penta- and hexa-benzoates were reacted with sulphuryl chloride at -75°C to synthesize penta-O-benzoyl-sucrose 1',6,6'-trichlorosulphate (59) and hexa-O-benzoylsucrose 6,6'-dichlorosulphate (60).



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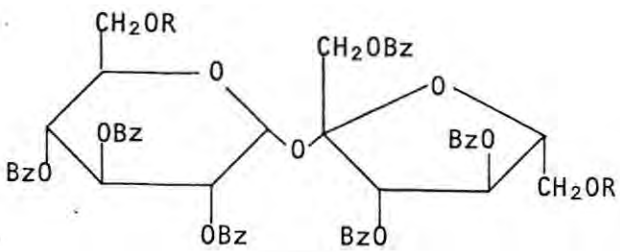

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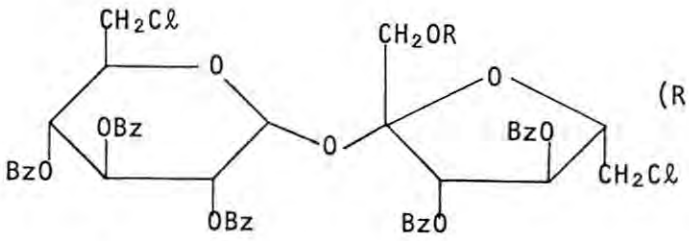


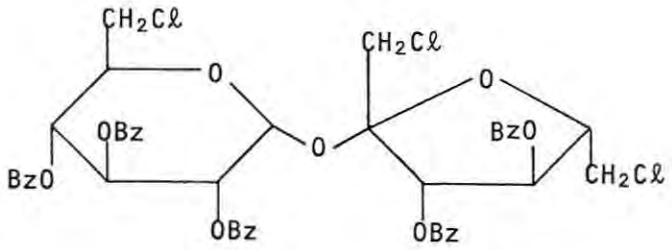
(R = $SO_2C\ell$)

(61)

When the former, trichlorosulphate was treated with pyridinium chloride at 50°C or with butanone under reflux (without any added nucleophile), the penta-O-benzoyl-6,6'-dichloro-6,6'-dideoxy 1'-chlorosulphate (61) was obtained. The higher reactivity of the chlorosulphate groups on C-6 and C-6' was comparable to the nucleophilic displacement of the sulphonyloxy groups of sucrose sulphonates.

Displacement of the 1'-chlorosulphate group in penta-O-benzoyl-6,6'-dichloro-6,6'-dideoxy-sucrose 1'-chlorosulphate[60] was found to be achieved

best with sodium chloride in a dipolar aprotic solvent such as hexamethylphosphoric triamide, to yield the penta-O-benzoyl-1',6,6'-trichloro-1',6,6'-trideoxy sucrose (62). Khan has emphasized that this displacement of the C-1'-chlorosulphate group had previously been unsuccessful and that this method had proved advantageous over standard types.

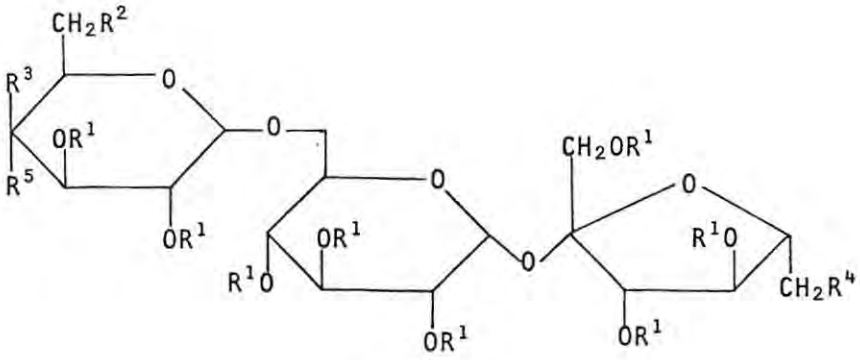


(62)

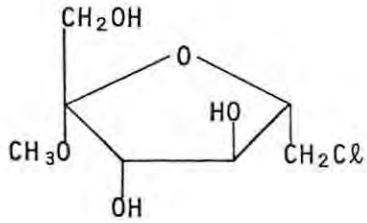
(The above reaction in hexamethylphosphoric triamide was also carried out on the penta-O-benzoyl trichlorosulphate, with and without sodium chloride, and was found to afford a higher yield of the trichlorotrideoxy sucrose in the presence of sodium chloride).

1.1.3 TRISACCHARIDES

The reaction of raffinose (6-O-α-D-galactopyranosylsucrose) (63a) with sulphuryl chloride at temperatures between -20°C and ambient, was reported by Hough and coworkers[62] to have formed several components after dechlorosulphation, namely, methyl 6-chloro-6-deoxy-β-D-fructofuranoside (64), its α-anomer, a trichloro derivative [6-O-(4,6-dichloro-4,6-dideoxy-α-D-glucopyranosyl)-α-D-glucopyranosyl 6-chloro-6-deoxy-β-D-fructofuranoside] (63b), 6'6''-dichloro-6'6''-dideoxyraffinose (63c) and 6'-chloro-6'-deoxyraffinose (63d).



(63)



(64)

(a) $R^1=R^5=H$, $R^2=R^3=R^4=OH$

(b) $R^1=R^3=H$, $R^2=R^5=R^4=Cl$

(c) $R^1=R^5=H$, $R^3=OH$, $R^2=R^4=Cl$

(d) $R^1=R^5=H$, $R^2=R^3=OH$, $R^4=Cl$

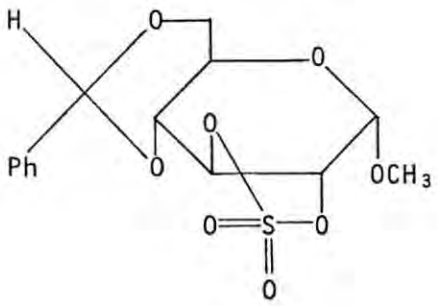
The relative proportions of these compounds were observed to be dependant upon the reaction conditions, in that higher temperatures and prolonged reaction times favoured the formation of the methyl fructofuranoside derivatives. The formation of the latter monosaccharide derivatives appeared to be a major pathway under these conditions, a phenomenon which was not observed to occur when sucrose was similarly treated with sulphuryl chloride.

1.2 REACTIONS OF SUGAR CHLOROSULPHATE ESTERS

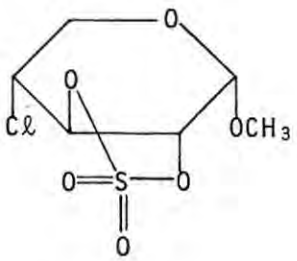
1.2.1 With base

Jennings and Jones[35] on comparing chlorosulphation reaction conditions which yielded cyclic sulphates[29,30], observed that when only a minimum amount of pyridine was used (pyridine-sulphuryl chloride ratio maintained at 1.5-2 mol/mol) at temperatures below zero, the reaction produced chlorosulphate esters instead of cyclic sulphates. They concluded that

in the presence of an excess of pyridine, suitably orientated chlorosulphates, especially those whose spatial arrangement was appropriate by being equatorially orientated, would undergo cyclization favourably. Thus when methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate[35] was reacted with pyridine, it was found to yield methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-cyclic sulphate (3). This was also found to occur when methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-dichlorosulphate was treated with pyridine in the cold, to form the corresponding 2,3 cyclic sulphate (65), or when a similar reaction (at room temperature) was carried out on methyl 4-chloro-4-deoxy-α-D-xylopyranoside 2,3-dichlorosulphate[41] to obtain its 2,3 cyclic sulphate derivative (66).



(65)

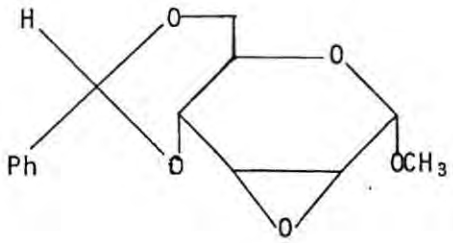


(66)

The actual mechanism proposed[28,35] for cyclization, suggests the basic hydrolysis of one of the chlorosulphate groups with S-O bond scission, to form a free hydroxyl group with retention of configuration, followed by attack by the latter of the remaining chlorosulphate group with S-Cl bond scission to form the cyclic sulphate.

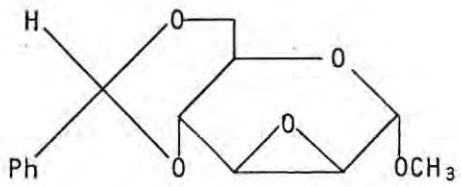
Treatment of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate[35], and methyl 4,6-O-benzylidene-α-D-glucopyranoside 2,3-dichlorosulphate[35], with a more basic reagent such as methanolic sodium methoxide was found to result in no cyclic sulphate formation and

a low yield of methyl 4,6-O-benzylidine-2,3-anhydro-α-D-alloside (67). This evidence thus indicated that the basicity of the reagent was an important factor in the formation of the cyclic sulphate ester, and mechanistic proposals for these reactions have been elaborated by Jennings and Jones[35].



(67)

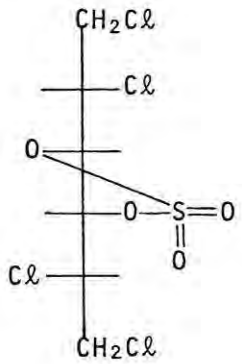
However, if the configuration of the ester groups was trans-diaxial as in the case of methyl 4,6-O-benzylidene-α-D-altropyranoside 2,3-dichlorosulphate[35], treatment with pyridine resulted in the formation of methyl 4,6-O-benzylidene-2,3-anhydro-α-D-mannopyranoside (68), thus indicating that the trans-axial configuration was the most favourable configuration for anhydro formation.



(68)

Favourable cyclization was also found to occur when vicinal dichlorosulphate esters in the open chain form were treated with pyridine; e.g. the tetrachloro-tetradeoxy dichlorosulphate of D-mannitol[35], afforded a tetrachloro-tetradeoxy cyclic sulphate ester (69). Jennings and Jones[35] have explained that the free rotation of the bond between C-3 and C-4 of the ester had enabled the two chlorosulphate groups to approach

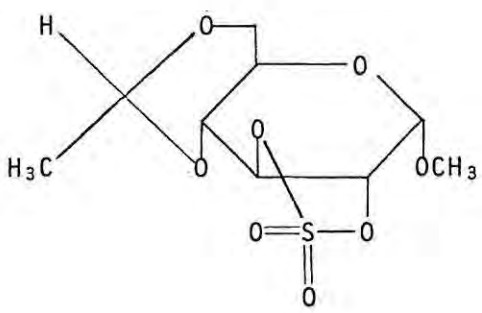
each other closely, thus facilitating cyclization.



(69)

They also observed an unusual phenomenon when treatment of the tetrachloro-tetradeoxy dichlorosulphate ester (mentioned above) with sodium iodide, was found to result in cyclic sulphate formation as well.

The reaction of pyridine on a 2,3-dichlorosulphate ester in the axial-equatorial configuration was also carried out, using the 2,3-dichloro-sulphate derivative of methyl 4,6-O-ethylidene-α-D-mannopyranoside[35] which was observed to form methyl 4,6-O-ethylidene-α-D-mannopyranoside 2,3-cyclic sulphate (70) and a 2-deoxy-3-keto compound, methyl 4,6-O-ethylidene-2-deoxy-3-keto-α-D-erythro-hexoside (71). Formation of the latter compound, was suggested to occur via the slow hydrolysis of the C-2 chlorosulphate group with the formation of an intermediate, which was rapidly converted to the 2-deoxy-3-keto compound.



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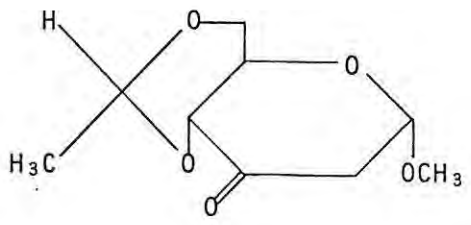
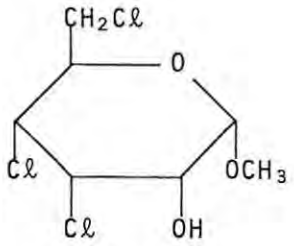


(71)

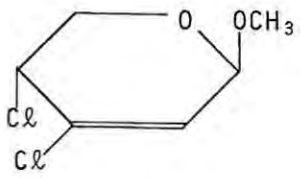
In the above reaction, sodium methoxide was found to produce no keto-deoxy compound.

Jennings and Jones[35] also observed that pyridine at 0°C was capable of hydrolyzing the chlorosulphate ester group in 1,2:5,6-di-O-isopropylidene-D-glucose 3-chlorosulphate, to yield di-O-isopropylidene-D-glucose. A similar phenomenon was later reported[41] by them, after observing the hydrolysis of the 2-chlorosulphate group in methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside 2-chlorosulphate, to form methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside (72).



(72)

Treatment of methyl 3,4-dichloro-3,4-dideoxy-β-D-ribopyranoside 2-chlorosulphate[41] with pyridine was found to result in the formation of a 2,3 trans elimination product, methyl 4-deoxy-3,4-dichloro-β-D-glycero-pent-2-enopyranoside (73). (A similar reaction with a ribopyranosyl monochlorosulphate ester was discussed earlier in this review.)



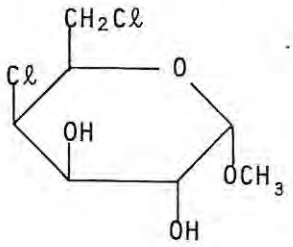
(73)

1.2.2 DECHLOROSULPHATION

Chlorosulphate groups may be easily removed with retention of

configuration to regenerate the sugar having corresponding hydroxyl groups. Dechlorosulphation can be accomplished through the reaction with an iodide ion, and is usually achieved by treatment of a methanolic solution of the sugar chlorosulphate ester, with sodium iodide in aqueous methanol. (Sodium methoxide may also remove these groups but could produce cyclic sulphates or epoxy derivatives from suitably orientated vicinal chlorosulphates[35].)

Chlorosulphated glycosides such as methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate[35,47], when treated with sodium iodide as above, was found to become dechlorosulphated to methyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (74).

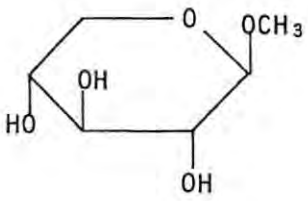


(74)

During the process, immediate liberation of iodine and evolution of sulphur dioxide was observed to occur. When the 2,3-dichlorosulphate-galactopyranoside ester was treated respectively with sodium bromide and sodium azide (in N,N-dimethylformamide), formation of the corresponding 2- and 3-monochlorosulphate esters, in addition to the completely dechlorosulphated compound was found to occur[63]. Parolis et al.[63] also found that the 3-monochlorosulphate-galactoside ester was readily dechlorosulphated with sodium iodide in acetone.

When glycosyl chlorides[40] containing chlorosulphate groups were treated with sodium iodide in aqueous acetone, the reaction also involved the hydrolysis of the anomeric chlorine atom, to yield the free sugar. Jennings[64], however, when investigating this reaction using

methanol as the solvent, observed that the treatment of α- and β-D-xylopyranosyl chloride 2,3,4-trichlorosulphate, and the corresponding α-D-lyxo derivative, with a catalytic amount of sodium iodide, (in the presence of barium carbonate) resulted in the removal of the chlorosulphate groups and rapid methanolysis of the anomeric chlorine atom. The resultant methyl glycosidation was found to occur with inversion of configuration at C-1 (75, 76, and 77 respectively).



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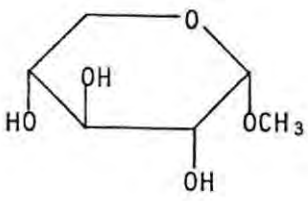

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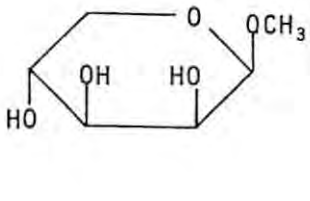
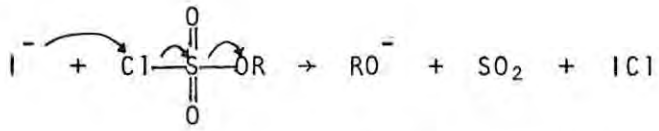


(77)

All mechanisms proposed for the dechlorosulphation reaction involve the attack by iodide ion of the chlorosulphate groups (S-O fission) to liberate iodine and sulphur dioxide. A possible mechanism[26,28] is the displacement by iodide of the chlorine, and subsequent formation of iodine monochloride, which reacts with iodide to give iodine and chloride ion. (Scheme 2)



(R = sugar moeity)

(Scheme 2)

The formation of an unstable iodosulphate intermediate has also been proposed by Buncel[26] as a possible alternative mechanism.

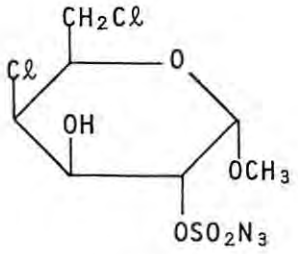
An exception to the general dechlorosulphation reaction pattern has been reported (as previously mentioned) by Jennings and Jones[35], who found that vicinal chlorosulphate ester groups in the open chain hexitol series

gave a cyclic sulphate ester derivative when treated with sodium iodide. They also observed that pyridine was capable of catalytically hydrolysing the chlorosulphate ester group in 1,2:5,6-di-O-isopropylidene-D-glucose 3-chlorosulphate[35] and methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside 2-chlorosulphate[41], to form the parent hydroxy sugars.

1.2.3 NUCLEOPHILIC DISPLACEMENT OF CHLORO GROUPS IN SUGAR CHLOROSULPHATE ESTERS

1.2.3.1 With azide

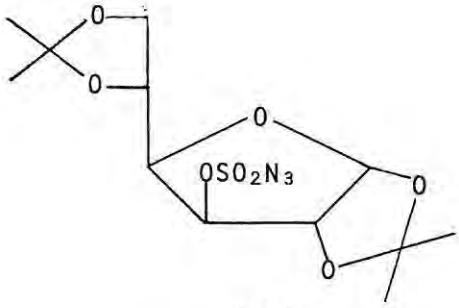
Parolis[63] found that treatment of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate with sodium azide in N,N-dimethylformamide at room temperature, afforded a mixture of four major products namely, methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside, its 2- and 3-monochlorosulphates, and an azidosulphate (78) for which a tentative assignment at C-2 was made.



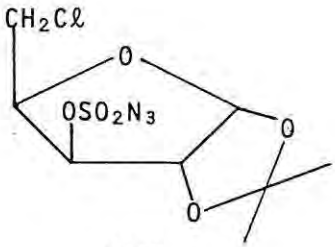
(78)

The synthesis of various carbohydrate azidosulphates and azidodeoxy sugars via the reaction of sugar chlorosulphates of varying reactivities such as, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-chlorosulphate, 5-chloro-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose 3-chlorosulphate, 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-chlorosulphate and 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone 5-chlorosulphate, with potassium azide in the presence of 18-crown-6-ether, has been reported in a preliminary communication[22], to yield, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-azidosulphate (79),

5-chloro-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose 3-azidosulphate (80), 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6-azidosulphate (81) [and the corresponding 6-azido-6-deoxy derivative (82)] and 5-azido-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono 6,3-lactone (83) [and a small proportion of the gluco-isomer (84)], respectively.



(79)



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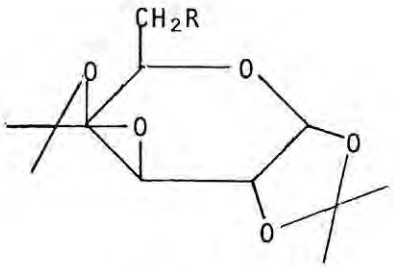
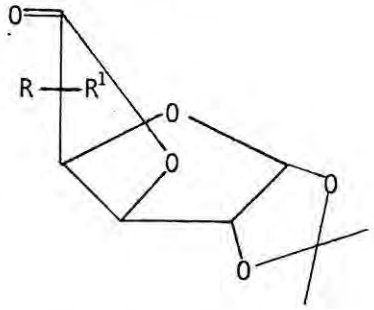


(81) R = OSO_2N_3

(82) R = N_3

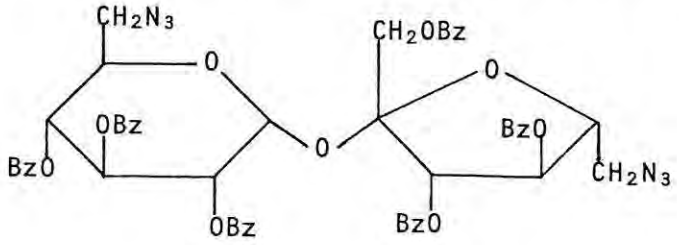


(83) $R^1 = N_3$, R = H

(84) R^1 = H, R = N_3

Khan[60] has questioned the bimolecular mechanism proposed for the chloride-displacement reaction, as chlorodeoxy and not azidodeoxy derivatives were obtained in the reaction with primary chlorosulphates[60] with sodium azide. When both sucrose derivatives, penta-O-benzoyl-trichlorosulphate and hexa-O-benzoyl-dichlorosulphate were treated under reflux with an excess of sodium azide in butanone, the 6,6'-dichlorides were obtained instead of the corresponding azides, and this phenomenon was suggested by Khan of being indicative of effective competition by the chloride ion which could only have originated from the chlorosulphonyloxy groups of the chlorosulphate ester precursor, thus possibly

involving an intramolecular process (S_Ni), but with inversion of configuration. In addition, however, the reaction of the hexa-O-benzoyl sucrose dichlorosulphate ester with sodium azide in hexamethyl phosphoric triamide was found to form the 6,6'-diazido-6,6'-dideoxy-benzoate (85), for which Khan[60] has suggested the initial formation of the 6,6'-dichloride by an S_Ni process, followed by a bimolecular (S_N2) displacement reaction with azide ion to afford the 6,6'-diazide.



