INTERACTION OF ELECTROPHILIC REAGENTS WITH CYCLIC ACETALS AND KETALS

A Thesis submitted by

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Doctor of Philosophy

JANUARY 1960

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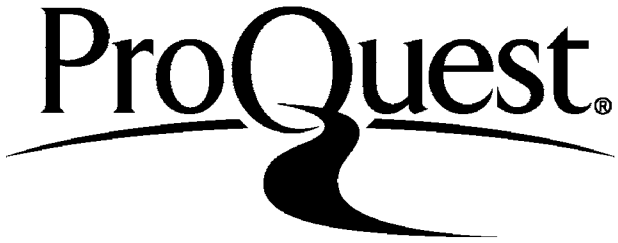

ACKNOWLEDGMENTS

The author would like to acknowledge the help of Professor E. J. Bourne and of her supervisor, Dr. T. G. Bonner, and to thank Mr. C. H. Miller for his continued interest.

ABSTRACT

The reactions of some electrophilic reagents with cyclic acetals and ketals and other derivatives of polyols have been investigated.

Friedel-Crafts reagents, such as acetic anhydride and methyl iodide in the presence of aluminium chloride, cause ring opening of cyclic acetals and ketals, but do not yield the expected acetates and methyl ethers. These may be formed during the reaction and then react further with the aluminium chloride; alternatively, aluminium chloride itself may cause ring opening.

Treatment with boron trichloride, followed by methanolysis, converts all except the most stable cyclic acetals and ketals into the parent polyols. The results of these reactions suggest that, of the different acetals and ketals, only the methylene acetals retain the alkylidene residue as an α-chloro ether group. Attempts have been made to replace the chlorine and obtain a more stable derivative and the reduction of the product of the reaction of boron trichloride with 2:5-O-methylene-D-mannitol

yielded 2-*O*-methyl-*D*-mannitol, a new compound. Further information about the mechanism of the reaction of boron trichloride with cyclic methylene acetals has been obtained from the infra-red spectrum of the product.

A mixture of a dicarboxylic acid and trifluoroacetic anhydride reacts with tri-*O*-methylene-*D*-glucitol to yield a linear polymer, containing free alcohol groups. Di-*O*-methylene pentaerythritol was expected to react similarly, but yielded a cross-linked polymer. The reaction of mono-carboxylic acids with this acetal and also with the benzylidene acetals and *iso*propylidene ketal of pentaerythritol has been investigated and compared with the reactions of the corresponding hexitol derivatives.

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INTRODUCTION

STRUCTURE OF CYCLIC ACETALS AND KETALS OF POLYOLS

Aldehydes react readily with alcohols in the presence of acid catalysts. Hemiacetals are probably formed but react further to give acetals:

$$R.CHO + R'.OH \rightarrow R.CH(OH).OR' \xrightarrow{R'.OH} R.CH(OR')_2 + H_2O \quad \text{(Equ.1)}$$

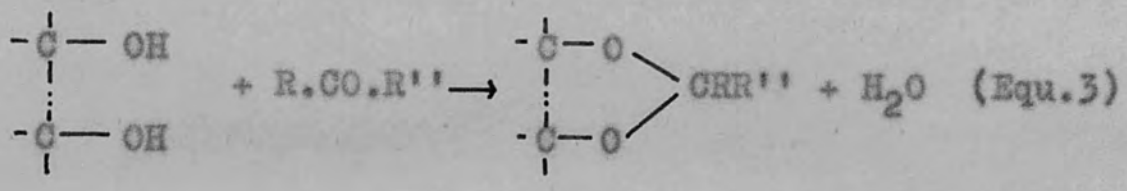
Ketones undergo a similar reaction but much less readily and ketals are usually prepared by reaction of the ketone with the orthoformate esters of the alcohols:

$$R.CO.R'' + CH(OR')_3 \rightarrow R.C(OR')_2R'' + H.CO_2R' \quad \text{(Equ.2)}$$

Acetals and ketals can be regarded as gemdiethers derived from the unstable hydrated carbonyl compounds.

A polyhydric alcohol may react with an aldehyde or ketone to give a cyclic product. This is found to occur readily in molecules where the two alcohol groups reacting with the carbonyl compound are on adjacent (α) carbon atoms, giving a five-membered ring, or attached to

the carbon chain in the β-position to each other, giving a six-membered ring. As the distance between the two groups increases, the chance of an intramolecular reaction decreases and an intermolecular reaction, forming a linear acetal, is more probable.



(Equ.3)

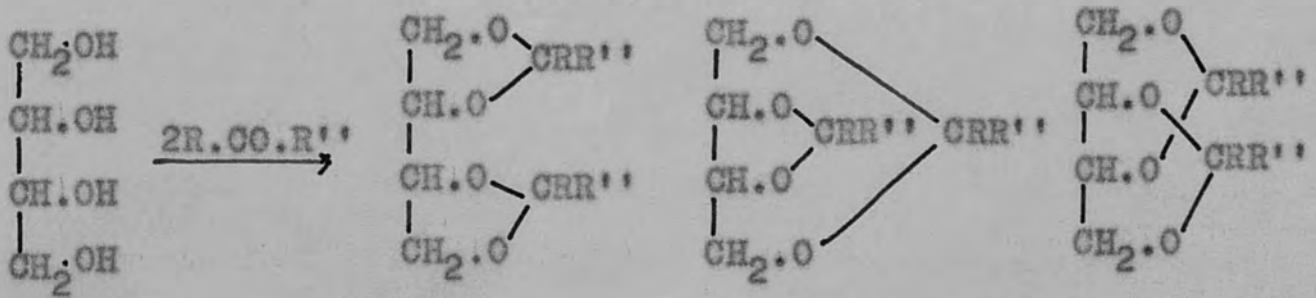
(The polyol need not be in the form of its ortho formate ester but reacts directly with a ketone to give a good yield of cyclic ketal)

The cyclic acetals and ketals have found wide use in carbohydrate chemistry, particularly as derivatives of the reduced monosaccharides or alditols[1]. They are usually crystalline with sharp melting points and relatively high specific rotations. In many cases, the positions of the acetal or ketal links in the molecule are known and partially substituted derivatives of the alditol can be prepared from them. If the acetal or ketal contains free alcohol groups in its molecule, these can be etherified or esterified and the carbonyl residues removed by acid

hydrolysis to give ethers or esters of known structure. Another type of reaction, which involves the opening of the dioxo rings to give alditol derivatives of known structure, will be discussed later.

Cyclic acetal and ketal derivatives have also been important in the chemistry of pentaerythritol[2]. Both mono- and di-substituted derivatives are known and are usually crystalline compounds with lower melting points than the free alcohol. They are used in the purification of pentaerythritol and in the preparation of partially substituted derivatives and played an important part in the proof of the tetrahedral configuration of the central carbon atom of the pentaerythritol molecule.

Alditols which contain three or more alcohol groups in their molecules might be expected to yield a mixture of products, formed by reaction of different pairs of alcohol groups with an excess of carbonyl compound:



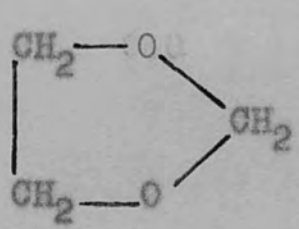
(Equ.4)

(In pentaerythritol all alcohol groups are in equivalent positions and only one product is possible). Investigations have been carried out to discover whether such mixtures are formed and it has been shown that in most reactions of a carbonyl compound with an alditol this is not the case. Even in reactions of the hexitols, where several products are possible, a good yield of a single product is obtained.

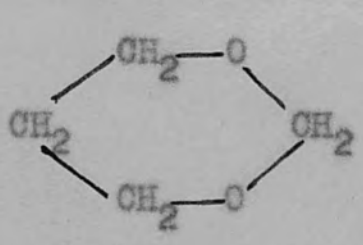
The arrangement of the dioxo rings has been worked out in many cases. Where all the alcohol groups have reacted with the carbonyl compound, as in the tri-acetals and tri-ketals of some hexitols, the positions of the rings have not been determined directly, although this may become possible from an examination of their infra-red absorption spectra. Instead, partially substituted compounds containing fewer rings and hence some free alcohol groups are examined. These can be obtained from the mother liquors of the preparation of the fully-substituted acetal or ketal and it is assumed that they are intermediates in the reaction and that the dioxo rings occupy the same position as those in the fully-substituted compound. Alternatively, one or more rings in the fully-substituted compound can be opened to give an acetal or ketal

containing free alcohol groups; again it is assumed that these contain the remaining rings in the same position as in the fully-substituted compound. The position of vicinal free alcohol groups can be shown by periodate oxidation and the presence of primary alcohols can be detected by their characteristic reactions. In this way, the structure of the partially substituted compounds can be determined and the arrangement of the rings in the fully-substituted compounds deduced. The Fischer projection formulae of some acetals and ketals are written out in Fig. I.

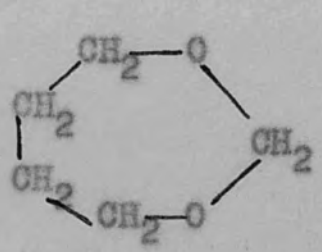
From these examples, it will be seen that five- and six-membered 1:3-dioxo rings are common, but that only ~~one~~ two compounds contain a seven-membered ring. These compounds are substituted derivatives of the heterocyclics:



1:3-dioxalan



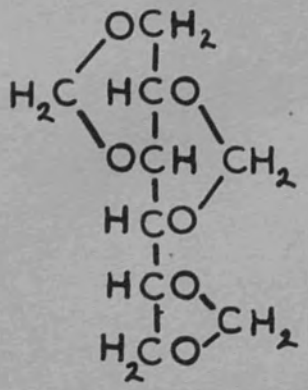
1:3-dioxan



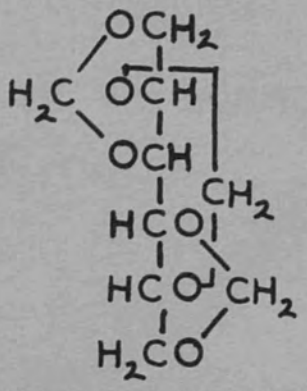
1:3-dioxepan

(Equ.5)

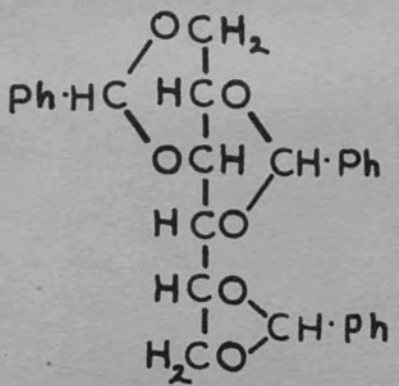
FIG. I



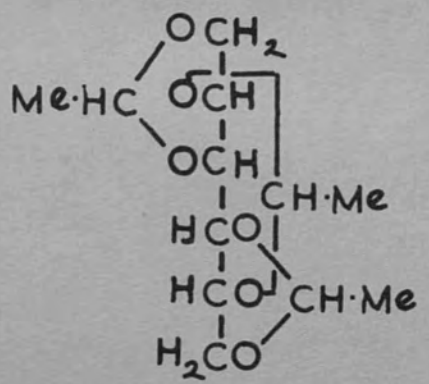
1:3-2:4-5:6-TRI-O-METHYLENE-D-GLUCITOL [3a,b.]



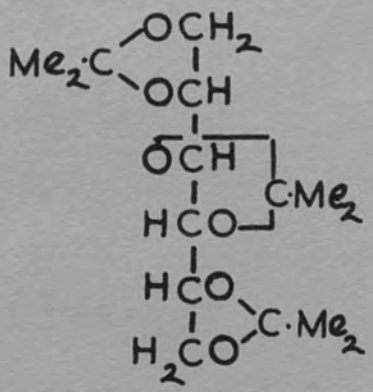
1:3-2:5-4:6-TRI-O-METHYLENE-D-MANNITOL [4,5.]



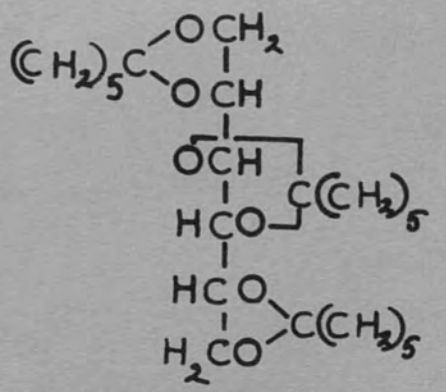
1:3-2:4-5:6-TRI-O-BENZYLIDENE-D-GLUCITOL [6]



1:3-2:5-4:6-TRI-O-ETHYLIDENE-D-MANNITOL [7]



1:2-3:4-5:6-TRI-O-ISOPROPYLIDENE-D-MANNITOL [8]



1:2-3:4-5:6-TRI-O-CYCLOHEXYLIDENE-D-MANNITOL [9]

No compounds have so far been prepared which contain larger rings. It will be noticed also that, although all the parent compounds are hexitols, the arrangement and size of the rings depends on the structure of the carbonyl compound and on the configuration of the reacting alcohol groups. Thus the aldehydes, formaldehyde and acetaldehyde, react with mannitol to give products containing two six-membered rings and one seven-membered ring, but the ketones, acetone and cyclohexanone, give products containing three five-membered rings. The configuration of the alcohol groups is seen to be important when the methylene acetals of D-mannitol and D-glucitol are compared. The two hexitols differ only in the configuration of one carbon atom but they give products with quite different arrangements of rings.

