REACTION OF CARBOHYDRATES WITH THE SULPHURYL CHLORIDE-N,N-DIMETHYL FORMAMIDE REAGENT

Dissertation
submitted in partial fulfilment of the
requirements for the degree of

MASTER OF SCIENCE
IN THE FACULTY OF PHARMACY
Rhodes University

by

WILFRED THOZAMILE MABUSELA B.Sc(Hons.), Fort Hare

January 1982

School of Pharmaceutical Sciences
Rhodes University
Grahamstown
Republic of South Africa

ACKNOWLEDGEMENTS

The author wishes to express his foremost thanks to Professor H. Parolis, under whose dedicated supervision this study was undertaken, for his indefatigable guidance, inspiring encouragement and sincere enthusiasm.

Gratitude is also expressed to the following:

Professors J.R. Nunn and T.M. Letcher for making available the required facilities of the Department of Chemistry, Rhodes University, where this investigation was undertaken.

Mr A.W. Sonemann and the technical staff of the Department of Chemistry, Rhodes University, for their valued assistance.

Professor L. Hough and the staff of the Department of Chemistry, Queen Elizabeth College, University of London, and Mr J. Brits, of the National Chemical Research Laboratory, Pretoria, for the elemental analysis of synthesized compounds.

Mrs S.A. Robertson for her patience and helpful suggestions in the layout and typing of this manuscript.

My parents, Mr and Mrs G.V. Mabusela, for their support and encouragement throughout the study that I have undertaken.

CONTENTS

SUMMARY

An investigation of the reaction of the sulphuryl chloride-N,N-dimethyl formamide reagent with several carbohydrate compounds, containing free hydroxyl groups, was undertaken, mainly with the view of looking at substitution of the hydroxyl groups with chlorine atoms.

The reaction was found to lead to substitution of both primary and secondary hydroxyl groups with chlorine, with inversion of configuration in the latter case. The reagent was further found to effect formylation and chlorosulphation of secondary hydroxyl groups, where nucleophilic substitution by a chlorine was not favourable.

Studies involving the methyl pentopyranosides, showed that the reagent was particularly useful in the chlorosulphation and chlorination of sugars, compared with the hexopyranosides.

1. INTRODUCTION

Halodeoxy sugars are known to be of great value in synthetic chemistry, because they are among the most versatile intermediates for the synthesis of other rare sugars such as aminodeoxy and deoxy sugars. In such syntheses advantage is taken of the ease of nucleophilic substitution of the halogeno substituents, or their reductive removal to afford deoxy sugars. Alternatively, a halodeoxy sugar may be induced to undergo 1,2-elimination of a hydrogen halide to give an unsaturated sugar.

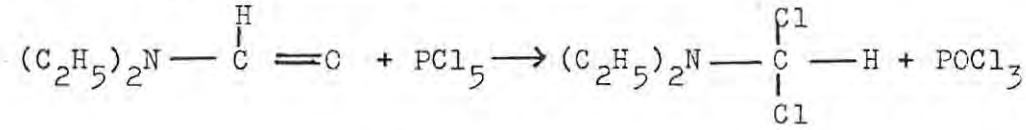
In several cases, halodeoxy sugars have been the ultimate target compounds, due, among other things, to the discovery that introduction of a halogen to the carbohydrate moieties of some antibiotic substances, imparts unique biological properties to the parent compounds.

The various methods and reagents that can be employed towards halogenation of sugars were reviewed by Barnett[1], Szarek[2] and Hanessian *et al.*[3]. The present review will be confined to the preparation of the Vilsmeier-Haack and related reagents and their reactions with carbohydrates.

1.1 Preparation of Vilsmeier-Haack and related reagents

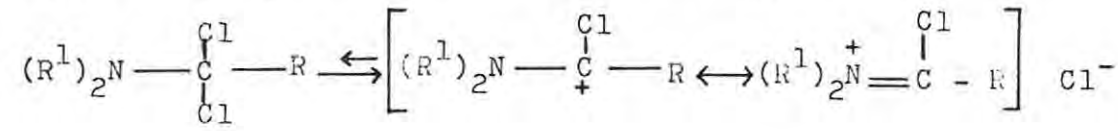
The reaction of carboxylic acid amides with inorganic acid chlorides is known to give rise to amide chlorides. A review on this type of reaction was undertaken by

Eilingsfeld et al.[4], in which they reported, as an example of the first reaction of this kind which had been conducted by earlier investigators, the reaction between N,N-diethyl formamide and phosphorus pentachloride, which gave N,N-diethyl formiminium chloride, thus;



These authors[4] further reported that, later investigators showed that the best method for the preparation of amide chlorides was that involving phosgene, as an inorganic acid chloride. N,N-dimethyl benzamide is one of the first acid amides to be used with the latter inorganic acid chloride, resulting in the formation of N,N-dimethyl-α-chlorobenzylidene ammonium chloride. Other acid chlorides found[5] to react in a similar manner with acid amides are thionyl chloride, phosphorus trichloride and oxalyl chloride. Vilsmeier and Haack[6] used both phosphorus pentachloride and phosphorus oxychloride in the preparation of amide chlorides.

Further investigations[4] revolved around establishing the structure of the amide chlorides produced. Some authors proposed the non-polar structure (1), whilst others suggested the polar or ionic structure (2).



(1) (2)

However, for the unsubstituted amide chloride, R^1 = H, the polar structure (2) appeared to be the appropriate one, as was established through conductivity measurements. Furthermore, the i.r. spectrum showed a band around 6 μm, which is indicative of a C = N bond. It has also been found that most amide chlorides are insoluble in non-polar solvents, whilst they are soluble in halogenated solvents such as chloroform. This solubility behaviour favours the polar structure. In addition, Bosshard and Zollinger[5], in their investigation of the catalytic effect of N,N-dimethyl formamide in the reaction of carboxylic and sulfonic acids with thionyl chloride, explained the effect as being due to the formation of a polar intermediate similar to (2), from dimethyl formamide and thionyl chloride;

$$(CH_3)_2N - \overset{H}{\underset{|}{C}} = O + SOCl_2 \longrightarrow \left[(CH_3)_2\overset{+}{N} = \overset{Cl}{\underset{|}{C}} - H \longleftrightarrow \right.$$
(3)

$$\left. (CH_3)_2N - \overset{Cl}{\underset{+}{\underset{|}{C}}} - H \right] Cl^- + SO_2$$

which subsequently reacts with the hydroxyl group of the acid. Even though they[5] could not establish whether the reactive species is (3) or the primary adduct (4), they did prove that when the adduct (4) is heated in vacuo (3) is formed.

$$\left[(CH_3)_2\overset{+}{N} = \overset{OSOCl}{\underset{|}{C}} - H \longleftrightarrow (CH_3)_2N - \overset{OSOCl}{\underset{+}{\underset{|}{C}}} - H \right] Cl^-$$
(4)

The preparation and isolation of a Vilsmeier-Haack type reagent using N,N-dimethyl formamide as amide, was first

accomplished by Arnold[7], through reacting the latter with phosgene, resulting in the formation of (3). Phosgene is the best acid chloride to use for the preparation of (3), because of the ready liberation of carbon dioxide from the analogous adduct (4) formed between dimethyl formamide and phosgene. Compound (3) has found much application in chemistry, and several methods have been used in its preparation.

Studies[4] involving phosphorus oxychloride as acid chloride did not lead to the formation of (3), but rather the reaction stopped with the formation of an adduct (5a), similar to (4).

$$(R^1)_2N - \overset{R}{\overset{|}{C}} = O + PCCl_3 \longrightarrow \left[(R^1)_2N - \overset{O\ PCCl_2}{\overset{|}{C}} - R\right]^+ \quad Cl^-$$

(5a)

However, further studies[8] on the structure of the dimethyl formamide-phosphorus oxychloride adduct, showed that the correct structure is (5b) and not (5a). This was later confirmed by

$$\left[(CH_3)_2N = \overset{Cl}{\overset{|}{C}} - H\right]^+ \quad OPOCl_2^-$$

(5b)

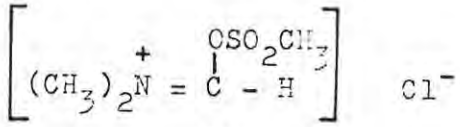
Filleux-Blanchard et al.[9] through n.m.r. studies of some of the Vilsmeier-Haack adducts.

Other methods for the preparation of (3) involved the use of thionyl chloride[4,5,10], phosphorus pentachloride[4]

and oxalyl chloride[4,5]. Morita and co-workers[11] also used phosgene in order to prepare (3), for use as a formylating agent in steroid alcohols.

The bromine analogue of (3) was first prepared by Arnold and Holý[12], by saturating compound (3) with gaseous hydrogen bromide, while Dods and Roth[10] prepared it by reacting thionyl bromide, $SOBr_2$, with N,N-dimethylformamide.

Since the first application of (3), in the chlorination of carbohydrates by Hanessian et al.[13], several similar adducts have been explored. The methanesulphonyl chloride-dimethyl formamide adduct, which has often been prepared in situ, was first used by Evans et al.[14], and is believed to have the structure shown below:-

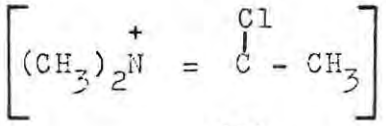


(6)

N,N-dimethyl-α-chlorobenzylidene ammonium chloride(7) had been first prepared and isolated at an earlier stage, as was reported in the review by Eilingsfeld et al.[4]. In later communications, Arnold[15] and Barton et al.[16] independently reported the same method for the preparation of the latter reagent, for synthetic use with carbohydrates[15]. Previously[4], the compound had been assigned the non-polar structure (7a), whereas Barton and co-workers[16] proposed the polar structure (7b). The only

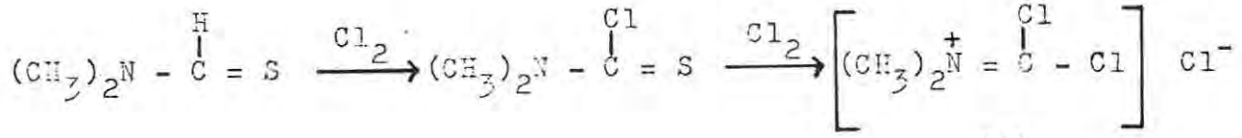
(7a) (7b)

other adduct, amongst those that have found application in carbohydrate chemistry, and which is prepared through the use of phosgene, is N,N-dimethyl-α-chloroethylidene ammonium chloride (8)[4,17], from N,N-dimethyl acetamide.



(8)

The preparation and isolation of N,N-dimethyl dichloromethylene ammonium chloride (9) was reported by Viehe et al.[18]. Various methods were used for its preparation. Of particular interest, is the one that shows the relationship with the Vilsmeier-Haack reagents, that is,

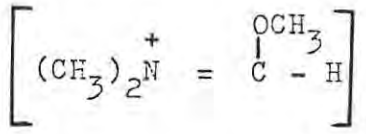


(9)

The bromo analogue was similarly prepared but found to be less reactive. The iodo compound was found to be unstable.

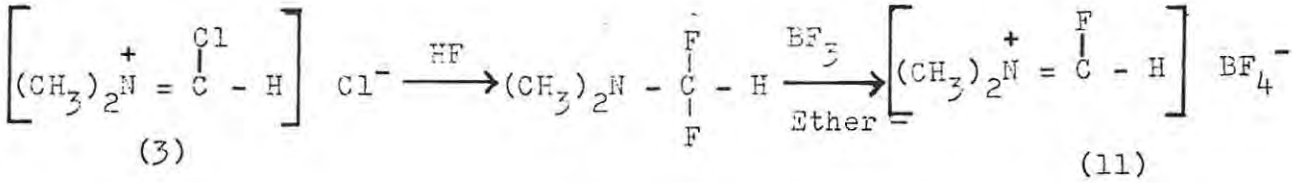
Bredereck et al.[19] were able to prepare N,N-dimethyl methoxymethylene ammonium methylsulphate (10) from dimethyl formamide and dimethyl sulphate. This found application as an acylating agent, rather than as a halogenating one, leading towards the formation of formylated

derivatives.



(10)

Even though N,N-dimethyl fluoromethylene ammonium tetrafluoroborate (11) was prepared by Arnold[15], nothing has been reported concerning its application in carbohydrate chemistry. The preparation involved treating compound (3) with dry gaseous hydrogen fluoride, and subsequent treatment of the product with boron trifluoride etherate. Compound (11) is known to lead to

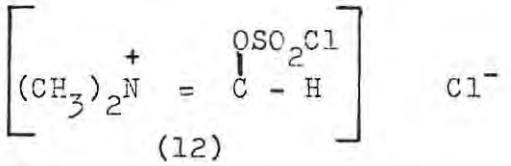


(3) (11)

the formation of acid fluorides[15], when reacted with carboxylic acids.

The preparation of an N,N-dimethyl formamide-arylsulphonyl chloride adduct, structurally related to the Vilsmeier-Haack reagents, was reported by Hall Jr.[20]. Although it has found use both as a formylating and chlorinating agent[21] with some hydroxyl containing compounds, it has not yet been exploited in the carbohydrate field.

In a review[22] on the synthetic uses of dimethyl formamide, Pizey reported the preparation of the dimethyl formamide-sulphuryl chloride adduct, which was assigned the structure (12).



(12)

Other halogenating reagents which reserble Vilsmeier-Haack reagents in the mechanistical aspects of their reactions with carbohydrates, are those involving triphenylphosphine. Various methods are known by which these can be prepared. Amongst these, the one that has found wide application, is where triphenyl phosphine is allowed to react with a carbon tetrahalide, first employed by Lee et al.[23] in the carbohydrate field using the chloride. However, nothing has been reported about the isolation of the resulting compound, probably due to its instability. Alternatively, triphenyl phosphine is reacted with an N-halosuccinimide, where again the isolation of the reagent formed has not been reported. Thus, for these two cases the reagents were prepared in situ. When Hagerlein et al.[24] used molecular halogens, they were able to isolate the triphenylphosphine dihalides, Ph_3PX_2, where X = Cl,Br as stable compounds.

1.2 Reaction of sugars with Vilsmeier-Haack and related reagents.

The selective replacement of hydroxyl groups in carbohydrates by a halogen may be achieved through the use of Vilsmeier-Haack and related reagents. Initially[22], Vilsmeier-Haack reagents were used for the preparation of

aldehydes and formate esters, where the reagent was found to react readily with an organic compound containing easily replaceable hydrogen atoms. However, the whole range of the reagents under discussion has found much application in the chemistry of polyols, towards the preparation of halogeno-deoxy derivatives. Generally, the reaction proceeds via the formation of an intermediate ester-like, salt-like, ionic species, where the polyol becomes the positive ion (see later), and the anion is the halide ion, which subsequently substitutes well placed ester-like groupings, referred to above. The electrophilic character of these reagents is the main determining factor in the formation of such intermediates, with the hydroxyl group acting as a nucleophile.

An earlier review on deoxyhalogeno sugars by Szarek[2] considered the direct replacement of hydroxyl groups through the reaction of these reagents with carbohydrate derivatives. These reactions are now reviewed under the following categories:

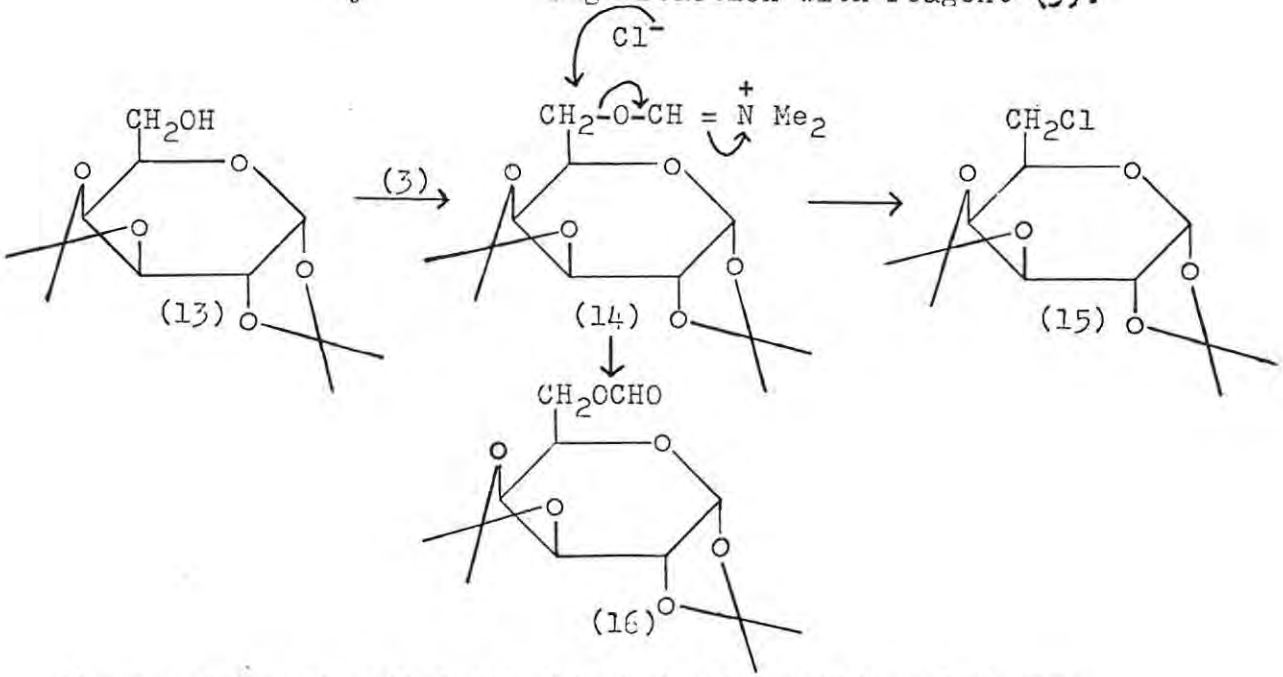
1.2.1 Monosaccharides

1.2.1.1. Glycosides

1.2.1.1.1. Pyranosides and other pyranoid sugars

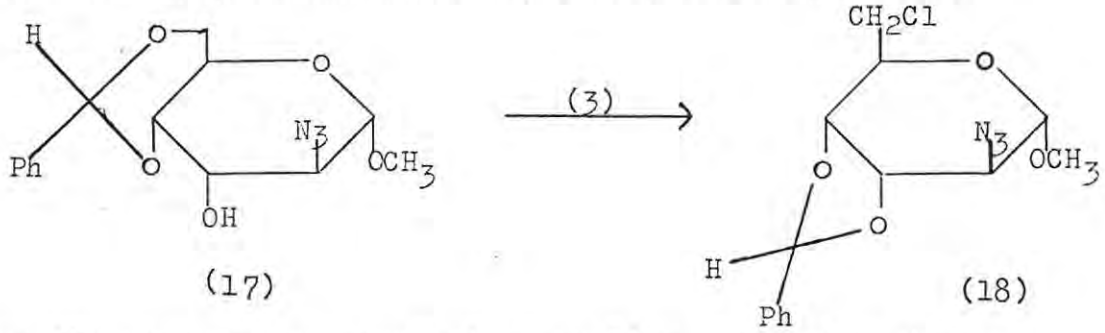
The reaction of a Vilsmeier-type reagent with pyranoid sugars, leading to the formation of products in which some hydroxyl groups were replaced by a halogen atom was first reported by Hanessian et al.[13]. Their investigation was

mainly on the use of N,N-dimethyl (chloromethylene) ammonium chloride (3), in the chlorination of sugars. Thus, treatment of 1,2:3,4-di-O-isopropylidene- α-D-galactopyranose (13) with (3) in a chlorinated solvent, like tetrachloroethane, at room temperature afforded the iminoester intermediate (14), which, upon heating under reflux, converted to 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene- α-D-galactopyranose (15). However, when (14) was treated with aqueous sodium hydrogen carbonate; the product was found to be the 6-O-formate ester (16). In fact, Arnold[25] had previously reported the synthesis of formate esters of carbohydrates through reaction with reagent (3).