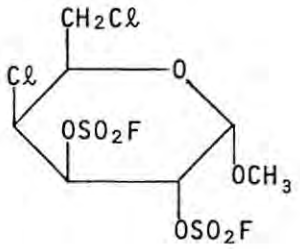
(85)

However, treatment of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6-monochlorosulphate[22] with azide, apparently affords the 6-azidodeoxy derivative via displacement of a 6-azidosulphate intermediate by azide. That this process probably occurs by an S_N2 mechanism, rather than an intramolecular S_Ni type, was demonstrated when the 6-chloro-6-deoxy derivative[22] was obtained by treatment of the 6-azidosulphate intermediate with pyridinium chloride. At no stage during this reaction was an intermediate chlorosulphate detected, thus indicating direct replacement of the azidosulphate group by chloride.

1.2.3.2 With Fluoride

Buncel and coworkers[65] have suggested that fluorosubstitution of chlorosulphate esters might enhance their characteristic as a leaving group during nucleophilic substitution reactions. They reported[67] the synthesis of several sugar fluorosulphate esters which were prepared by treatment of the corresponding chlorosulphate esters with silver

fluoride in methanolic solution. These reactions which were conducted at room temperature and observed to occur slowly via sulphur-chlorine bond scission, resulted in the synthesis of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-difluorosulphate (86), methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside 2-fluorosulphate (87), 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-fluorosulphate (88) and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-fluorosulphate (89), from their parent chlorosulphates.



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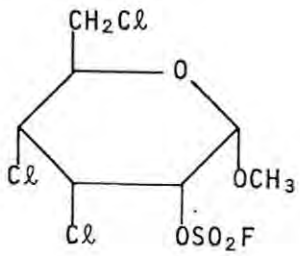

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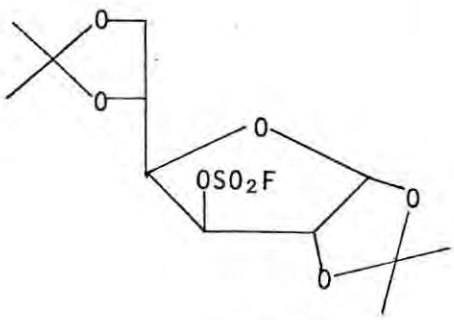

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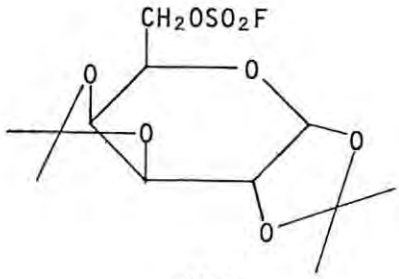
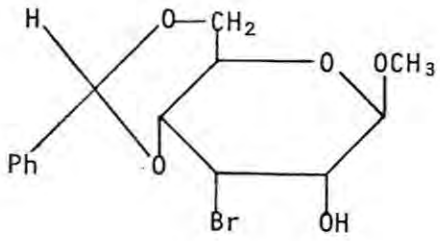


(89)

The latter primary fluorosulphate, was however, found to be unstable. (By analogy with other reactions involving silver ion catalysis, Buncel[26] has stated that these reactions could be presumed to have appreciable S_Ni characteristics.)

1.2.3.3 With Bromide

The reaction of the 2,3-dichlorosulphate ester of methyl 4,6-O-benzylidene-β-D-glucopyranoside with bromide at room temperature, was reported by Bundle[66] to yield methyl 4,6-O-benzylidene-3-bromo-3-deoxy-β-D-allopyranoside (90).



(90)

As previously mentioned, Parolis et al.[63] reported that treatment of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate with sodium bromide resulted in partial and complete dechlorosulphation to yield the corresponding 2- and 3- monochlorosulphate esters, as well as methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (74) respectively. They also observed that the latter compound had formed in greater proportion, than when a similar reaction was undertaken with sodium azide.

2. EXPERIMENTAL

2.1 General Procedures

Thin-layer chromatography (T.l.c.) was performed on glass plates with Kieselgel G (Merck) as adsorbent. The plates were developed with the following solvent systems: Solvents a, b, c, d, e, f and g were ether and petroleum ether (boiling point 40°-60°) in the proportions: 2:8, 3:7, 4:6, 5:5, 6:4. 7:3 and 8:2 respectively, while solvent (h) comprised ether and methanol 9:1. The separated components were detected by spraying the developed plates with spray reagent a (10% v/v sulphuric acid in ethanol) and followed by charring on a hot plate at ≈ 150° , or more specifically, chlorosulphate esters were detected with spray reagent b[67] (butanol-pyridine-aniline in a proportion of 8:2:1 respectively).

Dry column chromatography was performed on Kiesegel 60 (Merck) (70-230 mesh ASTM) using a 1-2% loading and fractions (15 ml) were collected automatically and monitored by t.l.c.

Gas liquid chromatography (G.l.c.) was performed with a Beckman GC-4 chromatograph equipped with dual f.i.d.; nitrogen was used as the carrier gas. Separation of the sugar derivatives was effected on a column containing 3% of ECNSS-M on Gas Chrom Q (100-120 mesh) at 145°, and at a flow rate of 60-80 ml/min. Retention times (T) of the sugar derivatives are quoted relative to 1,2-5,6-di-O-isopropylidene-α-D-glucofuranose, which was used as an internal standard.

Melting points (M.p.) were determined with a Gallenkamp melting point apparatus and are uncorrected.

Optical rotations were measured in chloroform solution (unless stated otherwise) at 23° ± 2° , with a Perkin-Elmer 141 automatic polarimeter using a 1.0 cc cell.

Infra-red (I.r.) spectra were recorded on a Beckman I.R.8 spectrophotometer using chloroform as solvent.

Nuclear magnetic resonance (N.m.r.) spectra were recorded on a Perkin-Elmer R-12 spectrometer at 60 MHz using chloroform-d as solvent with tetramethylsilane (t.m.s.) as the internal standard. Wherever possible, n.m.r. assignments were confirmed by decoupling experiments.

Mass spectra were determined with an A.E.I. MS-30 spectrometer at 70 eV.

Elemental analysis were performed by the microanalyst of the School of Pharmacy, University of London.

Evaporations were carried out under reduced pressure at room temperature or below 50° where indicated, using a Büchi Rotavapor outfit.

Unless otherwise stated, the term "petroleum ether" refers to the fraction of boiling point 40°-60°.

2.2 General Chlorosulphation Procedure

The reaction of carbohydrates with sulphuryl chloride was carried out according to the method of Jennings and Jones[47,35], by the dropwise addition of sulphuryl chloride to a cooled solution or suspension of the carbohydrate in pyridine-chloroform whilst accompanied by vigorous stirring. The pyridine-sulphuryl chloride ratio was maintained at 1.5 - 2.0 mol/mol[35] and the general proportions of reagents used[45] were as follows:

Pyridine 0.8 ml/OH group/1.0 g sugar

Sulphuryl Chloride 2.6 ml/4.0 ml pyridine

Chloroform 5-30 ml/g of sugar

All the above reagents were used in an anhydrous state. A portion (≃ 30%) of the total volume of chloroform was used to dilute the sulphuryl chloride prior to its addition. The reaction mixture was either maintained at various temperatures below zero or allowed to approach zero or room temperature over a period of time, after which it was diluted

with additional chloroform, and poured into chilled 10% sulphuric acid (equal volume) in a separating flask. The organic layer was separated from the aqueous phase, and washed successively with an equal volume of saturated sodium bicarbonate solution and water. The chloroform extract was then dried (anhydrous sodium sulphate), filtered, and concentrated under reduced pressure at 25°-30° to yield the product.

2.3.1 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose 3-chlorosulphate (1) - To a solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (5 g) in chloroform (40 ml) and pyridine (5.5 ml) at -10°, was added sulphuryl chloride (3.5 ml in chloroform 10 ml) as described over a period of 0.5 h. The reaction was continued at -10° for a further 1.5 h and then worked up as described, to yield (5.46 g, 79%) a crystalline product, t.l.c. examination of which revealed a single component (R_f 0.75, solvent d), and gave a positive reaction with spray reagent b. Recrystallization was from ether-petroleum ether; m.p. 92°-93°; $[\alpha]_D$ -55.95° (c 1.68) (Jennings et al.[35] reported $[\alpha]_D$ -40°, and m.p. 92° for compound 1); λ_{max} 7.13 μm ($OSO_2C\ell$), and 8.45 μm ($OSO_2C\ell$).

2.3.2 Reaction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-chlorosulphate (1) with potassium azide in the presence of 18-crown-6-ether. - To a solution of (1) (2.73 g) in acetone (20 ml) was added potassium azide (1.8 g, 3.0 molar equivalents) and 18-crown-6-ether (60 mg, 0.03 molar equivalent). The reaction mixture was stirred continuously at room temperature (20°) for 24 h, after which time it was filtered to remove insoluble salts and the filtrate evaporated to dryness. The residue was dissolved in chloroform and the solution was washed successively with saturated sodium bicarbonate solution and water and then dried (anhydrous sodium sulphate). Evaporation of the chloroform afforded a pale yellow syrup (1.68 g), t.l.c. examination (solvent a,

spray reagent b) of which indicated the absence of compound 1 and presence (spray reagent a) of two components (R_f 0.8 and 0.3, solvent a) which were separated by dry column chromatography (initial elution with solvent b and finally with solvent d) to afford: (i) compound 2, a yellow syrup (1.4 g, 66%) which was purified by distillation (98°-100°/0.05 mmHg); R_f 0.8 (solvent a); $[\alpha]_D$ -151.1° (c 1.91); λ_{max} 4.74 μm (N_3), 7.18 μm and 8.25 μm (OSO_2N_3). Anal. Calc. for $C_{12}H_{19}O_8N_3S$: C, 39.45; H, 5.21; N, 11.51; S, 8.77. Found : C, 40.63; H, 5.33; N, 10.78; S, 8,42.
(ii) a white crystalline compound (0.29 g, 14%); R_f 0.3 (solvent a); m.p. 106.5° (undepressed on admixture with authentic 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose.

2.3.3 Reaction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-azidosulphate (2) with potassium azide in the presence of 18-crown-6-ether. - Treatment of compound 2 (100 mg) with potassium azide (67 mg, 3.0 molar equivalents) and 18-crown-6-ether (75 mg, 1.0 molar equivalent) in acetone resulted after 64 h stirring at room temperature, in the formation of two components having R_f 0.62 (major) and 0 (minor) (solvent g, spray reagent a) which were identical to the Rf values (solvent g) of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose and 1,2-O-isopropylidene-α-D-glucofuranose respectively. The slower running component (R_f 0) was removed during washing of the chloroform solution of the mixture with water. Evaporation of the chloroform afforded a semi-crystalline syrup (60 mg); R_f 0.62 (solvent g); λ_{max} 3.0 μm (OH) and 7.3 μm [$(CH_3)_2C$].

2.3.4 Reduction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-azidosulphate (2).

(i) Catalytically[68] - A solution of compound 2 (0.75 g) in ethanol (25 ml) was hydrogenated with platinum(IV) oxide (75 mg) in a Cook's low pressure (30 p.s.i.g.) catalyst hydrpgenation plant, for 1 h at room temperature. The catalyst was removed by filtration and the ethanolic filtrate neutralized by addition of solid sodium bicarbonate (2 g), followed by filtration and evaporation of the filtrate to afford a foamy crystalline product, t.l.c. examination (solvent f, spray reagent a) of which revealed the presence of a major component (R_f 0.5) and a trace of a compound having R_f 0. The mixture was dissolved in ether (50 ml) and the solution was washed with water (50 ml) to remove the trace contaminant, dried (sodium sulphate), and evaporated to yield (0.54 g, 77.5%) a foamy crystalline product which was recrystallized from ether-petroleum ether to afford compound 3 as flat needle crystals, R_f 0.9 (ether); m.p. 141.5° - 142°; $[\alpha]_D$ -51.96° (c 1.84); λ_{max} 3.0 μm (NH_2), 7.15 μm and 8.25 μm (OSO_2NH_2).
Anal. Calc. for $C_{12}H_{21}O_8NS$: C, 42.48; H, 6.19; N, 4.13; S, 9.44.
Found : C, 42.28; H, 6.29; N, 3.89; S, 9.23.

(ii) With sodium borohydride - To a solution of compound 2 (0.45 g) in N,N-dimethylformamide (0.75 ml) and methanol (7.5 ml), was added sodium borohydride (0.36 g) in small portions. The reaction mixture was stirred continuously at room temperature for 1 h after addition of all the sodium borohydride. T.l.c. examination (solvent f, spray reagent a) revealed the presence of a major component (R_f 0.5) together with a small proportion of what was presumably a hydrolytic by-product (R_f 0). The reaction mixture was shaken with water (50 ml) and then extracted with chloroform (50 ml). The combined chloroform extracts were dried

(sodium sulphate) and finally evaporated under vacuum to remove N,N-dimethylformamide. The syrup obtained was redissolved in chloroform (50 ml) and the latter solution washed with water to remove all traces of hydrolytic by-products. The chloroform extract was dried as above and concentrated to yield a pale yellow syrup (0.38 g, 90.9%), which crystallized from chloroform-petroleum ether to form fine white needles (3) that were chromatographically pure (R_f 0.9, ether); m.p. 141° - 143°; $[\alpha]_D$ -52.78° (c 1.69).

2.3.5 Partial hydrolysis of 3-O-sulphamoyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (3). - Compound 3 (1 g) in methanol (5 ml) was acidified with 0.1 N hydrochloric acid (0.3 ml, in 5 ml water) and stirred at 50° for 30 h. The reaction mixture was neutralized with silver carbonate (0.1 g), filtered, and concentrated at 35° to afford a syrup. T.l.c. examination (solvent h, spray reagent a) revealed the presence of a major component (R_f 0.82), a trace of two components having R_f values of 0.62 (corresponded to that of 1,2-O-isopropylidene-α-D-glucofuranose) and 0.44 respectively, and a very slight trace of unreacted starting material (R_f 0.97). The main compound (4) was isolated by column chromatography (ether) and obtained as a pale yellow semi-crystalline syrup (0.8 g, 90.7%); $[\alpha]_D$ -23.27° (c 1.96), methanol); λ_{max} 3.05 μm (OH and NH_2), 7.35 μm [$(CH_3)_2C$], 7.1 μm and 8.4 μm (OSO_2NH_2). Anal. Calc. for $C_9H_{17}O_8NS$: C, 36.12; H, 5.69; N, 4.68; S 10.7. Found : C, 35.84, H, 5.97; N 4.36, S, 10.79.

2.3.6 Partial hydrolysis of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-azidosulphate (2) - An aqueous (5 ml) acidified (0.3 ml 0.1 N hydrochloric acid) methanolic (5 ml) solution of compound 2

(1.0 g) was stirred at 55° for 40 h. T.l.c. examination (solvent f, spray reagent a) revealed the presence of two components having R_f values of 0.4 (major) and zero respectively. The reaction mixture was worked up as described above and the main compound (5) isolated by column chromatography (solvent d) as a syrup (0.7 g, 78.8%); R_f 0.4 (solvent d) and 0.77 (ether); $[\alpha]_D$ -95.49° (c 1.95); λ_{max} 2.94 μm (OH), 4.68 μm (N_3), 7.25 μm [$(CH_3)_2C$], 7.0 μm and 8.15 μm (OSO_2N_3). Anal. Calc. for $C_9H_{15}O_8N_3S$: C, 33.23; H, 4.61; N, 12.92; S, 9.84. Found : C, 36.0; H, 5.07; N, 11.24; S, 8.83 (product underwent gradual decomposition).

2.3.7 Reduction of 1,2-O-isopropylidene-α-D-glucofuranose 3-azidosulphate (5) - Compound 5 (0.5 g) in ethanol (20 ml) containing platinum(IV) oxide (50 mg) was hydrogenated (30 p.s.i.g.) for 1.5 h at room temperature. The reaction mixture was worked up as previously described, to afford a yellow syrup. T.l.c. examination (ether, spray reagent a) indicated the presence of a major component (R_f 0.32) and a minor amount of a compound (R_f 0.19) which corresponded to 1,2-O-isopropylidene-α-D-glucofuranose. The main compound (4) was isolated by column chromatography (ether) as a semi-crystalline syrup (0.2 g, 43.5%); R_f 0.82 (solvent h); $[\alpha]_D$ -22.8° (c 2.01, methanol); λ_{max} 3.0 μm (OH and NH_2), 7.35 μm [$(CH_3)_2C$], 7.1 μm and 8.35 μm (OSO_2NH_2).

2.3.8 5,6-Di-O-acetyl-1,2-O-isopropylidene-α-D-glucofuranose 3-azidosulphate (6) - To a chilled solution of compound 5 (0.25 g) in pyridine (1.0 ml) was added acetic anhydride (1.0 ml) dropwise. The reaction mixture was allowed to stand at room temperature for 12 h, after

which it was poured into ice (50 g) and stirred. Compound 6 separated out as a syrup. The aqueous portion was decanted and the syrupy residue dissolved in chloroform. The chloroform solution was washed successively with 10% sulphuric acid (50 ml), saturated sodium bicarbonate solution (50 ml), and water, dried (sodium sulphate), filtered and concentrated to yield a pale yellow syrup (0.2 g, 63.6%). T.l.c. examination (solvent f, spray reagent a) indicated the presence of a single compound (R_f 0.62); $[\alpha]_D$ -14.11° (c 1.46) ; λ_{max} 4.68 μm (N_3), 5.8 μm (OAc), 7.15 μm and 8.25 μm (OSO_2N_3).

Anal. Calc. for $C_{13}H_{19}O_{10}N_3S$: C, 38.14; H, 4.65; N, 10.27; S, 7.82.
Found : C, 39.75; H, 4.67; N, 8.8; S, 6.78.

2.3.9. 5,6-Di-O-acetyl-3-O-sulphamoyl-1,2-O-isopropylidene-α-D-glucofuranose (7)

(i) Catalytically - Compound 6 (0.3 g) in ethanol (10 ml) containing platinum(IV) oxide (30 mg) was hydrogenated (30 p.s.i.g.) for 0.75 h at room temperature. The reaction mixture was worked up as previously described to afford a pale yellow syrup (0.26 g, 92.85%) which crystallized from chloroform-petroleum ether to form flat, granular off-white crystals. T.l.c. examination (solvent f, spray reagent a) revealed the presence of a single compound (7) having R_f 0.45; m.p. 146°-147°; $[\alpha]_D$ + 1.38° (c 1.44); λ_{max} 3.05 μm (OH and NH_2), 5.83 μm (OAc), 7.08 μm and 8.35 μm (OSO_2NH_2).

Anal. Calc. for $C_{13}H_{21}O_{10}NS$: C, 40.73; H, 5.48; N, 3.66; S, 8.36.
Found : C, 40.73; H, 5.54; N, 3.64; S, 8.33.

(ii) With sodium borohydride - To a solution of compound 6 (25 mg) in methanol (2 ml) and N,N-dimethylformamide (0.05 ml) was added sodium

borohydride (20 mg) as previously described. The mixture was stirred at room temperature for 1 h, after which t.l.c. examination (solvent f, spray reagent a) revealed the presence of a major component (R_f 0.45), and a trace quantity of a component at the origin (corresponded to 1,2-O-isopropylidene-α-D-glucofuranose). The reaction mixture was worked up as previously described to yield a pale yellow syrup (15 mg, 80%) which crystallized from chloroform-petroleum ether to form chromatographically pure crystals (7) having R_f 0.45 (solvent f), and m.p. 146°-147°.

2.4.1 5-Chloro-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone (8) - To a cooled (-10°) solution of 1,2-O-isopropylidene-α-D-glucofuranurono 6,3-lactone (10 g) in pyridine (16 ml) and chloroform (150 ml) was added sulphuryl chloride (10 ml, diluted with 50 ml chloroform) as described, over 4 h. The reaction mixture was allowed to stand at ≃ 5° overnight, after which t.l.c. examination (solvent g, spray reagent a) revealed the presence of a single component (R_f 0.93) which gave a negative reaction with spray reagent b. The product was isolated in the usual manner to yield a pale yellow amorphous powder (8.4 g, 77.7%), which on recrystallization from ether afforded white crystals; m.p. 135°-136°; $[\alpha]_D$ +52.93° (c 1.11); λ_{max} 5.56 μm (lactone, C=O) and 7.3 μm [$(CH_3)_2C$]. (Parolis[45] reported $[\alpha]_D$ +48.7° and m.p. 137°-139° for compound 8)

Anal. Calc. for $C_9H_{11}O_5Cl$: C, 46.06; H, 4.69; Cl, 15.14.
Found: C, 45.97; H, 4.67; Cl, 15.43.

2.4.2. 1,2-O-Isopropylidene-α-D-glucofuranurono-6,3-lactone 5-chloro-sulphate (9) - To a solution of 1,2-O-isopropylidene-α-D-

glucofuranurono 6,3-lactone (2 g) in chloroform (15 ml) and pyridine (2 ml) at -78° was added sulphuryl chloride (1.3 ml in chloroform 5 ml) as described. The temperature of the reaction mixture was allowed to rise to -20°, and work up followed (0.75 h after addition of sulphuryl chloride had commenced) by rapid dilution with chloroform (50 ml). The product was isolated in the usual way as fine feathery crystals (2.26 g, 78%) with a pungent odour. Recrystallization was effected from chloroform-petroleum ether. T.l.c. examination (solvent g, spray reagents a and b) revealed the presence of a single component (Rf 0.88); m.p. 141°-153° (with slow decomposition); $[\alpha]_D$ +64.5° (c 1.38). (Compound 9 decomposed on standing, thus precluding characterization by elemental analysis).