When the structure of several of these cyclic acetals and ketals had been worked out, it became clear that some types of dioxo ring were preferentially formed in reaction with a given carbonyl compound. It was then possible to draw up an order of preference for the formation of the different types of ring by comparing the possible products with those in fact formed[1,10]. To simplify the presentation of these results, a method of classifying the

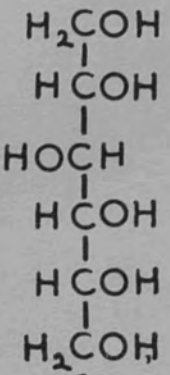
different types of ring has been worked out. The name of the ring depends on the relative positions and configurations of the two alcohol groups linked by the carbonyl residue. The smallest, five-membered ring results from the reaction of an alcohol group with a second alcohol attached to the adjacent carbon and is termed an α-ring. Similarly, six- and seven-membered rings are termed β and γ. If one of the reacting alcohol groups is primary, only one kind of a given size of ring is possible. If both are secondary, the arrangement of the ring substituents depends on the relative positions of the alcohol groups in the Fischer projection formula. Where these are on the same side of the carbon chain (cis), the ring is named αC, βC or γC, depending on its size; where the groups are on opposite sides (trans) the ring is named αT, βT or γT.

The structures of the chief products of the reaction of carbonyl compounds with alditols show that, with aldehydes, a βC ring is preferred. If there are no free alcohol groups in the positions required to give this type of ring, a β ring is formed and, where this is not possible, α, αT, βT, or γT rings are formed. When the carbonyl compound is a ketone, five-membered rings are

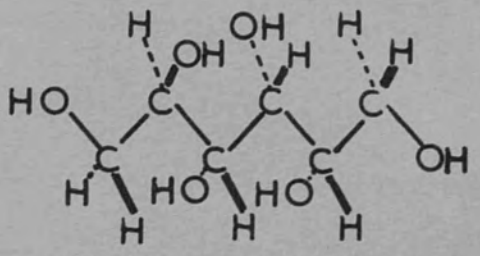
formed and an ^{a} ring is preferred to an ^{a}T ring, where either is possible. These rules have been modified slightly for the case of a particular aldehyde and are generally accurate in the prediction of the structure of a new acetal or ketal.

A theoretical basis for these rules has been suggested from a consideration of the relative ease with which the possible rings would be formed.[11] The alditol is assumed to be in a fully staggered conformation, in which the carbon-carbon bonds have rotated so that the distance between the atoms of the substituents on adjacent carbons is not less than the sum of their van der Waals radii. Non-bonded interactions between the substituents are then at a minimum and this is the most stable conformation of the molecule[12]. (It will be noticed [Fig.11] that the alcohol groups in the staggered conformation are in different relative positions to those in the Fischer projection formula. This is because, by convention, the projection is drawn from a three-dimensional model of the D-glucitol molecule in which the carbon-carbon bonds have not rotated to give the fully staggered form. In this model, the distance between adjacent substituents is less than the sum of their van der Waals radii. Therefore, to accommodate the substituents, the bond angles must become

FIG. II



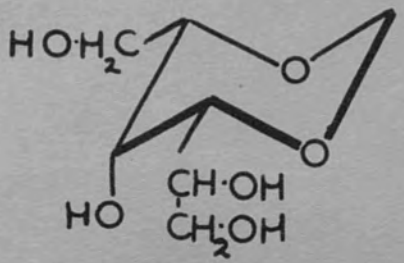
FISCHER PROJECTION



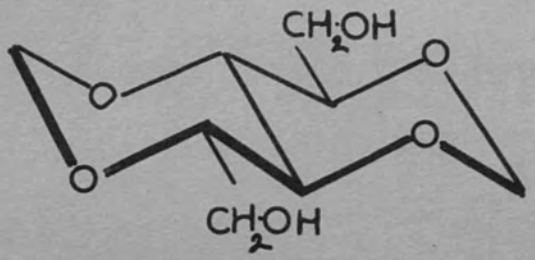
STAGGERED CONFORMATION

— in front of paper
— in plane of paper
··· behind paper

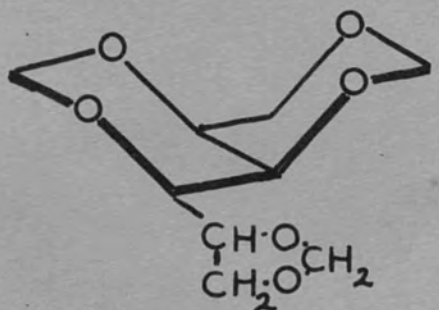
D-GLUCITOL



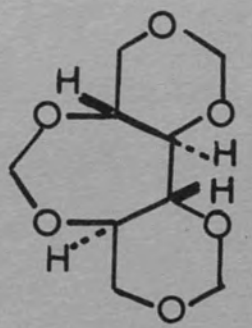
2:4-O-METHYLENE
-D-GLUCITOL



2:4-3:5-DI-O-METHYLENE ALLITOL



1:3-2:4-5:6-TRI-O-METHYLENE
-D-GLUCITOL



1:3-2:5-4:6-TRI-O-METHYLENE
-D-MANNITOL

deformed and this conformation is unlikely to be the most stable under normal conditions.) The distance between the two oxygen atoms in a 1:3-dioxo ring can be calculated from a knowledge of bond lengths and angles and it is assumed that rings are most readily formed from alcohol groups in which the oxygens are already in or near these positions. Pairs of alcohols can attain the required position by deformation of bond angles or rotation of carbon-carbon bonds, but these would be expected to react with the carbonyl compound less readily. In this way, the observed order of preference for the reactions with aldehydes can be explained, but it does not account for the formation of five-membered rings with ketones.

Another theoretical explanation has been suggested more recently[13]. The assumption made in this is that the product formed in greatest yield contains the most stable ring system: this is the system containing the least non-bonded interactions between substituents of the dioxo rings. Although much work has been carried out to discover the most stable conformations of alicyclic compounds, less is known about heterocyclics containing the 1:3-dioxo rings. The steric effect of the two unshared pairs of

electrons on the ring oxygen atoms is not known, but in many cases the most stable conformation of the rings is similar to that of the corresponding alicyclics. The five-membered 1:3-dioxalan ring is probably planar. The six-membered 1:3-dioxan ring, in its most stable conformation, takes up the chair form, in which the ring substituents are either axial or equatorial with respect to the ring. The bond linking any axial substituent to a ring carbon atom is perpendicular to the mean plane of the molecule and the bond linking an equatorial substituent is directed away from the ring at an angle of 60° or 120° to the axial bonds. Bulky substituents can occupy equatorial positions without approaching closely to other ring substituents, but if they are in axial positions, the distance between these and other axial substituents on the same side of the ring may be less than the sum of their van der Waals radii unless the bond angles become distorted and the ring unstable. One exception to this is found in the very stable βC-ring in 2:4-O-methylene-D-glucitol (Fig. II). If the two bulky substituents are in equatorial positions, the alcohol group on carbon 3 of the carbon chain must be in the axial position. This evidently does not cause any instability and it may be because the unshared pair of

electrons on the ring oxygens occupies less space than axial hydrogen atoms attached to carbon. The results from the study of alicyclic compounds cannot therefore always be applied to heterocyclic compounds.

The preferential formation of five-membered rings in the reaction of ketones with alditols may be because, if they were formed, six-membered rings must contain one of the alkyl substituents on the carbonyl residue in the axial position. This would render them unstable and may account for the greater stability of the smaller, planar ring.

The most stable conformation of the seven-membered 1:3-dioxepan ring probably resembles that of 1:3-dioxan, but is more flexible.

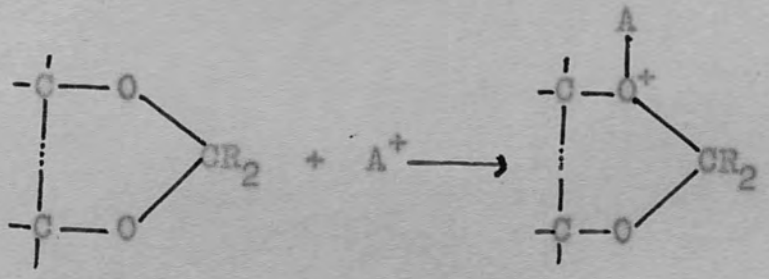
The preferred conformations of fused six- and seven-membered rings, often found in cyclic acetals, can be deduced by comparison with the decalins. Compounds in which, in the most stable conformation, all bulky substituents are in equatorial positions are again usually more stable than compounds which contain an axial substituent other than hydrogen. The ring fusion can be cis or trans, depending on the configuration of the alcohol groups involved in ring formation (Fig. II).

The first approach, to explain the preference for the formation of certain rings, makes the assumption that the chief product from the reaction of an aldehyde with an alditol will be the one which involves the least distortion of the alditol molecule in its most stable conformation. The second approach assumes that the chief product from a reaction which has come to equilibrium is that containing the most stable ring system, in which least non-bonded interactions occur. These both account for the observed order of preference in ring formation. In some reactions, the empirical rules cannot differentiate between two possible products and it is in these cases that the second approach is particularly useful. It has been applied successfully in the prediction of the most stable product from the reaction of the heptitol, volemitol[14]. The chief product was found to contain in its molecule two six-membered rings and one seven-membered ring, fused in the stable trans-anti-trans configuration.

REACTIONS OF CYCLIC ACETALS AND KETALS OF POLYOLS

It was mentioned earlier that acetals and ketals can be regarded as gemdiethers, derived from the alcohol and the hydrated carbonyl compound. They are stable to oxidation

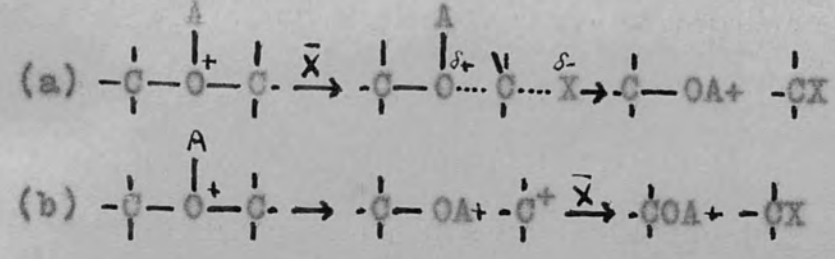
which would affect the free alcohol and are often used to protect some alcohol groups in a polyol molecule, while others are esterified or etherified under alkaline conditions. Thus, their reactions resemble those of aliphatic ethers and, when they do undergo reaction, the initial attack with both types of compound is probably by an electrophilic reagent on the unshared electrons of the oxygen atoms[15]. This gives a co-ordination compound, containing a trivalent oxygen atom, its bonds distributed pyramidally about it. Any electrophilic group in the molecule reduces the electron density on the oxygen and in such cases the co-ordination compound will be less readily formed.



(Equ.5)

These co-ordination compounds are seldom isolated, as they readily react with any nucleophilic reagents that are present. The ethers and cyclic acetals and ketals are usually unreactive towards all except very powerful nucleophilic reagents, but the formation of the third bond on the oxygen

atom alters the electron distribution in the molecule and reduces the electron density on the carbon atoms adjacent to the co-ordinated oxygen. One or both of these can be attacked and the alkoxide residue displaced by the nucleophilic group. Just as nucleophilic substitution at a saturated carbon atom can occur by two types of mechanism[16], here the carbon-oxygen bond may break heterolytically, as the new bond between the carbon and incoming group is formed, or it may break first, liberating a carbonium ion:



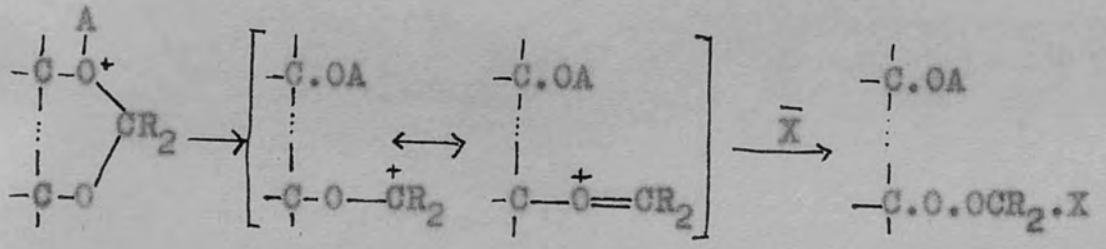
(Equ.6)

The operative mechanism will depend on the nature of the groups attached to the co-ordinated oxygen, on the strength of the nucleophilic reagent and also on the nature of the reaction solvent.

The carbon-oxygen bond most readily broken will depend on the mechanism of the reaction. If this is bi-molecular, as in (a), the nucleophilic attack will be directed towards the carbon with the lower electron density;

this is the carbon carrying the substituents with the smaller electron releasing power. (If these substituents are bulky, they may hinder attack at this carbon and reaction will then occur at the other carbon). If the reaction is unimolecular, as in (b), the carbon-oxygen bond which breaks will be the one which yields the most stable carbonium ion. In many reactions, the products are altered if the mechanism changes.