The reaction of methyl 2-azido-4,6-O-benzylidene-2-deoxy- α-D-altropyranoside (17) with (3) in refluxing 1,1,2,2-tetrachloroethane afforded a product, which was formulated[13b] as methyl-2-azido-3,4-O-benzylidene-6-chloro-2,6-dideoxy- α-D-altropyranoside (18). Initially[13a], the product was thought to be methyl 2-azido-4,6-O-benzylidene-3-chloro-

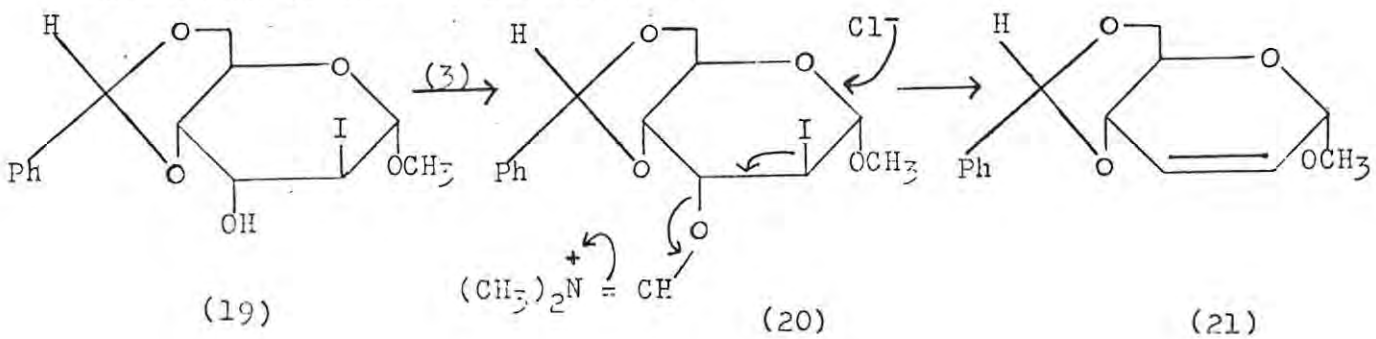
2,3-dideoxy-α-D-altropyranoside, based on the assumption that compound (17) had undergone a simple substitution at C-3. However, n.m.r. studies and transformations carried out[13b] on the product were in agreement with (18), rather



(17) (18)

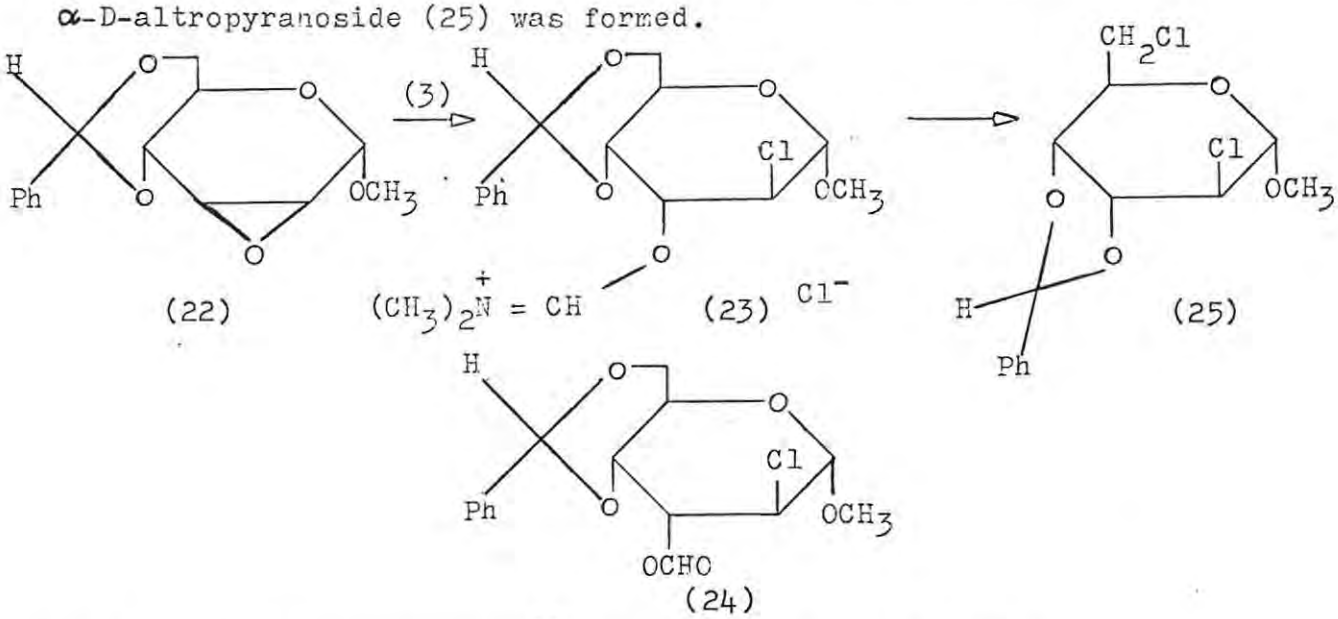
than the compound proposed at an earlier stage. Thus here, it is to be noted that acetal or even ketal migration may be a complicating factor, during the reaction of compounds such as (17) with (3). In fact, more such cases have been reported (see later).

Whereas the chlorination of (17) (via the intermediate 3-iminoester) proceeded with rearrangement, but with no accompanying side reactions, the reaction of (3) with methyl 4,6-O-benzylidene-2-deoxy-2-iodo-α-D-altropyranoside (19) gave rise to a complex mixture of compounds, amongst which one was identified as methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (21). The formation of (21) could be explained by attack of chloride ion on the iodine atom as in intermediate (20), with simultaneous elimination of the C-3 substituent.



(19) (20) (21)

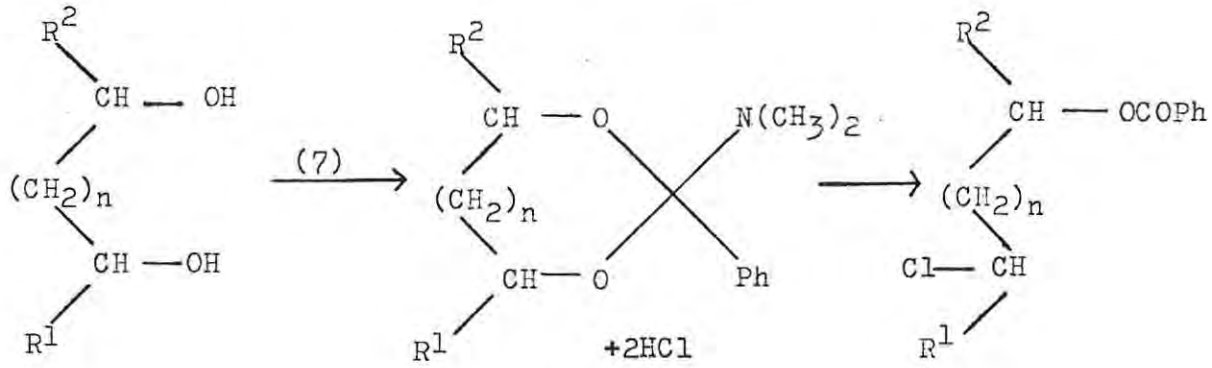
The reagent (3) reacts[13b] with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (22) to give monochlorodeoxy or dichlorodeoxy derivatives, depending upon the reaction conditions. At room temperature, the major product of the reaction is methyl 4,6-O-benzylidene-2-chloro-2-deoxy-3-O-formyl-α-D-altropyranoside (24). The conversion of the epoxide function in (22) into a vicinal trans-chloro formate system such as (24) under very mild conditions, demonstrates a further utility of halomethyleneiminium halide reagents in carbohydrate chemistry. When a solution of (22) and (3) was heated under reflux in 1,1,2,2-tetrachloroethane, methyl 3,4-O-benzylidene-2,6-dichloro-dideoxy-α-D-altropyranoside (25) was formed.



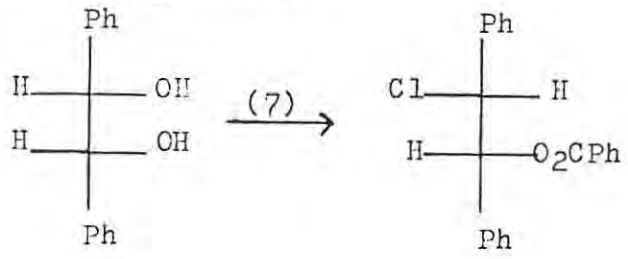
In a previous communication[13a], the product for the latter reaction was reported as being a methyl 2,3-dichloro-2,3-dideoxy-α-D-hexopyranoside, as would be expected if the reaction proceeded by a simple substitution at C-3 of the intermediate (23). However, it was established[13b], that in fact the reaction is accompanied by rearrangement of the

benzylidene acetal group to give (25). The structure of (25) was convincingly proved by Hanessian et al.[13b]

Back et al.[26] successfully applied N,N-dimethyl-α-chloro-benzylidene ammonium chloride (7) towards the preparation of chlorohydrin benzoates from 1,2- and 1,3-glycols. Thus, when 1,2-diphenyl ethane-1,2-diol(26) was treated with (7), 2-chloro-1,2-diphenylethyl benzoate (27) was formed. A mechanism for this kind of reaction was proposed, and it was suggested that the reaction proceeds via the formation of a cyclic intermediate as shown in the scheme:-



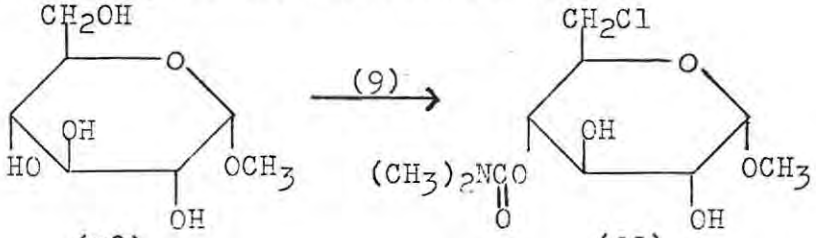
However, treatment of methyl 4,6-O-benzylidene-α-D-gluco-pyranoside with (7) afforded the 3-benzoate as the preponderant product. In order to explain why no chlorine was incorporated, they suggested that a cyclic intermediate of the type shown above would not be favoured, since it would be trans-fused.



Plus isomer and corresponding enantiomers

(26) (27)

The reaction of N,N-dimethyl N-dichloromethylene ammonium chloride (9) with the methyl pyranosides of D-glucose (28), D-mannose and D-galactose was investigated by Klemmer et al.[27]. Their findings showed that the reaction led towards the formation of the corresponding 4-carbamoyl-6-chloro-6-deoxy glycosides, designated (29) for the glucoside. Thus, the initial step in the reaction results



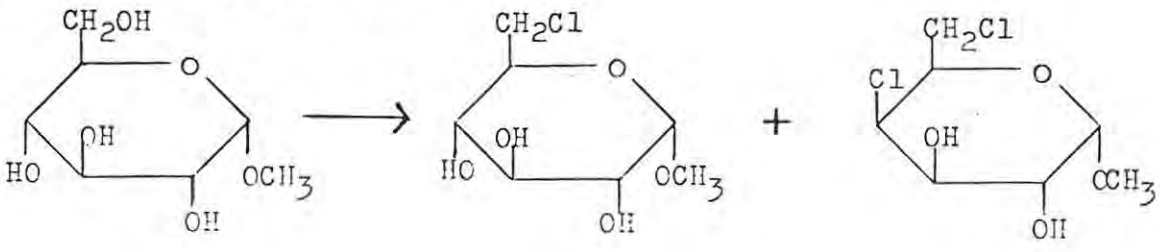
(28) (29)

in the formation of an imino-ester intermediate like (14) above, which upon decomposition gives rise to a still reactive carbamoyl chloride, and this subsequently reacts with the hydroxyl group at the 4- position.

Hanessian et al.[13b] had investigated the reaction of (13) above with N,N-dimethyl-α-chloroethylidene ammonium chloride (8) and N,N-dimethyl methoxymethylene ammonium chloride (10) respectively. With (8), the 6-O-formate ester (16) was formed predominantly, together with traces of (13) and the 6-chloro derivative (15). The low yield of (15) was attributed to steric hindrance, brought about by the presence of the methyl group, thus hindering approach by the incoming chlorine ion. However, the electronic effect due to the electron-donating ability of the methyl group, which tends to stabilize an intermediate like (14), could not be excluded. In the reaction with (10), t.l.c. analysis showed the presence of (16) and unchanged (13).

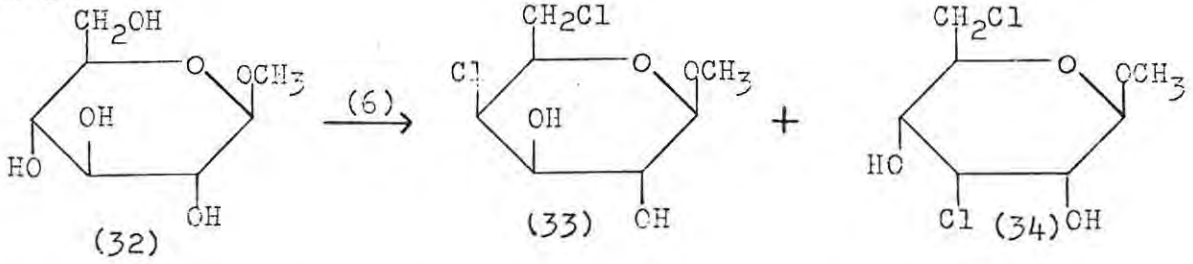
Furthermore, it was found that the latter reaction proceeded slower compared to the one involving reagent (3).

The reaction of the N,N-dimethyl formamide-methyl sulphonyl chloride reagent (6) with methyl α- and β-D-glucopyranoside was first investigated by Evans and co-workers[14]. Their findings showed that (6) always led to selective replacement of the primary hydroxyl group, with only trace amounts of compounds in which secondary hydroxyl groups had been substituted. Thus, they further claim that treatment of methyl α-D-xylopyranoside with (6) resulted in a 99% recovery of starting material. However, Edwards et al.[28] showed that, by increasing the amount of methyl sulphonyl chloride, the reaction time and temperature, substitution at secondary positions can be achieved. Such substitution was also found to proceed in a selective manner, and with inversion of configuration. Thus, treatment of methyl α-D-glucopyranoside (28) with 30 molar equivalents of mesyl chloride in N,N-dimethyl formamide at 70°C for 10 days[28], afforded methyl-6-chloro-6-deoxy-α-D-glucopyranoside (30) plus methyl 4,6-dichloro-4,6-dideoxy-α-D-galacto-pyranoside (31) in appreciable yields. Evans et al.[14] performed the reaction with 2 molar equivalents of mesyl chloride at 65°C for 16 hours, to afford (30) in almost quantitative yield. Reaction of

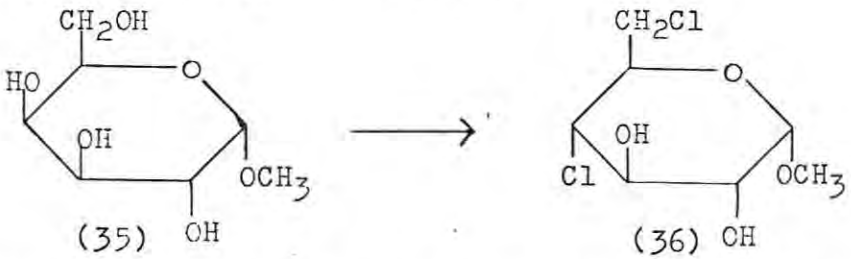


(28) (30) (31)

methyl β-D-glucopyranoside (32) and methyl α-D-manno-pyranoside with mesyl chloride via the latter method, gave the 6-chloro derivatives in good yields. Whereas methyl β-D-glucopyranoside (32) was reported[29] to give only methyl 4,6-dichloro-4,6-dideoxy- β-D-galacto-pyranoside (33) on reaction with sulphuryl chloride in pyridine/chloroform, Edwards et al.[28] found that on treating (32) with the mesyl chloride-N,N-dimethyl-formamide reagent (6), methyl 3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (34) was formed in addition to (33). These



authors[28] further showed that, the reaction carried out by Jennings et al.[29] with sulphuryl chloride and pyridine also produced both (33) and (34), but that the two isomers are difficult to separate. Reaction of methyl-α-D-galacto-pyranoside (35) with (6)[28] gave methyl 4,6-dichloro-4,6-dideoxy- α-D-glucopyranoside (36).



As have been stated above, reagents involving triphenyl-phosphine have found much application in carbohydrate

chemistry. Amongst these, the following are of interest;

(37) : Ph_3P/CX_4 ⎫ where (a) X = Cl; (b) X = Br and (c) X = I,

(38) : Ph_3P/NXS ⎭ NXS stands for N-halosuccinimide.

(39) : Ph_3P/X_2; (a) X = Cl, (b) X = Br

(40) : $Ph_3P/CHBr_3$

Lee et al.[23] were able to prepare 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (15) from (13) by refluxing a solution of the latter with triphenyl phosphine in carbon tetrachloride, thus using reagent (37a). That the reaction proceeds rapidly at reflux temperature, was noted in a preliminary investigation with primary and secondary alcohols, where chlorinated products were reportedly produced in good yields. Although still subject to verification, it is believed that halogenation with this type of reagent proceeds via the mechanism shown:[30]

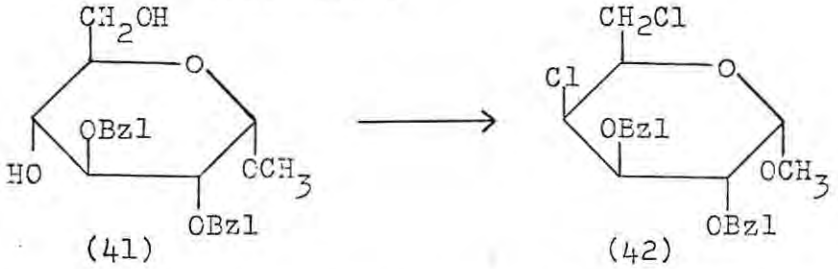
$$Ph_3P : XCX_3 \longrightarrow \left[Ph_3P^+ - CX_3X^-\right]$$

$$\xrightarrow{ROH} CHX_3 + Ph_3P^+ - OR\ X^- \longrightarrow Ph_3PO + RX$$

Assuming this mechanism to be true, then the relationship with Vilsmeier-Haack type reagents is self-evident, where triphenyl phosphine takes the place of N,N-dimethyl formamide and the tetrahalide replaces the inorganic acid halide.

The synthesis of 4,6-dideoxy-D-xylo-hexose has been of some interest, because of its occurrence as the 3-methyl ether in

certain antibiotics. Various methods have been used towards achieving its synthesis. Of interest is the one investigated by Lawton et al.[31] Thus treatment of methyl 2,3-di-O-benzyl-α-D-glucopyranoside (41) with triphenyl phosphine in carbon tetrachloride at reflux temperature, afforded methyl 2,3-di-O-benzyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (42), which served as a good intermediate for the preparation of 4,6-dideoxy-D-xylo-hexose.



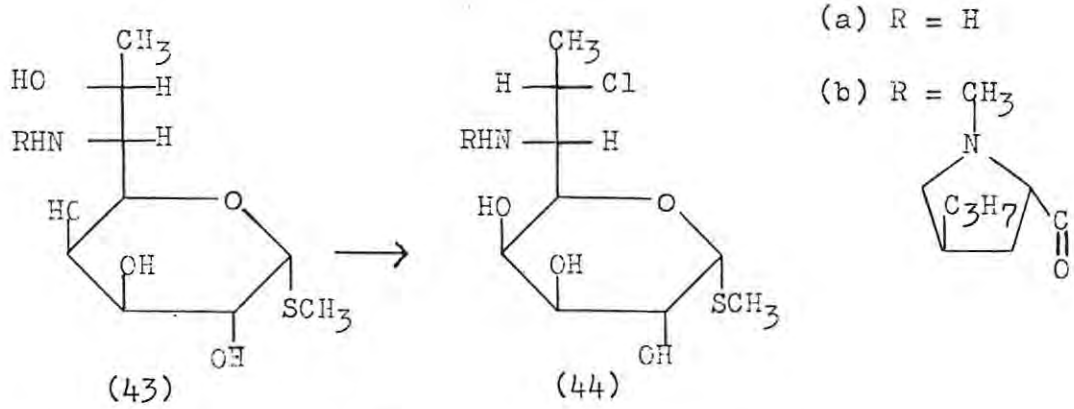
(41) (42)

This is but one of a few cases reported, where this reagent has effected substitution at a secondary position in pyranosides. The reaction of methyl α-D-glucopyranoside (28) with all three tetrahalides in reagents (37) was reported by Anisuzzaman and Whistler[32]. This resulted in the formation of methyl 6-chloro-6-deoxy-α-D-glucopyranoside (30), the bromo, and the iodo analogues respectively. Having conducted the reactions in pyridine as solvent, these authors proposed a different mechanism of halogenation to that suggested by Lee et al.[30]. Since two molar equivalents of triphenyl phosphine gave about twice the yield of product obtained with one molar equivalent, the following mechanism was proposed:-

$$2Ph_3P + CX_4 \longrightarrow Ph_3PC{=}X_2 + Ph_3X_2 \xrightarrow{\text{pyridine}} \text{Halogenating complex}$$

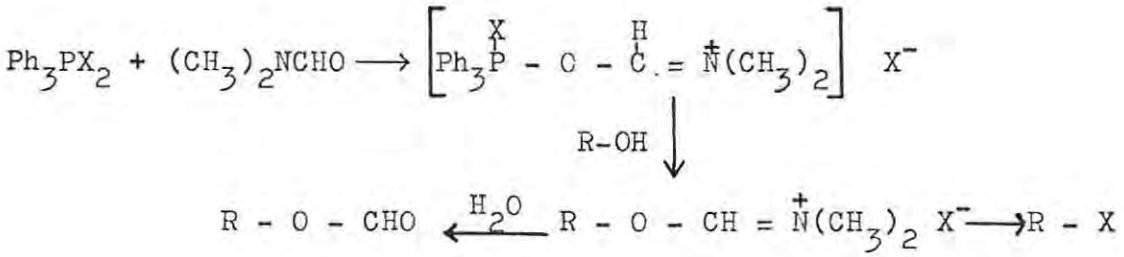
$$\xrightarrow{R\cdot CH_2\cdot OH} R\cdot CH_2\cdot X$$

Birkenmeyer et al.[33] reported the use of triphenyl phosphine in carbon tetrachloride in the chlorination of the carbohydrate moiety of the antibiotic lincomycin. HCl. Thus the reaction was found to lead to chlorination at C-7 of the sugar. Prior to this investigation, Magerlein et al.[24] had employed triphenyl phosphine dichloride (39a) to chlorinate methyl thiolincosaminide (43a) (carbohydrate moiety of lincomycin) at C-7, resulting in the formation of the chloro sugar (44a).



Whilst Magerlein et al.[24] performed the reaction on the independent sugar, Birkenmeyer and co-workers[33] performed it with lincomycin. HCl. 43(b). Compound (44b) and its bromo analogue could also be prepared using reagent (39). Furthermore, it was established[33] that each of the three halogens Cl, Br and I could be introduced at C-7 with the use of reagent (37).