2.4.3 Reaction of 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone 5-chlorosulphate (9) with potassium azide.

(a) In the presence of 18-crown-6-ether - Potassium azide (0.78 g, 3.0 molar equivalents) and 18-crown-6-ether (25.3 mg, 0.03 molar equivalent) were added to a solution of compound 9 (1 g) in acetone (8 ml). The reaction mixture was stirred at room temperature for 2 h, after which t.l.c. examination (solvent d, spray reagent b) revealed an absence of starting material. The reaction mixture was processed in the usual way to yield (0.49 g) white crystalline needles. T.l.c. examination (solvent d, spray reagent a) indicated the presence of a major compound namely, 10 (R_f 0.73) and a minor compound 11 (R_f 0.35), together with a trace of a compound having R_f 0.25. The crystalline mixture [λ_{max} 4.76 μm (N_3) and 5.6 μm (lactone, C=O)] was recrystallized from ether - petroleum ether to afford compound 10 (0.18 g); m.p. 110-113°; $[\alpha]_D$ +92.7° (c 1.41).

Anal. Calc. for (5-azido-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono

6,3-lactone) $C_9H_{11}O_5N_3$: C; 44.81; H, 4.56; N, 17.43. Found: C, 44.65; H, 4.62; N, 17.0. Compound 11 was isolated from the mother liquor by column chromatography (solvent d) and obtained as a syrup (8.6 mg); $[\alpha]_D$ +40.22° (c 0.46); λ_{max} 4.73 µm (N_3) and 5.6 µm (lactone, C=0).

(b) In the absence of 18-crown-6-ether - To a solution of compound 9 (0.2 g) in acetone (2 ml) was added potassium azide (0.156 g, 3.0 molar equivalents) with continuous stirring until all starting material was consumed (2.5 h). The reaction mixture was processed as before, to yield white crystalline needles (0.1 g). T.l.c. examination (solvent d, spray reagent a) revealed the presence of two major compounds namely 10 (R_f 0.73) (predominant) and 11 (R_f 0.35), together with a trace of a compound having R_f 0.23. (Recrystallization from ether-petroleum ether resulted in compound 11 and the latter being eliminated to a slight degree from compound 10). Compound 10 was separated by column chromatography (solvent d) and obtained as crystalline needles (0.06 g); m.p. 113°-115°; λ_{max} 4.73 µm (N_3) and 5.62 µm (lactone, C=0); $[\alpha]_D$ +93.5° (c 1.53).

2.4.4 Heating of 5-azido-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone (10) in N,N-dimethylformamide - Compound 10 (5 mg) was heated (85°C) in N,N-dimethylformamide for 10 h. T.l.c. examination (solvent d, spray reagent a) revealed the presence of some starting material and approximately 60% of the gluco-isomer (R_f 0.35) which had formed.

2.4.5 Reaction of 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone 5-chlorosulphate (9) with potassium fluoride in the presence of 18-crown-6-ether - To a solution of compound 9 (0.8 g) in acetone (6.5 ml), was added potassium fluoride (0.45 mg, 3.0 molar equivalents) and 18-crown-6-ether (20 mg. 0.03 molar equivalent). The reaction mixture was stirred continuously at room temperature and worked up after 6 h in the usual way, to yield (0.53 g) white granular crystals. T.l.c. examination (solvent d, spray reagent a) revealed the presence of two components with R_f 0.78 and 0.42, which were present in an approximate ratio of 60:40 respectively; the latter component was unreacted starting material which gave a positive reaction with spray reagent b, and was separated by column chromatography (solvent d) from the faster running component, which was isolated as a crystalline mass (0.3 g, 48.8%) that was recrystallized from ether to afford white crystals; m.p. 135°-137°; $[\alpha]_D$ +50.29° (c 1.52); λ_{max} 5.58 μm (lactone, C=O) and 7.3 μm $[(CH_3)_2C]$; (physical data obtained was similar to that reported for compound 8).

2.4.6 Methyl 5-chloro-5-deoxy-α-L-idofuranosidurono-6,3-lactone 2-chlorosulphate (13) - Sulphuryl chloride (10 ml) was added dropwise over 0.5 h to a cooled (below -40°) stirred solution of methyl-β-D-glucofuranosidurono-6,3-lactone (10 g) in pyridine (16 ml) and chloroform (80 ml). After a further 2 h below -40° the reaction temperature was raised to 0° for 2 h and then the mixture was allowed to stand at room temperature for 2 h. Work up as described afforded an off-white crystalline mass which was recrystallized from ether to afford compound 13 as colourless needles, m.p. 102°-103° and $[\alpha]_D$ -10.7° (c 1.2). (Parolis[45] reported m.p. 102°-104° and $[\alpha]_D$ -11°

for compound 13).

2.4.7 Reaction of methyl 5-chloro-5-deoxy-α-L-idofuranosidurono-6,3-lactone 2-chlorosulphate (13) with potassium azide - To compound 13 (100 mg) in acetone (10 ml) was added potassium azide (26 mg, 1.0 molar equivalent) with stirring. An immediate evolution of sulphur dioxide occurred and t.l.c. examination revealed the formation of a single compound. The reaction mixture was filtered and evaporated to dryness. The residue was extracted with warm ether and concentrated to a small volume which on cooling afforded colourless crystals (14) (40 mg, 58.8%) m.p. 136°-138°; $[\alpha]_D$ -85.8° (c 1.5). (Parolis[45] reported m.p. 137°-139° and $[\alpha]_D$ -87° for methyl 5-chloro-5-deoxy-α-L-idofuranosidurono-6,3-lactone). The mixed m.p. with authentic methyl 5-chloro-5-deoxy-α-L-idofuranosidurono-6,3-lactone was 136-138°.

2.5.1 5-Chloro-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose 3-chlorosulphate (15) - To a solution of 1,2-O-isopropylidene-α-D-xylofuranose (5 g) in chloroform (35 ml) and pyridine (15 ml) at -14°, was added sulphuryl chloride (7 ml in chloroform 15 ml) as described, over 0.5 h. The reaction was continued at -14° for 2 h and then at room temperature for 20 h, after which time it was worked up in the usual way, to yield a creamy-white solid (5.8 g, 73%) which crystallized from ether-petroleum ether. T.l.c. examination (solvent d, spray reagent a) revealed the presence of a single component (R_f 0.78) which gave a positive reaction with spray reagent b; m.p. 96.5°-97.5°; $[\alpha]_D$ -76.3° (c 1.76); λ_{max} 7.1 μm (OSO_2Cl) and 8.45 μm (OSO_2Cl). Anal. Calc. for $C_8H_{12}O_6Cl_2S$: C, 31.27; H, 3.92; C , 23.1; S, 10.42. Found: C, 31.53; H, 3.87; Cl, 23.57; S, 9.58.

2.5.2 5-Chloro-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (16) -

Compound 15 (2.3 g) was catalytically dechlorosulphated (This reaction was carried out essentially according to the method of Jennings and Jones[35] but as described by Lawton et al.[6]) by stirring a methanolic solution (70 ml) of it containing sodium bicarbonate (10 g), with addition of sodium iodide 10% in methanol (15 drops) at room temperature. The reaction was continued for an hour, after which t.l.c. examination (solvent d, spray reagent a) indicated the presence of a single compound (R_f 0.4) and an absence of starting material (spray reagent b). The reaction mixture was filtered and the filtrate concentrated to dryness. The residue was dissolved in water (50 ml) and extracted repeatedly with chloroform (50 ml portions), the extracts of which were bulked, dried (sodium sulphate), and concentrated to yield a white amorphous crystalline powder (1.35 g, 87%), which was recrystallized from ether-petroleum ether to form fine feathery needles; m.p. 98°-99°; $[\alpha]_D$ -40.07° (c 1.33); λ_{max} 2.9 μm (OH).

Anal. Calc. for $C_8H_{13}O_4Cl$: C, 46.04; H, 6.24; Cl, 17.03.

Found: C, 45.98; H, 6.22; Cl, 17.34.

2.5.3 Reaction of 5-chloro-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose 3-chlorosulphate (15) with potassium azide and 18-crown-6-ether -

To a solution of compound 15 (1 g) in acetone (8 ml) was added potassium azide (0.79 g, 3.0 molar equivalents) and 18-crown-6-ether (25.8 mg, 0.03 molar equivalent). The reaction mixture was stirred continuously at room temperature for 7 h, after which it was worked up in the usual manner to yield a pale yellow viscous syrup (0.74 g). T.l.c. examination (solvent d, spray reagent a) indicated the presence of two

components (R_f 0.77 and 0.4) (gave a negative result with spray reagent b) which were separated by column chromatography (solvents b and d) and obtained as:

(i) a yellow syrup (17) (0.43 g, 42%) which crystallized out from ether-petroleum ether; R_f 0.77 (solvent d); m.p. 46°-47°; $[\alpha]_D$ -153.16° (c 1.36); λ_{max} 4.68 μm (N_3) 7.1 μm and 8.2 μm (OSO_2N_3).

Anal. Calc. for $C_8H_{12}O_6C\ell N_3S$: C, 30.67; H, 3.73; Cℓ, 11.32; N, 13.41; S, 10.22. Found: C, 30.83; H, 3.84; Cℓ, 11.9; N, 13.05; S, 10.25.

(ii) a white crystalline compound (0.12 g, 17%); R_f 0.4 (solvent d) (corresponded to that of compound 16); m.p. 96°-97.5°.

2.6.1 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose 6-chlorosulphate (18) - To a solution of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (5 g) in chloroform (30 ml) and pyridine (4 ml) at -78°, was added sulphuryl chloride (2.6 ml in chloroform 20 ml) as described. The reaction mixture was allowed to approach -20° and 1 h after commencement, chilled 10% sulphuric acid was added to it rapidly followed by work up in the usual way to yield compound 18 as pungent, white crystalline needles (6.02 g. 87.5%). T.l.c. examination (solvent c, spray reagent a) revealed a single component (R_f 0.6), whilst spray reagent b gave a positive result for chlorosulphate ester. M.p. 83°-86° with slow decomposition; $[\alpha]_D$ -54.2° (c 1.68).

2.6.2 Reaction of 1,2:3.4-di-O-isopropylidene-α-D-galactopyranose-6-chlorosulphate (18) with 3.0 molar equivalents of potassium azide and (a) 3×10^{-3} molar equivalents of 18-crown-6-ether- To a solution of compound 18 (2 g) in acetone (20 ml), was added

potassium azide (1.36 g) and 18-crown-6-ether (4.5 mg). The reaction mixture was stirred continuously at room temperature for 140 h, after which time it was worked up as usual to yield a syrup (2.3 g) which crystallized out on refrigeration. T.l.c. examination (solvent c, spray reagent b) indicated an absence of starting material (18), whilst spray reagent a revealed the presence of three components, (i) R_f 0.67, (ii) R_f 0.57, (iii) R_f 0.13. Component (ii) was predominant, whereas (i) and (iii) were present in minor proportions, and were partially removed from the mixture by repeated recrystallization from ether-petroleum ether. Components (i), (ii) and (iii) were, however, separated by column chromatography (solvent a) and obtained as:

(i) a syrup (20) (0.1 g); λ_{max} 4.76 μm (N_3)

(ii) crystals (19) (1.21 g); m.p. 72°-73°; $[\alpha]_D$ -63.03° (c 1.09); λ_{max} 4.68 (N_3), 7.15 μm and 8.25 μm (OSO_2N_3).

Anal. Calc. for $C_{12}H_{19}O_8N_3S$: C, 39.45; H, 5.21; N, 11.5; S, 8.77. Found : C, 39.85; H, 5.31; N, 11.53; S, 8.88.

(iii) a syrup (0.08 g); R_f 0.13 (solvent c) (corresponded to that of authentic 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose).

(b) 1.0 molar equivalent of 18-crown-6-ether - To a solution of compound 18 (0.9 g) in acetone (15 ml), was added potassium azide (0.610 g) and 18-crown-6-ether (0.664 g), and reacted as before. All starting material (18) was observed by t.l.c. examination (solvent c, spray reagents a and b) to have been consumed after 21 h with predominant formation of compound 20 (R_f 0.67), and to a lesser degree that of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (R_f 0.13), while only a slight trace of compound 19 (R_f 0.57) was evident. No further change in the respective relative proportions of these components was observed after 67 h, after which time the reaction

mixture was processed in the usual manner to yield a syrup (0.69 g) which crystallized from ether-petroleum ether; g.l.c. examination of the crystalline mass revealed the presence of 6-azido-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (20) (T = 0.57), 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (T = 0.89) and 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose in a ratio of 80:19:1 respectively. Compound 20 present in the crystalline mixture was separated by column chromatography (solvent g) and isolated as a pale yellow syrup (0.25 g); $[\alpha]_D$ -90.1° (c 3.08) (Szarek and Jones[69] reported $[\alpha]_D$ -92.1° for compound 20); λ_{max} 4.78 μm (N_3).

Anal. Calc. for $C_{12}H_{19}O_5N_3$: C, 50.52; H, 6.67; N, 14.73.
Found: C, 50.28; H, 6.59; N, 14.96.

2.6.3 Heating of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6-chlorosulphate (18) with potassium azide and 18-crown-6-ether - Compound 18 (50 mg) was heated under reflux in acetone (1 ml) with potassium azide (32 mg, 3.0 molar equivalents), and 18-crown-6-ether (1.2 mg, 0.03 molar equivalent). After 1 h, t.l.c. examination (solvent c, spray reagents a and b) revealed an absence of starting material and the formation of mainly 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (R_f 0.13) and compound 19, with a trace amount of compound 20. After 64 h of refluxing a predominant amount of the parent hydroxy sugar (R_f 0.13) and a negligible trace of compound 20 were made evident by t.l.c. examination.

2.6.4 Reaction of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-azidosulphate (19) with 18-crown-6-ether - To a solution of compound 19 (30 mg) in acetone (1 ml), was added 18-crown-6-ether (15 mg, 0.75 molar equivalent). After continuous stirring at room temperature for 56 h, t.l.c. examination (solvent c, spray reagent a) revealed that the starting material (19) had remained unchanged.

2.6.5 Reaction of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-azidosulphate (19) with pyridinium chloride - To a solution of compound 19 (20 mg) in acetone (1 ml) was added pyridinium chloride (19 mg, 3.0 molar equivalents). The reaction mixture was stirred continuously at room temperature for 70 h, after which time t.l.c. examination (solvent c, spray reagent a) revealed the predominant presence of starting material (19) (R_f 0.57), and to a much lesser extent, the presence of a second component (R_f 0.7). The reaction mixture was then heated under reflux with further addition of pyridinium chloride (12.5 mg). T.l.c. examination after 70 h revealed the presence of a major compound (21) (R_f 0.7) and an absence of starting material, whilst a slight trace of a component near the origin (R_f 0.09) was apparent. The reaction mixture was processed in the usual way and afforded a yellow syrup (devoid of the latter trace component which was removed in the work up process), g.l.c. examination of which revealed the presence of a single peak (T = 0.34) for 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galacto-

pyranose (21).

2.6.6 Reaction of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-chlorosulphate (18) in the presence of 18-crown-6-ether with (a) Potassium Chloride - To a solution of compound 18 (50 mg) in acetone (1 ml), was added potassium chloride (31 mg, 3.0 molar equivalents) and 18-crown-6-ether (1.2 mg, 0.03 molar equivalent). The reaction mixture was stirred at room temperature for 234 h, after which time, t.l.c. examination (solvent c, spray reagents a and b) revealed an absence of starting material and the presence of compound 21 (R_f 0.7) and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (R_f 0.13). The reaction mixture was processed in the usual manner to afford a syrup, g.l.c. examination of which revealed the presence of 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (21) (T = 0.34) and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (T = 0.9) in a ratio of 55:45 respectively.

(b) Potassium Cyanide - Compound 18 (50 mg) was treated as above with potassium cyanide (27 mg, 3.0 molar equivalents). T.l.c. examination (as above) indicated that all starting material (18) had been consumed after 24 h, with the predominant formation of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (R_f 0.13), together with a negligible trace of a component having R_f 0.7.

(c) Potassium Cyanate - compound 18 (50 mg) was treated as above with potassium cyanate (34 mg, 3.0 molar equivalents). T.l.c. examination (as above) revealed that all starting material (18) had been consumed after 140 h, and that two components (R_f 0.7 and 0.13) as above were

present. The reaction mixture was processed in the usual manner, and the resulting syrup examined by g.l.c. which revealed the presence of 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (21) (T = 0.34), and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (T = 0.90) in a ratio of 66:34 respectively.

(d) Potassium Fluoride - A solution of compound 18 (0.8 g) in acetone 6.5 ml) was treated as above with potassium fluoride (0.39 g, 3.0 molar equivalents) and 18-crown-6-ether (18 mg, 0.03 molar equivalent). The reaction was continued for 140 h, after which time t.l.c. examination (as above) revealed an absence of starting material and the presence of a major amount of compound 22 (R_f 0.72), together with a trace of a faster running component (R_f 0.74), and a minor amount of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (R_f 0.13). The reaction mixture was worked up as before, and g.l.c. examination revealed the presence of a trace of 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (21) (T = 0.34), together with a minor amount of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (T = 0.89). Compound 22 was separated by column chromatography (solvent a), which afforded crystals (0.4 g, 52.4%) that were recrystallized from warm petroleum ether to afford clusters of colourless needles; m.p. 79°-80.5°; $[\alpha]_D$ -48.78° (c 1.23); λ_{max} 7.0 μm and 8.25 μm (OSO_2F).

2.7.1 Methyl 2,3,4-tri-O-methyl-6-O-trityl-α-D-glucopyranoside (23) - A solution of methyl-6-O-trityl-α-D-glucopyranoside[70] (10 g) in N,N-dimethylformamide (20 ml) was stirred at room temperature with methyl iodide (75 ml) (added in portions) and silver oxide (20 g) (added in portions), for 80 h. The reaction mixture was filtered and the filtrate concentrated by evaporating at 50° under vacuum, to a syrup

which was then dissolved in chloroform (200 ml). The chloroform solution was washed with 1% potassium cyanide solution (100 ml), then with water and dried (sodium sulphate). Evaporation of the chloroform yielded a syrup (9.44 g, 86%) which crystallized from ether-petroleum ether; R_f 0.88 (ether, spray reagent a); m.p. 104°-106°; (Lehmann[71] reported m.p. 109° for compound 23).

2.7.2 Detritylation[70] of methyl 2,3,4-tri-O-methyl-6-O-trityl-α-D-glucopyranoside (23) - A solution of compound 23 (10 g) in acetone (25 ml), acetic acid (45 ml) and water (5 ml), was heated at 90° with continuous stirring for 1.5 h. The acetone was evaporated from the reaction mixture which was then refrigerated for several hours to allow for the complete precipitation of tritanol. The latter was removed by filtration, and the aqueous acidic filtrate concentrated under reduced pressure at 50°-60°. The concentrate was dissolved in chloroform, dried (sodium sulphate), and filtered. Concentration of the filtrate afforded a pale yellow mobile syrup (3.47 g), t.l.c. examination (ether, spray reagent a) of which revealed the presence of a major component (R_f 0.22) and traces of two other components (R_f 0.57 and 0.04). The major compound (24) was isolated by column chromatography (ether) as a syrup (2.85 g, 57%); $[\alpha]_D$ +154° (c 1.41); (Robertson[72] reported $[\alpha]_D$ +156.6° for compound 24).

2.7.3 Methyl 2,3,4-tri-O-methyl-α-D-glucopyranoside 6-chlorosulphate (25) - To a solution of compound 24 (1.0 g) in chloroform (10 ml) and pyridine (0.8 ml) at -30°, was added sulphuryl chloride (0.52 ml in chloroform 2 ml) as described. After 0.5 h chilled 10% sulphuric acid was added rapidly to the reaction mixture, which was

then worked up in the usual way to afford a yellow syrup (1.38 g, 97.5%) t.l.c. examination (ether, spray reagent a) of which revealed a single compound (25) having R_f 0.86 and which gave a positive result with spray reagent b; $[\alpha]_D$ +113.9° (c 2.33); λ_{max} 7.0 μm and 8.3 μm (OSO_2Cl).

2.7.4 Reaction of methyl 2,3,4-tri-O-methyl-α-D-glucopyranoside 6-chlorosulphate (25) with potassium azide - A solution of compound (25) (0.58 g) in acetone (6 ml) was stirred with potassium azide (0.17 g, 1.2 molar equivalents) for 30 h at room temperature, after which time t.l.c. (ether, spray reagent b) revealed that all starting material had been consumed, whilst spray reagent a indicated the presence of a major component (R_f 0.86) and a trace amount of a component having R_f 0.3. The reaction was processed in the usual way to yield a yellow syrup (0.35 g) from which compound 26 (R_f 0.86) was isolated by column chromatography (solvent d) as a syrup (0.3 g); $[\alpha]_D$ +143.3° (c 1.71); λ_{max} 4.78 μm (N_3).

Anal. Calc for $C_{10}H_{19}O_8N_3S$: C, 35.19; H, 5.57; N, 12.32; S, 9.38. Found C, 49.72; H, 7.98; N, 10.14; S, 0.65.

2.7.5 Reaction of compound 26 with potassium azide and 18-crown-6-ether - A solution of compound 26 (0.17 g) in acetone (3 ml) was stirred with potassium azide (0.2 g, ≃ 5.0 molar equivalents) and 18-crown-6-ether (0.13 g, ≃ 1.0 molar equivalent) at room temperature for 120 h. The reaction mixture was worked up as before to yield a syrup (0.13 g) which was distilled at 83°-85°/0.3 mmHg; t.l.c. examination (ether, spray reagent a) revealed the presence of a single component (27), (R_f 0.85); $[\alpha]_D$ +136.8° (c 2.23); λ_{max} 4.8 μm (N_3).