In the reaction of cyclic acetals and ketals, the second oxygen can stabilise a positive charge on the carbon atom derived from the carbonyl residue. It seems probable, therefore, that fission occurs by a unimolecular mechanism to give this carbonium ion:



(Equ.7)

The presence of the second oxygen favours unimolecular fission and this may account for the much greater reactivity of the cyclic acetals and ketals compared to most ethers, which contain no such group. The unusual reactivity of benzyl and allyl ethers may also be due to the formation of stabilised

carbonium ions by heterolytic fission.

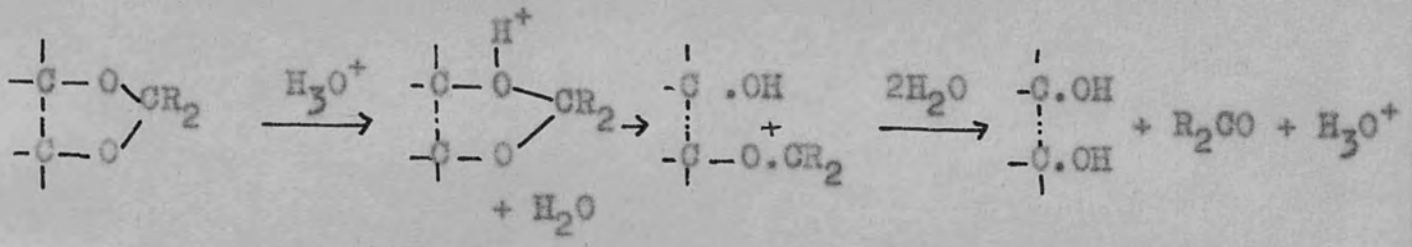
Aqueous acid hydrolysis is a typical reaction of cyclic acetals and ketals and with most compounds occurs readily. The ease of hydrolysis depends on the structure of the carbonyl compound from which the acetals and ketals are derived. In general, for alditol derivatives, methylene acetals are less readily hydrolysed, and ketals are more readily hydrolysed than other acetals. Because of this ready hydrolysis of ketals, acetone is often used to block some alcohol groups in an alditol molecule. The ketals derived from 1:1:1-trifluoroacetone are exceptionally stable to acid reagents.[17] This stability is thought to be due to the presence of the strongly electro-negative fluorines, which reduce the electron density on the ring oxygens and so render electrophilic attack on these less probable.

It has also been found that the rate of hydrolysis of rings derived from a given carbonyl compound depends on the size and substituents of the ring. Usually, the least reactive rings are those preferentially formed in reaction of the alditol with the carbonyl compound.

The hydrolysis of cyclic acetals and ketals of pentaerythritol has also been investigated[18]. Methylene acetals were again found to be the most slowly and iso-

propylidene ketals the most rapidly hydrolysed.

The kinetics of the hydrolysis of simple 1:3-dioxalans and 1:3-dioxans have been studied[19]. The energies of activation of substituted and unsubstituted rings have been compared and a mechanism proposed. In this, the initial attack is by the electrophilic reagent, the hydrated proton (A in equ.7), followed by formation of the carbonium ion and reaction of this with a water molecule (X in equ.7).



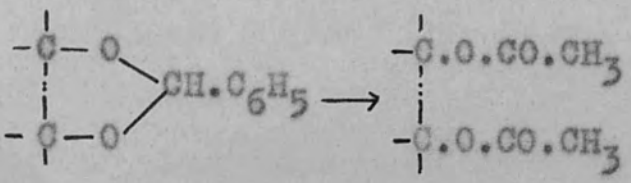
(Equ.8)

It has also been found that acetals of optically active alcohols are hydrolysed by aqueous acid without racemization, which shows that fission cannot occur at the other carbon-oxygen bond.[20]

Acetolysis of cyclic acetals and ketals, involving the fission of rings with the formation of acetyl derivatives, is a reaction which has found wide use. C. S. Hudson *et al.* have investigated the reaction of a mixture of acetic anhydride and acetic acid, containing 1-2% sulphuric acid, on

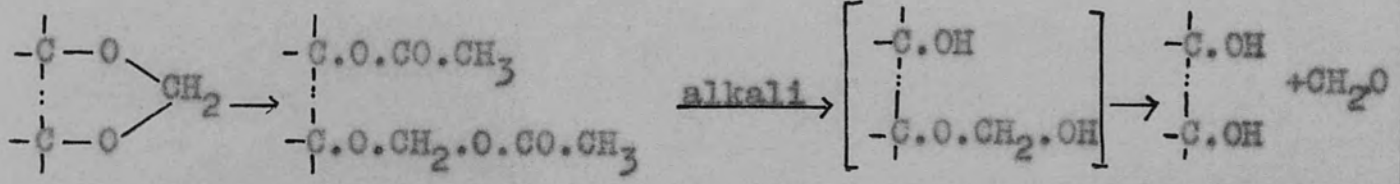
many alditol acetals and ketals.

Benzylidene acetals yield products containing acetyl groups in the positions originally linked by the benzylidene group, which is lost:[21]



(Equ.9)

Methylene acetals do not react completely, even under forcing conditions[22] but, on limited acetolysis at 0^{o}, a different type of product is obtained. This still contains the methylene residue and an acetyl and an acetoxymethyl group occupy the positions originally linked in the ring. Saponification yields the free alcohol groups and formaldehyde, as the intermediate product, the hemiacetal of formaldehyde, is unstable:



(Equ.10)

If the methylene acetal contains terminal rings, in which one of the primary alcohol groups is linked, these are preferentially attacked and ring opening occurs between the primary oxygen and the carbonyl carbon atom. For example, 1:3-2:4-5:6-tri-O-methylene-D-glucitol, after acetolysis and subsequent saponification, gave a 52% yield of 2:4-O-methylene-D-glucitol[3a] and 1:3-2:5-4:6-tri-O-methylene-D-mannitol gave 2:5-O-methylene--D-mannitol in 81% yield[4]. If both rings involve secondary alcohol groups, the least stable is attacked. 2:4-3:5-Di-O-methylene-D-glucitol contains a βC and a βT ring and only the latter, less stable ring, reacts, to give a product containing an acetyl group at position 5 and an acetoxymethyl group at position 3 in the carbon chain[22]. 2:4-3:5-Di-O-methylene-L-iditol contains βC rings and these are not attacked.[23]

The acetolysis of 1:3-dioxalan derivatives have been investigated, using acetic anhydride containing sulphuric acid.[24] Similar results were obtained and butyric anhydride and sulphuric acid were found to yield the corresponding butyrates. Acetic anhydride and zinc chloride have been reported to react with a tetrahydrofurfurylidene acetal of ethylene glycol to give an ester containing the furfurylidene residue.[25]

These reagents are probably all sources of the acetylium ion or similar electrophilic reagent.[26] The structures of the products are explained if the initial attack is by the acetylium ion (A in Equ.7) followed by ring fission and reaction of the carbonium ion with an acetate anion (X in Equ.7).

A more recent development has been the use of a mixture of equimolar quantities of a carboxylic acid and trifluoroacetic anhydride to cause ring opening of cyclic acetals and ketals. This reagent has been studied in the Birmingham University laboratories and its properties suggest that the reaction of the acid with the anhydride, to give the unsymmetrical anhydride, proceeds nearly to completion:[27]

$$R.CO_2H + (CF_3.CO)_2O \rightleftharpoons R.CO.O.CO.CF_3 + CF_3CO_2H \quad \text{(Equ.11)}$$

Its reactions also suggest that the unsymmetrical anhydride dissociates, perhaps only to a very small extent, into acylium and trifluoroacetate ions:[28]

$$R.CO.O.CO.CF_3 \rightleftharpoons R.CO^+ + CF_3.CO_2^- \quad \text{(Equ.12)}$$

The properties of other carboxylic unsymmetrical anhydrides

do not suggest that they dissociate, but that they react in molecular form.[29] The electronegative fluorine atoms cause trifluoroacetic acid to be a comparatively strong acid (Ka = 0.58), so the trifluoroacetate ion should be stabler and hence more readily formed than most carboxylate ions. The acylium ion liberated by this dissociation may be solvated as $R.CO_2H_2^+$, $(R.CO)_2OH^+$ or $(R.CO.O.CO.CF_3{:}H)^+$, but these will react in essentially the same way as the free ion.[30]

The unsymmetrical anhydride can be isolated, but is considerably less reactive than the unsymmetrical anhydride and trifluoroacetic acid mixture. The role of the acid is uncertain and one suggestion is that it catalyses the dissociation of the anhydride:[27]

$$R.CO.O.OC.CF_3 \xleftrightharpoons{H^+} (R.CO.O.CO.CF_3{:}H)^+ \rightleftharpoons R.CO^+ + CF_3CO_2H$$

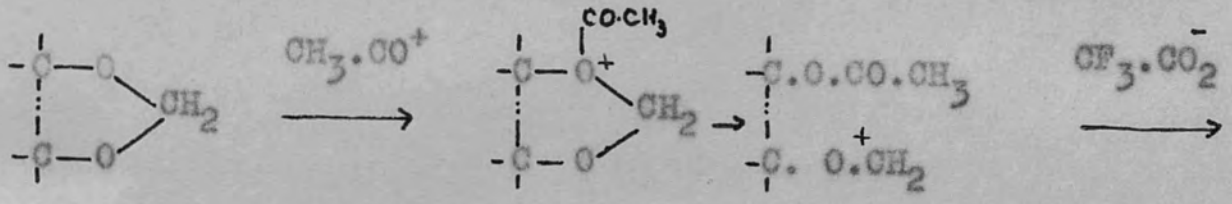
(Equ.13)

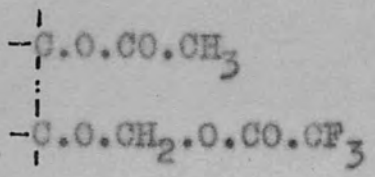
Alternatively, it may stabilise the trifluoroacetate ion by solvation and so promote the dissociation.[30]

The reagent therefore seemed a promising source of acylium ions, which would be expected to attack the oxygens of cyclic anetal and ketal rings. Its reactions with derivatives

of D-glucitol and D-mannitol have been investigated.[31,32]

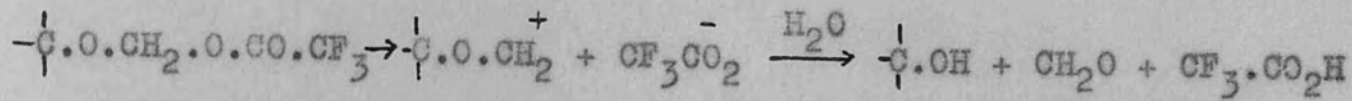
Methylene acetals, after reaction and treatment with aqueous sodium bicarbonate solution, yield products containing an acyl group and a free alcohol group in the positions originally linked by the methylene group. These products would result from attack by the acylium ion (A in Equ.7) on a ring oxygen atom, followed by ring opening to give a carbonium ion, which reacts with a trifluoroacetate ion (X in Equ.7):





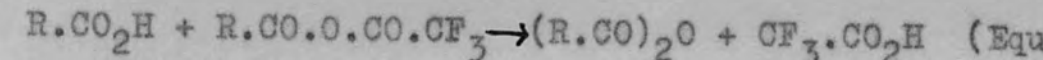
(Equ.14)

In contrast to ~~the~~ most carboxylic esters, the trifluoroacetates are hydrolysed in neutral aqueous solutions[33], so the trifluoroacetoxymethyl group would be expected to be very readily hydrolysed. The initial step may be an alkyl-oxygen bond fission to give a stabilised carbonium ion[34]:



(Equ.15)

If, instead of using equimolar mixtures of the acid and anhydride, excess carboxylic acid is present, the unsymmetrical anhydride reacts further with this:

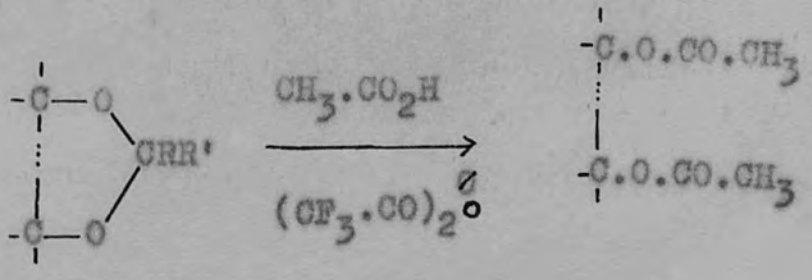


This reagent then contains a symmetrical carboxylic anhydride and a comparatively strong acid and, as might be expected, behaves similarly to the acetolysis reagents. Initial attack is again by the acylium ion but further reaction is with the anion , derived from the carboxylic acid; not with the trifluoroacetate ion (see Equ.10).