It appears that the mechanism followed by the reaction of alcohols and triphenyl phosphine dihalides, depends on the kind of solvent in which the reaction is conducted. A mechanism was proposed by Boekman Jr. et al.[34] for the reaction in N,N-dimethyl formamide:-

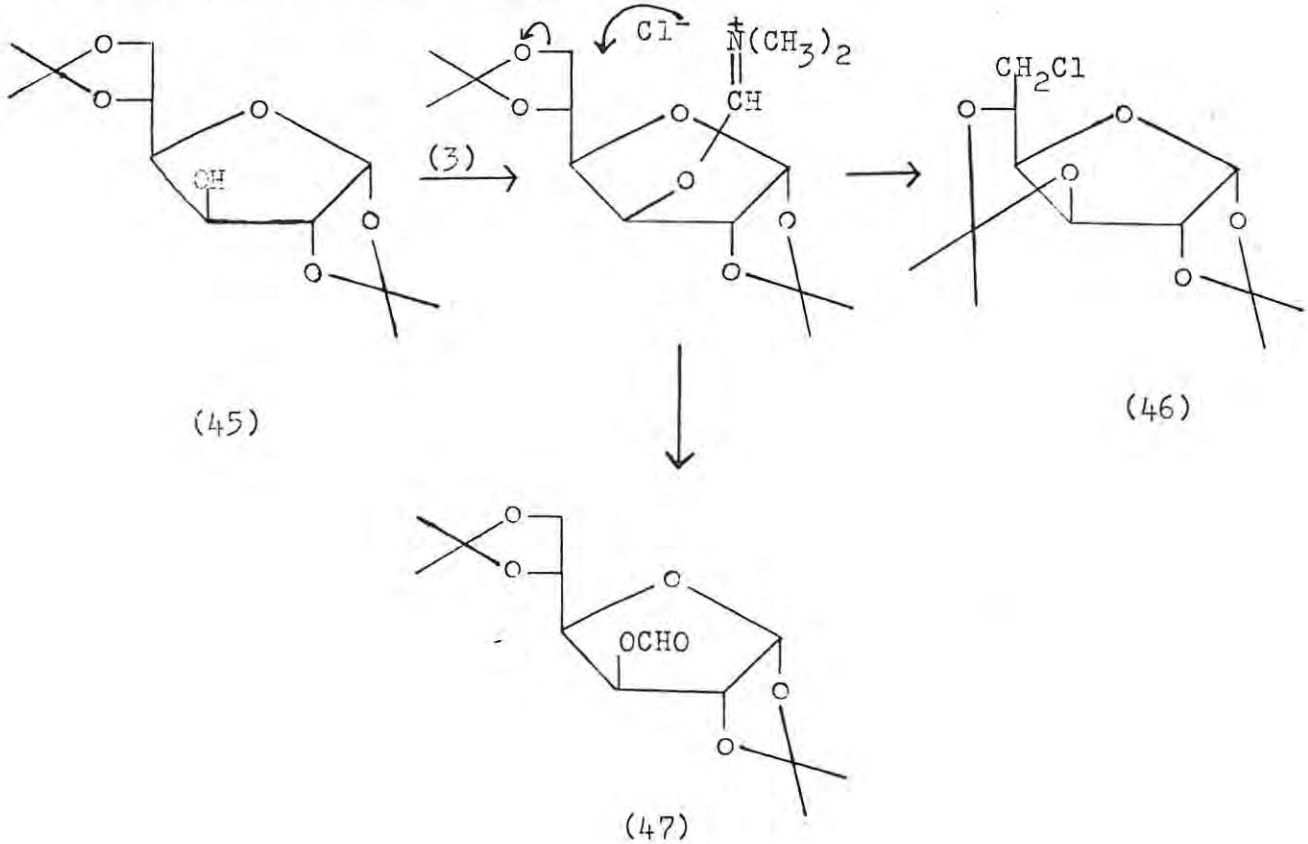


These authors used the reaction in order to differentiate between primary and secondary hydroxyl groups. Thus the former were found to be readily substituted by halide, whereas the latter were often converted into the formate esters. It is noteworthy that in lincomycin. HCl. and thiolincosaminide, substitution at a secondary position could be achieved. However, in the latter instances the halogen is chlorine, whereas in the former, it is bromine, which may imply that steric factors could play an important role.

The reaction of an N-halosuccinimide-triphenyl phosphine reagent (38) with a sugar in N,N-dimethyl formamide was investigated by Ponpipom et al.[3, 35, 36]. Analogously with the other reagents involving triphenyl phosphine, this reagent led to the selective substitution of primary hydroxyl groups. Thus 6-chloro-6-deoxy-1,2:3,4-di-O-isopropylidene α-D-galactopyranose (15) was easily prepared from the hydroxy compound (13) by this method in good yield. The bromo analogue of (15) was similarly prepared. Reaction of methyl α-D-glucopyranoside with (38b) led to selective bromination at C-6.

1.2.1.1.2 Furanosides and other furanoid sugars

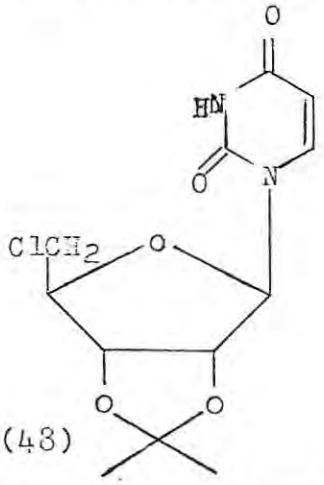
In the first investigation[13] of the reaction of Vilsmeier-Haack reagents with carbohydrates, 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (45) was selected as a model sugar derivative containing an isolated secondary hydroxyl group. When (45) was treated with reagent (3) in 1,1,2,2-tetrachloroethane at room temperature, it was converted to the 3-O-formate ester (47). However, heating a solution containing (45) and (3) under reflux afforded 6-chloro-6-deoxy-1,2:3,5-di-O-isopropylidene-α-D-glucofuranose (46). Compound (46) was produced through ketal migration as is indicated in the proposed mechanism. This was not unexpected, since reaction of (45) with phosphorus pentachloride had previously been shown to afford (46).



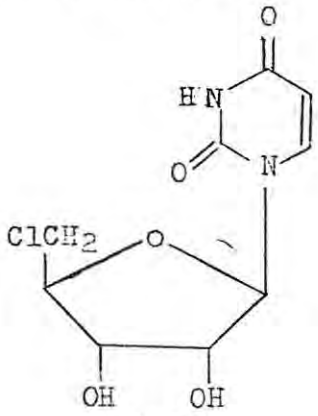
(45) (46)

(47)

Dods and oth[37] reported the synthesis of 5'-chloro-5'-deoxy-2',3'-O-isopropylidene uridine (48) and 5'-chloro-5'-deoxy uridine (49) and their bromo analogues from the corresponding hydroxy compounds, by reacting the latter with arsenic trichloride and arsenic tribromide respectively, in N,N-dimethyl formamide. Since many acid halides have been found [4,5] to react with N,N-dimethyl formamide leading to the formation of N,N-dimethyl (chloromethylene) ammonium chloride (3), it was proposed[37] that the arsenic halides could also lead to the formation of (3), and thus result in the halogenation of alcohols.



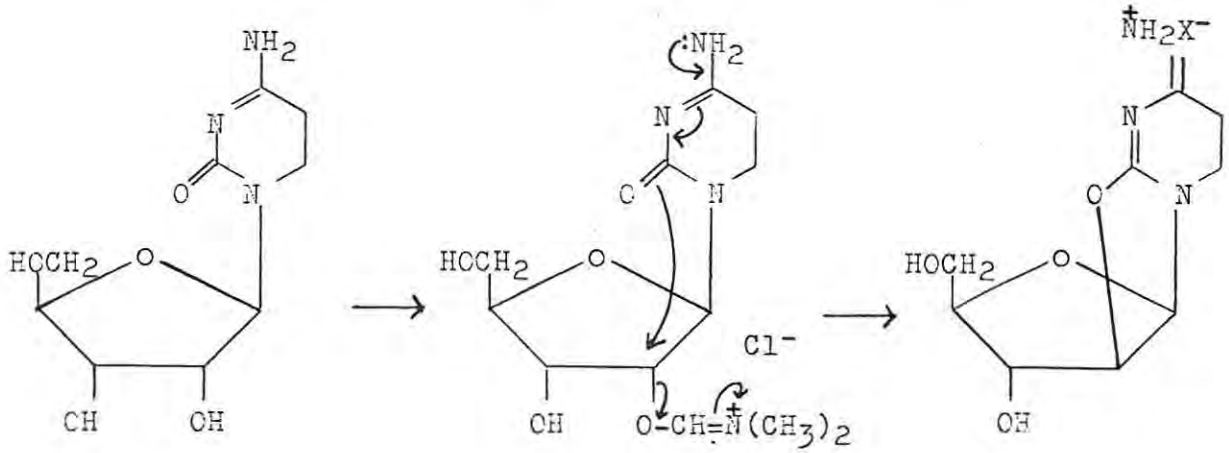
(48)



(49)

Arsenic triiodide was found to give poor yields of halogenated compounds. A report by these authors[37], that use of arsenic trichloride and N,N-dimethyl acetamide with uridine led to an additional product, which they assigned the 3-chloro-3-deoxy derivative structure, was proved incorrect by Verheyden et al.[38] (see later). However, the same authors[10] successfully employed thionyl chloride and thionyl bromide in the synthesis of (48) and (49) and their bromo analogues respectively, where the reactive intermediate is known to be (3) or its bromo analogue.

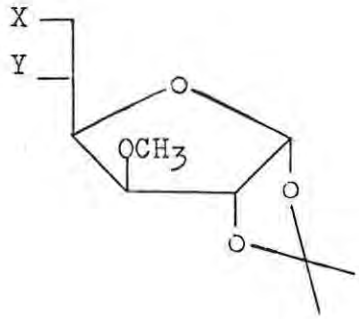
When cytidine (50) was treated[39] with thionyl chloride in N,N-dimethyl formamide, 2,2-cyclocytidine (52) was formed, and no chlorinated product was reported. The formation of (52) instead of a chlorinated product can be explained by assuming that in intermediate (51), before a chlorine ion can attack, the oxygen from the pyrimidine ring attacks to release a molecule of N,N-dimethyl formamide as shown below:



(50) (51) (52) X = Cl, HCOO

No reasons have been put forward as to why no chlorine substitution occurs at the primary hydroxyl group. Nevertheless (52) is known to be a novel intermediate in the chemical modification of the ribose or cytosine moiety of cytidine.

Reaction[26] of 1,2-O-isopropylidene-3-O-methyl-α-D-gluco-furanose (53a) with reagent (3) afforded the diformate derivative (53b), whereas when (53a) was treated with N,N-dimethyl-α-chlorobenzylidene ammonium chloride (7), the product was found to be the 6-chloro-6-deoxy-5-O-benzoate (53c).



(53)

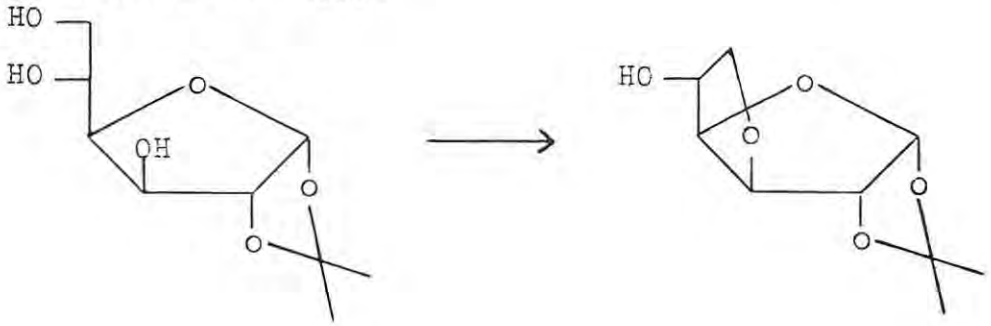
(a) X = Y = OH

(b) X = Y = OCHO

(c) X = Cl; Y = $PhCO_2$

(d) X = Cl; Y = $(CH_3)_2NCO_2$

The mechanism by which (53c) is formed has been explained above. Klemer and co-workers[27] reported the reaction of 1,2-O-isopropylidene-3-O-methyl- α-D-glucofuranose (53a) with N,N-dimethyl N-dichloromethylene ammonium chloride (9) resulting in the formation of the 5-carbamoyl-6-chloro-6-deoxy derivative (53d). Treatment of 1,2-O-isopropylidene-α-D-glucofuranose (54) with (9) afforded only the 3,6-anhydro derivative (55).

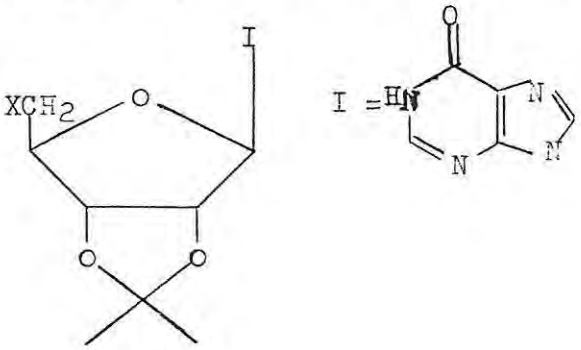


(54) (55)

Thus it is to be noted that in the latter reaction, chlorination at C-6 was followed by nucleophilic substitution of the chlorine by the hydroxyl group at C-3. Alternatively, (55) could have been formed via the intermediate imino ester, before incorporation of chlorine.

Haga et al.[40] reported the use of triphenyl phosphine and

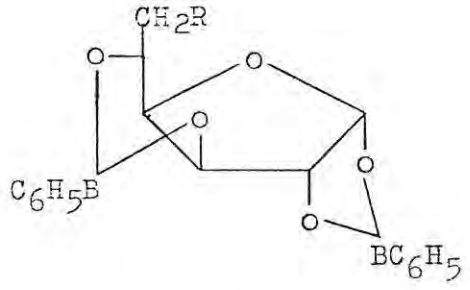
carbon tetrachloride in the chlorination of 2,3'-O-isopropylidene-inosine (56a) to give 5'-chloro-5'-deoxy-2',3'-O-isopropylidene (56b) in quantitative yield. The bromo (56c) and the iodo (56d) analogues were similarly prepared, using triphenyl phosphine with bromine, cyanogen bromide and iodine in triethyl phosphate as solvent. When 5'-O-acetyl inosine was treated with the same reagent, only the 3'-chloro-3-deoxy derivative could be isolated. The lack of substitution at C-2 was attributed to steric hindrance caused by the presence of the purine base.



(a) X = OH
(b) X = Cl
(c) X = Br
(d) X = I

(56)

Korgel et al.[41] treated the 1,2:3,5-diphenyl borate of α-D-glucofuranose (57a) with triphenyl phosphine in carbon tetrachloride to afford the chlorinated derivative (57b). Subsequent treatment of (57b) with propane-1,3-diol gave 6-chloro-6-deoxy-α-D-glucopyranose. It was also found that

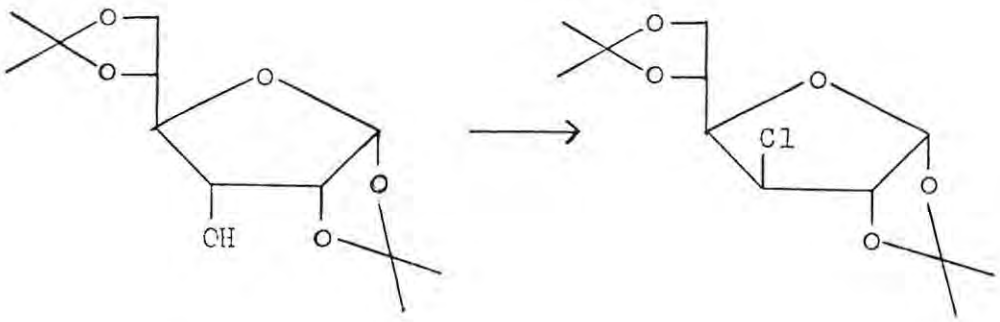


(a) R = OH
(b) R = Cl
(c) R = Br

(57)

treatment of (57c) with triphenyl phosphine in bromoform led to the formation of (57c), which could be similarly converted to 6-bromo-6-deoxy-D-glucose.

An investigation of the reaction of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (45), was undertaken by Haylock and co-workers[42]. They found that when, (45) was treated withtriphenyl phosphine in carbon tetrachloride, it led to chlorination at C-6, accompanied by rearrangement of the ketal group as had been reported before[13], resulting in the formation of (46). However, reaction of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (58), with the same reagent proceeded without rearrangement, but with effective substitution of the 3-hydroxyl group, affording the 3-chloro-3-deoxy-gluco derivative (59). Similarly, treatment[42, 43] of 1,2:5,6-di-O-isopropylidene-β-D-talofuranose afforded the 3-chloro-3-deoxy-ido derivative.

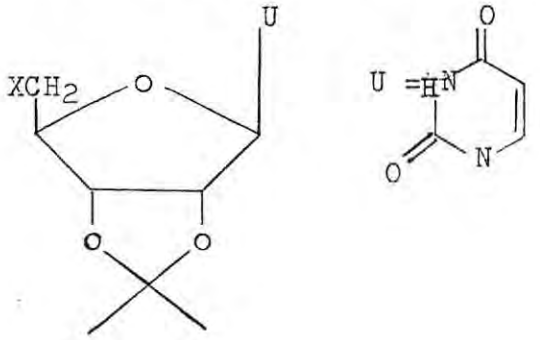


(58) (59)

The difference in the reactivity of the 3-hydroxyl group, comparing the latter two sugars and the former, was attributed to the difference in stereochemical relationship of the 3-hydroxyl group to the 1,2-O-isopropylidene group. Thus, in (45) the hydroxyl group is exo, and therefore approach by

an incoming nucleophile, would be sterically hindered by the 1,2-O-isopropylidene group. When the hydroxyl group is endo, as in (58), no such steric hindrance is possible, and substitution occurred readily. Furthermore, that chlorine had been incorporated at C-3 in the reaction of 1,2:5,6-di-O-isopropylidene-β-D-talofuranose, was unequivocally established by Einstein et al.[43], through crystallographic studies of the chlorinated compound.

Verheyden et al.[38] investigated the reactions of the reagents in (37), that is, Ph_3P/CX_4, with nucleosides. One of their objectives was to compare the relative efficiencies of the different tetrahalides. Thus, treatment of 2',3'-O-isopropylidene uridine (60a) under essentially the same conditions with reagents (37), a, b and c respectively in dimethyl formamide, afforded the 5'-halo nucleosides in varying yields, that of the chloro being the highest, while the iodo was the lowest. Reasons for the differences are presented[38].



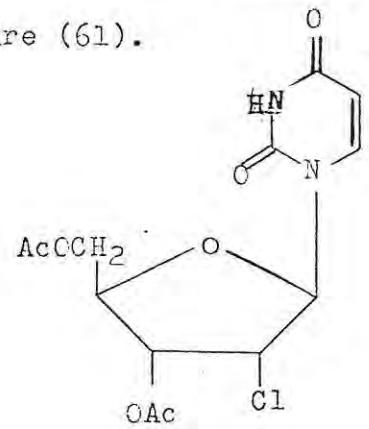
(a) X = OH
(b) X = Cl
(c) X = Br
(d) X = I

(60)

Prior to this publication, it had been claimed[40], that the reaction of (56a) to give (56b) did not proceed in dimethyl

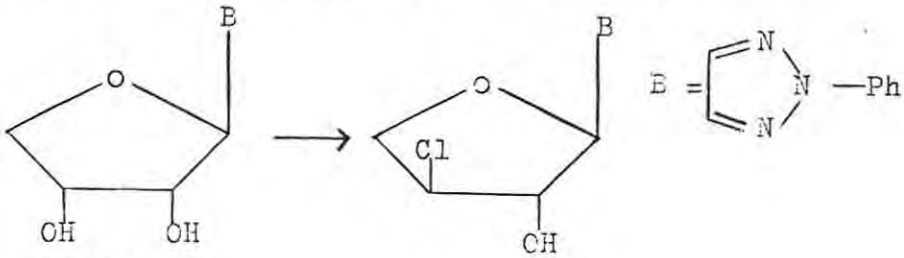
formamide. These authors[38] proved the claim to be incorrect, when they performed the reaction in almost a quantitative manner. Even though halogenation at secondary positions using these reagents is known to proceed with inversion of configuration, products in which retention had occurred were isolated, particularly in the case of uridine and thymidine and their derivatives. This was explained as being due to participation by the proximal oxygen atom in the pyrimidine base. Here again, the yields of such products were determined by the type of tetrahalide employed, and the kind of influence exerted by the latter has been extensively discussed[38].

In a previous communication by Dods and Roth[37], it had been reported that, reaction of uridine with arsenic trichloride in dimethyl acetamide gave, unexpectedly, a 3'-chloro compound, as an additional product to the expected 5'-chloro derivative. A careful reinvestigation[38] of the reaction was conducted, as motivated by an interest in the unusual role played by dimethyl acetamide. Thus, a close examination of the data obtained for the product, and some important experimental observations, were shown to be in disagreement with the proposed structure. Based on that, the compound was assigned structure (61).



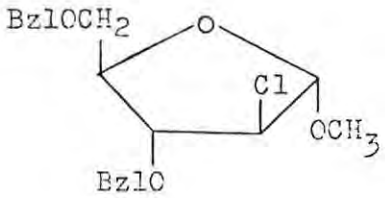
(61)

Nouaille and co-workers[44] investigated the chemical modification of derivatives of glycosides containing phenyl triazole. Amongst the series of reactions reported, is shown how the Ph_3P/CCl_4 reagent was employed in chlorination of 1-(2'-phenyl-1',2',3'-triazol-4-yl)-β-D-erythrofuranose (62), to afford the product (63) in the -α-L-threo configuration.