Anal. Calc. for $C_{10}H_{19}N_3O_5$: C, 45.97; H, 7.28; N, 16.09.
Found : C, 47.18; H, 7.61; N, 11.61.

2.8.1 Methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside (28) - A solution of methyl 4,6-O-benzylidene-α-D-glucopyranoside (15 g) in N,N-dimethylformamide (40 ml) and methyl iodide (120 ml), was stirred with silver oxide (20 g) at room temperature for 24 h, after which time the reaction mixture was filtered, and the filtrate concentrated under vacuum to yield a crystalline mass (11.4 g, 68.75%) that was recrystallized from ether-petroleum ether to afford white, flat needles; m.p. 121°-122°. (Akiya[73] reported m.p. 122°-123°).

2.8.2 Methyl 2,3-di-O-methyl-α-D-glucopyranoside (29) - Compound 28 (10 g) was heated on a boiling water bath for 15 minutes in the presence of aqueous acetic acid (60%) (50 ml). The latter was removed under vacuum at 50° and the residue was extracted with petroleum-ether (to remove benzaldehyde) and finally obtained as large colourless crystals (5.62 g, 82.2%); m.p. 80°-82° (White et al[74] reported m.p. 85°).

2.8.3 Methyl 2,3-di-O-methyl-6-O-trityl-α-D-glucopyranoside (30) - To a solution of compound 29 (1 g) in pyridine (20 ml) was added trityl chloride (1.4 g) and the mixture allowed to stand at room temperature for 48 h. Chloroform (50 ml) was then added to the reaction mixture, and the chloroform solution was washed successively with saturated aqueous sodium hydrogen sulphate, saturated sodium bicarbonate solution, and water. The chloroform extract was then dried (sodium sulphate) and concentrated to yield a crystalline mass (1.6 g, 77%) which was recrystallized from chloroform-petroleum ether, to afford

colourless plates; R_f 0.25 (solvent d); m.p. 167°-169° (lit.[72], m.p. 169°-170°); $[\alpha]_D$ +61.11° (c 1.74) (lit.[72], $[\alpha]_D$ +66°).

2.8.4 Chlorosulphation of methyl 2,3-di-O-methyl-6-O-trityl-α-D-glucopyranoside (30) - To a solution of compound 30 (0.5 g) in pyridine (0.4 ml) and chloroform (5 ml) at -10°, was added sulphuryl chloride (0.26 ml in chloroform 2.5 ml) as described. The reaction mixture was worked up in the usual way after 0.5 h to yield a foamy syrup (0.55 g). T.l.c. examination (solvent d, spray reagent a) revealed the presence of a major compound (31) (R_f 0.55), as well as two minor components having R_f 0.1 and 0.8 (tritanol). The compounds with R_f 0.55 and 0.1 gave a positive reaction with spray reagent b. Compound 31 was isolated by column chromatography (solvent b) as a syrup (0.38 g, 62.8%) which crystallized from chloroform-petroleum ether as cubes; m.p. 104°-106° (with gradual decomposition); $[\alpha]_D$ +78.75° (c 2.24); λ_{max} 7.0 μm and 8.3 μm (OSO_2Cl).

Anal. Calc. for $C_{28}H_{31}O_8ClS$: C, 59.78; H, 5.51; Cl, 6.31; S, 5.69.
Found : C, 59.78; H, 5.59; Cl, 6.49; S, 5.75.

2.8.5 Reaction of methyl 2,3-di-O-methyl-6-O-trityl-α-D-glucopyranoside 4-chlorosulphate (31) with potassium azide and 18-crown-6-ether - A solution of compound 31 (0.28 g) in acetone (5 ml), was stirred at room temperature in the presence of potassium azide (0.125 g, 3.0 molar equivalents) and 18-crown-6-ether (0.130 g, 1.0 molar equivalent). T.l.c. examination (solvent d, spray reagent b) indicated that a trace of starting material (R_f 0.55) was present after 1 h, at which stage, two major components (R_f 0.46 and 0.25) were

revealed with spray reagent a. The reaction was continued for 72 h, during which time incremental amounts of potassium azide (90 mg, 2.25 molar equivalents) and 18-crown-6-ether (130 mg, 1.0 molar equivalent) were added. T.l.c. (as above) indicated the presence of two compounds, 32 (R_f 0.46) and 30 (R_f 0.25), which were separated by column chromatography (solvent c) and isolated respectively as:

(i) a colourless syrup (0.14 g) R_f 0.46 (solvent d); $[\alpha]_D$ +57.06° (c 1.7); λ_{max} 4.78 μm (N_3).

Anal. Calc. for $C_{28}H_{31}O_5N_3$: C, 68.70; H, 6.34; N, 8.59.
Found : C, 68.25; H, 6.41; N, 8.29.

(ii) white granular crystals (0.08 g), R_f 0.25 (solvent d); m.p. 165-167°.

2.9.1 Methyl 2,3-di-O-methyl-α-D-glucopyranoside 4,6-dichlorosulphate (33) - To a solution of compound 29 (3 g) in pyridine (3 ml) and chloroform (10 ml) at -70°, was added sulphuryl chloride (2.5 ml in chloroform 10 ml) as described, over 30 mins. The reaction mixture was worked up by the rapid addition of chilled sulphuric acid 10%, and processed in the usual way, 5 minutes after all the sulphuryl chloride solution had been added, to yield a crystalline mass (5.51 g, 97.3%) that was recrystallized from ether to afford transparent needles, R_f 0.76 (solvent g, spray reagents a and b); m.p. 94°-96.5°; $[\alpha]_D$ +87.37° (c 1.9); λ_{max} 7.0 μm and 8.25 μm (OSO_2Cl).

Anal. Calc. for $C_9H_{16}O_{10}Cl_2S_2$: C, 26.47; H, 3.82; Cl, 16.95; S, 15.27.
Found : C, 26.21; H, 3.80; Cl, 17.76; S, 14.91.

2.9.2 Reaction of methyl 2,3-di-O-methyl-α-D-glucopyranoside 4,6-dichlorosulphate (33) with potassium azide - A solution of compound 33 (1 g) in acetone (20 ml), was stirred at room temperature in the presence of potassium azide (0.48 g, 2.5 molar equivalents) for 6.5 h. The reaction mixture was worked up in the usual way to yield a syrup (0.86 g), t.l.c. examination (solvent g, spray reagent a) of which showed the presence of a major compound (R_f 0.8) and a minor compound (R_f 0.45), which both gave a positive result with spray reagent b. The major component was isolated by column chromatography (solvent c) to give compound 34 as a syrup (0.67 g, 81.2%); $[\alpha]_D$ +97.95° (c 1.91); λ_{max} 4.8 μm (N_3), 7.0 μm and 8.3 μm (OSO_2Cl).

Anal. Calc. for $C_9H_{16}O_7ClN_3S$: C, 31.25; H, 4.64; Cl, 10.14; N, 12.15; S, 9.27. Found : C, 32.92; H, 5.19; Cl, 13.77; N, 9.5; S, 5.48.

2.9.3 Methyl 6-azido-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (35) - Compound 34 (0.33 g) was catalytically dechlorosulphated[6] by adding a methanolic solution of sodium iodide 10% (5 drops) to a solution of it in methanol (10 ml) to which sodium bicarbonate (2 g) was added. The reaction mixture was stirred at room temperature for 0.75 h, after which time it was worked up as before to yield compound 35 as a syrup (0.16 g, 67.8%). T.l.c. examination (solvent g, spray reagent a) revealed a single component (R_f 0.41) which gave a negative reaction with spray reagent b; $[\alpha]_D$ +101.3° (c 1.57); λ_{max} 2.95 μm (OH) and 4.83 μm (N_3).

Anal. Calc. for $C_9H_{17}O_5N_3$: C, 43.72; H, 6.88; N, 17.0.

Found : C, 44.06; H. 7.19; N, 15.86.

2.9.4 Methyl 4-O-acetyl-6-azido-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (36) - To a solution of compound 35 (60 mg) in pyridine (0.3 ml), was added acetic anhydride (0.3 ml) dropwise, and the mixture allowed to stand at room temperature for 6 h. The reaction mixture was poured into ice (50 g) and then extracted with chloroform (50 ml) after the ice had thawed. The chloroform extract was shaken with sulphuric acid 10% (50 ml), saturated sodium bicarbonate solution (50 ml), washed successively with water and dried (sodium sulphate). Evaporation of the chloroform yielded a yellow syrup (80 mg, 70.2%), which was distilled at 80°-83°/0.04 mmHg. T.l.c. examination (solvent g, spray reagent a) revealed a single compound (36); R_f 0.65; $[\alpha]_D$ +83.87° (c 1.55); λ_{max} 4.78 μm (N_3) and 5.83 μm (OAc).

Anal. Calc. for $C_{11}H_{19}O_6N_3$: C, 45.67; H, 6.57; N, 14.53.
Found : C, 45.49; H, 6.74; N, 13.56.

2.9.5 Reaction of methyl 6-azido-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside 4-chlorosulphate (34) with potassium azide and 18-crown-6-ether - To a solution of compound 34 (0.35 g) in acetone (7.5 ml), was added potassium azide (0.41 g, 5.0 molar equivalents) and 18-crown-6-ether (0.27 g, 1.0 molar equivalent). The reaction mixture was stirred at room temperature for 120 h [t.l.c. examination (solvent g, spray reagent b) indicated that all the starting material (34) had been consumed after 1 h], after which time it was worked up in the usual way to yield a pale yellow syrup (0.35 g). T.l.c. examination (solvent g, spray reagent a) revealed the presence of two major compounds, 37 (R_f 0.68) and 35 (R_f 0.41),

that were separated by column chromatography (solvent d), and obtained respectively as:

(i) a yellow syrup (0.13 g); $[\alpha]_D$ +95.25° (c 1.77); λ_{max} 4.83 μm (N_3).

Anal. Calc. for $C_9H_{16}O_4N_6$: C, 39.71; H, 5.88; N, 30.88.
Found : C, 39.81; H, 5.90; N, 28.64.

(ii) a pale yellow syrup (0.12 g); $[\alpha]_D$ +94° (c 1.48); λ_{max} 2.98 μm (OH) and 4.83 μm (N_3).

2.10.1 Benzylation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose -

To a solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (20 g) in N,N-dimethylformamide (300 ml), was added sodium hydride (8 g) (previously washed with petroleum-ether) in portions, and the mixture stirred at room temperature for an hour, after which time benzyl chloride (20 ml) (diluted with N,N-dimethylformamide 20 ml) was added dropwise with continuous stirring. The reaction was continued for 5 h and methanol (40 ml) then added dropwise with continuous stirring. The mixture was evaporated to afford an oily residue which was dissolved in chloroform (600 ml), and the chloroform extract was repeatedly washed with water, dried (sodium sulphate), and concentrated to a yellow-orange oily syrup (24.72 g). T.l.c. examination (solvent d, spray reagent a) revealed the presence of a major compound (38) (R_f 0.72) that was separated by column chromatography (solvent a) from trace amounts of components having R_f 0.86, 0.46 and 0.07, and isolated as a syrup (23.9 g, 88.8%); $[\alpha]_D$ -25.2° (c 1.56) (lit.[75], $[\alpha]_D$ -27.7°).

2.10.2 3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose (39) - Compound (38) (23.9 g) was added to methanol (150 ml) and water (50 ml). The suspension was stirred and warmed (≃55°), and Amberlite IR 120 (H^+) ion exchange resin (25 g) was added in portions (10 g) and stirred continuously for 15 h. The reaction mixture was filtered, and the methanol evaporated. Water (100 ml) was then added to the residue and the latter repeatedly extracted with chloroform (100 ml portions). The combined chloroform extracts were dried (sodium sulphate) and concentrated to yield a yellow syrup (18.06 g). T.l.c. examination (ether, spray reagent a) revealed the presence of a major compound (39) (R_f 0.64) that was separated by column chromatography (solvent d) from trace amounts of components having R_f 0.95 and 0.24. Compound 39 was obtained as a yellow syrup (17.45 g, 82.47%); $[\alpha]_D$ -41.2° (c 1.68) (lit.[76], $[\alpha]_D$ -35°).

2.10.3 3-O-Benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D glucofuranose 5-chlorosulphate (40) - To a solution of compound (39) (8 g) in pyridine (12.8 ml) and chloroform (120 ml) at -10°, was added sulphuryl chloride (8.32 ml in chloroform 40 ml) as described. The reaction was continued at -10° for 2 h and then at room temperature for an additional 3 h, after which time, it was worked up in the usual manner to yield a crystalline mass (10.17 g, 88.97%) that was recrystallized from ether-petroleum ether, to form white transparent needles; R_f 0.77 (solvent d, spray reagents a and b); m.p. 100°-100.5°; $[\alpha]_D$ -28.95° (c 1.52); λ_{max} 7.13 μm and 8.35 μm (OSO_2Cl).

Anal. Calc. for $C_{16}H_{20}O_7Cl_2S$: C, 44.96; H, 4.68; Cl, 16.62; S, 7.49.

Found : C, 45.30; H, 4.69; Cl, 16.79; S, 7.71.

2.10.4 3-O-Benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (41) - Compound 40 (1 g) in methanol was catalytically dechlorosulphated[6] as previously described, to yield a pale yellow syrup (0.74 g, 96.1%). T.l.c. examination (solvent d, spray reagent a) revealed the presence of a single compound (41) (R_f 0.54), which gave a negative reaction with spray reagent b; $[\alpha]_D$ -42.15° (c 1.44); λ_{max} 2.8 μm (OH).

Anal. Calc. for $C_{16}H_{21}O_5Cl$: C, 58.45; H, 6.39; Cl, 10.81.

Found : C, 58.64; H, 6.38; Cl, 10.65.

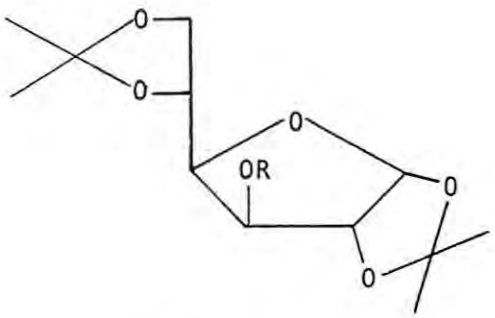
2.10.5 5-O-Acetyl-3-O-benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (42) - To compound (41) (0.26 g) in solution with pyridine (1.0 ml), was added acetic anhydride (1.0 ml). The reaction mixture was left to stand at room temperature overnight, after which it was poured into ice (50 g), and worked up in the usual way to afford a yellow syrup (0.23 g, 77.15%) which crystallized out on standing in the cold. Recrystallization from petroleum ether afforded transparent plates; m.p. 76°-77°; $[\alpha]_D$ -77.29° (c 1.29); λ_{max} 5.78 μm (OAc).

Anal. Calc. for $C_{18}H_{23}O_6Cl$: C, 58.39; H, 6.21; Cl, 9.58.

Found : C, 58.08; H, 6.2; Cl, 9.94.

3. DISCUSSION

3.1 The reaction of sulphuryl chloride with carbohydrates containing free hydroxyl groups has been extensively studied, and shown to give fully substituted derivatives containing both chlorodeoxy and chlorosulphate ester groups. Carbohydrate chlorosulphates react with a variety of nucleophilic agents[28], and these reactions may be conveniently divided into those occurring with (a) C-O bond fission, (b) S-O bond fission, (c) S-Cℓ bond fission and (d) those proceeding via (b) and (c). Various sugar chlorosulphate esters containing primary and secondary chlorosulphonyloxy groups in sterically favourable and unfavourable positions for nucleophilic displacement were synthesized, and their reactions with azide were investigated.



(1) R = $SO_2Cℓ$

(2) R = SO_2N_3

(3) R = SO_2NH_2

Chlorosulphation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose at -10° afforded the 3-chlorosulphate (1), the m.p. of which was consistent with that reported by Jennings and Jones[35]. The optical rotation (-55.95°), however, was somewhat higher than that reported[35] (-40°). This may be attributed to the higher proportion of sulphuryl

chloride employed by Jennings and Jones[35], which could have led to more impurities being present. The infra-red spectrum of 1 showed the characteristic absorbance peaks for chlorosulphate (7.13 μm and 8.45 μm). The n.m.r. data for 1 which has not previously been reported is given in Table 1. H-1, H-2 and H-3 appeared as three doublets, while H-4, H-5, H-6 and H-6' were observed as a complex multiplet. The doublet due to H-3 appeared as expected, further down field in comparison to that of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose[77], because of the deshielding effect of the electron withdrawing chlorosulphate group.

Table 1 - Chemical shifts (τ-values) and first-order coupling constants (Hz) for compounds 1-7

Compound	1	2	3	*4	5	6	7
H-1	3.97(d)	4.00(d)	4.00(d)	3.93(d)	4.06(d)	3.95(d)	3.91(d)
H-2	5.05(d)	5.15(d)	5.12(d)	5.07(d)	5.18(d)	5.11(d)	5.07(d)
H-3	4.70(d)	4.90(d)	4.96(d)	4.94(d)	4.84(d)	4.89(d)	4.92(d)
H-4	5.27-6.07 (cm)	5.07-6.20 (cm)	5.51-6.06 (cm)	5.68(dd)	5.70(dd)	5.47(dd)	5.50(dd)
H-5				6.05(m)	5.95-6.40 (cm)	4.71(m)	4.54(m)
H-6				6.15-6.65 (cm)		5.32(dd)	5.30(dd)
H-6'						5.83(dd)	5.82(dd)
CMe_2	8.46(s) 8.56(s) 8.65(s)(2x)	8.47(s) 8.53(s) 8.65(s)(2x)	8.48(s) 8.55(s) 8.67(s)(2x)	8.43(s) 8.60(s)	8.49(s) 8.68(s)	8.47(s) 8.64(s)	8.49(s) 8.64(s)
NH_2				≈4.60 (s) (broad)			
OH					≈7.28 (s)		
OAc						7.92(s) (2 x OAc)	7.89(s) 7.93(s)
$J_{1,2}$	3.3	4.7	4.0	3.3	4.0	4.0	4.0
$J_{3,4}$	≈1.4	2.3	2.3	2.7	2.3	2.4	2.7
$J_{4,5}$				8.7	8.7	8.7	8.7
$J_{5,6}$				2.7	2.7	2.7	2.7
$J_{5,6'}$				5.3	5.3	4.7	6.7
$J_{6,6'}$				-	-	12.6	12.0

Key: d = doublet, dd = double doublet, m = multiplet, cm = complex multiplet, s = singlet.
* (in deutero-acetone)

Reaction of 1 with potassium azide in the presence of 18-crown-6-ether in acetone for 24 h at room temperature, resulted in the replacement of the chloro group by azide and the formation of the azidosulphate (2) as a syrup. In addition, a small proportion (14%) of a crystalline

dechlorosulphated compound which had a similar R_f value and m.p. to that of the parent hydroxy sugar, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose was obtained. A similar dechlorosulphation phenomenon was also reported by Parolis et al.[63] who observed the formation of the 2- and 3-monochlorosulphate esters in addition to the completely dechlorosulphated compound upon treatment of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-dichlorosulphate with sodium azide. The infra-red spectrum of 2, with the exception of the absorbance peak for azide (4.74 μm) was similar to that of 1. The peak at 6.92 μm was assigned to azidosulphate. The n.m.r. spectrum of 2 (Table I) was comparable to that of 1, with the exception of the H-3 proton which was observed to resonate slightly upfield.

In the absence of 18-crown-6-ether, similar products (as above) were obtained in comparable yields, but the reaction time was found to have approximately doubled. The increase in rate of nucleophilic substitution in the presence of crown-ether is brought about by the enhancement of the nucleophilicity of azide. The increased nucleophilicity results in shorter reaction times and use of lower reaction temperatures in bimolecular nucleophilic substitution reactions[78]. Crown-ethers solubilize alkali metals by providing the cations with an organic mask by complex formation[79].

Whistler et al.[80,81] have reported the displacement of the p-tolylsulphonyloxy group in 1,2:5,6-di-O-isopropylidene-3-O-p-tolylsulphonyl-α-D-glucofuranose by azide, with inversion to give the corresponding 3-azido-3-deoxy allofuranose derivative after prolonged (15 days) reaction in N,N-dimethylformamide, or after 18 h in hexamethylphosphoramide. When 2 was treated with potassium azide and 18-crown-6-ether for a prolonged period (64 h) at room temperature, only S-O bond fission occurred with the

formation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose as the major product. T.l.c. of the reaction mixture failed to reveal any 3-azido-3-deoxy-allofuranose derivative. It has been shown[82-85] that in bicyclic compounds containing two cis-fused 5-membered rings, S_N2 displacement of an exo-sulphonate group with subsequent Walden inversion is sterically hindered, whereas endo-sulphonate groups are fairly susceptible to nucleophilic displacement.