As in acetolysis, terminal methylene rings are preferentially attacked and acyl groups introduced on the primary positions. For example, 1:3-2:4-5:6-tri-O-methylene-D-glucitol, after reaction with propionic acid and trifluoroacetic anhydride followed by hydrolysis, yields 2:4-O-methylene-1:6-di-O-propionyl-D-glucitol.[32] Also, if both rings are formed from secondary alcohols, the least stable may be

attacked. 1:6-Di-O-benzoyl-2:4-3:5-di-O-methylene-D-glucitol, after reaction with acetic acid and trifluoroacetic anhydride followed by hydrolysis, yields 5-O-acetyl-1:6-di-O-benzoyl-2:4-O-methylene-D-glucitol.[31] As in acetolysis, only βC rings are stable to the reagent. In each reaction, attack is directed towards one oxygen of a ring; in the reaction of the tri-O-methylene acetal, towards the primary oxygens and in the reaction of the di-O-methylene acetal, towards the oxygen linked to carbon five of the carbon chain. The direction of attack in the latter reaction has been explained by considering the steric hinderance to approach of the reagent to each of the four ring oxygens.

All the rings in the benzylidene and iso-propylidene derivatives of D-glucitol and D-mannitol which have been investigated react readily with an equimolar mixture of acetic acid and trifluoroacetic anhydride. As in acetolysis (Equ. 9) the products contain no benzylidene or iso-propylidene groups, which are replaced by acetyl residues:

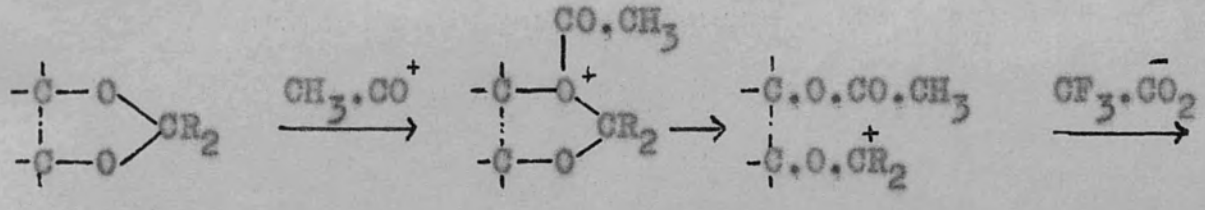


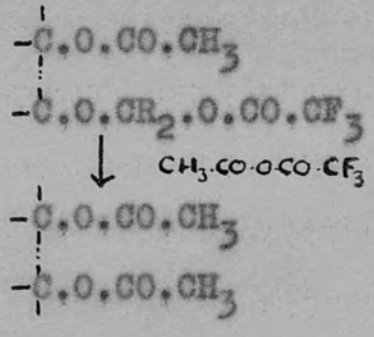
Benzylidene acetal, R = H, R'' = C_6H_5

isoPropylidene acetal, R = CH_3, R'' = CH_3.

(Equ.17)

The initial reaction is again probably the attack of an acetylium ion on a ring oxygen, followed by ring opening. The greater reactivity of these acetals and ketals, compared to the methylene acetals, may be because the carbonium ions, formed by ring opening, are stabilised in the former compounds by the phenyl and methyl groups attached to the trivalent carbon. The substituted trifluoroacetoxymethyl groups, formed by reaction of the carbonium ion with a trifluoroacetate anion, must then react further with the acetylium ion:





(Equ.18)

ELECTROPHILIC REAGENTS[35]

These results suggest that any reagent which liberates carbonium or acylium ions will cause ring opening of cyclic acetals and ketals. The production of compounds containing positively-charged, trivalent carbon atoms in their molecules has been postulated in many organic reactions but it is doubtful, except in the case of highly stabilised, unreactive ions, whether they are ever free. In such compounds, the valency electrons of the trivalent carbon are in sp^2 hybridization and a fourth bond is readily formed by acceptance of a pair of electrons from another atom, giving sp^3 hybridization. It is more probable that the ions are solvated, in the form of ion-pairs or even potentially available in a highly polarizable molecule. For simplicity, the reactions discussed here are assumed to involve free ions.

Analogues of carbonium ions would be expected to react similarly with cyclic acetals and ketals. The essential requirement is that the molecule should contain an atom which has more low energy orbitals than electrons to fill them. They are therefore strongly electrophilic and readily accept electrons to fill these orbitals. Boron

trichloride is an example of an uncharged electron deficient molecule. The bonds around boron are planar as a result of sp^2 hybridization and a fourth bond is readily formed, to give a tetragonal arrangement.[36] Positively charged dicovalent nitrogen compounds, such as the nitronium ion, are also electron deficient but oxonium ions contain an octet of valency electrons around the positively charged oxygen and would not be expected to react with dioxo rings.

The results of the reactions of this type of reagent with the cyclic acetals and ketals of D-glucitol, D-mannitol and pentaerythritol are recorded in this thesis. The cyclic compounds derived from these polyols contain 1:3-dioxo rings of different sizes and carrying different substituents and so the reactivity of the rings can be compared. It was hoped that, from the structure of the products, information could be obtained about the mechanism of the reactions and also that new, partially-substituted derivatives of the polyols could be prepared by these methods. The thesis is divided into three main sections, in each of which the reactions of one electrophilic reagent with these compounds are described and discussed.

REACTIONS OF ACETIC ANHYDRIDE AND METHYL IODIDE WITH TRI-O-METHYLENE HEXITOLS, IN PRESENCE OF ALUMINIUM CHLORIDE

FRIEDEL-CRAFTS REACTION

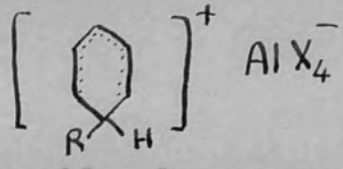
The reactions of alkyl and acyl halides with an aromatic compound, in the presence of a Lewis acid catalyst such as aluminium chloride, are examples of the Friedel-Crafts reaction. From investigations of the relative reactivities of the aromatic compounds, the conditions of the reaction and the structure of the products, a reaction mechanism has been suggested; this involves the formation of a carbonium or acylium ion by reaction of the halide with the catalyst, followed by preferential attack by this ion on the position of highest electron density in the aromatic nucleus:

$$RX + AlX_3 \rightarrow R^+ + AlX_4^-$$

$$R^+ + ArH \rightarrow ArR + H^+ \xrightarrow{AlX_4^-} ArR + HX + AlX_3 \qquad \text{(Equ.19)}$$

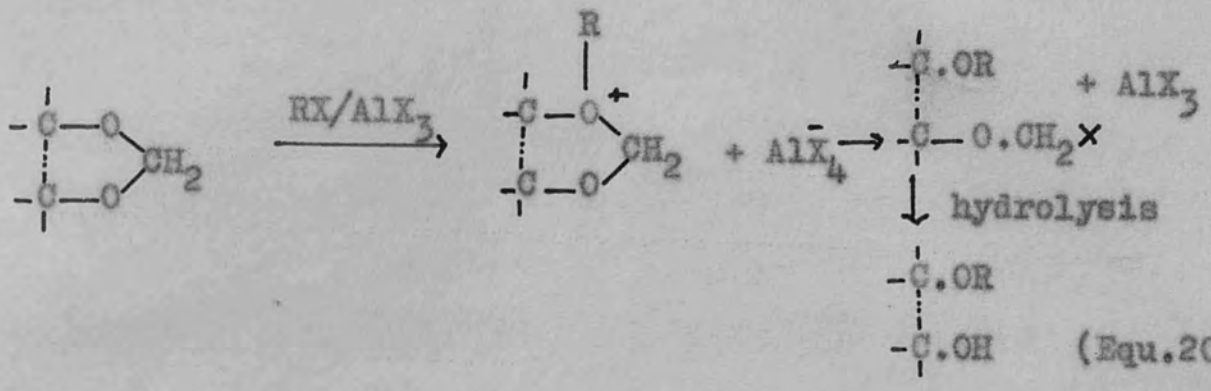
The system is probably more complex than this and several concurrent reactions may occur; the Lewis acid and the strong acid liberated in the reaction may co-ordinate with

the aromatic compound and so reduce its reactivity in the substitution reaction.[37] It is also doubtful whether the carbonium or acylium ions are liberated because, although acyl halides give conducting solutions in the presence of aluminium halides, alkyl halides do not ionise under these conditions. There is evidence, however, that a highly ionised σ-complex is formed between the halide, catalyst and aromatic compound:[38]



The alkyl or acyl residue becomes attached to the ring at the position of highest electron density and elimination of HX yields the aromatic product, so that the overall reaction may be termed an electrophilic substitution.

Alkyl and acyl halides, in the presence of aluminium chloride, might be expected to undergo a similar reaction with cyclic methylene acetal rings. The first step would involve the formation of an ionised complex, in which a bond had been formed between a cyclic oxygen atom and an alkyl or acyl residue, followed by ring opening, perhaps to give an α-halo ether, which would be hydrolysed to the alcohol:



(Equ.20)

(The reaction may be compared to equ.7, with R corresponding to A)

The reaction of acetic anhydride and methyl iodide, in the presence of aluminium chloride, with tri-O-methylene-D-glucitol and tri-O-methylene-D-mannitol has therefore been investigated. The anhydride has been used instead of acetyl chloride; it reacts with an equimolar proportion of aluminium chloride to yield the latter compound and is easier to handle. The reactions were carried out under the usual conditions for a Friedel-Crafts reaction, but the yields of the water-soluble products in most cases were not good. This was shown to be at least partly due to the adsorption of products on the precipitated alumina. In exp. 15 this was dissolved in concentrated hydrochloric acid and the solution eluted on a carbon/celite column; hexitol was detected in the eluent. In several experiments a brown solid, in which no carbohydrate was detected, was

isolated from the nitrobenzene layer, but the nature of this is not known.

RESULTS OF THE REACTION

1:3-2:4-5:6-Tri-O-methylene-D-glucitol (1) was treated with 2.4 molecular proprtions of acetic anhydride and 4.2 molecular proportions of aluminium chloride in nitrobenzene (exp. 7(a)). As it was hoped to isolate an acetate of glucitol, which would be expected to remain in the organic layer, only this was examined. It yielded a small amount of 2:4-O-methylene-D-glucitol. Similar reactions in sym-tetrachloroethane ~~(expt. 7c)~~ required higher temperatures, but again yielded 2:4-O-methylene-D-glucitol. As this monomethylene compound is readily soluble in water, experiment 7(b) was carried out, in which both organic and aqueous layers were investigated. This yielded a product, which, on acetylation, gave 1:3:5:6-tetra-O-acetyl-2:4-O-methylene-D-glucitol in 28.3% yield and a smaller amount of a second impure acetate (m.p. 137-145°). This may contain some 5:6-di-O-acetyl-1:3-2:4-di-O-methylene-D-glucitol, m.p. 135-136°.

1:3-2:5-4:6-Tri-O-methylene-D-mannitol (II) was

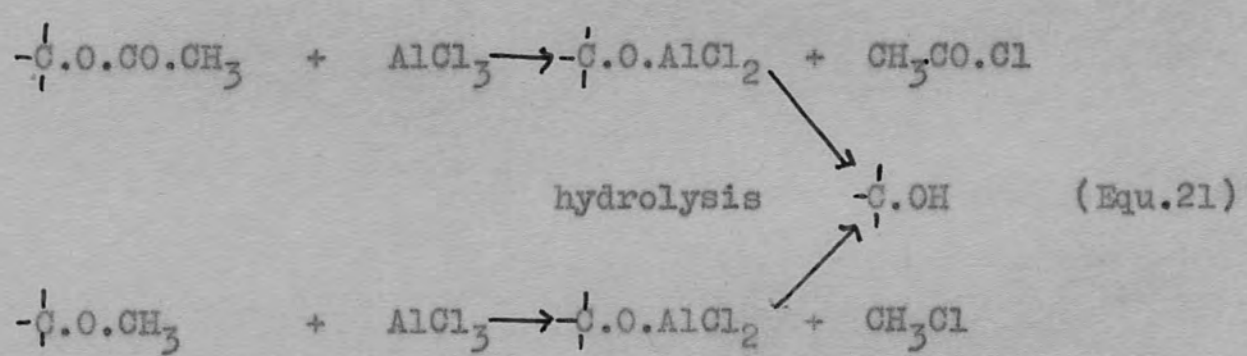
treated with 2 molecular proportions of acetic anhydride and 9 molecular proportions of aluminium chloride in nitrobenzene (exp. 8). Organic and aqueous layers were investigated. One product was identified as mannitol (11.1%) and a second was isolated, and acetylated to give tetra-acetate of 1:3-O-methylene-D-mannitol (7.2%).

Compound (I) was treated with 3 molecular proportions of methyl iodide and 1 molecular proportion of aluminium chloride in nitrobenzene (exp. 9a). Organic and aqueous layers were investigated and only unchanged starting material was isolated. The reaction was repeated, using 2.2 molecular proportions of each reagent and at a higher temperature (exp. 9b). Acetylation of the product yielded 1:3:5:6-tetra-O-acetyl-2:4-O-methylene-D-glucitol (5.6%) and a greater amount of a second acetate (m.p. 120-122°). Zeisel determinations on each product gave no evidence for the presence of methoxyl groups. Neither m.p. nor analysis suggests that the second acetate is 5:6-di-O-acetyl-1:3-2:4-di-O-methylene-D-glucitol, and it may be a partially acetylated derivative of 2:4-O-methylene-D-glucitol.