(62) (63)

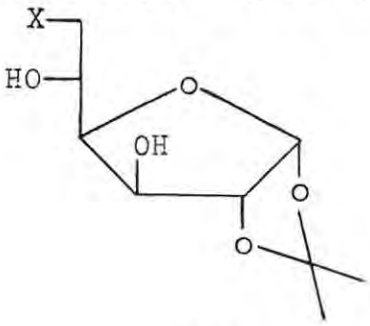
In another investigation involving drug synthesis, Ritzmann et al.[45] were able to prepare the important intermediate, methyl 3,5-di-O-benzyl-2-chloro-2-deoxy-α-D-arabinofuranoside (64) from methyl 3,5-di-O-benzyl-D-ribofuranoside, by using carbon tetrachloride and triphenyl phosphine in acetonitrile.



(64)

In an extension of their studies on the selective replacement of primary hydroxyl groups, Anisuzzaman and Whistler[32] reported the conversion of 1,2-O-isopropylidene-α-D-glucofuranose (54) into (65), through the use of reagents (37) a and b, in pyridine. Compound (65a) was subsequently

converted to the free sugar by treating with acid.

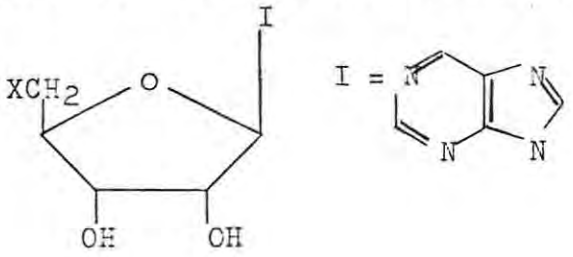


(a) X = Cl

(b) X = Br

(65)

The same authors successfully prepared 5'-chloro-5'-deoxy-2,3-O-isopropylidene inosine (56b) through acetalation of 5'-chloro-5'-deoxy inosine (66b), where the latter had been prepared from (66a) by reaction with (37a). Treatment of uridine with (37a) also afforded the



(a) X = OH

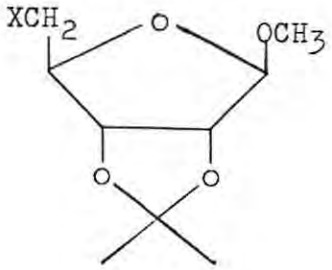
(b) X = Cl

(66)

5'-chloro derivative, as has been reported[37, 38] before by other authors using different methods described above.

The triphenyl phosphine-N-halosuccinimide reagent (38) has also found some application[35, 36] with furanoid sugars with good results. Thus, treatment of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (67a) with reagents (38) a, b and c respectively, afforded the halogenated derivatives (67) b, c and d in good yields. Other compounds similarly prepared through this method include 6-chloro-6-deoxy-1,2:3,5-di-O-isopropylidene-α-D-glucofuranose (46) and its bromo

analogue,



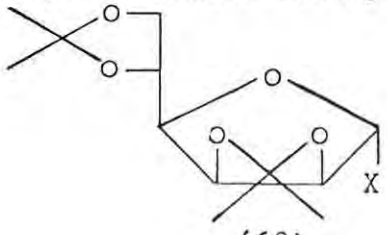
(a) X = OH
(b) X = Cl
(c) X = Br
(d) X = I

(67)

the 5'-halo-5'-deoxy derivatives of 2,3-O-isopropylidene uridine, and the 5'-bromo-5'-deoxy derivatives of inosine, 2',3'-O-benzylidene uridine and 2,3-di-O-acetyl-1-hypoxanthin-1-yl-β-D-ribofuranoside.

1.2.1.2 Free Sugars

The reaction of free sugars with reagents of the Vilsmeier type mentioned thus far, leads to halogenation at the C-1 position. Apparently, these reagents have not found much application with this class of substrate, since, as we shall see below, only reagents (37a) and (38b) have been used with free sugars. In order to prepare a good intermediate for the synthesis of a nucleoside containing mannofuranose, Lee and Nolan[46] treated 2,3:5,6-di-O-isopropylidene-α-D-mannose (68a) with triphenyl phosphine in carbon tetrachloride, to afford 2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl chloride (68b). The bromo analogue (68c) was

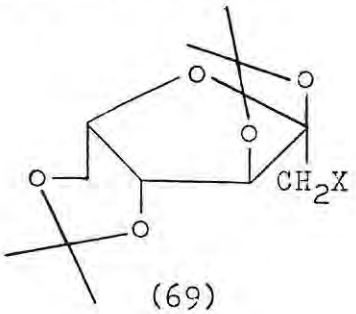


(a) X = OH
(b) X = Cl
(c) X = Br

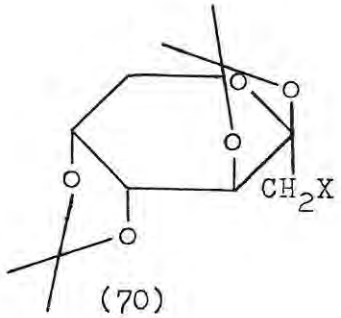
(68)

prepared by Hanessian and co-workers[35, 36], using triphenyl phosphine and N-bromosuccinimide in dimethyl formamide.

Treatment[42] of 2,3:4,6-di-O-isopropylidene-L-sorbofuranose (69a) with triphenyl phosphine in refluxing carbon tetrachloride afforded the 1-chloro-1-deoxy derivative (69b) as a crystalline compound. Similar treatment of 2,3:4,5-di-O-isopropylidene-D-fructose (70a) gave the chlorinated compound (70b) as a thick syrup.



(69)



(70)

(a) X = OH

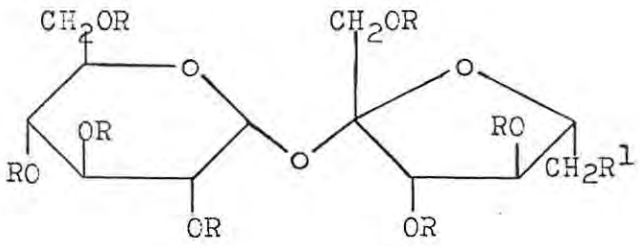
(b) X = Cl

It is noteworthy that in all the above reactions, the hydroxyl groups substituted are isolated.

1.2.2 Disaccharides

Amongst the early investigations, carried out for the reaction of disaccharides with Vilsmeier type reagents, is the one which was conducted by Ballard and co-workers[47]. While investigating the reaction of sucrose (71a) with sulphuryl chloride in pyridine-chloroform, they found as one of the products 6'-chloro-6'-deoxy sucrose (71b) characterized as its hepta-acetate (71c). The structure of (71c) was confirmed

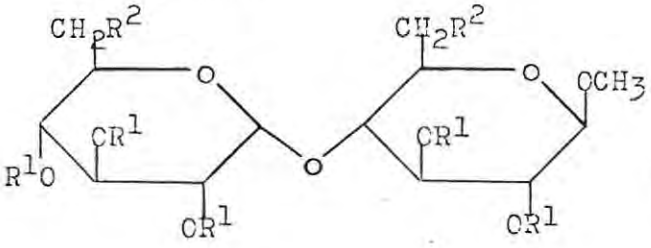
by its independent synthesis from 1',2,3,3',4,4',6-hepta-O-acetyl sucrose (71d) through reaction with the Vilsmeier type reagent, methane sulphonyl chloride-N,N-dimethyl formamide reagent (6) to afford (71c).



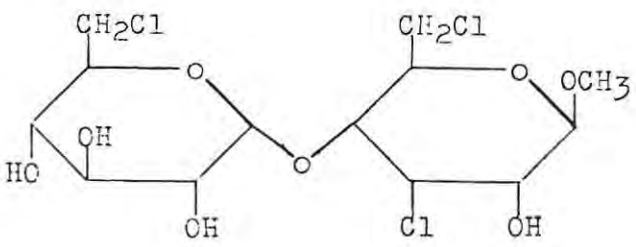
(a) R = H, R^1 = OH
(b) R = H, R^1 = Cl
(c) R = Ac, R^1 = Cl
(d) R = Ac, R^1 = H

(71)

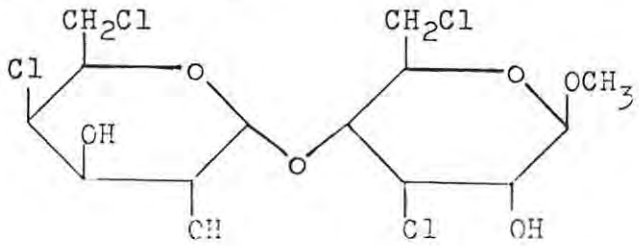
As it has been noted above, that the reaction of (6) with monosaccharides can effect substitution at secondary positions, (reported by Edwards et al.[28]) these same authors had initially found this to be true with disaccharides. However, in the latter case it often led to the production of more than one compound. Thus, reaction with methyl β-maltoside (72a) gave initially the 6,6'-dichloro derivative (72b), which



(72) (a) R^1 = H, R^2 = CH
(b) R^1 = H, R^2 = Cl



(73)



then, fairly rapidly converted to the 3,6,6'-trichloro derivative (73). Further reaction, rather at a slower rate, gave the 3,4',6,6'-tetrachloro derivative (74). The proportions in which the products appeared depended upon the reaction conditions. Mild conditions were found to be in favour of (72b), whereas more drastic conditions increased the amount of (74), even though not to an appreciable extent. Treatment of benzyl β-cellobioside with (6) afforded an even more complex mixture, from which the 6,6'-di-,3',6,6'-tri-,3,6,6'-tri-,4',6,6'-tri-,3,3',6,6'-tetra- and 3,4',6,6'-tetra-chloro derivatives were isolated. This is to be expected since with benzyl β-cellobioside, there is one more reactive site compared to methyl β-maltoside.

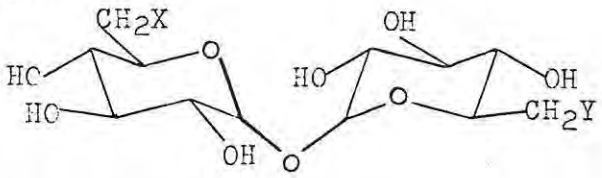
Khan and co-workers[48] also investigated the reaction of (6) with several partially esterified derivatives of sucrose. They also found mixtures of products, in which substitution at secondary positions had occurred. Both the latter groups of authors and the former, relied on n.m.r. and mass spectroscopic data for unambiguous assignment of structures to their fractionated product compounds.

An investigation of the reaction of methyl β-lactoside with (6) was undertaken by Bhatt and co-workers[49]. Under various reaction conditions, they found different distributions of chlorinated products. A particularly noteworthy feature among the reactions that they investigated, is the occurrence of nucleophilic displacement at C-3' of

the lactoside, in spite of the vicinal axial group at C-4', which should hinder such displacement at C-3'. The cause of this anomaly was extensively discussed[49].

Khan et al.[50] described the use of methane sulphonyl chloride and the corresponding bromide in the halogenation of sucrose (71a). Both reagents were found to effect substitution by the corresponding halogen at positions 6 and 6', and no substitution at secondary positions was reported.

The reaction of α,α-trehalose (75a) with triphenyl phosphine and N-bromosuccinimide in dimethyl formamide was reported by Hanessian et al.[51]. Depending upon the reaction conditions, either di- or monobromination could be achieved preferentially, at both or one of the primary positions. Thus, when two equivalents of the halogenating mixture was used, up to 40% yield of the



(75) (a) X = OH = Y

(b) X = OH, Y = Br

(c) X = Br = Y

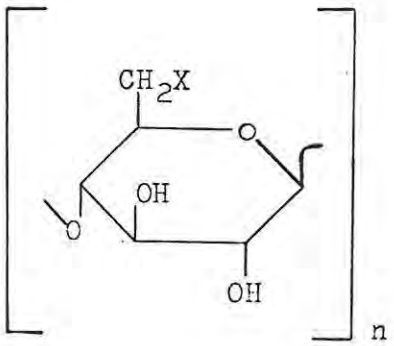
monobromo derivative (75b) could be obtained; (75b) is easily converted in high yield to 6-deoxy-α,α-trehalose, a known substrate for the enzyme trehalase Doubling of the amount of the halogenating mixture, led to the formation of the dibromo derivative (75c) in 62% overall yield after isolation as its acetate. The di- and monoiodo and the

monochloro derivatives could also be prepared, but in inferior yields.

Anisuzzaman et al.[32] were able to prepare 6,6'-dichloro-6,6'-dideoxy sucrose from sucrose, through reaction of the latter with the triphenyl phosphine - carbon tetrachloride reagent in pyridine. No report was given about isolation of any monochlorinated derivative, as was the case with α, α-trehalose.

1.2.3 Polysaccharides

The reaction of celluloses (76a) with the methanesulphonyl chloride - N,N-dimethyl formamide reagent (6), was reported by Horton and co-workers[52] to result in selective substitution of the hydroxyl groups at C-6. The reaction thus produced 6-chloro-6-deoxy celluloses (76b), without the need for protecting groups at secondary positions.

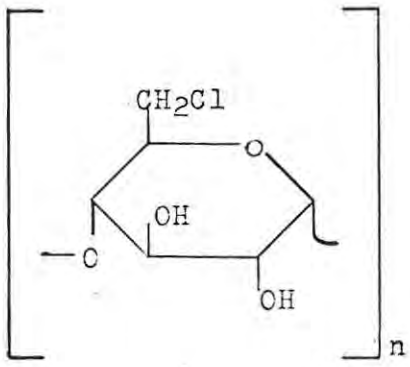


(a) X = OH

(b) X = Cl

(76)

6-Chloro-6-deoxy amylose (77)[53] was similarly prepared through reaction of amylose with reagent (6). However, the reaction with these polysaccharides did not proceed as easily as with monosaccharides, due to solubility problems associated with the former.



(77)

2. Experimental

2.1 General Procedures

Thin-layer chromatography (T.l.c.) was performed on glass plates with Kiesel gel G (Merck) as adsorbent. The plates were developed with the following solvent systems : solvents a, b, c, d, e and f were ether and petroleum ether (boiling point 40 - 60°) in the proportions : 9:1, 8:2, 7:3, 6:4, 5:5, and 4:6 respectively; g, ether; h and i were ether and acetone in the ratio 8:2 and 6:4 respectively, while solvent j was ethyl acetate 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°C, or more specifically, chlorosulphate esters were detected with spray reagent b[54] (butanol-pyridine-aniline in the ratio 8:2:1).

Dry-column chromatography was performed on Kiesel gel 60 (Merck) (70 - 230 mesh ASTM). In order to separate dechlosulphated products, the method used involved dissolving the sample in a suitable, volatile, solvent followed by treatment of the solution with a little silica gel, and subsequent evaporation of solvent to dryness. The residue was applied to the top of a dry-packed column of silica gel, and eluted with a suitable solvent system.

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

Optical rotations were measured in solvents, (a), chloroform and (b), methanol at 20°±3°, with a Perkin-Elmer 141 automatic polarimeter using a cell 1 cm long.

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

Nuclear magnetic resonance (N.m.r.) spectra were recorded on a Perkin-Elmer R-12 spectrometer at 60 MHz using solvents (a), chloroform-d, (b), acetone-d_6 or (c), dimethyl sulphoxide-d_6, with tetramethylsilane as internal standard.

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

Elemental analyses were performed by the microanalysts of the School of Pharmacy, University of London, and of the National Chemical Research Laboratory, Pretoria.

Evaporations were carried out under diminished pressure at room temperature or at below 60°, using a Büchi Rotavapor outfit or with the aid of a high vacuum pump where necessary. Unless otherwise stated, the term "petroleum ether" refers to the fraction of boiling point 40 - 60°.

2.2 General experimental procedure

Dimethyl formamide was dried over CaH_2 and sulphuryl chloride was used as supplied by the British Drug Houses.

The reaction of carbohydrates with the sulphuryl chloride - dimethyl formamide reagent, was carried out by the dropwise addition of sulphuryl chloride to a cooled solution (-20°C) of the carbohydrate in dimethyl formamide, whilst accompanied by vigorous stirring. Two molar proportions of sulphuryl chloride was used for each hydroxyl group present per mole of carbohydrate. The reaction mixture was allowed to stir at below 0° for a period ranging from 1 to 2 hours, and then to slowly warm up to room temperature, and stirring was continued until the reaction ceased. The work-up procedure was as follows:-

the reaction mixture was diluted, with cooling in an ice-water bath, with about 6 volumes of chilled chloroform, and transferred into a separating flask. This was followed by washing successively with an equal volume of ice-cold 10% sulphuric acid, water, saturated sodium bicarbonate solution and lastly twice with water. The chloroform extract was then dried over anhydrous sodium sulphate, filtered and concentrated under diminished pressure at 25 - 30° to yield the chlorosulphated material. Where the reaction mixture could not be evaporated to dryness, the residue was diluted with ether, washed twice with water, dried over sodium sulphate and then concentrated.

Dechlorosulphation was carried out by dissolving the residual material obtained above in methanol (about the same volume as dimethyl formamide used), followed by addition of solid sodium bicarbonate (about twice the mass of the starting sugar) and a few drops of 10% sodium iodide solution in methanol. The heterogeneous mixture was stirred at room temperature, until the reaction was complete (t.l.c.), after which it was filtered, and the filtrate concentrated to give the product. Alternatively, the reaction mixture was concentrated first, followed by extraction of the residue with hot ethyl acetate, which on subsequent evaporation gave the product.

Purification of contaminated products, which were ether insoluble was achieved by dissolving the compound in the minimum amount of a suitable solvent, and passing the solution through a short column containing a 1:1 (w/w) mixture of animal charcoal and silica gel. The column was eluted with ether. Concentration of the eluate gave the pure compound.

Acetylation of hydroxy compounds, where necessary, was achieved through dissolution of the compound in a 2:1, V/V mixture of pyridine and acetic anhydride, followed by stirring at room temperature, until the reaction was complete (t.l.c.). The reaction mixture was worked up by adding it into an excess amount of an ice-water mixture, whilst the latter was being stirred. The resulting mixture

was extracted with ether, and the extract was washed with water until free of pyridine and acetic acid. Drying of the ethereal layer over anhydrous sodium sulphate, followed by evaporation of solvent, gave the acetylated product.

2.3.1 Methyl 4,6-dichloro-4,6-dideoxy- α-D-galactopyranoside (1)

To a cooled solution of methyl α-D-glucopyranoside (1g) in dimethyl formamide (15 ml), was added sulphuryl chloride (3.3 ml) as described, over a period of 0.5 hr. Stirring at below 0° was for an hour and at room temperature for 10 hr., after which t.l.c. examination revealed the presence of traces of starting material (R_f 0.28 in solvent j) and material migrating with the solvent front. In solvent f t.l.c. showed that the fast-moving material contained one major component (R_f 0,43), giving a positive reaction with spray reagent b, and several minor components. Increasing the reaction time did not appear to change the composition of the reaction mixture. The reaction was worked up, and dechlorosulphated as described above. T.l.c. analysis showed the presence of one major component (R_f 0.52 in solvent g), which was contaminated with several fast- and slow-moving compounds. After processing the reaction mixture as described, the yellow syrup obtained was placed on a column and eluted successively with solvents b, a and g, to afford the major component. The compound was recovered as a white crystalline material. Recrystallization from chloroform-petrol ether afforded (1), (540 mg, 45%) as fine

needles; m.p. 157-158° (underpressed on admixture with an authentic sample) $[\alpha]_D$ + 186° (c 0,88 solvent a); λmax 2,95 µm lit.[29, 55] m.p. 159° $[\alpha]_D$ + 179° (c, 2.1 in water).

2.3.2 Reaction of methyl α-D-glucopyranoside in the presence of pyridine

To a cooled solution of methyl α-D-glucopyranoside, (1g), in a mixture of dimethyl formamide (10 ml) and pyridine (5 ml) was added sulphuryl chloride (3.3 ml) over 0.75 hr. as described. The reaction was shown (t.l.c.) to be complete within 3 hr. of stirring at room temperature. The reaction mixture was worked up and dechlorosulphated as described. T.l.c. analysis showed that there was more of the component of R_f 0.52 (in solvent g) and less of the minor components. Further processing of the reaction mixture, gave 1.13g of crude crystalline material, which was decolourised as described. Recrystallization from chloroform-petrol ether gave (1) (810 mg 68%) as fine needles; m.p. 157-158°; $[\alpha]_D$ + 187°(c 1.1 solvent a).

2.4.1 Methyl 4,6-dichloro-4,6-dideoxy- α-D-glucopyranoside (2)

To a cooled solution of methyl- α-D-galactopyranoside (2g) in dimethyl formamide (20 ml) was added sulphuryl chloride (6,6 ml) over a period of 50 min. as described. Stirring at below 0° was for an hr. and at room temperature for 72 hr., after which

t.l.c. showed that the reaction was complete. The reaction mixture was worked up and dechlorosulphated as described to afford 2.8g of crude crystalline material. T.l.c. examination revealed the presence of a major component (R_f 0.61 in solvent g) and a minor one (R_f 0.31). Chromatographic separation on a column was performed, eluting successively with solvents b and g. The major component was recovered as crystalline material (900 mg, 37%). Recrystallization from chloroform-petrol ether afforded (2) as needles; m.p. 122-124°; $[\alpha]_D$ + 129° (c 0.58 in solvent a); λ_{max} 3,0 µm. Jennings et al.[29] reported m.p. 119 - 121°, while Edwards et al.[28] reported m.p. 122 - 124° and $[\alpha]_D$ + 128 (c 1.25 solvent a).