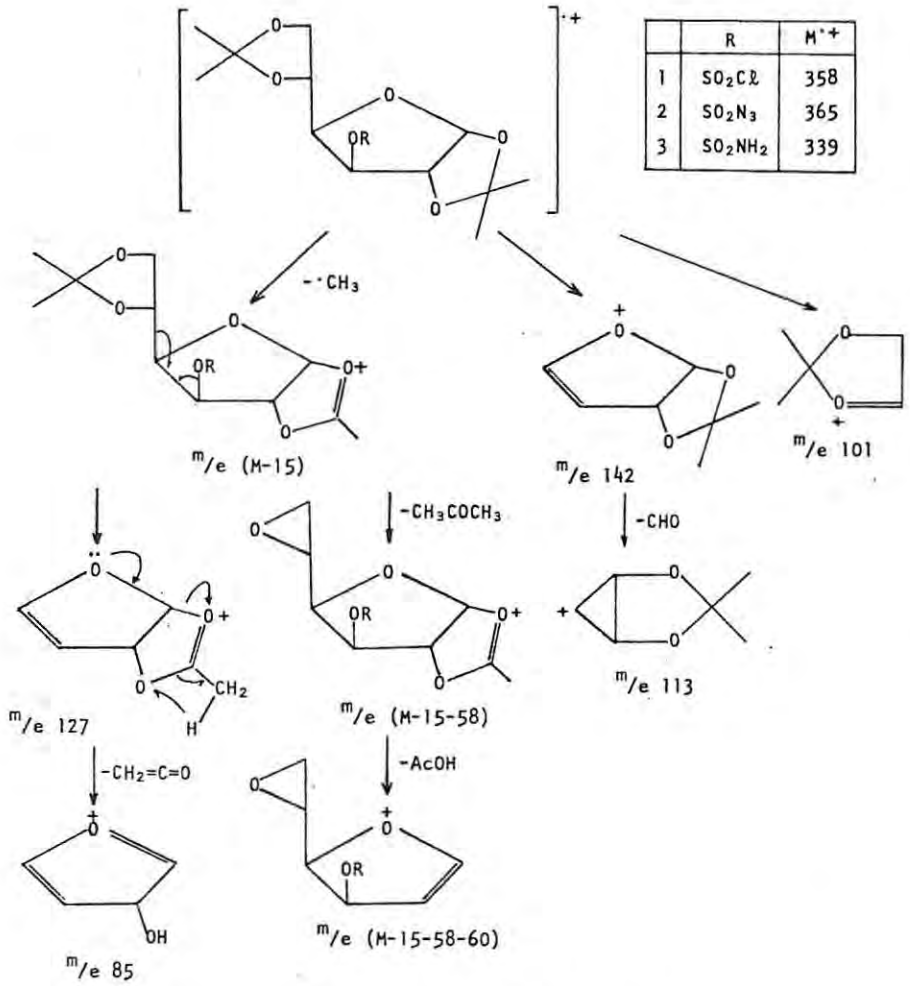
The replacement of potassium azide with potassium nitrite in the same molar proportion, also resulted in some dechlorosulphation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-chlorosulphate (1), during reaction with the latter in the presence of 0.03 molar equivalents of 18-crown-6-ether, but a greater proportion of the starting material (1) remained unchanged after 88 h.

Reduction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 3-azido-sulphate (2) either by hydrogenation in ethanol[86] with platinum oxide[68] as catalyst, or with sodium borohydride[87] in a mixture of N,N-dimethyl-formamide[88] and methanol afforded a crystalline 3-sulphamoyl derivative (3). In addition a small quantity of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose had formed as a result of removal of the azidosulphate group. The infra-red spectrum of 3 revealed the absence of the azide absorbance peak but showed an absorbance peak due to a sulphonyloxy and NH_2 group, while elemental analysis conformed with the assigned structure. The n.m.r. spectrum (Table I) was similar to the parent compound (2) with the exception of the appearance of a 2-proton singlet at τ 4.5 due to protons of the sulphamoyl group.

The synthesis of sulphamoyl carbohydrate derivatives is of interest since sulphamoyl nucleosides[23,24] have been shown to have biological activity. The synthetic routes employed here to afford the sulphamoyl

derivative (via reduction of the corresponding azidosulphate) was also preferred by Hedayatullah et al.[89] who synthesized aryl sulphamates via a similar reduction sequence, instead of through the use of sulphamoyl chloride or chlorosulphonyl isocyanate which are both highly toxic and difficult to manipulate.

The mass spectral data for compounds 1, 2 and 3 are given in Table II, and possible fragmentation pathways are shown in Scheme A.

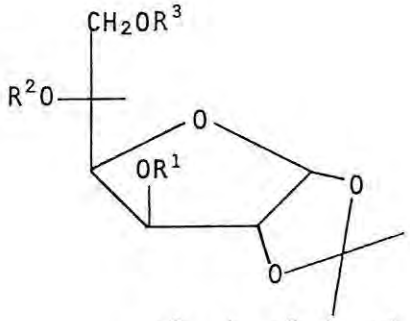


Scheme A - Mass spectral fragmentation pathways for compounds 1-3

Table II - Relative intensities of peaks in the mass spectra of compounds 1-3

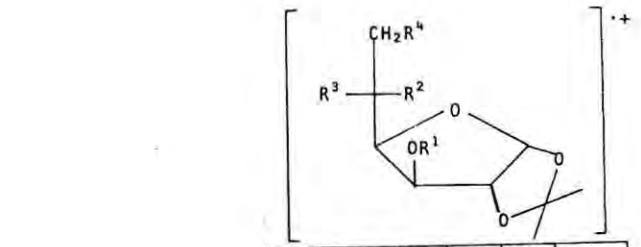
Compound	1	2	3
m/e	Relative	intensity	(%)
43	100.0	100.0	100.0
85	19.4	15.8	8.0
101	91.0	50.1	56.2
113	63.0	45.0	56.2
127	22.4	12.6	18.0
142	15.0	11.2	2.5
M-15	60.0	31.6	14.1
M-15-5	21.0	10.0	8.0
M-15-58-60	7.5	1.6	3.6

In each instance the major pathway appeared to be initiated by cleavage of the C-4 to C-5 bond with the formation of the ion m/e 101, while peaks common to the mass spectra of di-O-isopropylidene acetals[90,91] of the monosaccharides (M-15, M-15-58, M-15-58-60) were also evident. In the case of 1, these peaks were also associated with their diagnostic isotopic counterparts (M-15+2, M-15-58+2, M-15-58-60+2) in approximately 3:1 ratios indicating the presence of the chlorine atom.

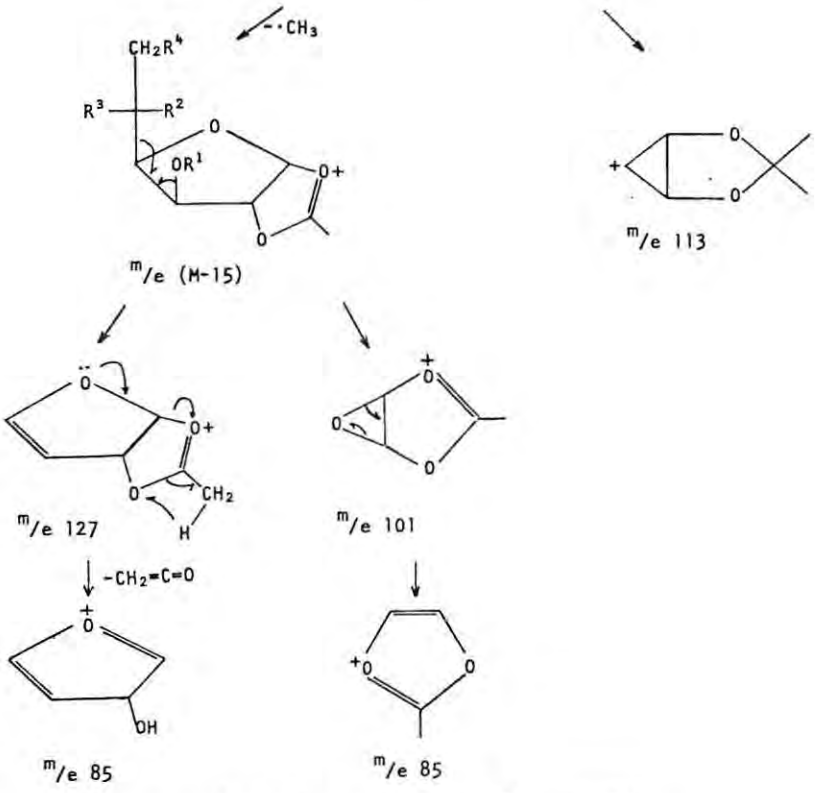


	R^1	R^2	R^3
(4)	SO_2NH_2	H	H
(5)	SO_2N_3	H	H
(6)	SO_2N_3	Ac	Ac
(7)	SO_2NH_2	Ac	Ac

Partial hydrolysis of compound 3 afforded 4 as a partially crystalline syrup after column chromatography on silica gel. The n.m.r. and infra-red spectra, and elemental analysis of compound 4 were consistent with the loss of the 5,6-isopropylidene group during hydrolysis with 0.01 M hydrochloric acid. In the n.m.r. spectrum of 4 (Table I) the resonances due to H-1, H-2, H-3 and H-4 were clearly resolved. The protons of the 5 and 6 hydroxyls and of the sulphamoyl amino group appeared as a very broad singlet centred at ca τ 4.30 and disappeared on addition of deuterium oxide. The major mass spectral fragmentation pattern for 4 is depicted in Scheme B.



	R^1	R^2	R^3	R^4	$M^{\cdot+}$
4.	SO_2NH_2	H	OH	OH	299
5.	SO_2N_3	H	OH	OH	325
6.	SO_2N_3	H	OAc	OAc	409
7.	SO_2NH_2	H	OAc	OAc	383



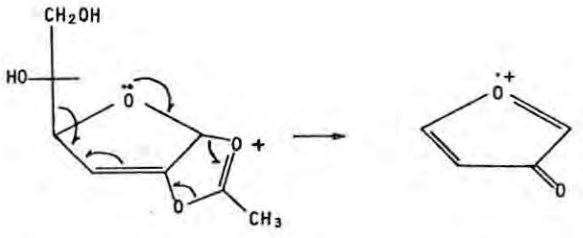
Scheme B - Mass spectral fragmentation pathways for compounds 4-7

Partial hydrolysis of 2 which was achieved under similar conditions as for the synthesis of 4, yielded 5 as a syrup. The formation of hydrolytic by-products was observed to occur at a faster rate than during the synthesis of 4. A satisfactory elemental analysis could not be obtained for 5 as the compound underwent gradual decomposition. The mass spectral (Scheme B, Table III), n.m.r. (Table I) and infra-red data for 5, however, are consistent with the structure shown.

Table III - Relative intensities of peaks in the mass spectra of compounds 4-7

Compound	4	5	6	7
m/e	Relative Intensity (%)			
43	100.0	100.0	100.0	100.0
83	2.5	56.2	2.0	1.0
85	50.1	31.6	5.6	9.0
113	71.0	22.4	5.0	4.5
127	18.0	5.6	3.2	9.0
M-15	11.2	2.0	7.1	10
M-15-HOR'	1.8	1.0	0.2	0.1

The infra-red spectrum of 5 revealed absorbances due to azide (4.68 μm) and hydroxyl (2.94 μm) groups, while the mass spectrum showed a peak at m/e 310 (M-15). In addition, a prominent peak situated at m/e 83 was observed for 5 and may be seen to have possibly arisen from the M-15-HOR fragment, as follows:



M-15-HOR (m/e 187)
(R = SO_2N_3)

m/e 83

The $^{m}/_{e}$ 83 peak was not very prominent in the mass spectra of compounds 4, 6 and 7. The n.m.r. spectrum of 5 (Table I) was very similar to that of 4.

Catalytic reduction of compound 5 resulted in the formation of a major product which was isolated by column chromatography as a semi-crystalline syrup. The optical rotation, and infra-red spectrum were found to be identical with that obtained for 4.

Compound 4 was thus obtained via two synthetic pathways, viz.,

(i) catalytic reduction of 2 and subsequent partial hydrolysis;

(ii) partial hydrolysis of 2, followed by catalytic reduction.

Pathway (i) appeared to be optimal as the overall effective yield of 4 from 2 was 71% compared to an effective yield of 34% obtained via pathway (ii), which resulted in extensive total hydrolysis of 2 and the formation of an unstable intermediate, 5.

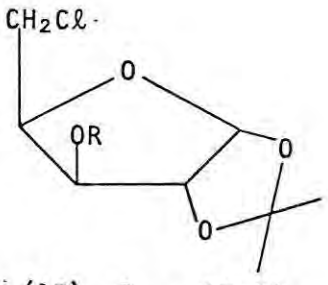
Acetylation of 5 afforded 6 as a syrup which showed some tendency to crystallize when scratched, but all attempts to recrystallize it were unsuccessful. Infra-red analysis revealed characteristic absorbance peaks for azide (4.68 μm) and acetate (5.8 μm). Elemental analysis of compound 6 as was the case with 5, was not entirely satisfactory due to its gradual decomposition. The n.m.r. spectrum (Table I) of 6 was completely amenable to first-order analysis and is consistent with the structure shown.

Catalytic reduction of 6 afforded a crystalline compound (7) in high yield. Infra-red analysis of 7 indicated that the azide group had been reduced, while a satisfactory elemental analysis was obtained for the assigned structure. The n.m.r. spectrum (Table I) of 7 was very similar to that of 6. The sulphamoyl protons were overlapped by the H-5 multiplet.

Reduction of 6 was also achieved with sodium borohydride in N,N-dimethylformamide and methanol at room temperature. The yield obtained, although high (80%), was less than that obtained by catalytic reduction. An attempt to synthesize 7 via acetylation of 4 was unsuccessful.

Compounds 6 and 7 in common with other sugar acetates[90] gave poor (low intensity) mass spectra (Table III). The fragmentation pathways for both compounds are characteristic of mono-isopropylidene hexoses[90] and are shown in Scheme B.

In order to establish whether the chlorine of the chlorosulphate ester can be replaced by azide in the presence of a S_N2 reactive C-Cℓ group, it was decided to synthesize 5-chloro-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose 3-chlorosulphate (15) by chlorosulphation of 1,2-O-isopropylidene-α-D-xylofuranose, and to react 15 with azide. Achmatowicz et al.[43] have previously shown that methyl pentofuranosides afford the 5-chloro-5-deoxy-2,3 dichlorosulphates only, on chlorosubstitution.



(15) R = $SO_2Cℓ$

(16) R = H

(17) R = SO_2N_3

The infra-red spectrum of 15 showed the characteristic absorbance peaks (7.1 μm and 8.45 μm) for chlorosulphate. The n.m.r. spectrum of 15 (Table IV) revealed the presence of doublets for H-1, H-2 and H-3, and a multiplet for H-4. Protons H-5 and H-5' occurred as a pair of overlapping doublets. Elemental analysis of 15 proved satisfactory for the assigned structure.

Table IV - Chemical shifts (τ-values) and first-order coupling constants (Hz) for compounds 15-17

Compound	15	16	16*	17
H-1	3.76(d)	4.20(d)	3.97(d)	3.92(d)
H-2	4.87(d)	5.40(d)	5.27(d)	5.06(d)
H-3	4.50(d)	5.49-5.75 (m)	4.57(d)	4.81(d)
H-4	5.27(m)		5.46(dd)	5.40(m)
H-5	6.18(d)	6.21(s)	6.17(s)	6.24(d)
H-5'	6.20(d)	6.27(d)	6.24(d)	6.26(d)
OH	-	7.66(s)(broad)	-	-
NH	-	-	1.27(s)	-
CMe_2	8.40(s) 8.59(s)	8.49(s) 8.68(s)	8.45(s) 8.66(s)	8.46(s) 8.65(s)
$J_{1,2}$	4.0	3.3	3.3	4.0
$J_{3,4}$	2.7		2.7	2.7
$J_{4,5}$	6.0	6.7	6.7	6.0
$J_{4,5'}$	8.0			8.0
$J_{5,5'}$				

Key: d = doublet, dd = double doublet, s = singlet, m = multiplet
* with shift reagent, Trichloro-acetyl-isocyanate

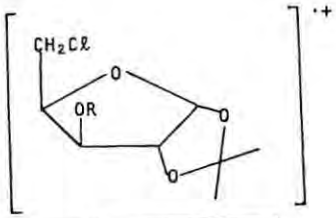
Reaction of 15 with potassium azide in the presence of 18-crown-6-ether for 7 h, resulted in the formation to a greater extent of the 3-azidosulphate derivative (17) together with a small proportion (17%) of 5-chloro-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (see later). Compound 17 which gave a negative test for chlorosulphate ester (spray reagent b) was isolated by column chromatography as a crystalline solid

with a low m.p. (46°-47°). The infra-red spectrum of 17 showed an azide absorbance peak (4.68 μm), while the n.m.r. spectrum (Table IV) was essentially similar to that of 15 with the exception of the H-3 proton, which in the case of 15 resonated at lower field (≃0.3 ppm) due to the greater deshielding influence of the chlorosulphate compared to the azidosulphate group. The elemental analysis of 17 was consistent with the assigned 3-azidosulphate structure.

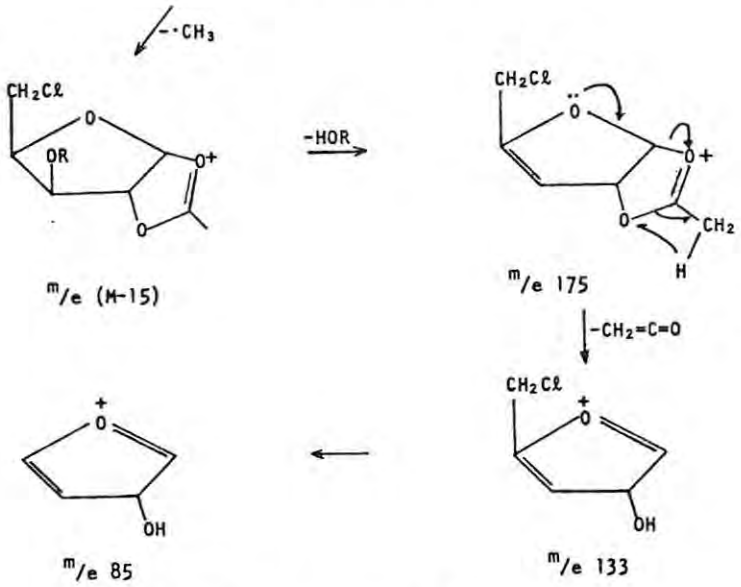
Removal of the chlorosulphate group from 15 was achieved by catalytic dechlorosulphation with methanolic sodium iodide which afforded a crystalline compound (16), the infra-red spectrum of which indicated the presence of a hydroxyl absorbance peak (2.9 μm). Compound 16 gave a satisfactory elemental analysis. The melting-point and t.l.c. mobility of 16 was identical to that observed for the minor compound isolated from the product mixture obtained after the treatment of 15 with potassium azide. The n.m.r. spectrum of 16 (Table IV) contained doublets for H-1 and H-2, while the signal for H-5 and H-5' appeared to consist of an overlapping singlet and doublet respectively. Addition of trichloroacetyl isocyanate to the solution resulted in the appearance of a 1-proton singlet at τ 1.26 due to the NH group of the resulting carbamate. Furthermore, H-4 was now revealed as a double-doublet at τ 5.46 with $J_{3,4}$ = 2.7, $J_{4,5}$ = 6.7 and $J_{4,5'}$ = 0.

The mass spectral fragmentation pattern for 15, 16 and 17 is depicted in Scheme C, and is in accordance with the fragments observed by Buchs *et al.*[92] for 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose. The M-15 peak (Table V) of 15 was associated with its respective isotopic counterparts (M-15+2, M-15+4) in approximate ratios of 9:6:1, while the M-15 peaks of 16 and 17 were associated with their isotopic counterpart (M-15+2) in a ratio of 3:1, indicating the presence of two and one

chlorine atoms respectively.



	R	$M^{\cdot+}$
15	SO_2Cl	306
16	H	208
17	SO_2N_3	313



Scheme C - Mass spectral fragmentation pathways for compounds 15-17

Table V - Relative intensities of peaks in the mass spectra of compounds 15-17

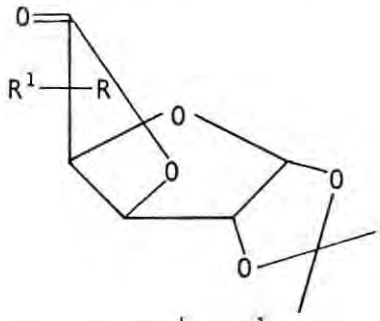
Compound	15	16	17
m/e	Relative intensity (%)		
43	100.0	100.0	100.0
85	17.8	8.0	11.8
133	70.8	20.0	76.4
175	14.1	4.0	20.8
M-15	31.6	15.9	34.7

In addition, 15, 16 and 17 gave rise to chlorine bearing peaks situated

at $^{m}/e$ 175 and $^{m}/e$ 133, which were also associated with their respective isotopic counterparts ($^{m}/e$ 177, $^{m}/e$ 135) in approximate ratios of 3:1.

1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone 5-chlorosulphate (9) was selected to investigate the effect of azide on a reactive 5-chlorosulphate group,while the 5-chloro-5-deoxy methyl ether (13) was used to examine the reaction of a 2-chlorosulphate group with azide.

1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone 5-chlorosulphate (9) was easily prepared as a crystalline compound by careful chlorosulphation of 1,2-O-isopropylidene-α-D-glucofuranurono-6,3 lactone at -78°.



	R	R^1
(9)	H	$OSO_2C\ell$
(10)	N_3	H
(11)	H	N_3
(12)	$C\ell$	H

Compound 9 which has not previously been reported, underwent slow decomposition during the determination of its melting-point. In the n.m.r. spectrum of 9 (Table VI), the resonances due to H-1, H-2, H-3 and H-5 appeared as doublets, while H-4 appeared as a double-doublet. H-5 resonated at low field (τ 4.49) due to the deshielding effect of the strongly electron withdrawing lactone carbonyl and chlorosulphate groups.