These reactions show that the cyclic methylene rings

open in the presence of acetic anhydride or methyl iodide and aluminium chloride, with loss of the formaldehyde residue. A product containing the βC ring was isolated from (I) and products containing no intact ring and containing a β ring from (II). This suggests that the βC ring is more stable than the α and β rings in (I) and that the β ring is more stable than the γT ring in (II). This agrees with the results of acid hydrolysis of both compounds and of acetolysis of compound (I). Acetolysis of (II), however, causes opening of the β rings only.

There is no evidence, however, for the introduction of acetyl or methyl groups. One explanation is that these cause ring opening, but that the products then undergo further reaction with aluminium chloride.



(Equ.21)

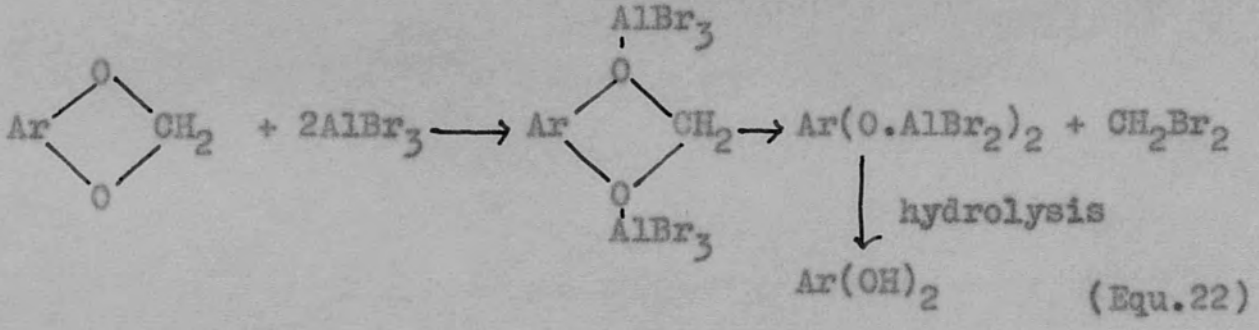
Experiments were therefore carried out to show if deacetylation and dealkylation could occur under the reaction conditions.

The deacylating power of aluminium chloride was investigated by treating the product of acetolysis of (I), 1:6-di-O-acetyl-3:5-di-O-acetoxymethyl-2:4-O-methylene-D-glucitol (III), with 4.6 molecular proportions of acetic anhydride and 9 molecular proportions of aluminium chloride in nitrobenzene (exp. 10). 2:4-O-Methylene-D-glucitol (21.8%) was isolated from the organic layer. Further evidence for the deacetylating properties of aluminium chloride was obtained by following the change in optical rotation on mixing alumium chloride and an acetate. With (III) (exp.11a), the specific rotation $[\alpha]_D^{21}$ + 26.2 (c 0.94 in $C_6H_5NO_2$) fell to -8.9 on mixing with the Lewis acid (5.3 molecular proportions). With mannitol hexa-acetate (exp. 11b) the specific rotation, $[\alpha]_D^{20}$ + 14.1 (c 0.99 in $C_6H_5NO_2$) fell to 0 on mixing with 7.7 molecular proportions of aluminium chloride. These changes suggest that reaction has occurred.

The demethylating power of aluminium chloride was investigated in its reaction with 2:3:4:6-tetra-O-methyl-D-glucose (exp. 13) under the conditions found to cause ring opening of (I) by methyl iodide and aluminium chloride. The products were investigated by paper chromatography and this showed the presence of unchanged starting material but of no demethylated products. Similar treatment of [illegible] methyl-α-D-

glucoside showed this to be converted into glucose (Exp. 12).

These results show that, under the reaction conditions, aluminium chloride can cause deacylation but not demethylation. It does, however, react with the methoxyl group of the glucoside. This compound is a mixed acetal and this suggests that aluminium chloride may react directly with the cyclic methylene acetal rings. This reaction has been used to liberate alcohols from a cyclic methylene derivative[39]. Aluminium bromide has been found more reactive and has been used at 0^{o} in nitrobenzene[40]. It was found that at least two molecular proportions of the bromide were needed and so the following mechanism was suggested:

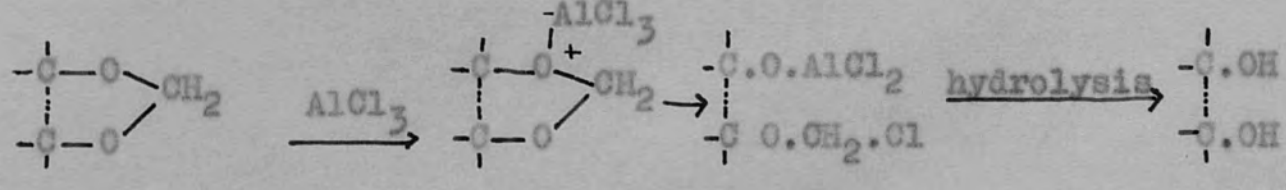


(Equ.22)

REACTION OF ALUMINIUM CHLORIDE WITH TRI-O-METHYLENE HEXITOLS

The reaction of aluminium chloride alone on the cyclic methylene acetals was then investigated. Compound (1), on treatment with two molecular proportions of chloride, gave 31% of unreacted acetal (exp. 14a). With nine molecular proportions of reagent, it gave 2:4-O-methylene-D-glucitol (64.2%) (exp. 14b) and a small amount of starting material. Compound (11), with four molecular proportions of reagent, gave a small amount of mannitol and some 1:3-O-methylene-D-mannitol (expt. 14c).

These results show that aluminium chloride can cause ring opening. It exists in solution in nitrobenzene in the monomeric form, $AlCl_3$, in which the aluminium atom contains only a sextet of valency electrons. It would therefore be expected to be an electrophilic reagent and to readily attack the cyclic oxygens of the acetal ring. If this reaction is similar to acid hydrolysis and other reactions of the cyclic methylene acetals (equ.7), ring opening will occur without the attack of a second molecule of aluminium chloride:



(Equ.23)

It was then decided to investigate the reactions of boron trichloride, a similar but more reactive compound, with cyclic acetals and ketals.

REACTION OF BORON TRICHLORIDE WITH CYCLIC ACETALS, KETALS AND OTHER DERIVATIVES OF POLYOLS

In these experiments, the polyol derivative, in some cases dissolved in dichloromethane, was treated with boron trichloride at -80° and the reaction mixture allowed to attain room temperature. The addition was carried out at this low temperature so that no volatile reagent should be lost. Reaction may have occurred at a higher temperature as in some reactions the polyol derivative, which was precipitated from solution at -80°, redissolved only as the reaction mixture warmed to room temperature. Excess reagent, solvent and any volatile products were removed under reduced pressure to leave an involatile residue. This was treated with various nucleophilic reagents and the products were investigated. In this way, it was hoped to gain information about the reaction of boron trichloride with the polyol derivatives and perhaps also to find new methods for the preparation of such derivatives.

REACTION OF AQUEOUS METHANOL ON THE PRODUCT OF THE REACTION OF BORON TRICHLORIDE WITH SOME POLYOL DERIVATIVES

1. Results of reaction

An excess of boron trichloride was used in the majority of these reactions, so that the number of molecules of reagent was greater than the number of ether oxygens linking carbon to carbon, or carbon to hydrogen in a molecule of the polyol derivative. Commercial methanol, which contains a small amount of water, was added to the involatile residue and the solution evaporated to dryness. This process was repeated until the turmeric test for the presence of boric acid was negative. The products were then investigated and characterised.

Tri-*O*-methylene-*D*-glucitol and tri-*O*-methylene-*D*-mannitol both yielded the corresponding hexitol, glucitol (exp. 17) (characterised as hexa-acetate) in 60.8% and mannitol (exp.18) in 52.8% yield. Paper chromatograms showed the presence of small amounts of fast-moving substituted hexitols, perhaps containing unopened acetal rings. One product from the reaction of the *D*-glucitol derivative

had the same R_g value as 2:4-O-methylene-D-glucitol and one from the reaction of the D-mannitol derivative had the R_m value expected for 1:3-O-methylene-D-mannitol.

The monomethylene acetals, 2:4-O-methylene-D-glucitol (exp.19a) and 2:5-O-methylene-D-mannitol (exp. 20), also yielded the corresponding hexitol as the chief product, glucitol in 61.0% and mannitol in 94.0% yield. No other product was detected from the reaction of the mannitol acetal but a small amount of unchanged acetal was isolated from the products of the glucitol acetal. This reaction (exp. 19b) was repeated under stronger conditions but unchanged acetal was again detected among the products.

Di-O-methylene pentaerythritol (exp.21) yielded pentaerythritol, isolated in 76.5% yield.

The reaction of tri-O-methylene-D-mannitol with one molecular proportion of boron trichloride (exp. 35) gave a mixture of products which was separated by elution on a celite column. This yielded unchanged acetal (0.6%), 1:3-4:6-di-O-methylene-D-mannitol (9.9%), 1:3-O-methylene-D-mannitol (5.0%) and D-mannitol (29.0%), giving a total yield of 44.5%. This rather low yield may be due to the

presence of boric acid in the mixture placed on the column. If the polyol products containing free alcohol groups were in the form of borate complexes, they would have been strongly held in the aqueous stationary phase on the column.

Tri-O-ethylidene-D-mannitol (exp. 22) and tri-O-benzylidene-D-mannitol (exp.23) yielded mannitol in 66.6% and 85.4% yield respectively. Small amounts of substituted hexitols were detected on the paper chromatograms. The reactions differed from those of the cyclic methylene acetals because the involatile residue from the treatment with aqueous methanol was only partially soluble in water. Chloroform extracts from both reactions yielded pleasant-smelling oils.

Di-O-benzylidene and mono-O-benzylidene pentaerythritol (exps. 24 and 25) both gave pentaerythritol in 91% yield and also a chloroform-soluble oil. The oil from the reaction of the diacetal was treated with aqueous sodium bicarbonate solution and yielded benzaldehyde.

Tri-O-isopropylidene-D-mannitol (exp. 26) and tri-O-cyclohexylidene-D-mannitol (exp. 27) yielded mannitol in 83.7% and 55.0%. Small amounts of substituted hexitols were detected on paper chromatograms. Chloroform extracts

of aqueous solutions of the products again gave pleasant-smelling oils but attempts to distil these resulted in charring as the temperature was raised. Chlorine was detected in the oil from the cyclohexylidene ketal.

Bis-O-(trifluoroisopropylidene)-D-mannitol (exp. 28) yielded only a trace of mannitol under the usual reaction conditions but when the reaction was carried out at a higher temperature and for a longer time, ring opening occurred more extensively. Paper chromatograms showed the presence of mannitol and some substituted mannitols.

D-Mannitol hexa-acetate (exp. 29) and 2:4-O-methylene-D-glucitol tri-benzoate (exp. 30) both gave the corresponding hexitols. The acetate yielded no other products but small amounts of substituted hexitols were detected among the products of the benzoate reaction. One of these had the same R_g value as 2:4-O-methylene-D-glucitol.

1:6-Di-O-toluene-p-sulphonyl-2:4-O-methylene-D-glucitol (exp. 31) gave an oily product, which contained only a trace of hexitol.

The reaction of methyl α-D-glucoside (exp. 34) was investigated, as this is strictly an acetal, the methoxyl group being in the β position to the pyranose ring oxygen in the glucoside molecule. The products from this reaction depended on the nature of the hydroxylic compound added to the involatile residue from the boron trichloride treatment. Water yielded glucose, and aqueous and absolute methanol both yielded a mixture of the glucoside and glucose.

D-Glucitol (exp. 32) and D-mannitol (exp. 33) were not affected by reaction with excess boron trichloride, followed by aqueous methanol.

Summarizing these results, the reaction of excess boron trichloride with the cyclic acetals and ketals, and carboxylic esters of these polyols, followed by treatment with aqueous methanol, yields the unsubstituted polyol as the chief product. The only exception to this, so far found, is the p-toluene sulphonic ester, which yielded a negligible amount of hexitol. This is therefore a useful general method for converting derivatives, in which the alcoholic hydrogen is replaced by a group of atoms, into the corresponding polyols.