The second component was obtained as an impure syrup (t.l.c.) (36%), thought to be methyl 6-chloro-6-deoxy-α-D-galacto-pyranoside. However, no attempt was made to purify the compound.

2.4.2 Reaction of methyl α-D-galactopyranoside at 60°

Essentially the same procedure as in 2.4.1 was followed, except that, after stirring at room temperature for 1 hr., the reaction mixture was heated to 60° for 21 hr., after which the usual work-up procedure was carried out. Upon dechlorosulphation, t.l.c. examination revealed the presence of one major component (R_f 0.55), a second minor one (R_f 0.76) in solvent b, and several trace components of lower mobilities. After separation on a column, eluting succesively with solvents c, a and g, the component with R_f 0.55 was identified as methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (2)

obtained in 32% yield. Physical constants were in agreement with those found in 2.4.1 above. The second component (R_f 0.76) was found to be methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside (3) obtained in 9% yield, after recrystallization from ether-petrol ether; m.p. 112 - 114°; $[\alpha]_D$ + 170° (c 0.57 in solvent a); λ max 2.81 µm; Jennings et al.[29] reported m.p. 116° and $[\alpha]_D$ + 159 (c 1.8 solvent b).

2.4.3 Reaction of methyl α-D-galactopyranoside in the presence of pyridine

To a cooled solution of methyl α-D-galactopyranoside (5g) in dimethyl formamide (50 ml) and pyridine (20 ml) was added sulphuryl chloride (18 ml) as described, over 3 hr. Stirring was continued for 2 hr. at below 0°, at room temperature for 21 hr. and at 60° for another 21 hr. At this stage t.l.c. analysis showed the presence of a new component (R_f 0.69 in solvent d) which gave a negative reaction with spray reagent b, apart from other components of lower mobilities. After the usual work-up, prior to dechlorosulphation, t.l.c. examination revealed that the component of R_f 0.69 was present as the major compound. Thus, it was isolated by column chromatography, eluting with solvent f. The compound was recovered as a clear syrup, (670 mg, 9%) and was characterized as methyl 4,6-dichloro-4,6-dideoxy-2,3-di-O-formyl-α-D-glucopyranoside (4); $[\alpha]_D$ + 96° (c 1.16 in solvent a) λ max 5.8 µm, -CHO.

Anal. Calc. for $C_9H_{12}Cl_2O_6$: C, 37.63; H, 4.18; Cl,24.74. Found: C,34.55; H, 4.66; Cl, 27.00 (The compound underwent gradual decomposition.)

Treatment of (4) with sodium iodide as described for the dechlorosulphation procedure, afforded the deformylated product, methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (2), the physical constants of which were consistent with those found in 2.4.1 above.

2.5 Methyl 6-chloro-6-deoxy-α-D-mannopyranoside-2,3,4-trichlorosulphate (5)

To a cooled solution of methyl α-D-mannopyranoside (1g) in dimethyl formamide (15 ml) was added sulphuryl chloride (3.3 ml) as described, in 45 min. Stirring was for 1.5 hr. at below C° and for 2 hr. at room temperature, after which t.l.c. examination revealed a single major component (R_f 0.51 solvent d), which gave a positive reaction with spray reagent b. Some slower moving contaminants, as revealed by t.l.c. analysis, were shown to have been removed after washing of the chloroform solution. Evaporation of solvent afforded (5) as crystalline material. Recrystallization from chloroform-petrol ether gave (5) (1.5g, 58%) as prisms; m.p. 132 - 133°; $[\alpha]_D$ + 21° (c 0.75 in solvent a); λ_{max} 7.1 μm and 8.41 μm ($-SO_2Cl$); lit.[29] m.p. 134° $[\alpha]_D$ + 19° (c 1.2 solvent a).

2.6.1 Reaction of methyl β-D-galactopyranoside

To a cooled solution of methyl β-D-galactopyranoside (6g) in dimethyl formamide (70 ml) was added sulphuryl chloride (18 ml) over 3 hr. as described. Stirring at below 0° was for 2 hr., at room temperature for 12 hr. and at 50° for 8 hr. After the work-up and dechlorosulphation as described, t.l.c. analysis showed the presence of one major component (R_f 0.84), and a second minor one (R_f 0.47) (in solvent g). Chromatographic separation on a column, eluting successively with solvents c, a and g gave 2.2g (29%) of the compound with R_f 0.84 as a syrup, which was characterized as methyl 3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranoside (8); $[\alpha]_D$ - 14° (c 0.91 in solvent b); λmax 2.91 μm (OH); lit.[29] $[\alpha]_D$ - 12.8° (c 1.18 solvent b). Compound with R_f 0.47 was recovered as crystalline material, 300 mg (4%), and was identified as methyl 3,6-dichloro-3,6-dideoxy-β-D-gulopyranoside (7). Recrystallization was from acetone-hexane; m.p. 163 - 165°; $[\alpha]_D$ - 35° (c 0.77 in solvent b); λmax 2.98 μm (OH).

Anal. calc. for $C_7H_{12}Cl_2O_4$: C, 36.36; H, 5.19; Cl, 30.74

Found: C, 36.24; H, 5.24; Cl, 32.02.

2.6.2 Methyl 2-O-benzoyl-3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranoside (8)

A solution of (8) (200 mg) in chloroform (1 ml), was added to a cooled (ice-water) stirring mixture of benzoyl chloride (0.5 ml), pyridine (0.5 ml) and chloroform (1 ml). The

reaction mixture was allowed to stand at 0° for 2 hr., after which t.l.c. examination revealed a single component (R_f 0.71 in solvent f). The reaction mixture was worked up as described by Vogel[56]. Evaporation of solvent afforded (8) as a cloudy syrup, (260 mg, 93%). The syrup crystallized from methanol-water; m.p. 114 - 115°; $[\alpha]_D$ - 51° (c 0.53 in solvent a); λ max 6.3 μm and 6.68 μm (aromatic ring).

Anal. calc. for $C_{14}H_{15}Cl_3O_4$: C, 47.66; H, 4.25; Cl, 30.21

Found: C, 48.03; H, 4.39; Cl, 32.66.

2.7. Methyl 4,6-dichloro-4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (10)

To a cooled solution of methyl β-D-glucopyranoside (3g) in dimethyl formamide (40 ml), was added sulphuryl chloride (10 ml) as described, in 2 hr. Stirring at below 0° was for 2 hr., at room temperature for 4 hr. and at 50° for 18 hr., after which the reaction mixture was worked up and dechlorosulphated as described. T.l.c. examination revealed one major component (R_f 0.51 in solvent g) with several fast-moving minor components. The major compound was isolated by column chromatography, eluting successively with solvents b and g. 900 mg (25%) of (10) was recovered as crystalline material. Recrystallization was from chloroform- petrol ether; m.p. 144 - 150° ; $[\alpha]_D$ + 7.8° (c 0.64 water); λ max 3.12 μm. (Jennings et al.[29] reported m.p. 144 - 146° ; $[\alpha]_D$ - 16°, whereas in an earlier communication[54], they had reported

m.p. 154° and $[\alpha]_D$ + 16°. Edwards et al.[28] reported m.p. 152 - 153° and $[\alpha]_D$ + 7°)

Anal. calc. for $C_7H_{12}Cl_2O_4$: C, 36.36; H, 5.19; Cl, 30.74

Found: C, 36.13; H, 5.32; Cl, 31.19.

2.8.1 Methyl 4-chloro-4-deoxy-β-L-arabinopyranoside (11)

To a cooled solution of methyl α-D-xylopyranoside (5g) in dimethyl formamide (70 ml), was added sulphuryl chloride (16 ml) as described, in 2.5 hr. Stirring at below 0° was for 1 hr. and at room temperature for 10 hr. After the usual work-up, concentration of the chloroform solution afforded 10.6g of crystalline material, which was shown to be chromatographically homogeneous (spray reagent a), and gave a positive reaction with spray reagent b. Without purification, the material was dechlorosulphated as described to afford (11) (4.9g, 88%) as colourless crystals. Compound (11) was shown (t.l.c.) to be homogeneous and had R_f 0.69 in solvent i. Recrystallization was from ethyl acetate; m.p. 147 - 148° ; $[\alpha]_D$ + 243°(c 1.27 in solvent b); lit.[55] m.p. 152°; $[\alpha]_D$ + 237°(c 0.96 in solvent b).

Anal. Calc. for $C_6H_{11}ClO_4$: C, 39.45; H, 6.03; Cl, 19.45

Found: C, 39.42; H, 5.94; Cl, 19.25.

2.8.2 Acetylation of methyl 4-chloro-4-deoxy-β-L-arabino-pyranoside

Compound (11) (0.5g) was dissolved in 9 ml of the acetylating mixture, and the solution was stirred for 5 hr., after which the reaction had gone to completion (t.l.c.) Further processing of the reaction mixture as described, afforded 571 mg (79%) of crystalline methyl 2,3-di-O-acetyl-4-chloro-4-deoxy-β-L-arabinoside (12). Recrystallization was from ether-petrol ether; m.p. 100 - 101° ; $[\alpha]_D$ + 240° (c 1.05 in solvent a); λmax 5.85 μm.

Anal. Calc. for $C_{10}H_{15}ClO_6$: C, 45.03; H, 5.63; Cl, 13.32

Found: C, 44.86; H, 5.65; 13.27.

2.9.1 Methyl 4-chloro-4-deoxy-α-L-arabinopyranoside (13)

Methyl β-D-xylopyranoside (5g) was treated in essentially the same manner as was the α-anomer in 2.8.1 above. The syrupy chlorosulphated material was found (t.l.c.) to be chromatographically homogeneous. Upon dechlorosulphation, t.l.c. analysis showed the presence of a single component (R_f 0.71 in solvent i). Further processing as described afforded (13) (2.85g, 51%) as white crystals. Recrystallization was from ethyl acetate; m.p. 105 - 106° $[\alpha]_D$ + 6° (c 1.38 in solvent b)

Anal. Calc. for $C_6H_{11}ClO_4$: C, 39.45; H, 6.03; Cl, 19.45

Found: C, 39.17; H, 6.02; Cl, 19.07

2.9.2 Acetylation of methyl 4-chloro-4-deoxy-α-L-arabinopyranoside

Compound (13) (0.5g) was acetylated as described for the corresponding β-anomer (11) in 2.8.2 above. Methyl 2,3-di-O-acetyl-4-chloro-4-deoxy-α-L-arabinopyranoside (14) was obtained crystalline in 82% yield. Recrystallization was from ether-petrol ether; m.p. 110 - 111°; $[\alpha]_D$ - 3.2° (c 1.09 in solvent a); λ_{max} 5.89 μm.

Anal. Calc. for $C_{10}H_{15}ClO_6$: C, 45.03; H, 5.63; Cl, 13.32

Found: C, 44.95; H, 5.67; Cl, 13.25

2.10.1 Methyl 4-chloro-4-deoxy-α-L-xylopyranoside

Methyl β-D-arabinopyranoside (5g) was reacted in essentially the same manner as was methyl α-D-xylopyranoside in 2.8.1 above. The chlorosulphated material could be obtained crystalline, and was shown (t.l.c.) to be chromatographically homogeneous. Dechlorosulphation in the usual way gave a single compound (R_f 0.44 in solvent g) as was shown by t.l.c. Further processing as described afforded (15) (4.8g, 85%) as colourless prisms, after recrystallization from ethyl acetate; m.p. 104 - 105°; $[\alpha]_D$ - 130 (c 1.24 in solvent b).

Anal. Calc. for $C_6H_{11}ClO_4$: C, 39.45; H, 6.03; Cl, 19.45

Found: C, 39.15; H, 6.24; Cl, 19.17

2.10.2 Acetylation of methyl 4-chloro-4-deoxy-α-L-xylopyranoside

Compound (15), (0.5g) was acetylated as described for methyl 4-chloro-4-deoxy-β-L-arabinopyranoside (11) in 2.8.2 above. Methyl 2,3-di-O-acetyl-4-chloro-4-deoxy-α-L-xylopyranoside (16) was obtained crystalline in 71% yield. The compound was recrystallized from ether-petrol ether; m.p. 137 - 138°; $[\alpha]_D$ - 80° (c 0.97 in solvent a); λ_{max} 5.94 μm.

Anal. Calc. for $C_{10}H_{15}ClO_4$: C, 45.03; H, 5.63; Cl, 13.32.

Found: C, 44.93; H, 5.71; Cl, 13.18

2.11 Reaction of D(+) galactose in the presence of pyridine

To a cooled solution of D(+) galactose (5g) in dimethyl formamide (80 ml), and pyridine (20 ml), was added sulphuryl chloride (18 ml) as described, in 3 hr. Stirring at below 0° was for 3 hr. and at room temperature for 16 hr., after which t.l.c. examination revealed 3 components (R_f's 0.82, 0.74 and 0.56 in solvent d), all of which gave a positive reaction with spray reagent b. After the usual work-up, t.l.c. analysis showed that all 3 compounds had been retained in the chloroform layer, concentration of which afforded a pale yellow syrup. Dechlorosulphation was carried out as described to give a range of products (t.l.c.), amongst which 4 were isolated by column chromatography; elution was with solvents e, c, a and g respectively. The compounds had the following R_f values: (a) 0.70; (b) 0.44; (c) 0.25 and (d) 0.17 in solvent b. The one with R_f 0.70 was methyl3,4,6-trichloro

-3,4,6-trideoxy-α-D-allopyranoside (3) of which 400 mg (6%) was recovered. The physical constants were in agreement with those of an authentic sample. The R_f value of 0.44 was that of 3,4,6-trichloro-3,4,6-trideoxy-allopyranose (17), which was obtained in less than 1% yield, after recrystallization from acetone-hexane; m.p. 143 - 144°; $[\alpha]_D$ (equilibrium) + 9.2° (c 0.65 in solvent b); lit.[29] m.p. 170 - 171°.

Anal. Calc. for $C_6H_9Cl_3O_3$: C, 30.57; H, 3.82; Cl, 45.22

Found: C, 30.50; H, 3.94; Cl, 46.98

Methyl 4,6-dichloro-4,6-dideoxy-β-D-glucopyranoside (18) had R_f 0,25, and was obtained in 9% yield, after recrystallization from chloroform-petrol ether; m.p. 143 - 144°; $[\alpha]_D$ - 63° (c 1.26 in solvent b).

Anal. Calc. for $C_7H_{12}Cl_2O_4$: C, 36.36; H, 5.19; Cl, 30.74

Found: C, 36.63; H, 5.35; Cl, 32.01.

The compound with R_f 0.17 was methyl 4,6-dichloro-4,6-deoxy-α-D-glucopyranoside (2), and was recovered in less than 1% yield. The physical constants measured for (2), were consistent with those obtained previously.

2.12 Reaction of D-glucose in the presence of pyridine

To a cooled solution of D-glucose (5g) in dimethyl formamide (50 ml) and pyridine (5 ml), was added sulphuryl chloride (18 ml) as described, in 3 hr. Stirring was continued at

below 0° for 2 hr. and at room temperature for 20 hr., after which t.l.c. examination revealed 3 major components (R_f's 0.72, 0.53 and 0.45 in solvent f), all of which gave a positive reaction with spray reagent b. However, dechlorosulphation as described, produced one major component (R_f 0.23 in solvent g) with several minor components of higher mobilities, as observed on t.l.c. The compound was isolated by column chromatography, eluting successively with solvents b, a and g. When recovered, the compound was contaminated with some monoformyl ester, as was evident from its mass spectrum. Thus, further treatment with 1-propanol afforded, after removal of solvent and recrystallization (3X) from chloroform-petrol ether, methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (10) in 16% yield. The physical constants measured for (10) were in agreement with those obtained previously.

2.13 Reaction of D(+) xylose

To a cooled solution of D(+) xylose (5g) in dimethyl formamide (70 ml) was added sulphuryl chloride (13 ml), as described, in 3 hr. Stirring at below 0° was continued for 2 hr. and at room temperature for 19 hr., after which t.l.c. analysis showed the presence of a single component (R_f 0.65 in solvent e), which gave a positive reaction with spray reagent b. Dechlorosulphation as described afforded 2,7g (44%) of what appeared like a single compound (t.l.c.) with R_f 0.59 in solvent h. The syrup obtained crystallized upon

standing.The optical rotation of +47° obtained initially indicated that the major compond was methyl 4-chloro-[illegible]-deoxy-α-L-arabinopyranoside (13) which was probably contaminated with the β-anomer (11).Carefull recrystallization (2X) from ethyl acetate afforded (13)as colourless needles. The physical constants measured for (13)were consistent with those obtained previously.

Anal. Calc. for $C_6H_{11}ClO_4$: C, 39.45; H, 6.03; Cl, 19.45

Found: C, 39.61; H, 6.05; Cl, 19.01

Compound (13) was further characterized as its crystalline acetate (14) for which the spectral data were identical with those obtained before.

Anal. Calc. for $C_{10}H_{15}ClO_8$: C, 45.03; H, 5.63; Cl, 13.32

Found: C, 44.97; H, 5.69; Cl, 13.28

The dibenzoyl derivative of (13) was also prepared, and was obtained as a clear syrup which crystallized after standing in the refrigerator for 5 days. Recrystallization from ether-petrol ether gave the compound as fine crystals; m.p. 104 - 105°C; $[\alpha]_D$ + 93° (c 1.25 in solvent a).

Anal. Calc. for $C_{20}H_{19}ClO_6$: C, 61.46; H, 4.87; Cl, 9.09

Found: C, 61.39; H, 4.97; Cl, 6.35

2.14.1 Reaction of L(+) Arabinose

To a cooled solution of L(+) Arabinose (5g) in dimethyl formamide (70 ml) was added sulphuryl chloride (18 ml),

as described, in 3 hr. Stirring was continued at below 0° for 2 hr. and at room temperature for 12 hr., after which t.l.c. examination revealed what appeared like a single component (R_f 0.53 in solvent e), which gave a positive reaction with spray reagent b. However, upon dechlorosulphation, t.l.c. analysis showed the presence of 3 components (R_f's 0.80, 0.55 and 0.44 in solvent g). Chromatographic separation on a column, eluting successively with solvents c, a and g, afforded 70 mg (0.6%) of 4-deoxy-3,4-dichloro-D-glycero-pent-2-enopyranosyl 3',4'-dichloro-3',4'-dideoxy-α-D-ribopyranoside (19) for the compound with R_f 0.8. Recrystallization from ether-petrol ether yielded (19) as white needles; m.p. 129 - 130°; $[\alpha]_D$ + 133° (c 0.85 in solvent b).

N.m.r. data: τ 3.80 (d), olefinic proton; τ 5.50 (m), H-4; τ 5.42 (dd), H-5; τ 6.03 (dd); H-5', $J_{4,5}$ 11.3 Hz; $J_{4,5'}$ 13.0 Hz; $J_{5,5'}$ 2.0 Hz.

I.r. : λ_{max}^{Nujol} 3.08 μm (OH); 6.10 μm C-C double bond.

Anal. Calc. for $C_{10}H_{12}Cl_4O_4$: C, 35.50; H, 3.55; Cl, 42.01

Found: C, 35.30; H, 3.64; Cl, 43.46

The second component, of R_f 0.55, was recovered as white amorphous material weighing 1,2g (19.7%), and was identified as methyl 5-chloro-5-deoxy-α-L-arabinofuranoside (20). Repeated attempts to recrystallize (20) often afforded amorphous material; m.p. 93 - 95°; $[\alpha]_D$ - 104° (c 1.05 in solvent a).

N.m.r. data: τ 5.25 (d), H-1; τ 5.66 - 5.86 (cm), includes H-2, 3, 4, 5, 5', OCH_3 and 2X OH; $J_{1,2}$ 2,0 Hz.

Anal. Calc. for $C_6H_{11}ClO_4$: C, 39.45; H, 6.03; Cl, 19.45

Found: C, 39.82; H, 6.03; Cl, 19.21

The third component of R_f 0.44, was obtained as a syrup 300 mg (5), which crystallized after standing at room temperature for 24 hr. Recrystallization (2X) from ethyl acetate-petrol ether gave methyl 4-chloro-4-deoxy-α-D-xylopyranoside (21) as fine crystals; m.p. 89 - 91°
$[\alpha]_D$ + 140° (c 0.84 solvent b); lit.[58] m.p. 102 - 103°;
$[\alpha]_D$ + 135° (c 0.9 solvent b).

N.m.r. data: τ 5.15 (d), H-1; τ 6.0 - 6.9 (cm), H-2, 3, 4, 5, 5'; τ 6.5 (s), OCH_3; τ 7.8 (s), 2XOH; $J_{1,2}$ 3.3 Hz.

Anal.Calc. for $C_6H_{11}ClO_4$: C, 39.45; H, 6.03; Cl, 19.45

Found: C, 39.25; H, 5.83; Cl, 18.79

All n.m.r. spectra were measured in solvent b.

2.14.2 Acetylation of methyl-5-chloro-5-deoxy-α-L-arabinofuranoside.

Compound (20) (0.2g) was dissolved in 6 ml of the acetylating mixture, followed by stirring of the solution. The reaction was complete (t.l.c.) within 5 hr. Further processing of the reaction mixture as described, afforded 210 mg (72%) of methyl 2,3-di-O-acetyl-5-chloro-5-deoxy-α-L-arabinofuranoside

as fine crystals. Recrystallization was from ether-petrol ether; m.p. 141 - 142°; $[\alpha]_D$ - 120° (c 1.03 in solvent a); λ_{max} 5.91 μm.