Table VI - Chemical shifts (τ-values) and first-order coupling constants (Hz) for compounds 9 and 10

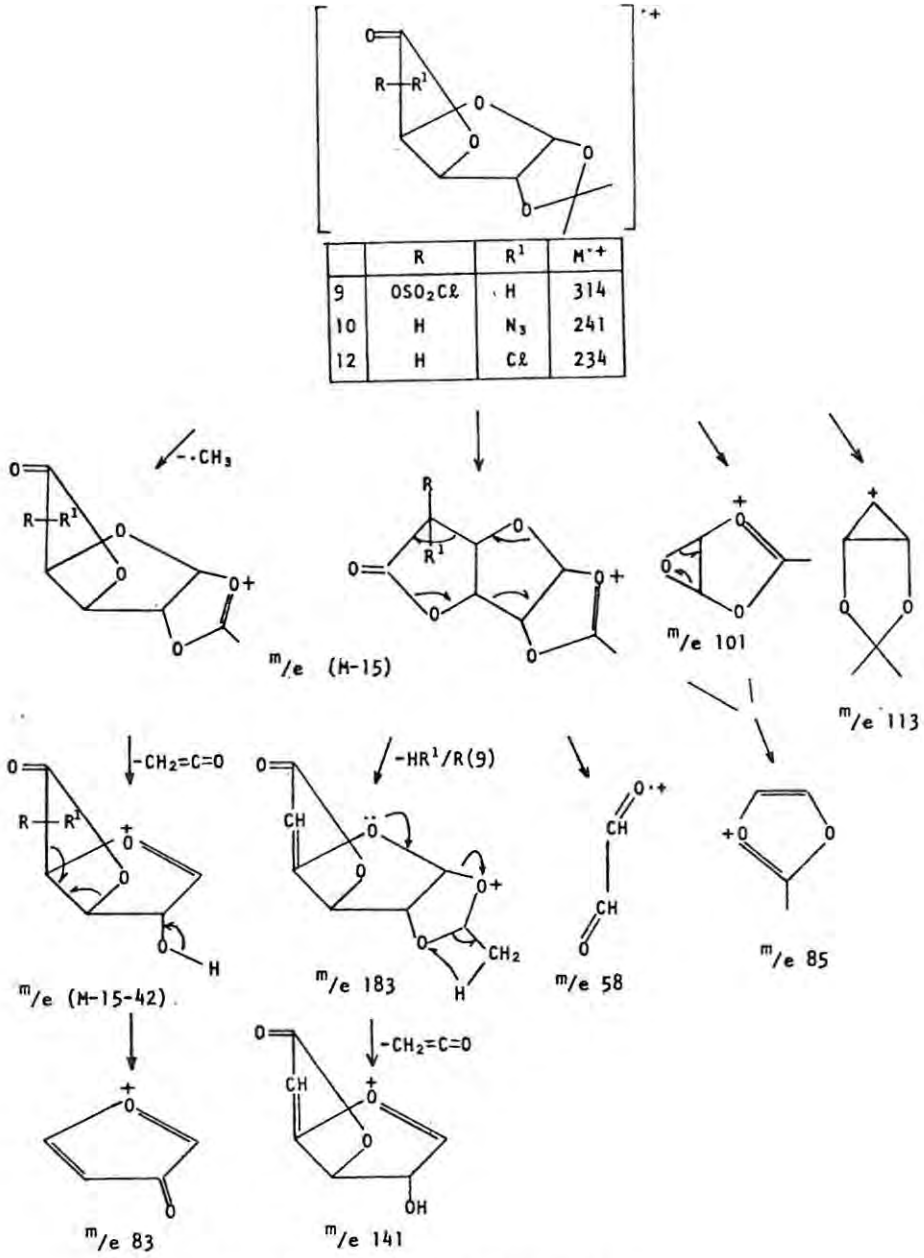
Compound	9	10
H-1	3.90(d)	4.10(d)
H-2	5.09(d)	5.14(d)
H-3	5.00(d)	5.10(d)
H-4	4.78(dd)	5.31(d)
H-5	4.49(d)	5.74(s)
CMe_2	8.47(s) 8.63(s)	8.58(s) 8.64(s)
$J_{1,2}$	3.3	3.3
$J_{3,4}$	2.7	2.7
$J_{4,5}$	4.7	-

Key: d = doublet, dd = double-doublet
s = singlet.

The mass spectrum of 9 (Scheme D, Table VII) showed the presence of the M-15 peak in association with its isotopic counterpart (M-15+2) in a ratio of 3:1 which indicated the presence of a chlorine aton. The fragmentation pattern followed that of a cis-dioxapentalane ring system[90] such as is found in 3,6-anhydro-glucofuranosides.

Table VII - Relative intensities of peaks in the mass spectra of compounds 9, 10 and 12.

Compound	9	10	12
m/e	Relative intensity (%)		
43	100.0	100.0	100.0
58	28.2	9.0	20.0
83	6.0	6.0	12.6
85	11.2	28.2	9.0
101	1.4	1.4	4.5
113	5.0	14.1	7.0
141	4.5	5.6	20.0
183	6.3	2.0	7.0
M-15	5.0	17.4	35.5
M-15-42	1.0	1.3	28.2



Scheme D - Mass spectral fragmentation pathways for compounds 9, 10 and 12

Reaction of 9 with potassium azide in the presence of 18-crown-6-ether, afforded a crystalline product composed of 10 and 11 (R_f 0.73 and 0.35 respectively), which were separated by fractional crystallization and column chromatography. Compound 10 was present in greater proportion and was isolated as crystalline needles. The infra-red spectrum of 10

revealed the presence of azide (4.76 μm) and lactone (C=O) (5.6 μm) absorbance peaks. The n.m.r. spectrum of 10 (Table VI) was different from that of 9 with regard to the resonance signals of H-4 and H-5, which in the case of 10, the latter signal appeared at higher field (1.25 ppm) as a singlet (τ 5.74, $J_{4,5}$ = 0), and the former as a doublet. The data indicates that 10 has the L-ido configuration and is consistent with the inversion of configuration that occurs when a chlorosulphate group is replaced by chloride. Similar observations were made by Schweng et al.[93] who synthesized 10 via the reaction of 1,2-O-isopropylidene-α-D-gluco-furanurono-6,3-lactone with a triphenylphosphine-azidocarboxylic ester - HN_3 complex. Wolfrom et al.[85] have also reported on the effectiveness of the azide ion in displacing the 5-substituent of 3,6-anhydro-1,2-O-isopropylidene-5-O-p-tolylsulphonyl-α-D-glucofuranose, to give derivatives with the L-ido configuration. The elemental analysis of 10 conformed to the proposed 5-azido-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone. The mass spectral fragmentation pattern of 10 is described in Scheme D.

The infra-red spectrum of 11 which was isolated as a syrup from the mixture obtained in the above reaction, was found to be similar to that of 10, and assumed to be the corresponding gluco-isomer. The lower t.l.c. mobility of the gluco-isomer (11) (R_f 0.35) was also observed by Irimajiri et al.[94], who reported that the 5-bromodeoxy-L-ido-isomer had a t.l.c. mobility twice that of the corresponding 5-bromodeoxy-D-gluco-isomer.

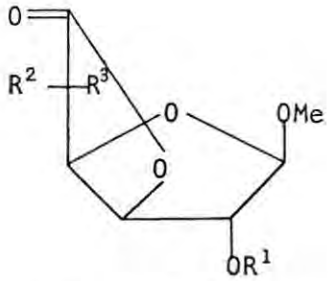
A similar reaction to the above, carried out in the absence of 18-crown-6-ether took 30 minutes longer for completion, and yielded a mixture containing a major compound which was isolated as crystalline needles through fractional crystallization and column chromatography. The t.l.c. mobility, melting-point, optical rotation and infra-red spectrum, were

identical to that of 10, thus the rate of nucleophilic substitution at the chiral centre of 9 appeared to be almost as fast in the absence of the phase-transfer catalyst. The relatively short reaction time in both instances may be attributed to the electron withdrawing effect of the lactone (C=O) group, with subsequent enhanced electrophilicity of C-5, with a resulting enhanced nucleophilic substitution at the reactive chiral site. In addition, the chlorosulphate group at C-5 of the starting material (9) is endo, since it projects into the V formed by the furanose and the lactone rings, and is thus more readily displaced by nucleophilic reagents due to the less hindered rear side approach of the nucleophile.

Isomerization of the L-ido derivative (10) to the corresponding D-gluco derivative (11) was observed after heating in the presence of N,N-dimethylformamide.

Reaction of 9 with potassium fluoride in the presence of 18-crown-6-ether afforded after 6 h, a crystalline mixture comprising approximately 40% of unreacted starting material (positive reaction for chlorosulphate ester), and a compound (12) having a faster t.l.c. mobility. The latter compound which was isolated by column chromatography and obtained in crystalline form, was found to have a similar melting-point and optical rotation to that of 5-chloro-5-deoxy-β-L-idofuranurono-6,3-lactone (8) which was synthesized by chlorosulphation of 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone at -10° essentially according to the method of Parolis[45]. In addition, the mass spectrum of 12 (Scheme D, Table VII) revealed fragments which correspond to the M-15 ion of 5-chloro-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone and its isotopic counterpart (M-15+2) in a 3:1 ratio that indicated the presence of a chlorine atom. No fragments relating to the corresponding 5-fluorosulphate or 5-fluoro-5-deoxy derivatives were observed.

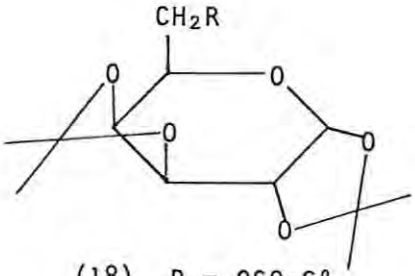
Chlorosulphation of methyl β-D-glucofuranosidurono-6,3-lactone afforded crystalline 13, the melting-point and optical rotation of which was similar to that reported by Parolis[45].



(13) $R^1 = SO_2Cl$, $R^2 = H$, $R^3 = Cl$
(14) $R^1 = H$, $R^2 = H$, $R^3 = Cl$

Reaction of 13 with potassium azide in the presence and absence of 18-crown-6-ether resulted in its dechlorosulphation to yield crystalline 14, the melting-point and optical rotation of which agreed with that reported by Parolis[45] for the compound obtained after dechlorosulphation of 13 with methanolic sodium iodide.

Chlorosulphation of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose afforded an unstable pungent crystalline compound (18) which melted with slow decomposition.



(18) R = OSO_2Cl
(19) R = OSO_2N_3
(20) R = N_3
(21) R = Cl
(22) R = OSO_2F

The n.m.r. data for 18 is shown in Table VIII. Only H-1 which appeared as a doublet and H-3 which appeared as a double-doublet were discernable. The rest of the signals were overlapped. The C-6, 6' protons which usually resonate at $\tau \simeq 6.25$ in galacto compounds,[95,96] were deshielded and therefore overlapped with the H-2 , H-4 and H-5 signals.

Table VIII - Chemical shifts (τ-values) and first-order coupling constants (Hz) for compounds 18, 19 and 20.

Compound	18	19	20
H-1	4.4(d)	4.42(d)	4.41(d)
H-3	5.26(dd)	5.30(dd)	5.30(dd)
H-2	5.32-5.85 (cm)	5.30-5.92 (cm)	5.64(dd
H-4			5.80(dd)
H-5			6.1(m)
H-6			6.4(dd)
H-6'			6.73(dd)
CMe_2	8.45(s) 8.53(s) 8.63(s)(2x)	8.45(s) 8.53(s) 8.65(s)(2x)	8.46(s) 8.54(s) 8.68(s)(2x)
$J_{1,2}$	5.3	5.3	5.3
$J_{2,3}$	2.7	2.7	2.7
$J_{3,4}$	5.7	7.3	8.0
$J_{4,5}$			2.0
$J_{5,6}$			6.7
$J_{5,6'}$			13.3
$J_{6,6'}$			15.3

Key: s = singlet, d = doublet, dd = double-doublet, m = multiplet, cm = complex multiplet.

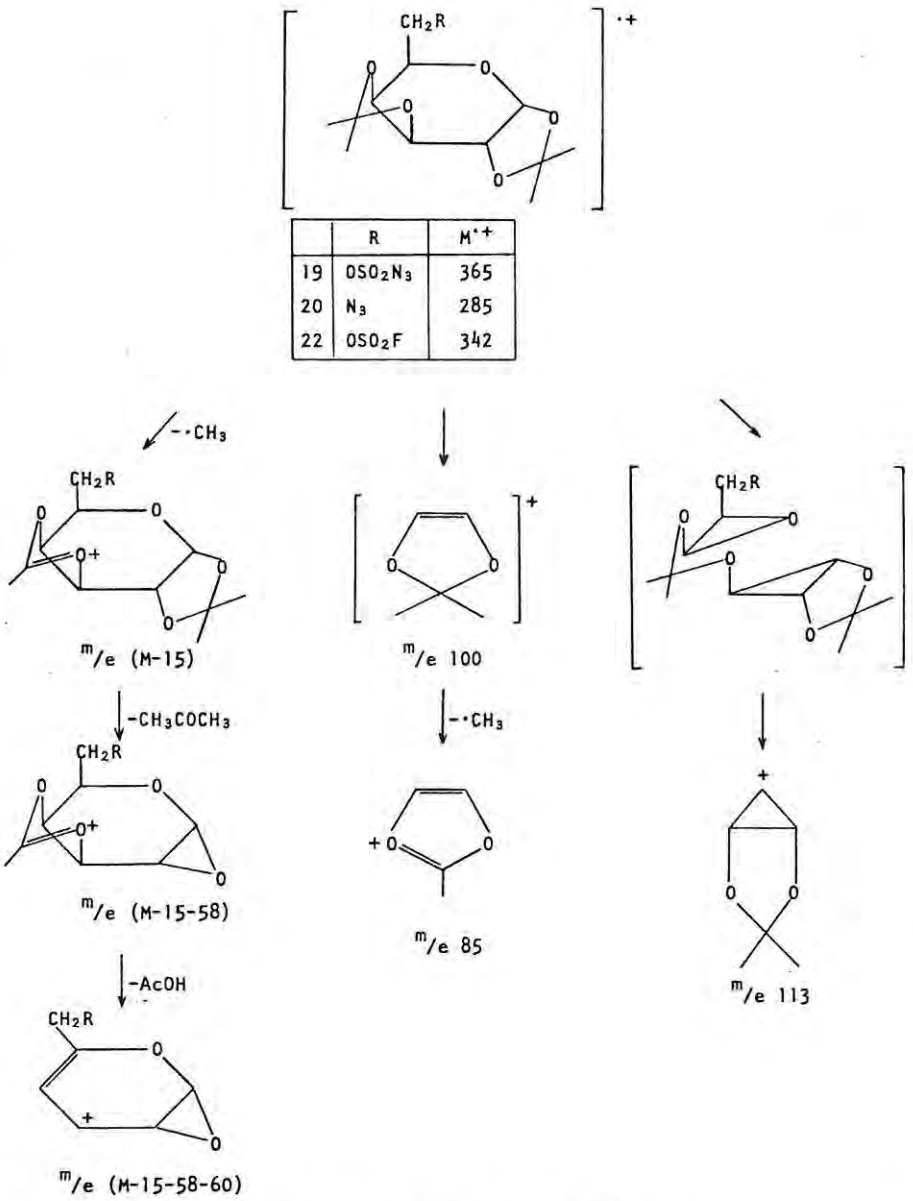
Reaction of 18 with potassium azide (3.0 molar equivalents) in the presence of 18-crown-6-ether (3.0×10^{-3} molar equivalents) for 140 h at room temperature gave rise to a major compound (19) having R_f 0.57 (t.l.c.) which was obtained crystalline, and two minor compounds having R_f 0.67 and 0.13 (the latter corresponding to that of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose), that were separated by column chromatography and isolated as syrups. The infra-red spectrum of the

compound (20) having R_f 0.67 revealed the presence of an azide absorbance peak (4.67 μm) and the absence of sulphonyloxy absorbance peaks. The infra-red spectrum of 19 indicated the presence of an azide absorbance peak (4.68 μm) as well, in addition to those of a sulphonyloxy group (7.13 μm, and 8.25 μm), while the elemental analysis was consistent with the proposed azidosulphonyloxy structure. The n.m.r. spectrum of 19 was very similar to 18, with the signals due to H-6 and H-6' being slightly deshielded and overlapped.

The formation of the 6-azidodeoxy derivative (20) appeared to be dependent upon the concentration of 18-crown-6-ether. The presence of the latter at a concentration of 1.0 molar equivalent in a reaction with 18 afforded after 21 h, a mixture, t.l.c. examination of which revealed a major proportion of 20 (R_f 0.67) with minor amounts of the 6-azidosulphate 19 (R_f 0.57) and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (R_f 0.13). G.l.c. examination of the mixture revealed that the 6-azidodeoxy derivative (20) was associated with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose and the 6-chlorodeoxy compound (21) in a ratio of 80:19:1 respectively. [The 6-azidosulphate derivative (19) was not detectable by g.l.c.]. The latter compound (21) was not detected by t.l.c. The n.m.r. spectrum of 20 (Table VIII) appeared to be similar to that of the 6-iodo-6-deoxy galactopyranoside derivative described by Cone *et al.*[95]. H-1 gave rise to a doublet while H-2, and H-4 each appeared as double-doublets, with those of H-2 partly overlapping that of H-4. H-5 appeared as a multiplet, while the signals due to H-6 and H-6' gave rise to overlapping double-doublets. The small coupling constant (2 Hz) observed for $J_{4,5}$ is a common feature of the galacto configuration[97].

The mass spectra of 19 and 20 (Scheme E, Table IX) revealed fragments that are in accordance with the fragmentation pattern of 1,2:3,4-di-O-

isopropylidene-α-D-galactopyranose[90], and involved elimination of acetone and acetic acid from the M-15 fragment.



	R	M·+
19	OSO_2N_3	365
20	N_3	285
22	OSO_2F	342

Scheme E - Mass spectral fragmentation pathways for compounds 19, 20 and 22.

Table IX - Relative intensities of peaks in the mass spectra of compounds 19, 20 and 22.

Compound	19	20	22
m/e	Relative intensity (%)		
43	100.0	100.0	100.0
85	35.5	8.9	11.2
100	35.5	11.2	10.0
113	20.0	7.1	3.2
M-15	20.0	8.9	14.1
M-15-58	2.2	6.3	2.8
M-15-58-60	1.8	0.7	2.2

In addition, 20 gave rise to a fragment of low abundance situated at m/e 263 in association with m/e 265 in a ratio of 3:1, which was indicative of the M-15 ion and its respective isotopic counterpart for the 6-chlorodeoxy compound (21), which was detected by g.l.c. examination prior to isolation of 20 by column chromatography. Although 21 was present as a trace contaminant in 20, elemental analysis of the latter proved to be satisfactory for the assigned 6-azidodeoxy structure.

Further experiments undertaken with various concentrations of potassium azide and 18-crown-6-ether, indicated that use of a 0.5 molar equivalent of the latter with 3.0 molar equivalents of potassium azide, resulted in all the starting material (18) being consumed after 21 h as well, with the formation of 19 and 20 in equal concentration. Continuation of this reaction over a period of thirty days at room temperature, resulted in most of the intermediate 6-azidosulphonyloxy compound (19) being converted to the 6-azidodeoxy derivative (20). Reduced concentrations of potassium azide (1.2 molar equivalents) and

18-crown-6-ether (0.012 molar equivalent), however, resulted in the starting material (18) being consumed after 95 h with predominant formation of 19 and a minor amount of 20. When 19 was stirred with 18-crown-6-ether alone, no 6-azidodeoxy derivative (20) was formed. In addition, reaction of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-chlorosulphate (18) with 3.0 molar equivalents of potassium azide and 0.03 molar equivalent of 18-crown-6-ether under refluxing conditions, accelerated dechlorosulphation of the starting material and possibly deazidosulphation of 19 which had formed, resulting after 64 h in the predominance of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose and a negligible amount of the 6-azidodeoxy compound (20).

From the above reactions, it seems evident that the rate-limiting step in the production of the 6-azidodeoxy derivative (20) from 19 is the displacement of the azidosulphonyloxy group by azide. Although Khan[60] has questioned the bimolecular mechanism proposed for chloride displacement reactions, the above process probably occurred via an intermolecular (S_N2) mechanism, rather than an intramolecular (S_Ni) type. This was demonstrated when the 6-chlorodeoxy derivative (21) was obtained by reaction of the azidosulphate derivative (19) with pyridinium chloride. At no stage during this reaction was an intermediate chlorosulphate ester detected (spray reagent b), thus suggesting direct replacement of the azidosulphonyloxy group by chloride. The presence of a negligible trace (≃1%) of the 6-chlorodeoxy derivative (21) (as revealed by mass spectroscopy and g.l.c.) in association with the 6-azidodeoxy compound (20), after synthesis of the latter, however, seems to indicate a competing intramolecular (S_Ni) mechanism due to competing chloride ions originating from the chlorosulphate group, and resulting in the formation of some 6-chlorodeoxy compound (21), which in turn could also undergo

C-Cℓ bond fission accompanied by bimolecular (S_N2) displacement by azide to yield the 6-azidodeoxy compound (20). In the latter respect, an analogous phenomenon has been reported by Khan[60] who observed that treatment of the hexa-O-benzoyl sucrose dichlorosulphate ester with sodium azide in hexamethylphosphoric triamide, afforded the 6,6'-diazido-6,6'-dideoxy benzoate, for which he has suggested the initial formation of the 6,6'-dichloride by an S_Ni process, followed by a bimolecular (S_N2) displacement reaction with azide ion to form the 6,6'-diazide derivative.