This reaction has been carried out on several

cyclic acetals and ketals, derived from the reaction of the polyols with different carbonyl compounds, and in most cases a good yield of polyol was obtained. It is therefore difficult to arrange the compounds in an order to stability towards boron trichloride, although towards aqueous acid hydrolysis there are marked differences in the stability of different derivatives of the same polyol[1]. The difference in stability of the two monomethylene acetals is marked, however, 2:5-O-Methylene-D-mannitol gave an almost quantitative yield of mannitol but 2:4-O-methylene-D-glucitol gave unchanged acetal, in addition to glucitol, even after prolonged reaction. This suggests that the βC ring in the molecule of the glucitol acetal is considerably more stable than the γT ring in the mannitol acetal. The only compound found to be unreactive under the normal reaction conditions was bis-O-(trifluoroisopropylidene)-D-mannitol. This is in accord with its exceptional stability which has been mentioned in the Introduction p.24

Another example of varying stabilities toward boron trichloride, due to differing stabilities of the ring conformations and not to differing electron densities on the ring oxygens, was found in the reaction of the three acetal rings of tri-O-methylene-D-mannitol. One molecular proportion of boron trichloride was used so that there was a competitive reaction between the three rings for reaction with this. None of the products, except a trace of unreacted acetal, contained the 2:5(γT)-ring. This suggests that this ring is more rapidly attacked and opened than the 1:3- and 4:6-(β) rings and is therefore less stable. A similar result was found on acid hydrolysis[5] and also in the reaction of aluminium chloride.
Limited acetolysis, however, gave a product containing the γT ring, but no β rings[4]. These results are understandable if the seven-membered ring is less stable than the six-membered rings and is more readily attacked by electrophilic reagents. Approach to this ring is sterically more hindered than to the terminal β rings and, if the attacking group is bulky, reaction with this ring may be prevented. The terminal rings will then react more rapidly with the reagent and the relative reactivities of the two kinds of ring will be apparently reversed. The acetylium ion, assumed to be the

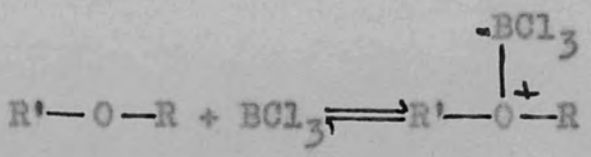
attacking group in the acetolysis reactions, may be solvated or in the form of an ion pair, and if this is more bulky than the hydrated proton, the attacking group in acid hydrolysis, boron trichloride or monomeric aluminium chloride reactions, then its preferential attack on the terminal rings is explained. A similar situation does not arise in the reactions of tri-O-methylene-D-glucitol, as in this molecule the terminal rings are preferentially attacked by all the reagents.

2. Possible reaction mechanisms

These results alone give little information about the reaction of boron trichloride with the cyclic acetals and ketals, and esters of polyols and with methyl α-D-glucoside. It is possible, however, to predict a reaction mechanism in analogy with the known reactions of boron trichloride with oxygen-containing organic compounds.[41]

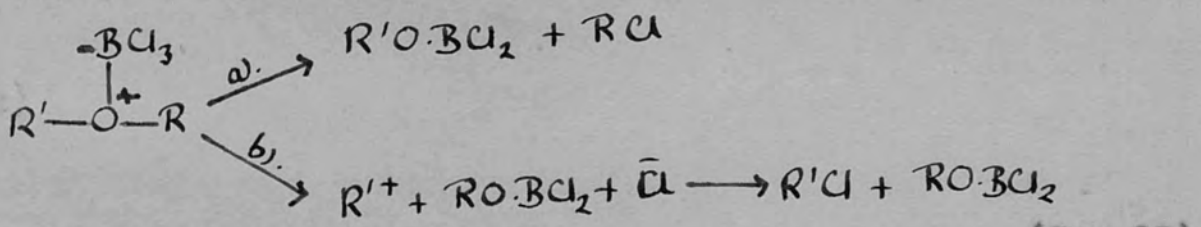
The reaction of boron trichloride with the cyclic acetals and ketals and methyl α-D-glucoside can be compared with the reaction of this reagent with aliphatic and cyclic ethers.[47,42] This has been studied in detail and, with few exceptions, the ethers have been found to undergo fission, in some cases at -80° and in others at 100°,

depending on the stability of the ether. When fission occurs only at the high temperatures, complexes of the ether with boron trichloride can be isolated at lower temperatures. The first step in all the reactions is assumed to be the formation of a bond between the ether oxygen and boron:



(Equ.24)

Fission of the carbon-oxygen bond can then occur by simultaneous attack by a chloride ion on the carbon and fission of this bond, or the carbon-oxygen bond can break first, to liberate the alkyl group as a carbonium ion, which subsequently reacts with a chloride ion (compare with Equ. 6, p. 22).

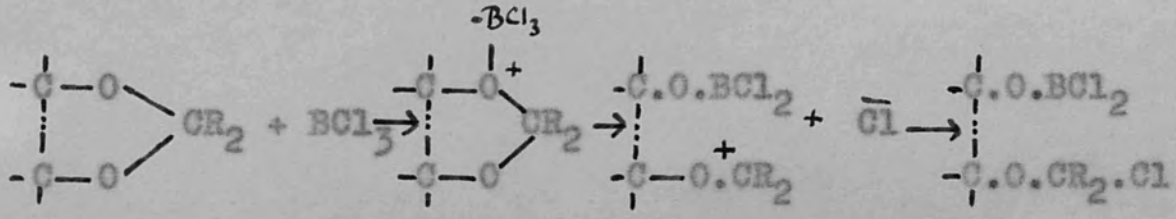


(Equ.25)

In the majority of the ether fission reactions caused by boron trichloride, the alkyl group with the greatest electron releasing properties is found in the alkyl halide product. This suggests that the initial reaction is carbonium ion

formation, as in (b). The racemisation and rearrangement of some alkyl groups in the alkyl halide products support this mechanism.

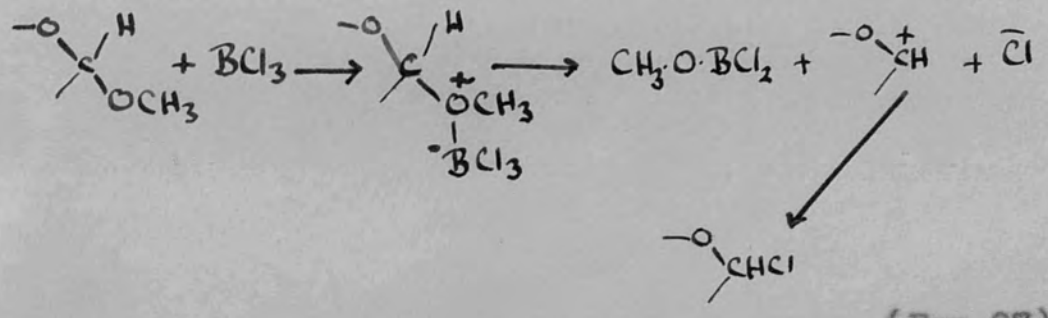
It seems probable, therefore, that boron trichloride will first react with cyclic acetals and ketals to give an oxonium compound and, as in other reactions of these compounds with electrophilic reagents, ring opening will then occur to give a carbonium ion, which subsequently reacts with a chloride ion (see equ.7, p.24):



(Equ.26)

The product then contains dichloroboronite and α-chloro ether groups in the positions originally occupied by the ring. Methyl α-D-glucoside would be expected to react similarly and, in analogy with its acid hydrolysis[43], attack

would be expected to be directed on the acyclic acetal oxygen. Fission would then occur between carbon-1 of the glucose residue and co-ordinated oxygen to give a stabilised carbonium ion, which can react with chloride ion to give D-glucopyranosyl chloride:



(Equ.27)

Dichloroboronites are sufficiently electrophilic to cause further fission of carbon-oxygen bonds[44]:

$$R'OR + RO.BCl_2 \longrightarrow (RO)_2BCl + R'Cl \qquad \text{(Equ.28)}$$

They can also yield the corresponding chloroboronates by disproportionation, favoured by reduced pressure[44]:

$$2RO.BCl_2 \longrightarrow (RO)_2BCl + BCl_3 \qquad \text{(Equ.29)}$$

In a poly-substituted polyol, reaction may occur intramolecularily to give a cyclic chloroboronate. The chloroboronates are only weakly electrophilic, because of the back co-ordination of the two oxygen atoms with the boron, and are unlikely to cause further fission of acetal links, but

they may disproportionate to the borate ester[45]:

$$2(RO)_2BCl \longrightarrow (RO)_3B + RO.BCl_2 \qquad \text{(Equ.30)}$$

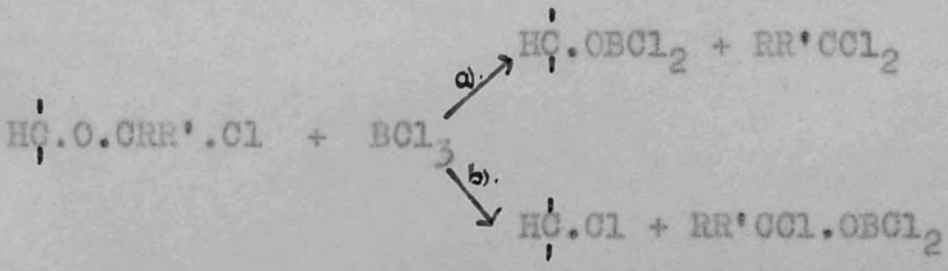
Dichloroboronates and chloroboronates are known to undergo one further type of reaction. When heated under atmospheric pressure or in the presence of traces of Lewis acid catalyst, alkyl halides are produced:[44,45]

$$3RO.BCl_2 \longrightarrow 3RCl + B_2O_3 + BCl_3$$
$$3(RO)_2BCl \longrightarrow 3RCl + B_2O_3 + (RO)_3B \qquad \text{(Equ.31)}$$

Exceptions to this are the thermally-stable cyclic chloroboronates of ethylene glycol and of catechol[46]. Polyol derivatives would be expected to yield similar cyclic compounds and this decomposition to give the chlorodeoxy derivatives may not occur.

α-Chloro ethers, the other postulated products from the reaction of boron trichloride with cyclic acetals and ketals, may also undergo further reaction. Investigations of the reactions of boron trichlorode with α-chloromethyl methyl ether[47] have shown that a stable complex is formed, which only

decomposes with fission at 100°. It is unlikely, therefore, that the α-chloromethyl ethers, postulated prpducts in the reaction of cyclic methylene acetals, would undergo reaction in the conditions used in the experiment. The presence of alkyl or aryl substituents on the α-carbon in the products of reaction of the other acetals and ketals, may affect the reactivity of these ethers and fission may then occur to give one or both of the possible products:



(Equ.32)

(The dichloroboronites can then react further, as described above)

The reaction of the acetates and benzoates of the polyols can be compared with the known reaction of boron trichloride with the carboxylic esters of mono-functional alcohols[48]. These yield complexes with the reagent, many of which are stable at room temperature. On heating, reaction occurs and the products depend on the nature of the alcohol

residue. If it is primary, the reaction is:

$$CH_2.O.CO.R + BCl_3 \longrightarrow CH_2.O.BCl_2 + RCO.Cl \quad \text{(Equ.33)}$$

If it is secondary or tertiary, the overall reaction is:

$$3CH.O.CO.R + 2BCl_3 \longrightarrow R.CO.OBCl.O.BCl.O.CO.R + RCO.Cl + 3CH.Cl$$

(Equ.34)

The first step may again be the formation of a dichloroboronite, but, as the secondary and tertiary alkyl dichloroboronites are known to be more reactive than the primary, they may react further with the acyl chloride to give the products isolated. If this is so, the initial fission in all esters is between the acyl group and the oxygen derived from the alcohol. From these results, the carboxylate esters of polyols would be expected to react:

$$\begin{array}{l} CH_2.O.CO.R \\ | \\ CH.O.CO.R \end{array} \xrightarrow{BCl_3} \begin{array}{l} CH_2.OBCl_2 \\ | \\ CH.Cl \end{array} \qquad \text{(Equ.35)}$$

The reaction of sulphonic esters with boron trichloride has not previously been investigated.

Any free alcohols in these compounds will react with boron trichloride with the evolution of hydrogen chloride:[49]

$$ROH + BCl_3 \rightarrow RO.BCl_2 \xrightarrow{ROH} (RO)_2BCl \xrightarrow{ROH} (RO)_3B.$$

(Equ.36)

The dichloroboronite and chloroboronate may react further by disproportionation or decomposition, as mentioned above.

The next step in the reaction of boron trichloride with these compounds was the removal of excess reagent, solvent and any volatile products. Commercial methanol was then added and its reaction with the compounds postulated as present in the involatile residue can be predicted.

All boron derivatives of alcohols will give the free alcohol:

$$\left(-\overset{1}{C}\cdot O\right)_x BCl_{3-x} + 3CH_3OH \rightarrow x\,-\overset{1}{C}OH + (CH_3O)_3B + (3-x)HCl$$

(Equ.37).