N.m.r. data: τ 4.55 - 5.35 (m), H-2, 3; τ 5.43 - 5.95 (m), H-1, 4; τ 5.95 - 6.54 (m), H-5,5'; τ 6.47 (s), OCH_3; τ 7.91 (s) and τ 7.95 (s), 2X OAC.

Anal. Calc. for $C_{10}H_{15}ClO_6$: C, 45.03; H, 5.63; Cl, 13.32

Found: C, 44.83; H, 5.46; Cl, 13.26

The n.m.r. spectrum was measured in solvent a.

2.14.3 Hydrolysis of methyl 5-chloro-5-deoxy-α-L-arabinofuranoside.

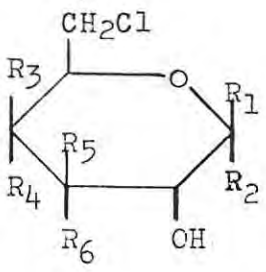
A solution of (20) (0.4g) in 1N sulphuric acid (10 ml) was heated under reflux, at 115 - 120°, for 10 hr, after which t.l.c. examination revealed a single component (R_f 0.44 in solvent i). The reaction mixture was allowed to cool down to room temperature, and was neutralized with barium carbonate, filtered and concentrated to a yellow syrup. The syrup was dissolved in a 1:1 - V/V mixture of methanol and ether, and the solution was treated with animal charcoal, filtered and concentrated to a clear syrup which crystallized on standing. Recrystallization from acetone-ether afforded 5-chloro-5-deoxy-L-arabinofuranose as fine crystals; m.p. 121 - 122°(decomp.); $[\alpha]_D$ - 64°(5 min) ⟶ -2°(equilibrium, 24 hr.) (c 0.7 in solvent b).

Anal. Calc. for $C_5H_9ClO_4$: C, 35.61; H, 5.34; Cl, 21.06

Found: C, 36.50; H, 5.82; Cl, 20.70.

3. Discussion

The reaction of the sulphuryl chloride - dimethyl formamide reagent with some carbohydrates containing free hydroxyl groups has been investigated. As with other Vilsmeier-Haack reagents[59], the reaction has been shown to give rise to chlorodeoxy derivatives. Furthermore, the formation of chlorosulphate esters with the reagent was indicated. Chlorosubstitution was shown to occur at both primary and secondary positions, with inversion of configuration at the latter centre, indicating that the reaction probably proceeds by a nucleophilic bimolecular substitution mechanism. The selectivity of substitution at secondary centres is subject to constraints involving steric and polar effects, in a manner similar to that described by Richardson[60] for the replacement reactions of sulphonates.



(1) $R_1 = R_4 = R_6 = H$, $R_2 = OCH_3$, $R_3 = Cl$

(2) $R_1 = R_3 = R_6 = H$, $R_2 = OCH_3$, $R_4 = Cl$

(10) $R_2 = R_4 = R_6 = H$, $R_1 = OCH_3$, $R_3 = Cl$

(18) $R_2 = R_3 = R_6 = H$, $R_1 = OCH_3$, $R_4 = Cl$

} $R_5 = OH$

(7) $R_2 = R_4 = R_5 = H$, $R_3 = OH$, $R_6 = Cl$, $R_1 = OCH_3$

Reaction of methyl α-D-glucopyranoside at room temperature gave methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (1), the m.p. of which was consistent with that reported by Jennings et al.[29]. When the reaction was conducted in the presence of a little pyridine, the yield of (1) was raised

Table I - Chemical shifts (τ-values) and first-order coupling constants (Hz) for (1), (2), (10), (18) and (7)

Compound	1[b]	1*	2[a]	2*	10[b]	10*	18[b]	7[c]
H-1	5.15(d)	4.47-4.9(cm)	5.05(d)	4.72(d)	5.5(d)	4.94(d)	5.27(d)	4.17(d)
H-2	5.59-6.2(cm) includes H-5 and OH's		5.80-6.35(cm)	4.98(dd)	5.93(dd)	4.52-7.3(m)	see below	4.95-5.7(cm) includes OH's
H-3				4.26(t)	5.52-5.75 (cm) includes OH's		5.6(dd)	
H-4	5.38(dd)	5.05(d)		5.7-6.15(cm)		5.19(dd)	5.92-6.91(cm) includes H-2 and OH's	6.06-6.6(cm)
H-5	see above	5.5(m)			6.05-6.34(m)	5.53(m)		
H-6	6.3(d)	6.16(d)				6.1(d)		
H-6'								
OCH_3	6.55(s)	6.4[illegible](s)	6.47(s)	6.45(s)	6.47(s)	6.77(s)	6.58(s)	[illegible]
CH	see above	-1.17(s)and -1.03(s)	6.98(s)	1.31(s)& 1.21(s)	see above	-1.46(s)and -0.78	see above	see above
$J_{1,2}$	2.7	4.0	3.3	3.3	9.3		12.6	5.7
$J_{2,3}$				12.0	6.7			
$J_{3,4}$	2.8	3.5						
$J_{4,5}$	1.3	1.3						

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

*with trichloroacetyl isocyanate

The superscripts (a), (b) and (c) denote solvents as described in the experimental.

from 45 to 68%. The superior yield in the latter reaction over the former, may be attributed to a control over the side-reactions ensuing from the growing acidity of the reaction mixture as more sulphuryl chloride is added. The infra-red spectrum of (1) showed the presence of hydroxyl groups. The n.m.r. data is given in table 1. The H-2 and H-3 signals merge with the H-1 signal upon addition of trichloroacetyl isocyanate, due to the deshielding effect brought about by the electron withdrawing group introduced.

Methyl 4,6-dichloro-4,6-dideoxy- α-D-glucopyranoside (2) and methyl 4,6-dichloro-4,6-dideoxy- β-D-galactopyranoside (10) were similarly obtained by reacting methyl α-D-galacto- and β-D-glucopyranosides respectively. The m.p. and optical rotation for compound (2) were consistent with those reported by Edwards et al.[28], whereas the m.p. (148 - 150°) of (10) was somewhat lower than that reported (152 - 153), and remained so even after successive recrystallizations. This may be due to a slight contamination with the 3,6-dichloro-3,6-dideoxy derivative, which was somehow not detectable by t.l.c. The latter compound was reported[28] as being the major product in the reaction with the methanesulphonyl chloride - dimethyl formamide reagent, whilst it appeared as a minor with the sulphuryl chloride - pyridine reagent. However, in another investigation conducted with the latter reagent, by Dean and co-workers[61], the compound appeared as the preponderant product.

The n.m.r. spectrum of (2) showed much overlapping of the ring proton signals except for H-1, which appeared as a doublet farthest downfield. Some slight resolution was achieved in the presence of trichloroacetyl isocyanate. H-3 appeared as a broad triplet at τ 4.26. A double-doublet due to the resonance of H-2 was observed at τ 4.98, at slightly higher field with respect to the H-1 doublet, which was centred atτ4.72. Compound (10) also showed a poorly resolved spectrum, with the H-1 signal partially overlapping with the complex multiplet due to H-3 and H-4, and a double-doublet at τ 5.93 due to the H-2 resonance. A noteworthy feature in the n.m.r. spectra of sugars with the galacto configuration [62], is the appearance of H-5 as an apparent triplet, whilst in actual fact, the signal is a multiplet due to additional narrow coupling with H-4, the appearance of the H-6,6 signal as a doublet and that of H-4 as a narrow double-doublet with $J_{4,5}$ = 1.3Hz. This phenomenon was only observed with the two galacto sugars (1) and (10) synthesized by the present method in the presence of the shift reagent.

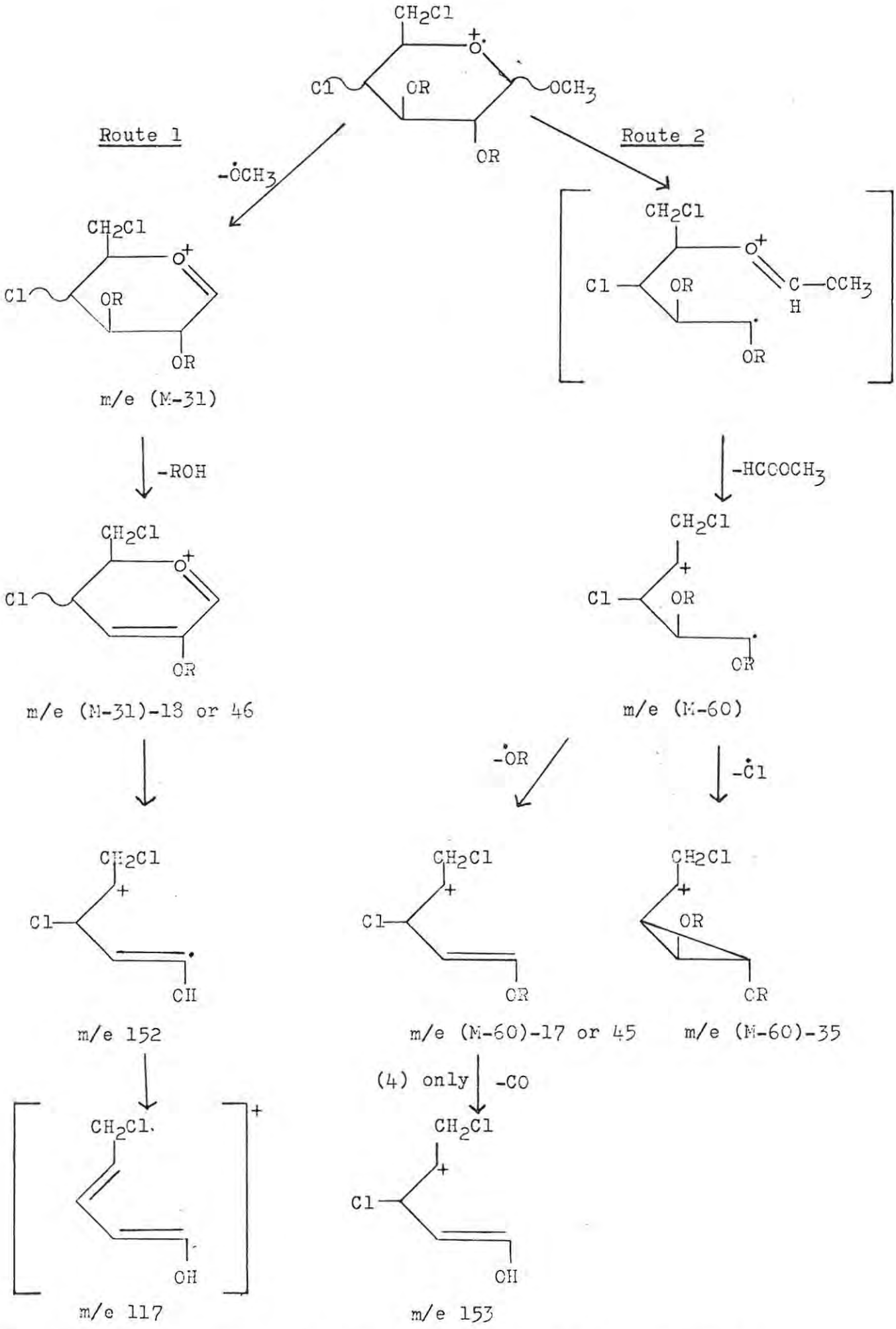
When free D(+) galactose was reacted with the reagent in the presence of a little pyridine, the major product, amongst other minors, was found to be methyl 4,6-dichloro-4,6-dideoxy-β -D-glucopyranoside (18), for which no physical constants have been reported. The assignment of compound (18) as methyl 4,6-dichloro-4,6-dideoxy-β -D-glucopyranoside, was mainly from its mass and n.m.r.

Table II - Relative intensities in the mass spectra of compounds (1), (2), (10), (18) and (7)

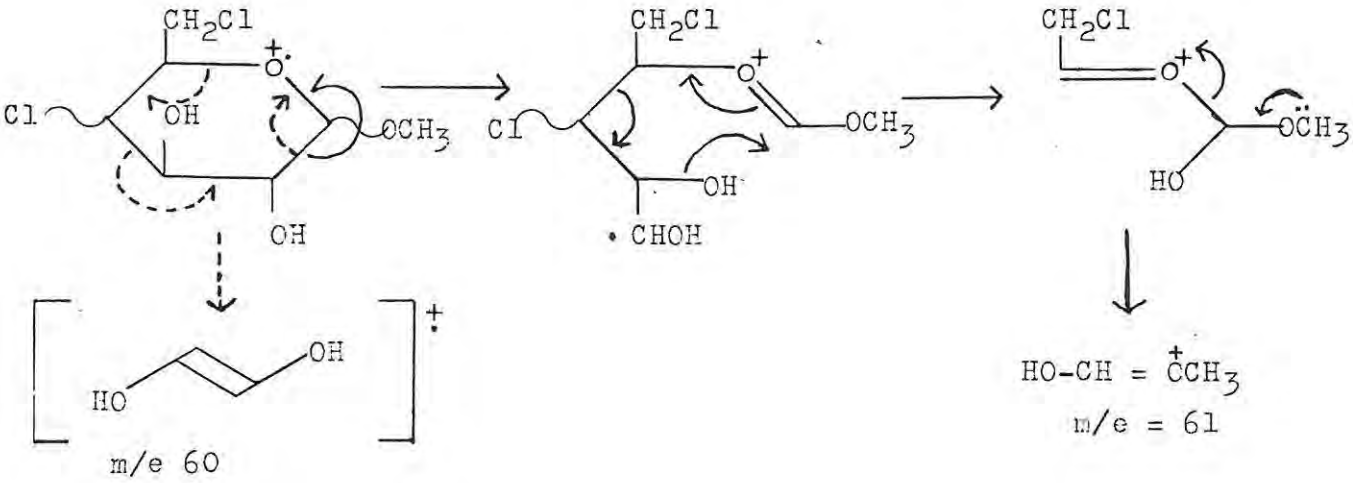
Compound		1	2	10	18	7
m/e		Relative intensity %				
M-31	199	0.89	0.2	0.19	1.58	2.51
(M-31)-18	181	0.13	0.25	0.28	0.60	0.67
M-60	170	0.08	0.45	0.51	1.50	
M-60)-17	163	0.24	0.35	1.40	0.60	8.91
	152	0.56	1.0	1.68	1.41	
	139	2.99	1.59	1.84		
(M-60)-35	135	1.59	1.99	2.37	14.12	14.13
	117	3.59	2.24	2.86	14.12	15.85
	105	7.94	2.99	3.52	16.7	11.22
	99					63.08
	61	83.18	39.81	43.57	89	100
	60	100	100	100	100	

spectral data and its optical rotation. The mass spectrum showed m/e 199 (M-31) as the fragment of highest mass, in association with its isotopic counterparts (M-31+2, M-31+4) in the ratio of 9:6:1 confirming the presence of two chlorine atoms. The mass spectral fragmentation pathway was basically similar to that depicted in scheme A and table II. The n.m.r. spectrum showed a relatively high coupling constant between H-1 and H-2 ($J_{1,2}$ = 12,6), which is indicative of ring protons that are trans-diaxially related, which would be the case for a β-D-glucopyranosyl sugar. The optical rotation obtained was -70°, in contrast to that found for the α-sugar which is +129°.

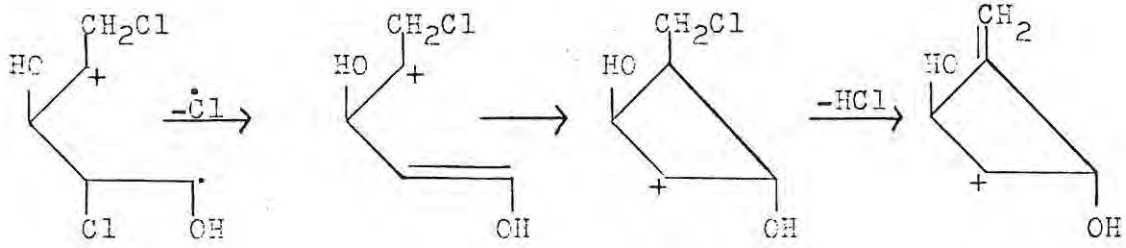
Reaction of methyl β-D-galactopyranoside afforded, as a minor product, after column chromatography, methyl 3,6-dichloro-3,6-dideoxy-β-D-gulopyranoside (7) in 4% yield. The identity of compound (7) was not readily apparent from its n.m.r. spectrum, whilst its mass spectrum (table II and scheme B) showed a fragmentation pattern, unique to the compound, and different from that of the 4,6-dichloro-4,6-dideoxy derivatives. Thus m/e = 60 could not be observed as a base peak in the spectrum of (7), because no stable fragment ion with m/e = 60 can be formed from the compound according to the mechanism shown. In the n.m.r. spectrum of (7)(table I), H-1 was observed as a doublet at τ 4.13, whilst H-2, 3, 4 and one -OH proton appeared at τ 4.95 - 5.76 as a complex multiplet. The signals due to H-5, H-6,6', one OH and OCH_3 were observed over the range τ 6.00 - 6.80.

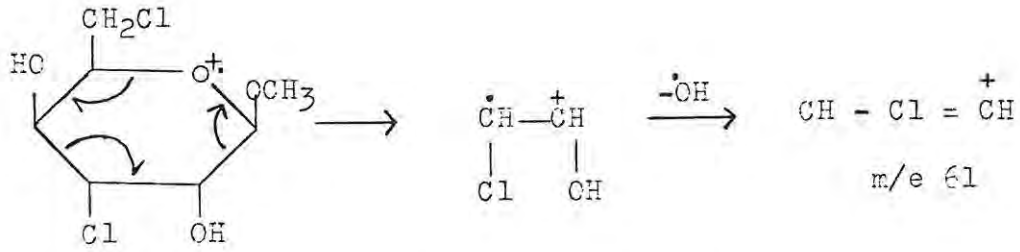


Scheme A : Mass spectral fragmentation pathways for compounds (1), (2), (10); (12), (R = H) and (4), (R = CHC)

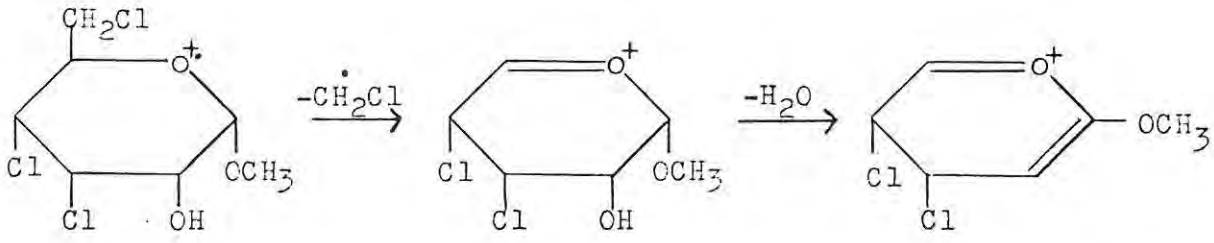


Scheme A (continued)



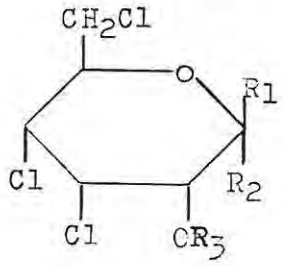


Scheme B : Some mass fragmentation pathways for compound (7)



Scheme C : Characteristic mass spectral fragmentation pathways for compound (7)

When (7) was acetylated, the n.m.r. of the acetate measured in chloroform-d showed H-1, 2 and 4 as a singlet at τ 5.13, H-3 and 5 as a doublet at τ 5,59 and H-6,6' as a doublet at 5.73. Additional evidence in support of structure (7), was revealed when the compound was found not to be affected, after treatment with sodium periodate for 72 hr. Compound (18) was found (t.l.c.) to react with sodium periodate to give, mainly, a component of higher chromatographic mobility, thus confirming the presence of vicinal hydroxyl groups. The n.m.r. and mass spectral data for (1), (2), (7), (10) and (18) are presented in tables I and II respectively. The mass fragmentation pathways are given in schemes A and B. The elemental analyses of (7) and (18) were in accord with the expected structures.



(3) $R_1 = R_3 = H$; $R_2 = OCH_3$

(6) $R_1 = OCH_3$; $R_2 = R_3 = H$

(8) $R_1 = OCH_3$; $R_2 = H$; $R_3 = Bz$

In an endeavour to improve the yield of methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (2) in the reaction of methyl α-D-galactopyranoside, the reaction mixture was heated at 60° as described. However, this resulted, unexpectedly, in a lower yield of (2), accompanied by the production of another compound, which was characterized as methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside (3). The m.p. and optical rotation of (3) were consistent with those reported in the literature[29]. In the n.m.r. spectrum of (3), H-1 was observed as a doublet at τ 5.13, H-3 as a not

Table III - Chemical shifts (τ-values) and first-order coupling constants (Hz) for (3), (4), (6), (8) and (17)

Compound	3	3*	4	6	6*	8	17
H-1	5.13(d)	4.9(d)	4.86(d)	5.23(d)	4.94-5.15(m)		5.1(d)
H-2	see below	4.85(q)	4.89(dd)	see below			5.9(q)
H-3	5.31(bs)	5.16(bs)	4.26(t)	5.22(t)			5.3(t)
H-4	5.59-5.75(m)	5.46-5.65(m)	5.76-6.17(cm)	5.65-5.83(m)	5.42-5.78(m)	5.52-5.75(m)	5.40-5.72(m)
H-5							
H-6	6.79-6.12(m) includes H-2	6.05(d)		5.99-6.39(m) includes H-2	6.06(m)	6.05(d)	6.18(d)
H-6'							
OH	7.28(s)	1.7(s)		7.35(s)	1.25(s)		4.06(s) 6.37(s)
-C(=O)-R			1.75(s) 1.85(s)			1.79(m) 2.43(m)	
OCH_3	6.50(s)	6.47(s)	6.50(s)	6.39(s)	6.41(s)	6.42(s)	
$J_{1,2}$	4	4	3.3	8			7.5
$J_{2,3}$			12	2.7			2.5
$J_{3,4}$				2.7			2.5
$J_{4,5}$							10

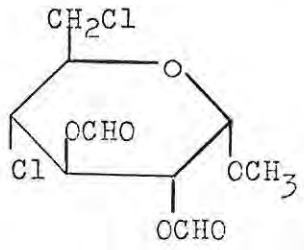
Key: d = doublet; bs = broad singlet; m = multiplet; s = singlet; q = quartet; dd = double doublet; t = triplet; cm = complex multiplet

All spectra measured in deuterochloroform except for (17) which was done in hexadeutero-acetone.