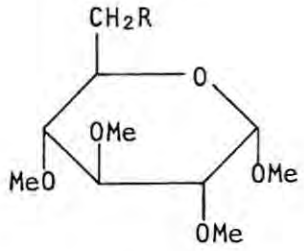
Reaction of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-chlorosulphate (18) with 3.0 molar equivalents of potassium chloride in the presence of 0.03 molar equivalents of 18-crown-6-ether afforded after 234 h, the 6-chlorodeoxy derivative (21) and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose which were shown by g.l.c. examination to be present in a ratio of 55:45 respectively. A similar reaction with potassium cyanide, however, gave rise predominantly to 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose after 21 h, whereas reaction with a less powerful nucleophile such as potassium cyanate was shown by g.l.c. examination to afford a 66:34 ratio of compound 21 and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose after 140 h, thus suggesting that substitution occurred via an intramolecular (S_Ni) mechanism to form the 6-chlorodeoxy derivative (21). In the presence of potassium fluoride, the reaction afforded after 140 h a mixture having three components (R_f 0.74, 0.72, and 0.14) (t.l.c.). G.l.c. examination indicated that the compound with the fastest t.l.c. mobility (R_f 0.74) was 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (21) which was present in a trace amount, while the compound having R_f 0.14 was 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose. The proportions of these two

could not be determined relative to that of the fluorosulphate compound (22) (R_f 0.72) in the mixture, as the latter compound was not sufficiently volatile to be detected by g.l.c. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose was, however, present in a ratio of 92:8 with the 6-chlorodeoxy compound (21). The presence of a trace amount of 21 suggests either the presence of a competing intramolecular (S_Ni) mechanism or less likely the bimolecular (S_N2) displacement of the fluorosulphate group by chloride ion which originated from the chlorosulphonyloxy group of 18. The infra-red spectrum of 22, which was isolated by column chromatography as needle-like crystals, indicated the presence of absorbance peaks at 7.0 μm and 8.25 μm that are characteristic for the fluorosulphate group, while the mass spectrum (Scheme E, Table IX) revealed a peak situated at $^m/e$ 327 (M-15) (based on 6-fluorosulphate) and a fragmentation pattern that conforms with that of the galacto-compounds, 19 and 20. Buncel *et al.*[65] have reported the synthesis of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 6-fluorosulphate (22), by treatment of 18 with methanolic silver fluoride, but found that the resulting primary fluorosulphate (22) had decomposed on standing, a phenomenon which was observed here as well.

The chlorosulphate ester of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose is particularly resistant to replacement reactions in comparison with the corresponding glucopyranosides[34]. This difference in activity has been attributed to the difference in location of the oxygen at C-4[98,99], (Unfavourable polar and steric factors are likely to exist due to the electronic field effect of the lone pair of electrons of the ring oxygen and the axial C-4 oxygen, thus causing repulsion of an approaching nucleophile.) thus resulting in the hindered replacement of the primary chlorosulphonyloxy group. The reactivity of a chlorosulphate ester in an

unhindered, reactive, primary position, such as is found in methyl 2,3,4-tri-O-methyl-α-D-glucopyranoside 6-chlorosulphate (25), was hence investigated with regard to its nucleophilic replacement by azide.

Methyl 2,3,4-tri-O-methyl-α-D-glucopyranoside (24) which was obtained by detritylating 23, was chlorosulphated at -30° for 0.5 h to afford a chromatographically pure syrup (25) which gave a positive test for chlorosulphate ester.



(23) R = $O(C_6H_5)_3C$

(24) R = OH

(25) R = OSO_2Cl

(26) R = $OSO_2N_3/N_3/Cl$

(27) R = N_3/Cl

The infra-red spectrum of 25 showed the characteristic absorbance peaks for chlorosulphate at 7.0 μm and 8.25 μm. The n.m.r. spectrum (Table X) of 25 showed H-1 as a doublet at τ 5.10. H-2 appeared as an overlapped double-doublet, while H-3, H-4 and H-5 gave rise to a complex multiplet. H-6 and H-6' appeared as a low field doublet at τ 5.25 due to the marked deshielding influence of the 6-chlorosulphate group. Compound 25 underwent decomposition on standing thus precluding an elemental analysis.

Table X - Chemical shifts (τ-values) and first-order coupling constants (Hz) for compounds 25 and 26

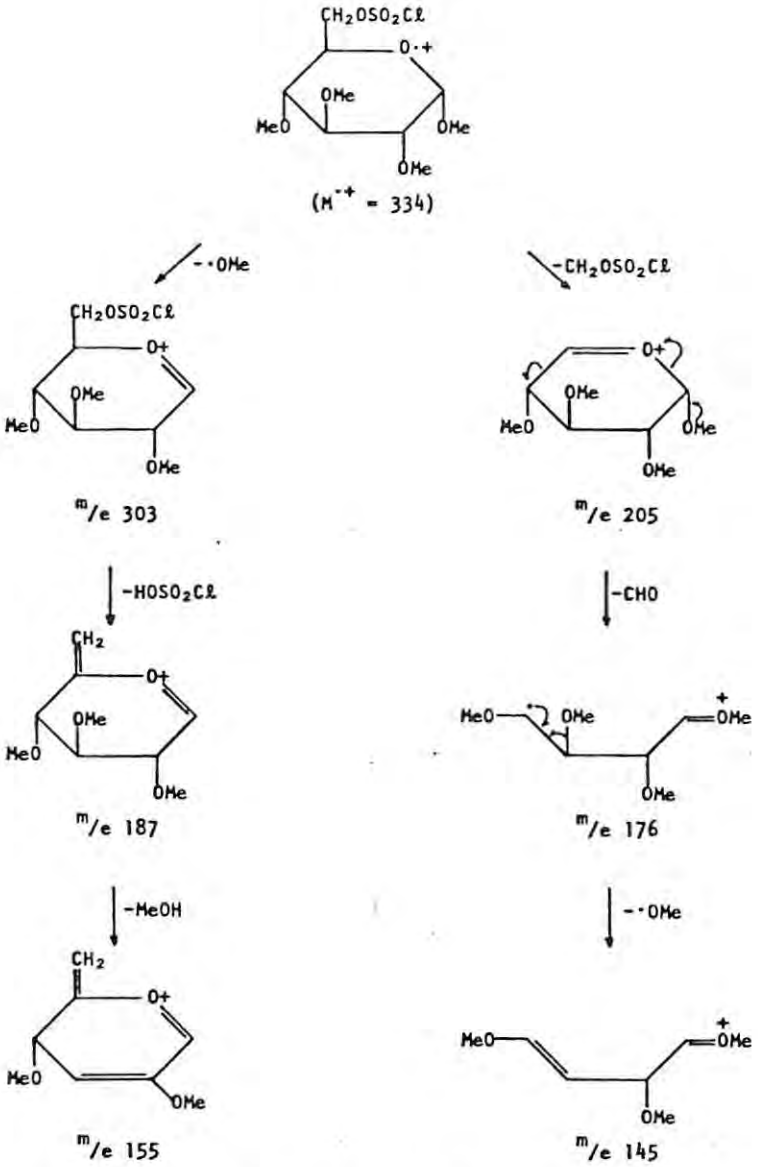
Compound	25	26
H-1	5.10(d)	5.12(d)
H-2	5.95-6.68(cm)	6.75(dd)
H-3		6.11-6.55(cm)
H-4		
H-5		
H-6	5.25(d)	
H-6'		
OMe	6.42(s) (3H) 6.47(s) (3H) 6.53(s) (3H) 6.62(s) (3H)	6.34(s) (3H) 6.37(s) (3H) 6.43(s) (3H) 6.53(s) (3H)
$J_{1,2}$	3.3	3.3
$J_{2,3}$	-	8.7

Key: d = doublet, dd = double-doublet
s = singlet, cm = complex multiplet.

The mass spectrum of 25 (Table XI) revealed a low intensity peak at $^{m}/e$ 303 (M-31) in association with its isotopic counterpart ($^{m}/e$ 305) in a ratio of 3:1, indicating the presence of a chlorine atom.

Table XI - Relative intensities of peaks in the mass spectra of compounds 25 and 26

Compound	25	26
$^{m}/e$	Relative Intensity (%)	
45	14.1	23.7
71	11.2	18.8
73	11.2	16.8
75	20.0	47.3
88	100.0	100.0
101	71.0	100.0
145	0.5	-
155	0.5	-
176	1.0	-
187	0.5	-
205	0.11	-
M-31		
303	0.4	-
310	-	0.8(6-OSO_2N_3)
230	-	0.3 (6-N_3)
223	-	1.7 (6-Cℓ)



Scheme F - Mass spectral fragmentation pathways for compound 25

The major fragmentation pathways (Scheme F) were observed to occur according to those proposed by Kochetkov et al.[100], for methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside. Fragment ions of mass numbers greater than $^{m}/e$ 101 had very low relative abundances.

Treatment of methyl 2,3,4-tri-O-methyl-α-D-glucopyranoside 6 chlorosulphate (25), with 1.2 molar equivalents of potassium azide, afforded 26 as a syrup after 30 h. Although the latter appeared to be chromatographically pure, its elemental analysis revealed the possibility

of it being a mixture consisting of a minor quantity of the 6-azido-sulphate derivative (calc. sulphur for azido-sulphate: 9.38%, found 0.65%) in association with the 6-azidodeoxy derivative. The infra-red spectrum revealed negligible absorbance peaks for a sulphonyloxy group, but a strong absorbance peak for azide at 4.78 μm. The presence, however, of some 6-chlorodeoxy derivative in addition to the aforementioned, was established after the syrup gave a positive Beilstein test for halogen, and the mass spectrum of the syrup (26) gave rise to a peak at $^{m}/e$ 223 (M-31 for the 6-chlorodeoxy derivative) in association with its isotopic counterpart ($^{m}/e$ 225) in a ratio of 3:1, thus confirming the presence of a chlorine atom. The presence of the 6-azidodeoxy derivative in the syrup (26) was also evident from its mass spectrum, as a low intensity peak situated at $^{m}/e$ 230 (M-31) was present. The n.m.r. spectrum of 26 (Table X) revealed H-1 as a doublet and H-2 as a double-doublet. The signals due to H-3, H-4, H-5, H-6 and H-6' were unresolved due to overlap with the methoxyl protons. From the n.m.r. spectrum it is also evident that the syrup was mainly the azidodeoxy derivative.

In an attempt to convert the trace of the azidosulphate derivative present in 26, to the azidodeoxy compound, the syrup was treated with an additional 5.0 molar equivalents of potassium azide in the presence of 1.0 molar equivalent of 18-crown-6-ether for 120 h at room temperature, to afford a syrup (27). Compound 27 was found to have the same t.l.c. mobility as 26, and its infra-red spectrum revealed a strong absorbance peak for azide (4.8 μm), while none was observed for a sulphonyloxy group. The n.m.r. data was the same as that of 26, while the mass spectrum (Table XI) still revealed low intensity peaks corresponding to the M-31 ion of the 6-chlorodeoxy derivative ($^{m}/e$ 223) in association with its isotopic counterpart ($^{m}/e$ 225) in a ratio of 3:1. The M-31

ion of the 6-azidodeoxy derivative gave rise to a peak of low intensity at $^{m}/e$ 230. The elemental analysis of 27 was not in accord with the 6-azidodeoxy structure. If it is assumed that 27 consisted of a mixture of the 6-azidodeoxy, and 6-chlorodeoxy derivatives, then these are present in a ratio of 70:30 respectively.

Since retreatment of 26 with azide did not remove the chlorodeoxy derivative, it is obvious that in this case the reaction did not occur as suggested by Khan[60] for the 6,6' dichloride and diazide derivatives of sucrose (i.e. $-SO_2C\ell \xrightarrow{S_Ni} -C\ell \xrightarrow{S_N2} -N_3$), but by either of the following sequences:

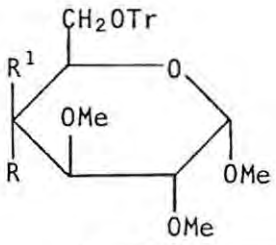
$$-SO_2C\ell \xrightarrow{S_N2} -N_3 \qquad \text{or}$$

$$-SO_2C\ell \xrightarrow{S_N2} -SO_2N_3 \xrightarrow{S_N} -N_3$$

The presence, however, of the 6-chlorodeoxy derivative in 26 suggests a competing intramolecular (S_Ni) reaction during the reaction of 25 with azide. Such a competing reaction was not observed with the less reactive 6-chlorosulphate of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose, where only a negligible trace of the 6-chlorodeoxy derivative was detected together with 6-azido-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (20). It could presumably be rationalized that the more reactive the site, the greater the possibility of competing internal reactions.

Methyl 2,3-di-O-methyl-6-O-trityl-α-D-glucopyranoside 4-chlorosulphate (31) was prepared in order to determine the extent of substitution by azide at a reactive secondary position. Compound 31 was synthesized by chlorosulpating methyl-2,3-di-O-methyl-6-O-trityl-α-D-glucopyranoside (30) at -10°. [Compound 30 was obtained by tritylating methyl 2,3-di-O-methyl-α-D-glucopyranoside (29)]. Compound 31 was obtained crystalline

and gave a positive test reaction for chlorosulphate ester.



	R	R^1
(31)	$OSO_2C\ell$	H
(32)	H	N_3

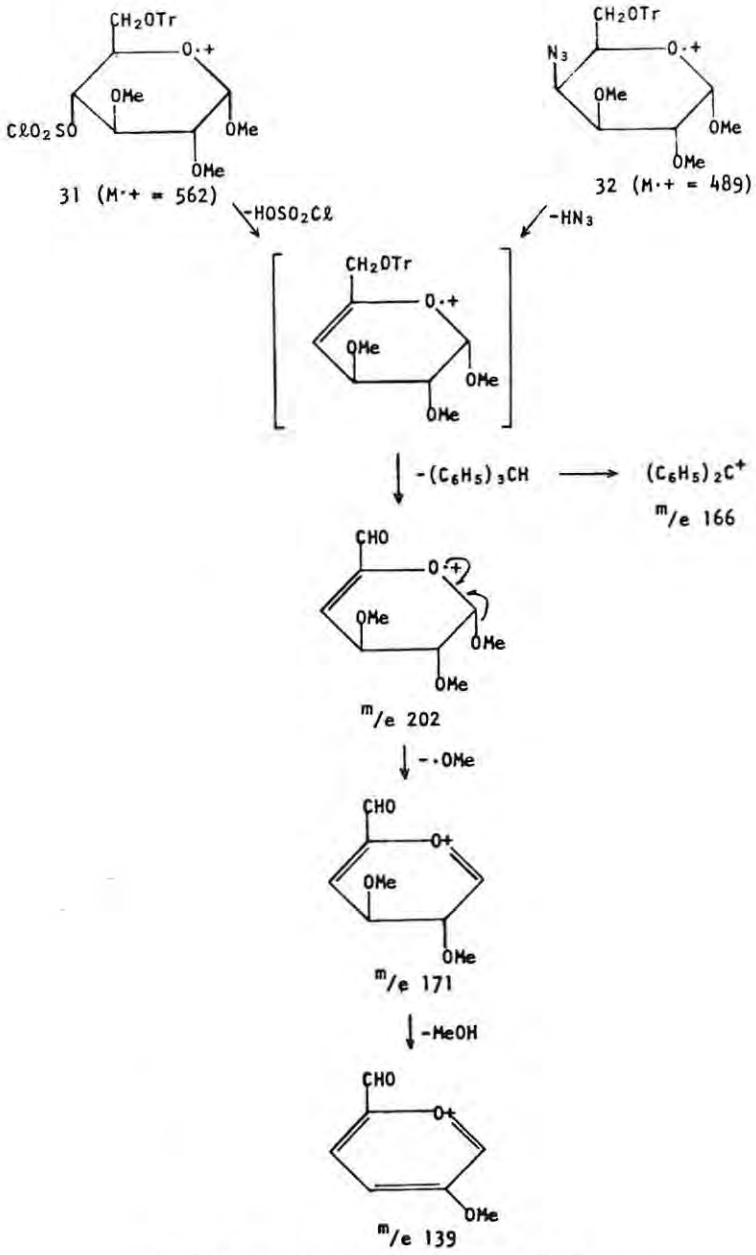
During the chlorosulphation reaction, some detritylation occurred, giving rise to a trace amount of the 4,6-dichlorosulphate ester. The infra-red spectrum of 31 revealed the characteristic absorbance peaks for the chlorosulphonyloxy group (7.0 μm, 8.35 μm), while the elemental analysis was in accord with the expected structure. The n.m.r. spectrum of 31 (Table XII) showed H-4 as a triplet at τ 5.15.

Table XII - Chemical shifts (τ-values) and first-order coupling constants (Hz) for compounds 31 and 32

Compound	31	32
H-1	5.02(d)	5.17(d)
H-2	6.62(dd)	see below
H-3	see below	see below
H-4	5.15(t)	5.9(dd)
H-5	6.07-6.47(cm) (includes H-3)	6.27-6.67(cm) (includes H-2 and H-3)
H-6		
H-6'		
OMe	6.37(s) (3H) 6.40(s) (3H) 6.44(s) (3H)	6.44(s) (3H) 6.47(s) (3H) 6.49(s) (3H)
$(C_6H_5)_3C$	2.30-2.87(m)	2.37-2.72(m)
$J_{1,2}$	3.3	3.3
$J_{2,3}$	8.7	-
$J_{3,4}$	9.0	2.7
$J_{4,5}$	9.0	1.3

Key: d = doublet, dd = double-doublet, m = multiplet, s = singlet, cm = complex multiplet.

The appearance of H-4 at low field clearly indicates the presence of the chlorosulphonyloxy group at C-4. H-1 appeared as a doublet and H-2 as a double-doublet, while the signals due to H-3, H-5, H-6 and H-6' were not clearly discernable. The mass spectrum of 31 (Scheme G, Table XIII) was characterised by the absence of isotopic cluster peaks that occur with chlorine bearing fragments, thus indicating that initial fragmentation had occurred with the loss of the chlorosulphate group.



Scheme G - Mass spectral fragmentation pathways for compounds 31 and 32

Table XIII - Relative intensities of peaks in the mass spectra of compounds 31 and 32

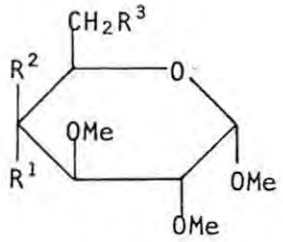
Compound	31	32
m/e	Relative Intensity (%)	
45	56.3	20.0
73	35.5	10.0
75	63.1	35.5
88	100.0	71.0
101	100.0	14.1
139	1.4	25.12
166	8.0	16.0
171	1.0	0.5
202	1.0	3.5
243	9.0	100.0

The general fragmentation pattern was similar to that proposed for methylated pyranosides[100], with high intensity ions being of low mass numbers.

Reaction of methyl 2,3-di-O-methyl-6-O-trityl-α-D-glucopyranoside 4-chlorosulphate (31) with 5.25 molar equivalents of potassium azide and 2.0 molar equivalents of 18-crown-6-ether, afforded methyl 4-azido-4-deoxy-2,3-di-O-methyl-6-O-trityl-α-D-galactopyranoside (32), after stirring at room temperature for approximately 72 h. [A preliminary reaction using a lower concentration of potassium azide (1.2 molar equivalents) in the absence of 18-crown-6-ether resulted in some unreacted starting material (31) remaining after stirring at room temperature for 44 h.] Examination of the reaction mixture by t.l.c., indicated that all the starting material (31) had been consumed after 1 h, and during this period, some of the starting material had become dechlorosulphated as evidenced by the isolation of a compound having the same t.l.c. mobility and melting-point as that of 30. No further increases in the concentration of the dechlorosulphated compound occurred after the first hour of the reaction, suggesting that 30 did not

arise from what appeared to be the 4-azidosulphate intermediate which had formed as well. The latter compound persisted in diminishing concentration throughout the reaction until all of it was converted to the 4-azido-4-deoxy derivative (32). Within the first hour of the reaction, compound 32 and its intermediate 4-azidosulphate appeared to be present in an approximate ratio of 7:3. Even at the lower concentration of azide (1.2 molar equivalents) both the 4-azidodeoxy and 4-azidosulphate formed. Compound 32 is thus probably formed by both direct S_N2 displacement of the chlorosulphate group by azide and the S_N displacement of the azidosulphate group by azide. Mass spectral evidence did not suggest the presence of a 4-chloro-4-deoxy derivative in association with 32. Compound 32 which was present with the dechlorosulphated starting material in a ratio of 64:36 respectively, was isolated by column chromatography, as a syrup. The infra-red spectrum of 32 showed the presence of an absorbance peak for azide (4.78 μm), while its elemental analysis was consistent with the assigned structure. The mass spectrum of 32 (Table XIII) showed a base peak situated at $^m/e$ 243 $[(C_6H_5)_3C^+]$, and a possible fragmentation pathway is shown in Scheme G. The galacto configuration for 32 is clearly established by its n.m.r. spectrum (Table XII) which revealed a characteristic[97] narrow double-doublet for H-4, with $J_{4,5}$ = 1.3 Hz. H-1 appeared as a doublet, while H-2, H-3, H-5, H-6 and H-6' could not be assigned.

The reaction of azide with a compound possessing both a reactive primary chlorosulphate group and a replaceable secondary chlorosulphate group was investigated with methyl 2,3-di-O-methyl-α-D-glucopyranoside 4,6-dichlorosulphate (33).



	R^1	R^2	R^3
(33)	$OSO_2C\ell$	H	$OSO_2C\ell$
(34)	$OSO_2C\ell$	H	N_3
(35)	OH	H	N_3
(36)	OAc	H	N_3
(37)	H	N_3	N_3

Compound 33 was synthesized by chlorosulphating methyl 2,3-di-O-methyl-α-D-glucopyranoside (29), and obtained crystalline. The infra-red spectrum of 33 revealed absorbance peaks for chlorosulphate ester (7.0 μm, 8.25 μm), and the elemental analysis was satisfactory for the assigned structure. The n.m.r. spectrum of 33 (Table XIV) contained a doublet for H-1, a double-doublet for H-2, and a triplet for each of H-3 and H-4.