Any chlorine attached to carbon, as in the chlorodeoxy derivatives of the polyols, is unlikely to react under these conditions[50], but the chlorine in α-chloro ethers is particularly reactive and this would be expected to react with methanol.[53] This would yield the mixed acetal, which would probable be hydrolysed in the presence of hydrochloric acid:[57]

$$-O.CRR'.Cl + CH_3OH \longrightarrow -O.CRR'.O.CH_3 + HCl$$

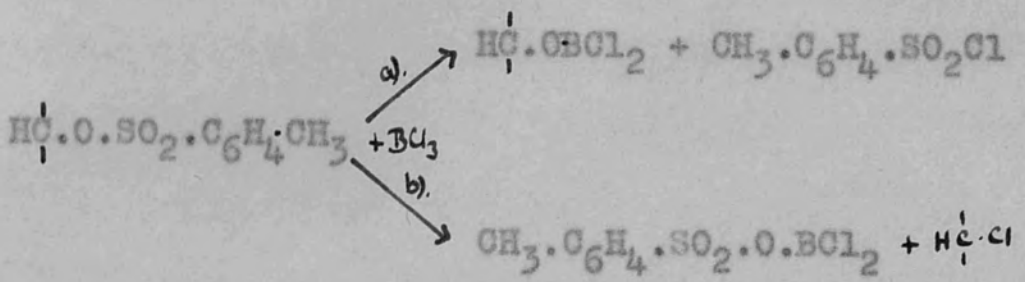
$$\downarrow H_2O, HCl$$

$$-OH + RR'CO + CH_3.OH \qquad \text{(Equ.38)}$$

From the structure of the isolated products, it is possible to eliminate some of the postulated reactions. Cyclic acetals and ketals give fairly high yields of the corresponding polyols and this suggests, therefore, that no chlorodeoxy derivatives are formed during the reaction. Decomposition of dichloroboronite and chloroboronate or fission of α-chloro ether, which would yield these derivatives, cannot have occurred. This is understandable if stable cyclic chloroboronates, which do not undergo this decomposition, are formed from the dichloroboronites and also that, if fission

of the α-chloro ethers does occur, it must yield the dichloroboronite and gemdichloro derivative of the carbonyl compound (see equ.32). Similarly, the products from the reaction of methyl α-D-glucoside could arise by reaction of aqueous methanol with D-glucopyranosyl chloride. The formation of glucose in the reaction with absolute methanol is probably due to incomplete reaction of the chloride and subsequent hydrolyses of the unreacted material. (This type of reaction has been found to go to completion only in the presence of a basic catalyst).

Polyols were also isolated from the carboxylic esters, although from the known reactions of ~~the~~ such compounds chlorodeoxy derivatives of the polyols were expected. The reaction of the esters of secondary alcohols must therefore be similar to that of the esters of primary alcohols and this may be because the initially-formed dichloroboronites react further to give the stable cyclic chloroboronates instead of yielding the corresponding alkyl halide. Sulphonic esters, however, yielded little polyol and it is possible that chlorodeoxy derivatives were formed in this case. The fission of these esters can be postulated as occurring in one of two ways:



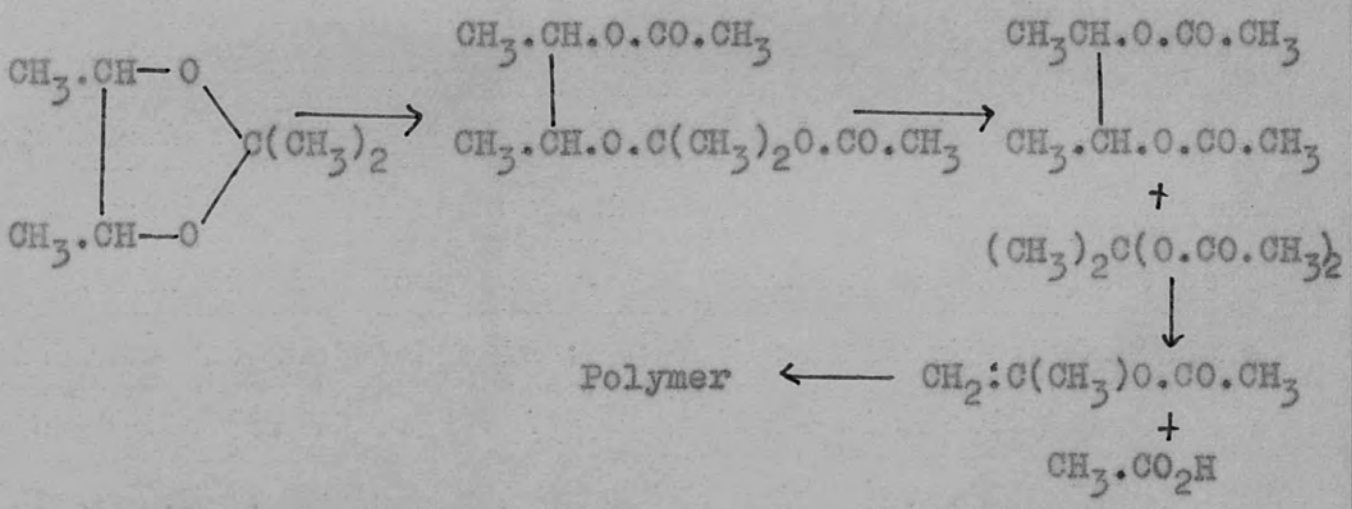
(Equ.39)

As these esters are known to undergo alkyl-, rather than acyl-oxygen fission, reaction (b) may predominate[34].

From these considerations, it is not possible to decide whether the α-chloro ethers, the postulated products from the ring opening of cyclic acetals and ketals, undergo further reaction with boron trichloride. ~~Hydrolysis of~~ The chloro ether and the product of its reaction with boron trichloride will both yield the alcohol on treatment with commercial methanol and so this does not distinguish between them. If fission does occur, the carbonyl residue must be liberated as the dichloride; methylene chloride, ethylidene dichloride (b.p. 57.3°), isopropylidene dichloride (b.p. 69.7°), cyclohexylidene dichloride (b.p. 169-173°) or benzylidene chloride. Methylene chloride would not be detected, as this is the solvent of the reaction, but benzylidene chloride was isolated from the reaction of a

cyclic benzylidene acetal. The other acetals and ketals yielded high-boiling, coloured oils and the relatively volatile dichlorides were not detected.

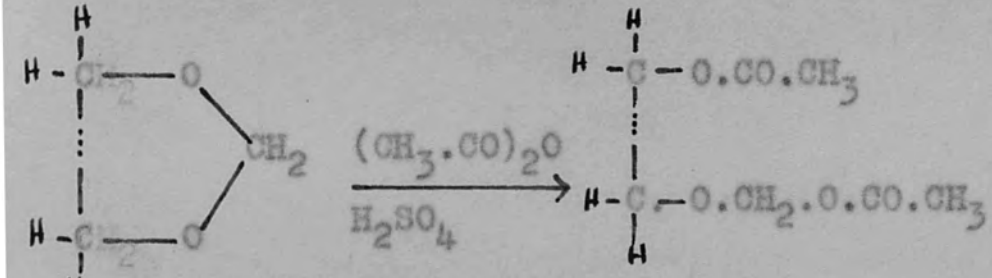
Similar results have been obtained i n the reaction of acetic anhydride and sulphuric acid with this type of compound[24]. The di-acetates of the diols originally linked in a dioxo ring and tars are the products: Senkus suggests that the gemdi-acetates of the carbonyl compounds were first formed but that acetic acid was then eliminated from these to give vinyl esters, which polymerised in the presence of the strong acid:



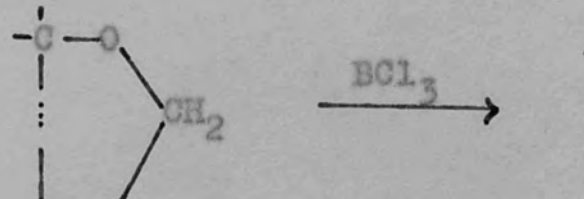
(Equ.40)

~~(Equ.40)~~

The gemhalides, postulated as products in the reaction of boron trichloride with the cyclic acetals and ketals, could, with the exceptions of methylene dichloride and benzylidene chloride, lose hydrogen chloride to give vinyl chlorides, which would polymerise in the presence of boron trichloride. This would explain the production of high-boiling products in the reactions of ethylidene, isopropylidene and cyclohexylidene derivatives and suggests that, in the reaction of these compounds and of the benzylidene acetal, the α-chloro ethers undergo further reaction with boron trichloride. If the reaction of the methylene acetals with boron trichloride is similar to their reaction with acetic anhydride and sulphuric acid, further reaction of the α-chloromethyl ether will not occur:



(75% yield)



(Equ.41)

This reaction has therefore been investigated in greater detail.

ANALYSIS OF THE PRODUCTS OF HYDROLYSIS OF THE COMPOUND OR MIXTURE OF COMPOUNDS FORMED IN THE REACTION OF EXCESS BORON TRICHLORIDE WITH TRI-O-METHYLENE-D-MANNITOL

Weighed amounts of acetal (exp.36) were treated with excess of boron trichloride and the products evaporated to constant weight under reduced pressure. If the increase in weight is assumed to arise from addition of boron trichloride to the acetal, with no subsequent elimination reaction, the average number of molecular proportions of boron trichloride reacting with one molecular proportion of acetal can be calculated (Column III, Table I). This value was found to depend on the pressure used in the evaporation of the products. When the oil pump was used, the average value was 1.8 and with the water pump it was 2.3. This is understandable if a disproportionation, known to be favoured by reduced pressure[44], occurs more readily at the lower pressures (equ.29). It will be

Sample	I Acetal (milli mols.)	II Added BCl_3 (millimols.)	III Mols. BCl_3/ mol. acetal	IV $\bar{C}l$ (milli mols.) (i)	(ii)	(iii)	V Acid (milli mols.)	VI H_3BO_3 (milli mols.)	VII Mols. $\bar{C}l$/ mol. acetal (i)	(ii)	(iii)	VIII Mols. H_3BO_3/ mol. acetal	IX Mols. CH_2O/ mol. acetal
A	3.10	5.70	1.84	15.1	-	16.7	21.60	6.50	4.89	-	5.39	2.10	-
B	3.00	5.42	1.81	14.1	-	16.1	20.10	6.00	4.70	-	5.36	2.00	-
C	2.47	5.72	2.32	13.1	-	-	-	-	5.30	-	-	-	-
D	2.63	5.73	2.18	-	14.0	-	-	-	-	5.33	-	-	-
E	2.06	4.50	2.18	-	-	13.1	-	-	-	-	5.58	-	-
F	2.45	5.86	2.39	-	-	-	-	-	-	-	-	-	1.89
G	2.54	5.61	2.21	-	-	-	-	-	-	-	-	-	1.85

TABLE I

noticed that, although three acetal rings are present in each molecule of polyol derivative, the average number of molecules of boron trichloride associated with this is always less than three. This may be because not all rings are attacked. If reaction is complete, it may be caused by disproportionation of dichloroboronites (see equ.29) or by reaction of dichloroboronites with an acetal ring, causing fission (equ.28).

The products were treated with measured volumes of water. Hydrolysis of dichloroboronites, chloroboronates and borates will yield the hexitol, and boric acid. Hydrochloric acid will also be produced from the first two types of compound. α-Chloromethyl ethers, if present, will be hydrolysed to the alcohol, formaldehyde and hydrochloric acid.

Boric acid is dissociated to a very small extent in aqueous solution (K_a: 5.8×10^{-10}), but in the presence of polyols, such as mannitol, it forms a strongly acid complex[52]. As mannitol was one of the hydrolysis products, some of the boric acid was already complexed. It was therefore not possible to titrate the hydrochloric acid and then add mannitol and titrate the boric acid complex,

so obtaining values for the concentrations of both acids[45]. Instead, additional mannitol was added, to ensure that all the boric acid was complexed, and the total strong acid concentration, due to the boric and hydrochloric acids, was determined by titration against standard alkali (Column V).

The concentration of chloride ion, liberated by the hydrolysis of boron-chlorine and carbon-chlorine bonds, was determined by the Volhard method. This concentration was found to depend on the pH values of the sample titrated. Acid samples, taken from the solution of hydrolysis products, gave a lower value than samples which had been made alkaline. Determinations were therefore carried out on samples which were initially (i) acid, (ii) neutral and (iii) alkaline (Column IV).

The boric acid concentration was calculated from the difference between the total strong acid concentration and the chloride ion concentration, measured in an acid sample. This value of the chloride ion concentration was assumed to approximate most closely to the hydrochloric acid concentration, which had been determined on an acid sample having a pH value near to 7 only for a short time

at the end point of the titration (Column VI).

The formaldehyde concentration was determined gravimetrically by precipitation of the dimedone derivative at pH 4.6 (Column IX).

The titration results are only strictly comparable if the difference in the average number of molecular proportions of boron trichloride associated with one molecular proportion of acetal is taken into account. Analysis of the hydrolysis products of samples A and B gave values of 2.10 and 2.00 for the average number of molecular proportions of boric acid/molecular proportion of acetal (Column VIII). From this, it can be deduced that an average of 2.10 and 2.00 molecular proportions of boron trichloride were associated with one molecular proportion of acetal. These values do not show very close agreement with the figures in Column III, but again are less than three and the same conclusions can be drawn.

Analysis of samples A, B, C, D and E showed that the values obtained for the average number of molecular proportions of chloride ion/molecular proportion of acetal (Column VII) depended on the pH values of the samples. The value obtained for C can be directly compared

with those for D and E if a correction is made for the smaller amount of boron trichloride co-ordinated with the acetals in D and E. The average number of molecular proportions of chloride ion/molecular proportion of acetal is then found to increase from 4.98 in acid solution to 5.33 in neutral and 5.58 in alkaline solution. A similar increase is seen in the results for A and B. This suggests that not all the covalently-bound chlorine is ionized on the addition of water. Boron-chlorine bonds are known to break readily in the presence of water so this chlorine would be expected to be fully ionised at any pH. If all the boron is in the form of dichloroboronites, the ratio of molecular proportions of chloride ion/ boric acid will be 2/1 but the presence of chloroboronates will reduce the relative amount of chloride ion. This ratio was found to be greater than 2/1 even in the acid solution obtained by addition of water to the product. This suggests therefore that some carbon-chloride bonds must also hydrolyse under these conditions. In alkaline solution, the hydrolysis of these bonds will presumably be complete. Chlorine attached to primary or secondary carbon atoms is hydrolysed only in alkaline solutions, but the chlorine in an α-chloromethyl ether is as

reactive as that in a tertiary chloride and will be hydrolysed in the presence of water by an S_NI mechanism:[16]

$$RO.CH_2.Cl + H_2O \rightleftharpoons R.OH + CH_2O + HCl \quad \text{(Equ.42)}$$

The high concentration of hydrochloric acid, produced in the aqueous solution, will prevent the reaction from going to completion but addition of alkali should upset the equilibrium. The results are therefore explained if α-chloromethyl ether groups are present, which are partially hydrolysed in acid and completely in alkaline solution.