* with trichloroacetyl isocyanate

well-defined singlet at τ 5.31 and H-6,6' appeared with H-2 as a complex multiplet. However, in the presence of trichloroacetyl isocyanate, H-2 was shifted to lower field, and appeared as a quartet at τ 4.85, beyond H-1, for which the signal was centred at τ 4.9. More n.m.r. spectral data for (3) are presented in table III.

The i.r. spectrum showed the presence of a hydroxyl group. In the mass spectrum of (3), the peak at m/e 199 was found to be due to a fragment ion containing two chlorine atoms, which could not have been formed via a route similar to (1) in scheme A. Thus, a probable pathway leading to the formation of the fragment ion, is depicted in scheme (C). The other fragmentation pathways followed by (3) were similar to those shown in scheme A, route (1) and (2).



(4)

When methy α-D-galactopyranoside was heated at 60° with the reagent in the presence of pyridine, no formation of (3) could be detected. Rather, the major compound produced, before dechlorosulphation, was methyl 4,6-dichloro-4,6-dideoxy-2,3-di-O-formyl-α-D-glucopyranoside (4). The n.m.r. data for (4) (table III) showed that the compound was in the gluco- configuration, as was evident from the $J_{2,3}$

value of 12.0Hz, which is typical of trans-diaxial ring protons. Furthermore, the mass spectral fragmentation pathways followed by (4) were analogous to those followed by the other 4,6-dichloro-4,6-dideoxy-D-gluco- derivatives. The relative intensities in the mass spectrum of (4) are presented in table (V).

The i.r. spectrum of (4) showed the presence of an unconjugated carbon - oxygen double bond due to the formyl ester group. The structure of (4) was further confirmed through deformylation using sodium iodide in methanol which resulted in the formation of (2) above, for which the physical constants were consistent with those obtained at an earlier stage.

Reaction of methyl β-D-galactopyranoside at 50°, afforded as a major product, after column chromatography, methyl 3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranoside (6) as a pale yellow syrup, which was shown to be chromatographically homogeneous.

The n.m.r. spectrum of (6) (table III) assumed the same appearance, basically, as that of the α-anomer (3) except for the features characteristic of the β-configuration, and a little contamination with the solvent, dimethyl formamide. Thus H-1 resonated at slightly lower field (τ 5.23), with a splitting of 8 Hz, compared to its counterpart in (3), which appeared at about 0.1 ppm higher field, with a spacing of 4 Hz. The signal due to H-3 was

Table IV - Relative intensities in the mass spectra of compounds (3) and (17)

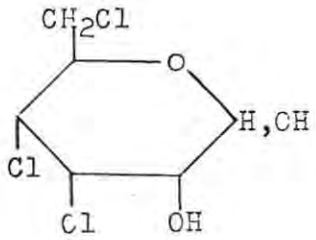
Compound		3	17
m/e		Relative intensity %	
M-31/17	217	2.51	2.82
M-49	199	0.22	
	181	1.78	1.0
	153	22.39	2.82
	117	35.49	21.14
	61	100	
	53		100

Table V - Relative intensities in the mass spectrum of compound (4)

m/e	255	209	191	181	163	153	117	61
	M-31	(M-31) -46	(M-60) -35	(M-60) -45				
Relative Intensity	3.16	3.76	3.35	4.22	2.8	9.44	16.79	100

found to be a well-defined triplet at τ 5.22 with a coupling constant of 2,7 Hz. Addition of trichloroacetyl isocyanate would not simplify the spectrum any further, other than shifting the hydroxyl peak from τ 7.35, to farthest downfield at τ 1.25.

Compound (6) was further characterized as its crystalline benzoyl (8) and syruppy acetyl esters, for which the n.m.r. spectra appeared almost similar, with respect to the resonances due to the protons of the sugar moiety, and were no simpler than that of the parent compound. The elemental analysis of (8) was in accord with the expected structure.



(17)

Amongst the minor products formed in the reaction of D(+) galactose, were methyl 4,6-dichloro-4,6-dideoxy-α-D-glucopyranoside (2), obtained in less than 1% yield, and methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside (5), which was obtained crystalline in 6% yield. The physical constants measured agreed well with those obtained before.

Another product isolated from this reaction was 3,4,6-trichloro-3,4,6-trideoxy-D-allopyranose (17), obtained in

less than 1% yield. The melting point of (17), (143 - 144°) was found to be somewhat low compared to that reported in the literature, (170 - 171°)[29]. Since the compound was recrystallized from a solvent system different from that used by Jennings et al.[29], the discrepancy in the melting points may be attributed either to a difference in the distribution ratio of the α- and the β-anomers in the respective crystalline samples, or to a difference in the basic crystal structures of the samples. The latter phenomenon is illustrated by the report[63] on the melting points of the β-anomers of D- and L- allose, which were shown to be dimorphic. Furthermore, it is known[64] that some reducing sugars may often crystallize as solvated adducts.

The n.m.r. spectrum (table III) of (17), showed that the compound was present almost entirely in the β- configuration; a similar phenomenon was observed[65] in the spectrum of D-allopyranose. Thus, H-1 appeared as a doublet of spacing 7.5 Hz at τ 5.1. The highly deshielded hydroxyl proton at the anomeric position was found to resonate farthest downfield at τ 4.06, appearing as a broad singlet. H-3 was observed as a triplet at τ 5.30, while H-2 appeared as a quartet at τ 5.90. The non-appearance of the signal, m/e 61, (table IV), as a peak of significant intensity was indicative of the fact that (17) is not a methyl glycoside. More evidence in support of structure (17) was achieved when the compound was shown to reduce Fehling's solution. Furthermore,

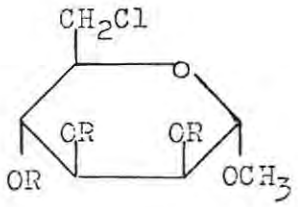
treatment with sodium periodate resulted in the disappearance (t.l.c.) of (17) after 24 hr. The elemental analysis of (17) was in accord with the expected structure.

When D-glucose was reacted with the reagent in the presence of pyridine, the major product formed, had the same chromatographic mobility as methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside. However, the mass spectrum showed that the compound was contaminated with some compound of higher molecular mass. The appearance of an additional peak of m/e 258, indicated that the contaminant was probably a monoformyl ester of the methyl dichloro-dideoxy-glycoside. Subsequent treatment of the material with 1-propanol for 24 hr afforded, after evaporation of the solvent and recrystallization (2X), methyl 4,6-dichloro-4,6-dideoxy-β-D-galactopyranoside (10), the physical constants of which were in agreement with those obtained before.

The preferential formation of the methyl B-glycosides as major products in the reaction of D(+) galactose and D-glucose was particularly noteworthy. Haynes et al.[66] reported that substitution reactions of glycosyl halides at C-1, often led to the formation of products with the α-configuration, for which they claim more stability over the β-sugars, irrespective of what the configuration at C-1 of the halide was. Thus the α-anomer of (10) was obtained after reaction at the reflux temperature of methanol, whereas (10) was produced at room temperature in the presence of silver oxide as catalyst [55]. Therefore, the preponderant formation of (10), in the reaction of D-glucose may be attributable

to the fact that dechlorosulphation was carried out at room temperature, if the sodium bicarbonate, also present in the reaction mixture, cannot be implicated. However, since the formation of the α-anomer as minor product was observed, a difference in the distribution of the different anomeric halides prior to dechlorosulphation, could be the determining factor towards the observed distribution of the anomeric methyl glycosides.

Ligman et al.[64] showed that in aqueous equilibrium solutions of D-glucose and D-galactose, the β-anomer occurred as the preponderant species over the α-anomer. Assuming the same phenomenon occurs in dimethyl formamide, then the formation of more halides with the α-configuration, from which the methyl β-glycosides would be readily formed at room temperature, is understandable. The preferential formation of methyl 4,6-dichloro-4,6-dideoxy-β-glucopyranoside from D(+) galactose could be similarly explained.



(5) R = SO_2Cl

Treatment of methyl α-D-mannopyranoside with the reagent at room temperature was shown (t.l.c.) to result in the formation of a single compound in 2 hr. Because this was the only reaction, amongst those investigated with hexopyranosides,

Table VI - Chemical shifts (τ-values) and first-order coupling constants (Hz) for (5)

	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	OCH_3
τ	4.80(d)	4.41 - 5.06(m)			5.76(m)	6.17(m)		6.40(s)

$J_{1,2}$ = 1.3 Hz

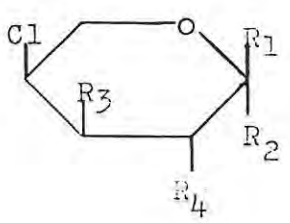
Key: d = doublet; m = multiplet; s = singlet

Spectrum measured in deuterochloroform.

which produced a single compound, further shown to be a chlorosulphate ester, there was some interest to isolate it. Thus methyl 6-chloro-6-deoxy- α-D-mannopyranoside-2,3,4-trichlorosulphate (5) was obtained crystalline in 58% yield. This represented an improved method for the synthesis of (5), since Jennings et al.[29] obtained the compound in 29% yield, in the reaction with the sulphuryl chloride-pyridine reagent. The m.p. and optical rotation of (5) were consistent with those reported in the literature[29].

The i.r. spectrum of (5) showed the presence of chlorosulphonyloxy groups. In the n.m.r. spectrum, (table VI), H-1 was observed as a doublet of narrow splitting at τ 4.80, while H-2, 3 and 4 appeared as a complex multiplet farthest downfield at τ 4.41 - 5.06, due to the deshielding effect of the chlorosulphonyloxy groups. The signal due to H-5 appeared as a multiplet at τ 5.76, slightly lower field to the resonance signal due to H-6,6' which was centred at τ 6.17.

An investigation of the reaction of D-mannose was undertaken and, contrary to that of the methyl glycoside, was shown (t.l.c.) to produce a very wide range of compounds of closely related chromatographic mobilities. Thus, no attempt was made to separate the products.



(11) $R_1 = R_3 = R_4 = H$; $R_2 = OCH_3$

(12) $R_1 = H$; $R_2 = OCH_3$; $R_3 = R_4 = Ac$

(13) $R_1 = OCH_3$; $R_2 = R_3 = R_4 = H$

(14) $R_1 = OCH_3$; $R_2 = H$; $R_3 = R_4 = Ac$

Reaction of methyl α- and β-Dxylopyranoside afforded methyl 4-chloro-4-deoxy-β-L-arabinopyranoside (11) and the corresponding α-anomer (13) respectively. The chlorosulphate ester from methyl α-D-xylopyranoside could be obtained crystalline and chromatographically homogeneous, even though it was dechlorosulphated without prior purification. From methyl β-D-xylopyranoside the chlorosulphate ester was found to be a syruppy compound. The m.p. and optical rotation of (11) were consistent with those reported in the literature[55].

The mass spectra of (11) and (13) showed that each of them contained a single chlorine atom, as was evident from the (M-31) and (M-31)+2 peak intensities, which were in the ratio of 3:1. For the diacetylated derivative of (11), that is, compound (12), the n.m.r. spectrum showed H-1 and H-3 as a multiplet at τ 4.70 - 5.07. H-2 and H-4 also appeared as a multiplet at τ 5.34 - 5.94, partially overlapping with the double doublet due to H-5, which appeared slightly lower field than was expected, because of the deshielding effect caused by the axially orientated acetoxy group at C-3. The deshielding effect of an axially orientated acetoxy group, on an axially orientated proton located at a position β to that of the acetoxy group was described by Lemieux et al.[67]. H-5' was also observed as a double doublet at 6.39.

The n.m.r. spectrum of (13) showed H-1 as a doublet centred at τ 5.26. The signal due to H-3 was observed at τ 5.46 as

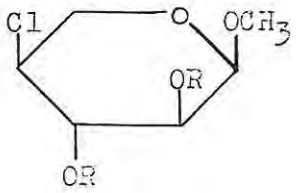
Table VII - Chemical shifts (τ-values) and first-order coupling constants (Hz) for (12), (13), (14), (15) and (16)

Compound	12[a]	13[b]	14[a]	15[b]	16[a]
H-1	4.48-4.76(m) includes H-3	5.26(d)	4.70-5.07(m) includes H-3	5.27(d)	5.09(d)
H-2	4.97(q)	see below	5.43-5.94(m) includes H-4	see below	5.15(dd)
H-3		5.46(bs)		5.50(bs)	4.47(t)
H-4	5.43(q)	5.98-6.81(cm) includes H-2		5.75-6.93(cm) includes H-2	5.87-6.38(cm)
H-5	5.80(dd)		5.82(dd)		
H-5'	6.24(dd)		6.25(dd)		
OH					
OCH_3	6.56(s)	6.59(s)	6.54(s)	6.61(s)	6.57(s)
OAc	7.89(s)		7.91(s)		7.91(s)
$J_{1,2}$		3.2	3.0	3.1	3.0
$J_{2,3}$					12.7
$J_{3,4}$					9.3
$J_{4,5}$	2.4		2.9		
$J_{4,5'}$	1.5		6.0		
$J_{5,5'}$	12.7		12.0		

Key: d = doublet; m = multiplet; q = quartet; dd = double doublet; s = singlet; cm = complex multiplet; bs = broad singlet; t = triplet

The superscripts (a) and (b) denote solvents as described in the experimental

a broad singlet. The rest of the ring protons appeared together with the hydroxyl protons as a complex multiplet at τ 5.98 to 6.81. The n.m.r. spectrum of the acetate (14) appeared, basically, similar to that of the acetate (12), except that H-2 and H-4 appeared as separate signals at τ 4.97 and 5.43 respectively, and none of them overlapped with the H-5 peak, which appeared without any deshielding effect due to an acetoxy group, since (14) is in the C-1 conformation. The n.m.r. spectral data for (12), (13) and (14) are presented in table VII, and the mass spectral data for (11) and (13) in table VIII. The elemental analyses for (11), (12), (13) and (14) were in accord with the expected structures.

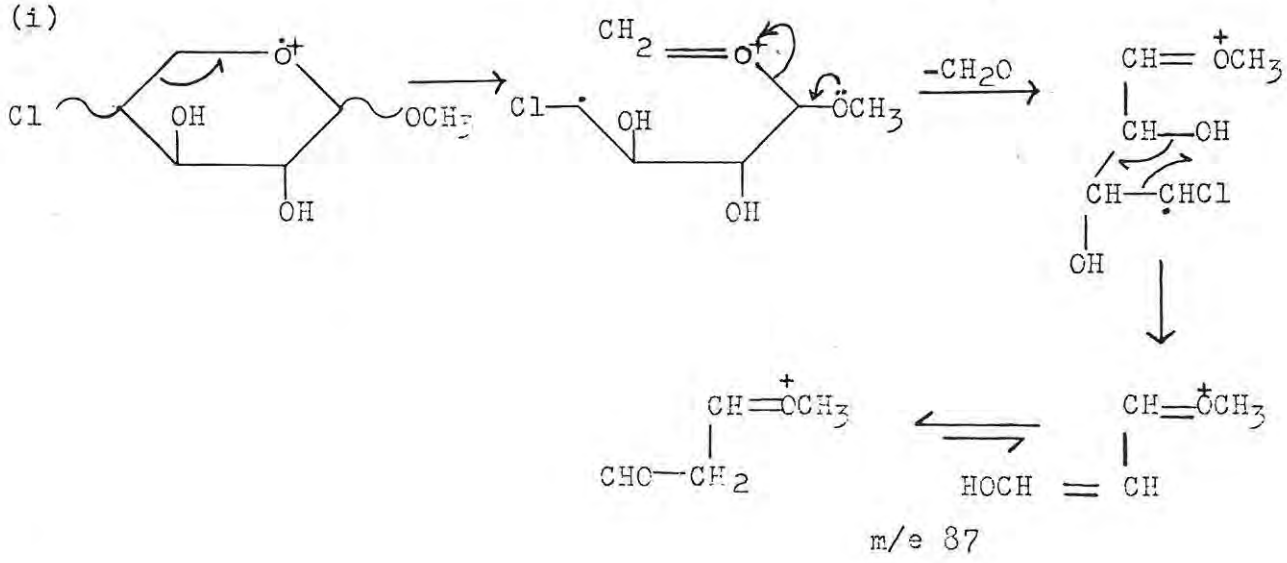


(15) R = H

(16) R = Ac

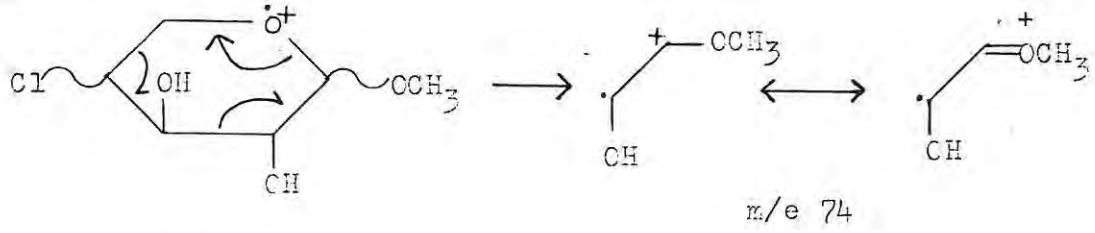
Methyl 4-chloro-4-deoxy- α- L-xylopyranoside (15) was obtained from the reaction of methyl β-D-arabinopyranoside. As in the reaction of methyl α-D-xylopyranoside, the chlorosulphate ester could be obtained crystalline and chromatographically homogeneous. In the n.m.r. spectrum of (15) (table VII) the only signals which could be clearly observed, besides that for the methoxyl protons, were those due to H-1 and H-3, and the former appeared as a doublet at τ 5.27, while the latter was observed as a broad singlet at τ 5.90. The rest of the ring protons, plus the hydroxyl protons, appeared as a complex multiplet over the range

(i)



m/e 87

(ii)



m/e 74

Scheme D : Some mass spectral fragmentation pathways for (11), (13), (15) and (21)

Table VIII -

Relative intensities in the mass spectra of (11), (13), (15), (20) and (21).

Compound		11	13	15	20	21
m/e		Relative intensity %				
M-31	151	1.60	4.47	4.73	21.14	10.60
(M-31)-18	133	0.32	0.30	1.00	5.01	2.00
M-60	122	1.12	5.01	1.00	2.11	4.47
	117	2.99	1.41	0.94	2.37	3.55
	104	3.76	2.50	2.51	5.62	11.22
	91	6.68	3.98	2.37	6.31	8.91
(M-60)-35	87	8.91	5.96	8.91	10.05	39.81
	74	10.0	10.0	10.0	11.22	19.96
	60	12.59	8.91	13.34	20.39	25.12
	61	79.43	44.67	46.24	70.79	75.03
	60	100	100	100	100	100

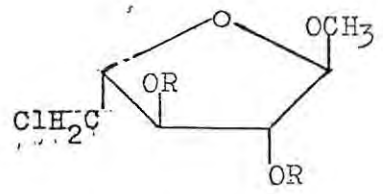
τ 5.95 - 6.93.

In the n.m.r. spectrum of (16) (table VII), H-3 was observed as a triplet, farthest downfield at τ 4.47, due to the deshielding effect of the acetoxy group. H-1 appeared as a doublet at τ 5.00, whilst H-2 was found to resonate at τ 5.15, appearing as a double doublet. A complex multiplet due to H-4, 5 and 5' was observed in the range of τ 5.87 - 6.38. The elemental analyses of (15) and (16) were in accord with the expected structures. Some important mass spectral fragmentation pathways followed by (11), (13) and (15) are given in scheme D. The other fragmentation pathways followed by these compounds are similar to those shown for the methyl hexopyranosides in scheme A.

The reaction was found to be particularly useful with the methyl pentopyranosides compared with the methyl hexopyranosides. Thus, yields of up to 88% could be obtained from reactions with the former, whereas with the latter the yields never exceeded 50%, with the exception of methyl α-D-mannopyranoside.

Reaction of D-xylose yielded methyl 4-chloro-4-deoxy-α-L-arabinopyranoside (13) as major product, together with the β-anomer (11) as a minor product. The kind of distribution of the anomeric products, observed in this reaction could be explained in a manner similar to that

described for the reaction of D-glucose and D-galactose.