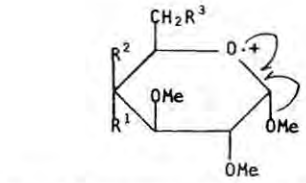
Table XIV - Chemical shifts (τ-values) and first-order coupling constants (Hz) for Compounds 33-37

Compound	33	34	35	35*	36	37
H-1	5.02(d)	5.02(d)	5.06(d)	5.06(d)	5.04(d)	5.07(d)
H-2	6.63(dd)	6.63(dd)	6.57(dd)	6.67(dd)	see below	see below
H-3	6.21(t)	see below	6.06-6.50(cm)	see below	see below	see below
H-4	5.18(t)	5.16(t)		5.09(t)	5.12(t)	6.11(dd)
H-5	5.63-6.23(m)	5.80-6.46(cm) (includes H-3)		5.73-6.49(cm) (includes H-3)	5.97-6.82(cm) (includes H-2 and H-3)	6.17-6.72(cm) (includes H-2 and H-3)
H-6	5.13-5.37(cm)					
H-6'						
OMe	6.31(s) (3H) 6.39(s) (3H) 6.46(s) (3H)	6.31(s) (3H) 6.39(s) (3H) 6.46(s) (3H)	6.31(s) (3H) 6.46(s) (3H) 6.49(s) (3H)	6.39(s) (3H) 6.43(s) (3H) 6.48(s) (3H)	6.42(s) (3H) 6.47(s) (6H)	6.40(s) (3H) 6.49(s) (6H)
OH	-	-	7.56(s)	-	-	-
NH	-	-	-	1.32(s)	-	-
OAc	-	-	-	-	7.85(s)	-
$J_{1,2}$	3.3	3.3	2.7	3.3	3.3	3.3
$J_{2,3}$	9.3	9.3	6.7	9.3	-	-
$J_{3,4}$	9.3	9.3	-	9.3	9.3	5.0
$J_{4,5}$	9.3	9.3	-	9.3	9.3	2.0

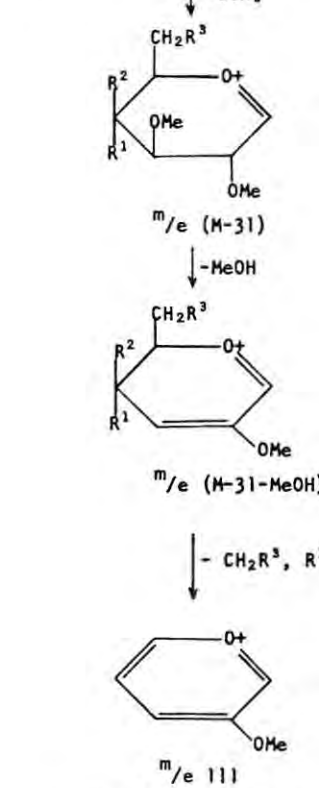
Key: d = doublet, dd = double-doublet, cm = complex multiplet, m = multiplet, s = singlet, t = triplet.

* with shift reagent, trichloro-acetyl-isocyanate.

H-4, H-6 and H-6' appeared to be deshielded due to the proximity of the chlorosulphate groups at C-4 and C-6. H-6 and H-6' gave rise to a complex multiplet downfield (τ 5.13-5.37), while H-5 which appeared to be deshielded to a lesser extent, afforded a low intensity multiplet. The mass spectrum (Scheme H, Table XV) showed an M-31 ion ($^{m}/e$ 387) in association with its isotopic counterparts ($^{m}/e$ 389 and $^{m}/e$ 391) in a ratio of 9:6:1, indicating the presence of the two chlorine atoms. The fragmentation occurred according to that proposed by Kochetkov et al.[100], with ions of high mass numbers being present in low intensities.



	R^1	R^2	R^3	$M^{\cdot+}$
33	OSO_2Cl	H	OSO_2Cl	418
34	OSO_2Cl	H	N_3	345
35	OH	H	N_3	247
36	OAc	H	N_3	289
37	H	N_3	N_3	272



Scheme H - Mass spectral fragmentation pathways for compounds 33-37

Table XV - Relative intensities of peaks in the mass spectra of compounds 33 - 37

Compound	33	34	35	36	37
m/e	Relative Intensity (%)				
43	-	-	-	80.0	-
45	100.0	44.7	35.5	18.0	20.0
73	31.6	25.1	22.4	14.1	16.0
75	100.0	71.0	56.2	71.0	35.5
88	100.0	100.0	100.0	100.0	100.0
101	31.6	25.1	14.1	7.1	12.6
111	14.1	2.5	1.4	1.0	0.5
M-31	0.13	0.12	0.1	0.03	0.03
M-31-MeOH	0.16	0.1	0.11	0.03	0.06
*M-31	-	0.1	0.35	0.06	0.06

* corresponding 6-chlorodeoxy derivative

Treatment of methyl 2,3-di-O-methyl-α-D-glucopyranoside 4,6-dichlorosulphate (33) with 2.5 molar equivalents of potassium azide in the absence of crown-ether, afforded 34 as an unstable syrup (elemental analysis was unsatisfactory) which gave a positive reaction for chlorosulphate ester. The infra-red spectrum of 34, which was isolated by column chromatography, revealed characteristic absorbance peaks for chlorosulphate (7.0 μm, 8.3 μm) and azide groups (4.8 μm). The formation of 34 with its intact chlorosulphate group at position C-4 indicated the low degree of activity at this site under the present reaction conditions. It is interesting to note that the 4-chlorosulphonyloxy group is readily substituted by chloride in gluco compounds at room temperature[32].

The n.m.r. spectrum of 34 (Table XIV) was essentially similar to that of 33, with the exception of H-6 and H-6', and shows that the 4-chlorosulphate group is still intact, as the H-4 triplet of 34 occurred in the same position as in the spectrum of the 4,6-dichlorosulphate ester (33). The spectrum also indicated that removal of the 6-chlorosulphate group

had occurred, as evidenced by the fact that H-6 and H-6' occurred at a much higher field in 34 than in 33. It is also clear that the chlorosulphate group had been replaced by an azide group to afford the 6-azidodeoxy and not the 6-azidosulphate derivative,as H-6 and H-6' would have resonated further downfield in the case of the latter. The mass spectrum of 34 is described in Table XV and Scheme H. All high mass number ions were present in low intensity. The M-31 ion was associated with its isotopic counterpart in a ration of 3:1, indicating the presence of a chlorine atom. In addition, the M-31 ion (^{m}/e 307) for the corresponding 6-chlorodeoxy derivative in association with its isotopic counterparts ^{m}/e 309 and ^{m}/e 311 in an approximate ratio of 9:6:1, which indicated the presence of two chlorine atoms, suggested that a small amount of the 6-chlorodeoxy derivative was associated with 34. Further indications as to the presence of a trace of the 6-chlorodeoxy compound were obtained from the elemental analysis, which although unsatisfactory as a result of the instability of 34, indicated a slightly higher chlorine and lower nitrogen content.

Catalytic dechlorosulphation of methyl 6-azido-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside 4-chlorosulphate (34) gave methyl 6-azido-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (35) as a syrup. The infra-red spectrum of 35 showed the presence of an hydroxyl (2.95 μm) and an azide group (4.8 μm). The n.m.r. data of 35 is given in Table XIV. H-1 appeared as a doublet, while the double-doublet due to H-2 partly overlapped with a methoxyl signal. H-3, H-4, H-5, H-6 and H-6' could not be assigned, but the signal due to the hydroxyl group appeared as a broad singlet at τ 7.56. The addition of trichloro-acetyl-isocyanate resulted in the appearance of a broad singlet at τ 1.32 due to the NH of the resulting carbamate complex, while H-4 was strongly

deshielded and appeared as a triplet centered at τ 5.09. The mass spectrum of 35 (Table XV, Scheme H) revealed the presence of some of the corresponding 6-chlorodeoxy compound associated with it, as a peak situated at $^{m}/e$ 209 (M-31) in association with its isotopic counterpart ($^{m}/e$ 211) in a ratio of 3:1 was present. This was reflected in the elemental analysis of 35 which gave a marginally lower nitrogen content, but was otherwise satisfactory.

Acetylation of methyl-6-azido-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (35) afforded methyl 4-O-acetyl-6-azido-6-deoxy 2,3-di-O-methyl-α-D-glucopyranoside (36) as a syrup which was purified by distillation. The infra-red spectrum of 36 showed absorbance peaks for the acetyl (5.85 μm) and azide (4.78 μm) groups. The n.m.r. data of 36 is given in Table XIV. H-1 afforded a doublet and H-4 which was deshielded by the 4-acetoxy group, appeared as a triplet (τ5.12). The remaining signals were overlapped by the methoxyls and could not be assigned. The mass spectrum (Scheme H, Table XV) of 36 differed from those of 33, 34 and 35, by giving rise to a strong peak at $^{m}/e$ 43 (CH_3CO^{+}). The M-31 ion ($^{m}/e$ 251) for the corresponding 6-chlorodeoxy derivative of which there appeared to be a trace, was associated with its isotopic counterpart $^{m}/e$ 253 in a ratio of 3:1, indicating the presence of a chlorine atom. This was also reflected in the elemental analysis, which gave a slightly low nitrogen content, but was otherwise in accord with the assigned structure.

Reaction of methyl 6-azido-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside 4 chlorosulphate (34) with 5.0 molar equivalents of potassium azide and 1.0 molar equivalent of 18-crown-6-ether for 120 h at room temperature, resulted in the formation of methyl 4,6-diazido-4,6-dideoxy-2,3-di-O-methyl-α-D-galactopyranoside (37), in addition to

a similar amount of 35. During the reaction the starting material (34) was consumed (t.l.c.) within an hour of commencement; at this stage, most of the dechlorosulphation had occurred, and the presence of 37 (t.l.c.) and a lesser amount of a compound that appeared to be the intermediate azidosulphate, which had a similar t.l.c. mobility as that of its 4-chlorosulphate precursor (34) was also evident. The intermediate azidosulphate persisted with diminishing concentration until all of it had been converted to the 4,6-diazido-dideoxy derivative (37).

Compounds 35 and 37 were isolated by column chromatography. Compound 37 was obtained as a pale yellow syrup, the infra-red spectrum of which showed an absorbance peak for the azide (4.83 μm) group. The n.m.r. spectrum (Table XIV) revealed a doublet for H-1, while the resonance signal for H-4 appeared as a narrow double-doublet at τ 6.11 with a coupling constant ($J_{4,5}$ = 2.0 Hz) that is characteristic of the galacto configuration[97]. The remaining signals could not be assigned. The mass spectral data[100] for 37 (Table XV, Scheme H) contained a low intensity M-31 peak ($^{m}/e$ 234) for the corresponding 4-azido-6-chloro-dideoxy derivative which was associated with its isotopic counterpart in a ratio of 3:1, indicating the presence of a chlorine atom. This was also shown by the elemental analysis which revealed a slightly lower nitrogen content. There was no mass spectral evidence to suggest the presence of any of the 4,6-dichloro-dideoxy compound.

Further experiments were undertaken with 34, using potassium azide concentrations of 1.2 and 3.0 molar equivalents respectively in the absence of 18-crown-6-ether. The results obtained indicated that when the lower concentration of potassium azide was used, a large portion of the starting material (34) remained unreacted after a 30 h period, with the formation of trace amounts of the diazido-dideoxy

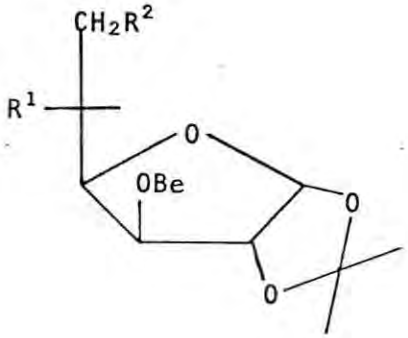
compound (37) and its intermediate azidosulphate. A significant amount of dechlorosulphation of the starting material was, however, observed to occur. At the higher azide concentration (3.0 molar equivalents) the starting material was completely consumed after 10 h with formation of equal but minor amounts of 37 and its intermediate azidosulphate, while dechlorosulphation of the starting material appeared to be as extensive as before.

In all of the above azide reactions, dechlorosulphation of the starting material (34) was observed to occur in the initial stage of the reaction, with no apparent increase in the amount of dechlorosulphated material occurring as the reactions progressed. Formation of the 4,6-diazido-dideoxy compound (37) seemed to occur via two possible concurrent mechanisms as was suggested for the formation of 32 from 31. The presence of a small amount of the 6-chlorodeoxy derivative in association with 34 indicates that the above reactions have some S_Ni characteristics.

3.2 A small part of the present work was concerned with the synthesis of furanosidic sugars for evaluation as potential anti-inflammatory agents. Tribenoside[101] (ethyl 3,5,6-tri-O-benzyl-α-D-glucofuranoside) which is marketed under the name of Glyvenol ^{R}, is a multipotent drug exhibiting both anti-inflammatory and anti-allergic properties[102 103]. Its exact mode of action has not been reported. Structure-activity studies have shown that many furanosides possess anti-inflammatory properties, however, the influence of a halogen atom in the sugar molecule on the activity, has not been investigated. We were required to synthesize 3-O-benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (41) and its 5-acetate (42) for comparison of their

anti-inflammatory properties with that of tribenoside.

3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose (39) which was obtained via the partial hydrolysis of 3-O-benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (38) was allowed to react with sulphuryl chloride at -10° to yield 3-O-benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose 5-chlorosulphate (40) as a crystalline compound.



	R^1	R^2
(39)	OH	OH
(40)	OSO_2Cl	Cl
(41)	OH	Cl
(42)	OAc	Cl

The infra-red spectrum of 40 revealed absorbance peaks (7.13 μm, 8.35 μm) for the chlorosulphate group. The n.m.r. data for 40 is shown in Table XVI. H-5 appeared as a deshielded multiplet at τ 4.56 due to the chlorosulphate group at C-5.

Table XVI - Chemical shifts (τ-values) and first-order coupling constants (Hz) for compounds 40-42

Compound	40	41	41*	42
H-1	4.07(d)	3.88(d)	3.87(d)	3.87(d)
H-2	see below	5.24(d)	5.19(d)	5.23(d)
H-3	5.87(d)	5.09-6.29(cm) (includes CH_2)	5.82(d)	5.88(d)
H-4	5.19-5.54(cm) (includes H-2)		≈5.38(dd)	≈5.41(dd)
H-5	4.56(m)		4.43(m)	4.48(m)
H-6	5.78(dd)		5.76(dd)	5.81(dd)
H-6'	6.02(dd)		6.06(dd)	6.10(dd)
CMe_2	8.49(s) (3H)	8.47(s) (3H)	8.46(s) (3H)	8.46(s) (3H)
	8.69(s) (3H)	8.65(s) (3H)	8.63(s) (3H)	8.64(s) (3H)
CH_2	≈5.35(s) (2H)	see above	5.22(s) (2H)	5.27(s) (2H)
C_6H_5	2.6 (s) (5H)	2.39(s) (5H)	2.40(s) (5H)	2.41(s) (5H)
OH	-	7.6(s)	-	-
NH	-	-	1.33(s)	-
OAc	-	-	-	7.98(s) (3H)
$J_{1,2}$	3.6	3.7	3.6	3.3
$J_{3,4}$	3.0		3.3	3.0
$J_{4,5}$	8.0		8.0	8.0
$J_{5,6}$	2.7		2.7	3.0
$J_{5,6'}$	4.7		4.7	4.7
$J_{6,6'}$	12.8		13.3	13.3

Key: d = doublet, dd = double doublet, s = singlet, m = multiplet, cm = complex multiplet

* with shift reagent trichloro-acetyl-isocyanate.

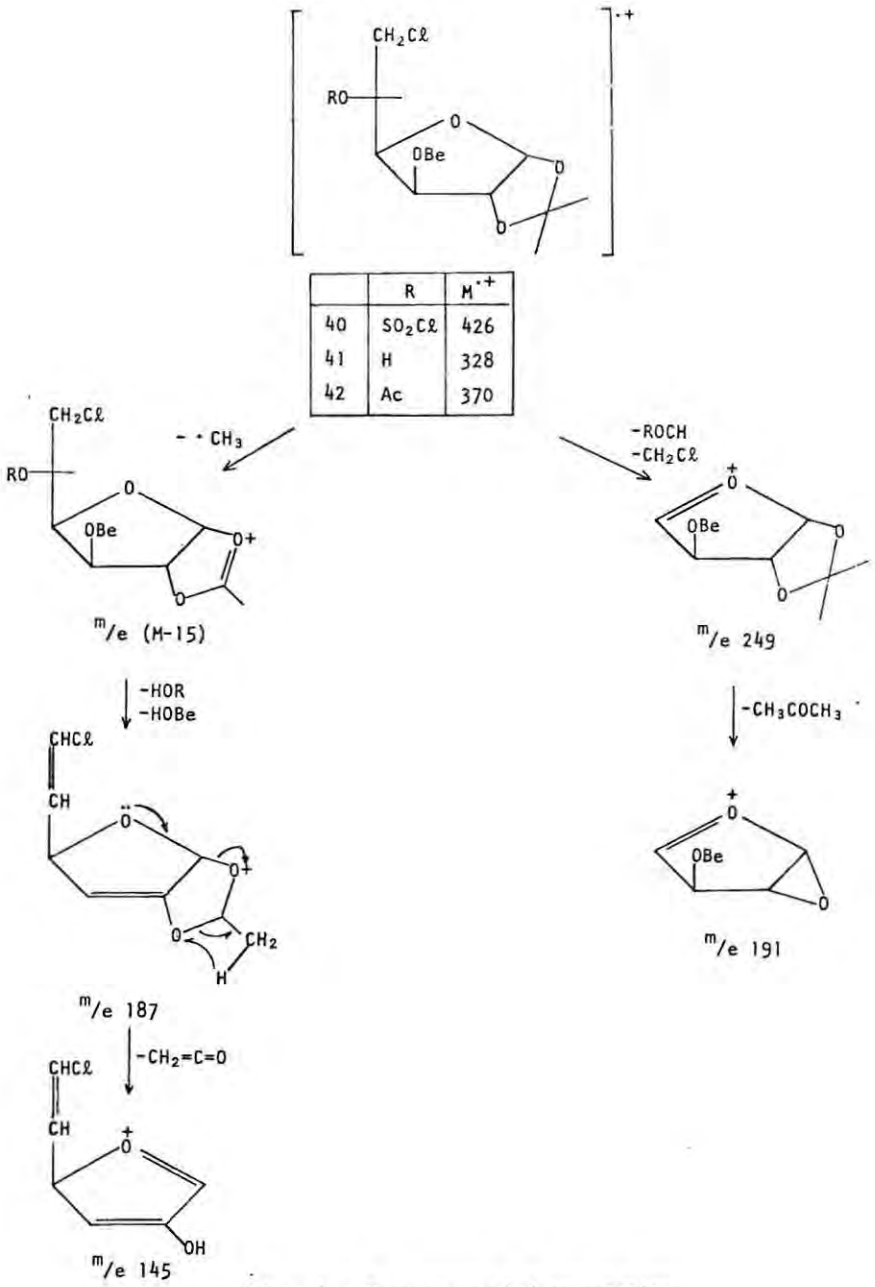
Dechlorosulphation of 40 afforded 3-O-benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (41) as a syrup. The infra-red spectrum of 41 showed the presence of a hydroxyl absorbance peak (2.8 μm). The n.m.r. spectrum of 41 (Table XVI) showed a broad singlet for the hydroxyl proton at τ 7.6. Addition of trichloro-acetyl-isocyanate resulted in the appearance of a 1-proton singlet (τ 1.33) due to the NH group of the resulting carbamate. The spectrum obtained showed a multiplet due to H-5 (τ 4.43), and the overall profile appeared to be similar to that of 40. The deshielding of H-5 after addition of the shift reagent, confirms that the free hydroxyl group in 41 is located at C-5.

Acetylation of 41 afforded 5-O-acetyl-3-O-benzyl-6-chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (42) as a crystalline compound, the infra-red spectrum of which revealed an absorbance peak (5.78 μm) for the acetyl group. The n.m.r. spectrum of 42 (Table XVI) contained a multiplet at τ 4.48, that was assigned to H-5. The latter was deshielded, due to the electron withdrawing effect of the acetyl group. It is noteworthy that the deshielding influence of the electron withdrawing group at C-5 of compounds 40 and 42, on H-6 and H-6', and the shielding influence of the benzyl group at C-3 on H-3, resulted in the overlap of the H-3, H-6 and H-6' resonance signals.

The mass spectra of 40, 41 and 42 (Table XVII, Scheme I) revealed a base peak situated at $^{m}/e$ 91 ($C_6H_5CH_2^+$). The M-15 peak of 40 was associated with its isotopic counterparts, (M-15+2, M-15+4) in a ratio of 9:6:1, indicating the presence of two chlorine atoms, while the M-15 peaks of 41 and 42 were associated with their isotopic counterparts (M-15+2) in a 3:1 ratio, which indicates the presence of 1 chlorine atom in each of these compounds. All three compounds gave rise to peaks situated at $^{m}/e$ 187 and $^{m}/e$ 145 that were associated with peaks at $^{m}/e$ 189 and $^{m}/e$ 147 in ratios of 3:1, which indicated that these were due to fragments bearing a single chlorine atom.

Table XVII - Relative intensities of peaks in the mass spectra of compounds 40-42

Compounds	40	41	42
$^{m}/e$	Relative Intensity (%)		
91	100.0	100.0	100.0
145	3.6	4.5	6.3
187	6.3	3.6	3.6
191	2.5	5.0	5.0
249	2.2	6.3	2.8
M-15	9.0	7.1	5.6



	R	$M^{\cdot+}$
40	$SO_2C\ell$	426
41	H	328
42	Ac	370

Scheme I - Mass spectral fragmentation pathways for compounds 40-42

The biological activity of 41 and 42 is at present being compared with that of tribenoside.

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