(20) R = H

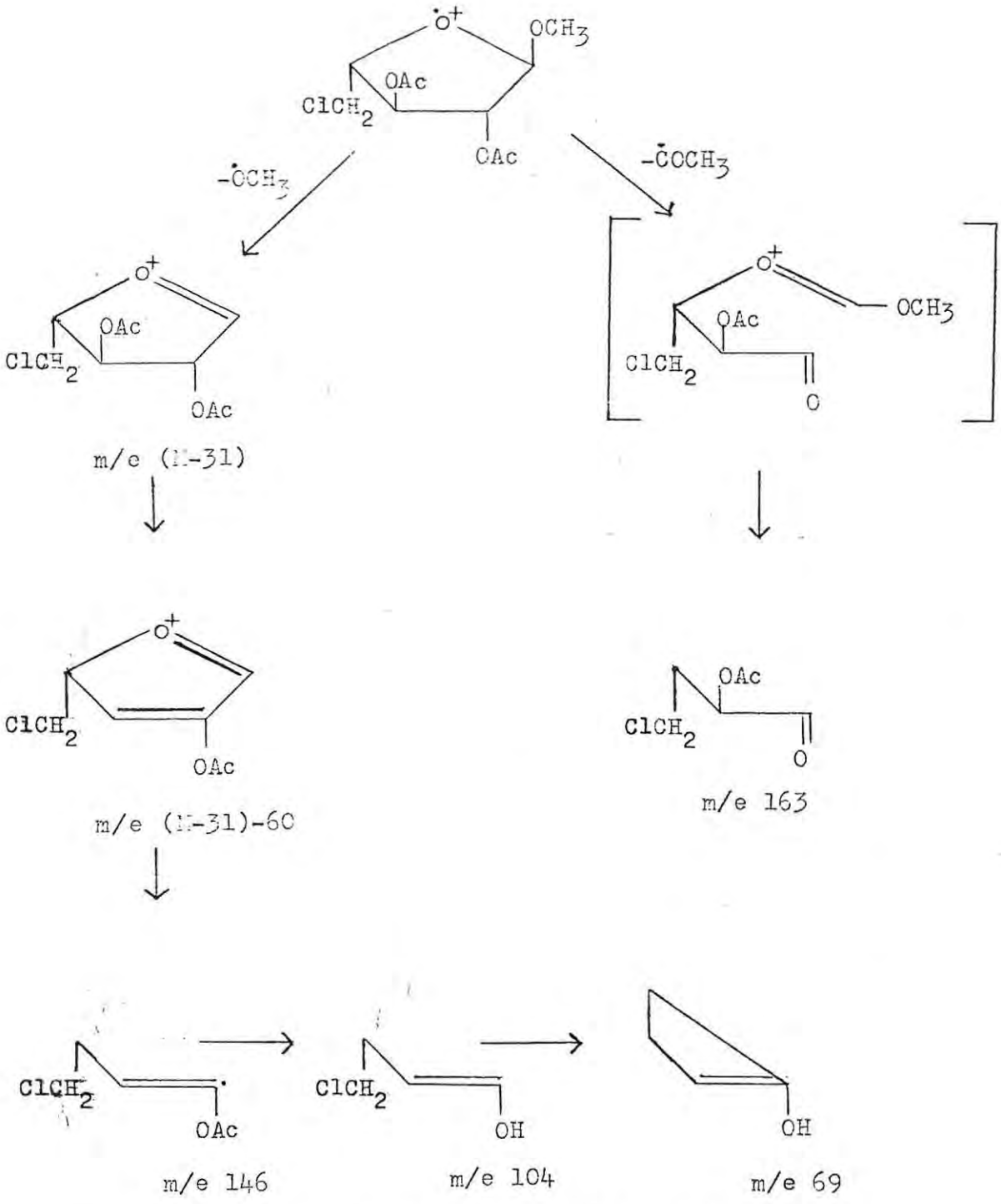
(22) R = Ac

When L(+)arabinose was reacted with the reagent, three products were formed, amongst which methyl 5-chloro-5-deoxy-α-L-arabinofuranoside (20) was obtained as the major one, in 19.7% yield. The optical rotation of (20) compared well with the one reported[57] for methyl α-L-arabinofuranoside.

In the n.m.r. spectrum of (20), H-1 was observed as a doublet at τ5.25 with a coupling constant of $J_{1,2}$ = 2.0 Hz. The other protons appeared as a complex multiplet over the range τ5.66 - 6.86. The mass spectral data (table VIII) were not that different from those of the pentopyranosides.

That compound (20) was a furanoid sugar was also supported by its chromatographic mobility relative to that of the pentopyranoside (21).

It is noteworthy that in this reaction a furanoid sugar was the major product. This may be explained by the observation[64] that L(+) arabinose is one of the free sugars, which has a greater tendency to form furanoses during mutarotation in solution. The fact that no formation of (20) was reported in



Scheme E : Mass spectral fragmentation pathways for compound (22).

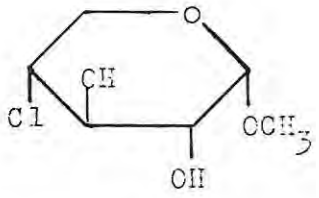
Table IX

Relative intensities in the mass spectrum of compound (22)

m/e	235	175	163	146	129	104	69	43
	M-31	(M-31)						
		-60						
Relative intensity	0.11	0.75	0.24	11.89	2.66	3.55	6.31	100

the reaction of L(+) arabinose with the sulphuryl chloride - pyridine reagent[58] could be explained by the difference in the solvent properties of pyridine and dimethyl formamide. L(+) arabinose dissolved readily in the latter solvent, thus encouraging mutarotation to occur before reaction with the reagent, whereas in the former solvent, the sugar was only partially dissolved[58] and thus, the reaction was virtually heterogeneous.

In the n.m.r. spectrum of the acetate (22), H-2 and H-3 appeared as a multiplet farthest downfield at τ 4.55 - 5.35. H-1 and H-4 were also observed as a multiplet slightly higher field at τ 5.43 - 5.95. The multiplet due to H-5,5' appeared at τ 5.95 - 6.54, overlapping with the methoxyl protons singlet, which was observed at τ 6.47. The mass spectral fragmentation pathways for (22) are given in scheme E and the relative peak intensities are presented in table IX.

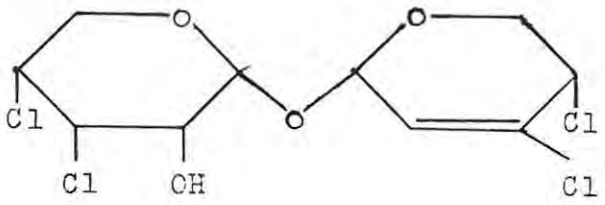


(21)

One of the minor products formed in the reaction of L(+) arabinose was methyl 4-chloro-4-deoxy-α-D-xylopyranoside (21) for which, the optical rotation was consistent with that reported by Jennings et al.[58]. The m.p. (89 - 91°), however,

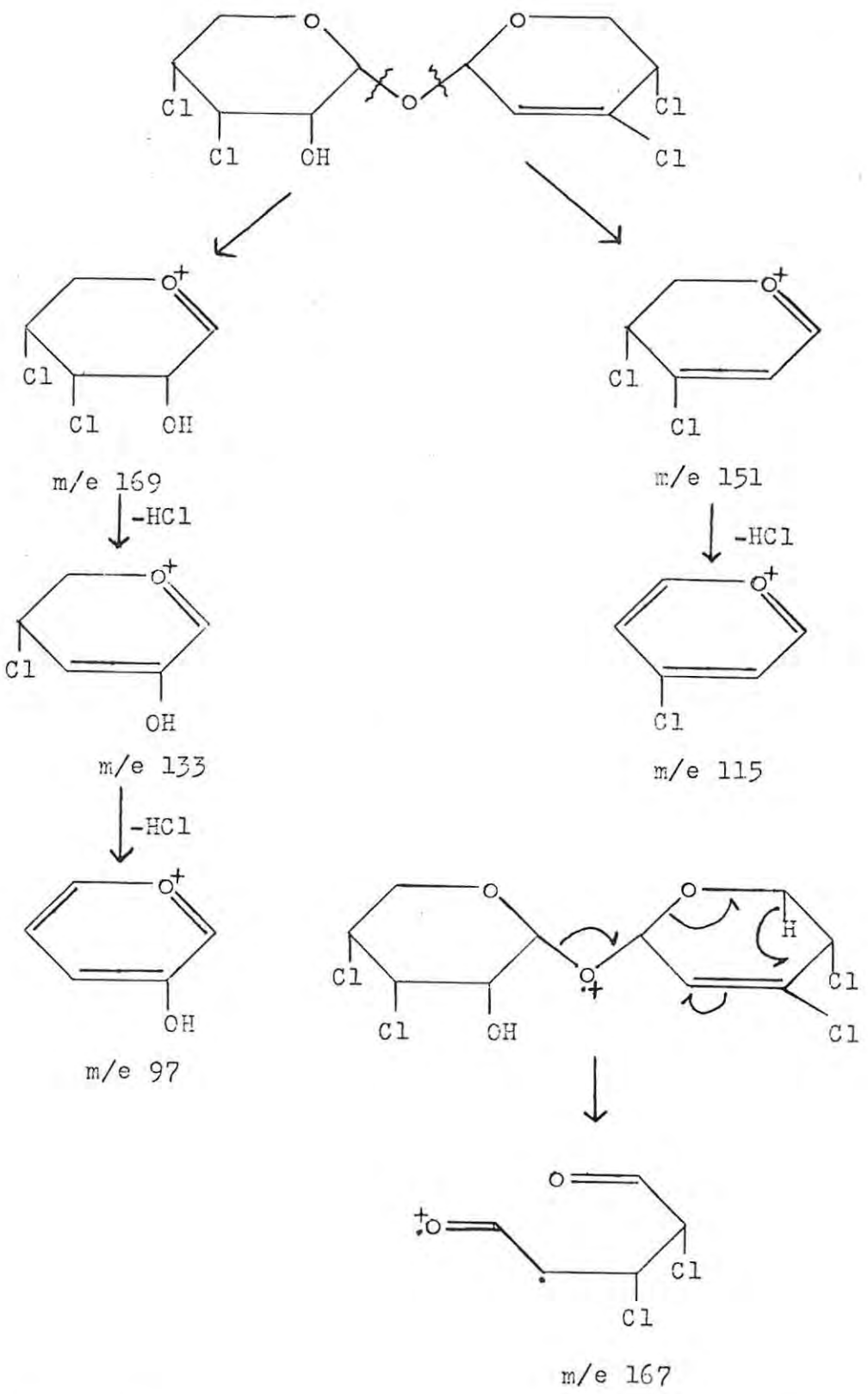
was somewhat lower than the one reported (102 - 103°). This may be due to contamination either with the β-anomer or with the free sugar derived from compound (20). The latter compound may be formed during dechlorosulphation, due to the presence of traces of water in methanol, and it has about the same R_f value as compound (21).

The n.m.r. spectrum of (21) did not show much, except for the doublet due to H-1, which appeared at τ 5.15 with splitting of $J_{1,2}$ = 3.3 Hz, a singlet due to the 2 hydroxyl protons at τ 7.8 and a singlet at τ 6.5 due to the resonance of the methoxyl protons. The other protons were observed as a complex multiplet at τ 6.0 - 6.9.



(19)

Compound (19), 4-deoxy-3,4-dichloro-D-glycero-pent-2-enopyranosyl 3',4'-dichloro-3',4'-dideoxy-α-D-ribopyranoside, was obtained crystalline in less than 1% yield. The i.r. spectrum of (19) showed a broad peak at 3.08 μm, which was indicative of the presence of a hydroxyl group, and the peak of moderate intensity at 6.10 μm was due to the presence of a C-C double bond. The mass spectral fragmentation pathways for (19) are shown in scheme F. No molecular ion peak could be observed in the mass spectrum, thus implying



Scheme F - Mass spectral fragmentation pathways for compound (19)

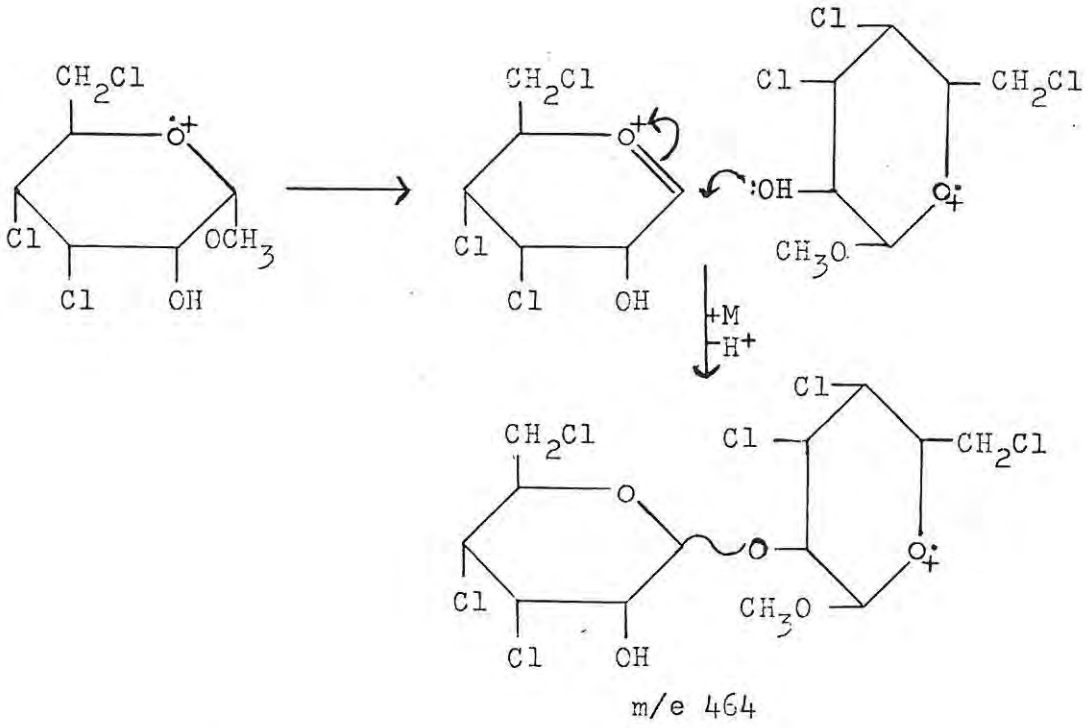
Table X -
Relative intensities in the mass spectrum of compound (19)

m/e	169	167	151	133	131	115	103	97	55
relative intensity	1.03	2.11	7.05	14.16	99.56	6.81	5.16	87.52	100

that fragmentation began with the breaking of the inter-glycosidic bond. The relative peak intensities in the mass spectrum are presented in table X. In the n.m.r. spectrum of (19) the olefinic proton was observed as a doublet at 3.80 with a coupling constant of 2.9 Hz. Unexpectedly, the spectrum appeared like that of a symmetric disaccharide, and thus, H-5 appeared as a double doublet at τ 5.42, partially overlapping with H-4, which was centred at τ 5.50. The double doublet due to H-5' was observed at τ 6.03.

The fact that no signal due to a methoxyl group could be observed, and that the compound was non-reducing, suggested that it was a trehalo-type dimer similar to the one described by Jennings et al.[58]. Even though the location of the double bond could not be established with absolute certainty, the presence of a hydroxyl group was clearly evident from the i.r. spectrum. Furthermore, treatment of a small amount of (19) with the acetylating mixture, was shown by t.l.c. to give rise to a component of higher chromatographic mobility. The n.m.r. data for (19), (20), (21) and (22) are presented in the experimental section. The elemental analyses of the compounds, (19), (20), (21) and (22), were in accord with the expected structures.

The characteristic feature[68] of the mass spectra of methyl glycopyranosides, that is, the presence of peaks M+1, was well noted in the mass spectra recorded for the compounds synthesized in the present work. Another feature, well



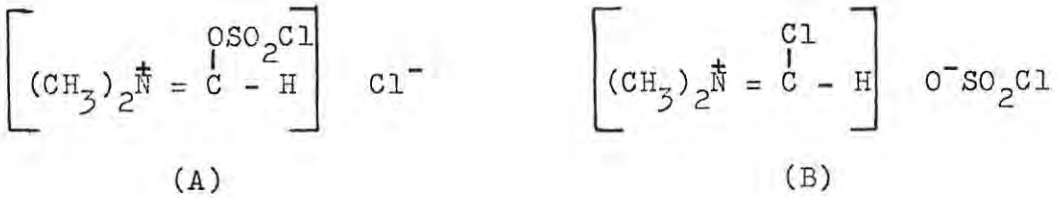
Scheme G - An illustration of the dimerization in the mass spectrometer

noted in the mass spectra of a few methyl glycosides was dimerization, which apparently occurred inside the mass spectrometer. This was well pronounced in the mass spectra of methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside (3), methyl 3,6-dichloro-3,6-dideoxy-β-D-gulopyranoside (7), methyl 5-chloro-5-deoxy-β-D-xylofuranoside (20) and methyl 4-chloro-4-deoxy-α-xylopyranoside (21). Thus, the mass spectrum of (3), showed a peak at m/e 464. A mechanism leading to the formation of such an ion was proposed, and is given in scheme G. It was further observed, that such an ion, upon formation, is then fragmented in a manner analogous to that of disaccharides. Since there is no common structural feature in the above sugars, which could account for such a phenomenon, it is likely that whether dimerization will occur or not, would depend on the temperature at which the probe is heated.

In the way of a conclusion to this section, some aspects about the sulphuryl chloride - dimethyl formamide reagent will be discussed.

The reagent was first prepared by Kühle et al.[69], and was obtained as a hygroscopic, crystalline compound of m.p. 40 - 41°. On the basis of its infra-red spectrum, they assigned to it the structure (A) which they found to be stable up to 170 -180°, whereupon it decomposes into sulphur dioxide, hydrogen chloride and N,N-dimethyl carbamyl chloride. However, a later investigation into the structure of the

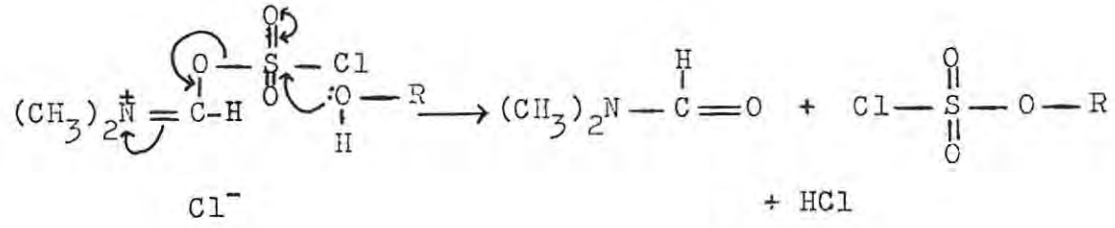
reagent by Lehmann and co-workers[70] showed that the correct structure was (B). Thus when



(A) (B)

(B) was reacted with $NaClO_4$ in dry acetonitrile, a precipitate of $NaSO_3Cl$ was formed.

In the investigation just undertaken, of the reaction of the reagent with carbohydrates, the reagent was prepared <u>in situ</u>. That, therefore, brings about a possibility of having both species (A) and (B) existing in equilibrium with each other. The fact that the reaction led mainly to the formation of chlorosulphate esters, suggests that the predominant and probably the most reactive species is (A). A proposed mechanism for the reaction with (A) is given below:



Cl^- + HCl

Thus it appears that in (A), the sulphur atom is still more electrophilic compared to the carbon atom, in contrast to the methanesulphonyl chloride - dimethyl formamide

reagent (14), in which nucleophilic attack occurs at the latter centre. This is, however, understandable if the electron-withdrawing properties of the chlorine atom in (A) are considered. Furthermore, the bulky methyl group would be likely to exert some steric hindrance to an approaching nucleophile.

On certain occasions the formation of formyl esters was noted. That may be attributable to the presence of the species (B) of the reagent, in which nucleophilic attack would occur at the carbon atom, in the same manner as was proposed by Hanessian et al.[13] for the reaction with the N,N-dimethyl (chloromethylene) ammonium chloride reagent.

At this stage, the formation of methyl 4,6-dichloro-4,6-dideoxy-2,3-di-O-formyl-α-D-glucopyranoside (4) may be readily explained, thus, upon heating, chlorosulphate esters became dechlorosulphated, because of their thermodynamic instability, while the formyl esters were unaffected.

With the mechanism thus proposed for the initial reaction of the reagent with carbohydrates, it becomes clear that subsequent chlorination at secondary positions with inversion of configuration, would occur by a nucleophilic bimolecular substitution S_N2 mechanism.

The unfavourable substitution[60] at C-3 of methyl β-D-galactopyranoside resulting in the formation of methyl

3,6-dichloro-3,6-dideoxy-β-D-gulopyranoside (7), was unexpected. But Bhatt et al.[49] reported substitution at C-3 of the galacto-monosaccharide unit of methyl -β lactoside, in the reaction with methanesulphonyl chloride in dimethyl formamide. This, they attributed to an abnormally high reactivity of the 3-hydroxyl group towards esterification, and since chlorine-substitution is not rate-limiting, such anomalous substitution at C-3 should not be surprising. A similar explanation could be offered for the formation of (7). Furthermore, the good solvating properties of dimethyl formamide for the S_N2 transition state may be of importance.

The unexpected formation of methyl 3,4,6-trichloro-3,4,6-trideoxy-α-D-allopyranoside (3), when methyl α-D-galactopyranoside was heated with the reagent, was found to have occurred via hydrolysis of the methyl glycosidic bond with the formation of a β-D-glycosyl chloride. This could be expected, when the acidity of the reaction mixture was coupled with heating. Thus, subsequent dechlorosulphation in methanol afforded (3), in which chlorination at C-3 had occurred in the intermediate glycosyl chloride. This was confirmed when (3) could not be detected when the reaction was conducted in the presence of pyridine.

One of the advantages of using this reagent, is that reactions are performed at moderate temperatures, where temperature control is more manageable. The colouring of

reaction mixtures, which often required treatment of products with animal charcoal was one major disadvantage. However, it is hoped that the reagent will find much use in future, both as a chlorosulphating and a chlorinating reagent.

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