The values for the average number of molecular proportions of formaldehyde/molecular proportion of acetal (Column IX) in samples F and G were found to be 1.89 and 1.85. The maximum theoretical value is 3.0 and these low values may be caused by incomplete reaction of the acetal rings with boron trichloride or by incomplete hydrolysis of the α-chloromethyl ether at pH 4.6.

These results give further information about the reaction of excess boron trichloride with tri-O-methylene-D-mannitol. The presence of the α-chloromethyl ether is

indicated by the isolation of formaldehyde from the hydrolysis products. The values obtained for the chloride ion concentration in the aqueous solution of the products can also be explained by the presence of such a compound.

The isolation and characterisation of the α-chloromethyl ether would be difficult, as any method used to remove boron and give the alcohol would also cause reaction of the reactive chlorine in the ether group. It was therefore decided to replace the chlorine by another, less reactive atom or group. In this way it was hoped to obtain a stable derivative of the polyol and to show that it contained the methylene residue, originally in the acetal ring.

REACTION OF SOME NUCLEOPHILIC REAGENTS ON THE PRODUCTS OF THE REACTION OF EXCESS BORON TRICHLORIDE WITH CYCLIC METHYLENE ACETALS

The replacement of the reactive chlorine in the simple α-chloro ethers, such as α-chloromethyl ether, is a well known reaction. In the presence of sodium acetate, the acetoxymethyl derivative is formed:[54]

$CH_3.O.CH_2.Cl + CH_3.CO_2Na \longrightarrow CH_3.O.CH_2.O.CO.CH_3 + NaCl$ (Equ.43)

Similarly, with sodium methoxide the acetal is formed:[55,53]

$CH_3.O.CH_2.Cl + CH_3.ONa \longrightarrow CH_3.O.CH_2.O.CH_3 + NaCl$ (Equ.44)

The chlorine attached to boron may also react with these reagents. Dichloroboronites and chloroboronates are known to react with acetic acid[56] and analagous reaction may occur with sodium acetate, to give the polyol borates. Sodium methoxide would be expected to react with the chlorine attached to boron, giving mixed borates. In either case, treatment with methanol should remove boron and give the polyol derivatives, containing in their molecules one acetoxymethyl or one unsymmetrical acetal group for every acetal ring opened.

1. Reaction of Sodium Acetate

Anhydrous sodium acetate, in suspension in chloroform, was added to the products of the reactions of tri-O-methylene-D-mannitol (exp. 37a) and tri-O-methylene-D-glucitol (expt. 37b) with excess boron trichloride. After removal of solvent and volatile products, an attempt was made to remove the

boron residues by adding methanol and then distilling it off under atmospheric pressure. The involatile residue was extracted with chloroform, in which highly substituted organic derivatives of hexitols are soluble. The insoluble residue was extracted with boiling pyridine, in which substituted hexitols and the hexitols themselves are soluble. The concentrated extracts were examined by paper chromatography using solvent (a) and the silver nitrate spray, which detects compounds containing free and esterified vicinal glycol groups. The chloroform extracts were shown to contain a mixture of fast-moving, and therefore highly substituted, hexitol products. Similar products and some unsubstituted hexitol were detected in the pyridine extracts.

Predicted products of the reaction are triacetoxymethyl hexitols, when three rings have been attacked, and diacetoxymonomethylene hexitols and monacetoxydimethylene hexitols, where not all the rings have reacted. These are all highly substituted hexitols and would be expected to be eluted together, near the solvent front, in this solvent. The presence of fast-moving products from these reactions therefore suggests that acetoxymethyl derivatives have been formed. In addition, slower-moving compounds and hexitols were

detected. This is understandable if the acetoxymethyl derivatives were hydrolysed during the reaction or if the replacement of the chlorine was not complete and the unreacted α-chloromethyl ether groups were subsequently hydrolysed.

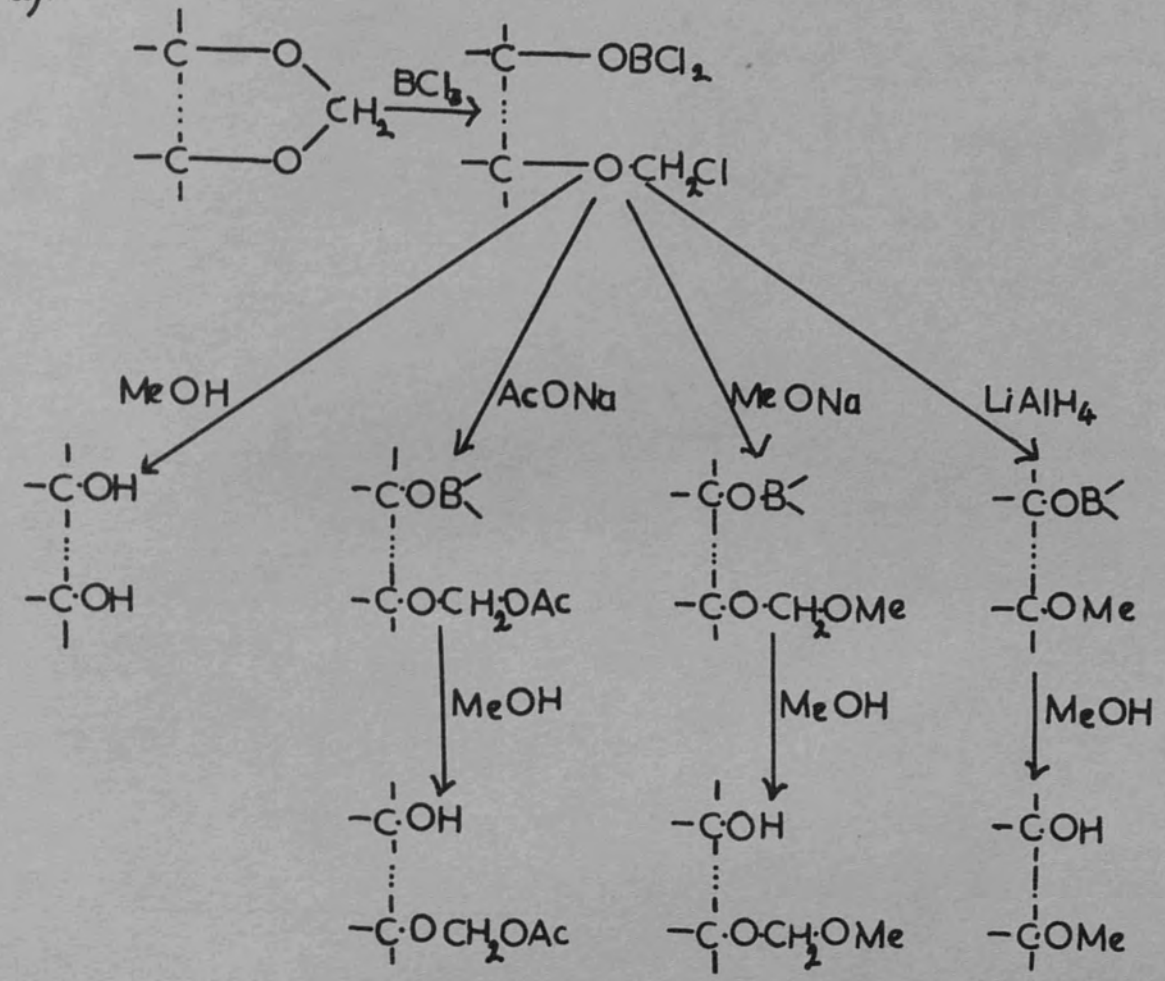
2:4-O-Methylene-D-glucitol (exp. 37c), on similar treatment, yielded hexitol, a product which, on a paper chromatogram, moved at the same rate as the original acetal, and a third product, which may be the acetoxymethyl derivative. The production of acetoxymethyl compounds can be explained by the reaction shown in Fig. III.

2. Reaction of Sodium Methoxide

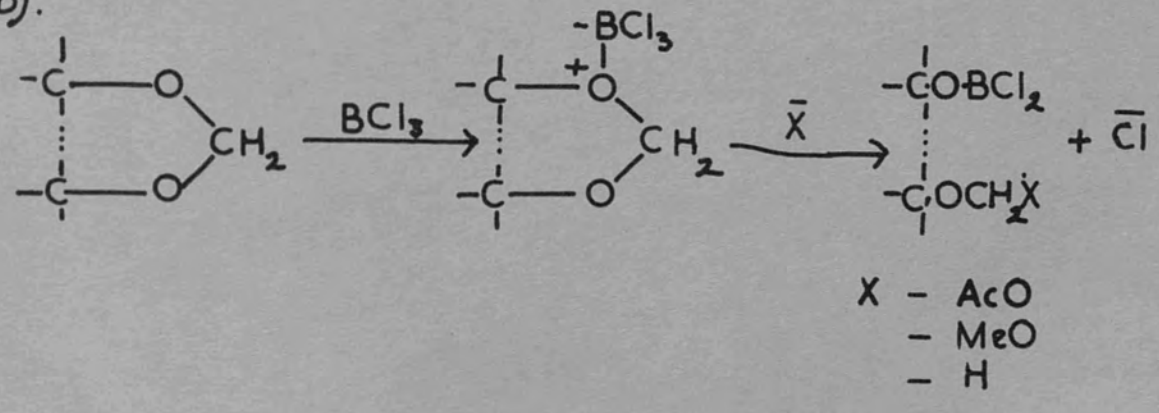
Sodium methoxide, in methanol, was added to the products of the reaction of excess boron trichloride with tri-O-methylene-D-mannitol (exp.38a) and tri-O-methylene-D-glucitol (exp.38b). After removal of precipitated sodium chloride, the solution was treated with acid to give a pH value of 8 and then evaporated to dryness, in an attempt to remove the boron residues and give the unsymmetrical acetal derivatives of the hexitols. The involatile residue was extracted with

FIG. III

a).



b).



X - AcO
- MeO
- H

chloroform, to obtain the highly substituted products, and then with n-butanol, to obtain any remaining substituted hexitol products and hexitols. The extracts were investigated by paper chromatography, as before, but the products from these reactions would be expected to be stable to the alkaline conditions of the spray, and only compounds containing glycol groups should be detected. The chloroform extracts contained a mixture of fast-running products and the n-butanol extracts slower-moving products, including hexitol and compounds moving slower than this. These latter products may be the borate complexes of the hexitols.

These results suggest that the unsymmetrical acetals have been formed and again the presence of hexitol can be explained if the acetal products were hydrolysed during the reaction or if some α-chloromethyl ether remained unreacted and was later hydrolysed.

2:4-O-Methylene-D-glucitol (exp. 38c), on similar treatment, yielded hexitol, a product which, on a paper chromatogram, moved at the same rate as the original acetal,

and a third product, which may be the unsymmetrical acetal. The production of the mixed acetals can be explained by the reactions shown in Fig. III p.78

Although these reaction products are more stable to hydrolysis than the postulated α-chloromethyl ether products, the results suggest that some hydrolysis may have occurred. This instability is not surprising as both the acetoxymethyl and the unsymmetrical acetal compounds are related to the hydrated form of formaldehyde and can be theoretically prepared from this by esterification and etherification. Similar compounds are known to hydrolyse readily, liberating formaldehyde:

$$RO.CH_2.O.CO.CH_3 + H_2O \xrightarrow[\text{alkali}]{\text{acid or}} ROH + CH_2O + CH_3.CO_2H \quad ^{54b,57}$$

$$RO.CH_2.O.CH_3 + H_2O \xrightarrow{\text{acid}} ROH + CH_2O + CH_3.OH \quad ^{57}$$

(Equ.45)

Another derivative, not related in this way to formaldehyde, can be prepared by reduction of the α-chloromethyl ether, to give the methyl ether. The methyl ethers of hexitols are known to be resistant to hydrolysis, so it

was decided to carry out a reduction of the products from the reaction of excess boron trichloride with cyclic methylene acetals.

The reducing agent selected was lithium aluminium hydride. This compound is known to reduce chlorine attached to carbon whereas sodium borohydride, for example, will not effect this reduction.[58] The reaction is a chemical reduction and is thought to be a bimolecular nucleophilic replacement of chlorine by the hydride ion:[59]

$$RO.CH_2.Cl + \overline{AlH_4} \xrightarrow{fast} RO.CH_3 + AlH_3 + \overline{Cl}$$

$$3RO.CH_2.Cl + AlH_3 \xrightarrow{slower} 3RO.CH_3 + AlCl_3 \qquad \text{(Equ.46)}$$

Ether and acetal groups are not attacked by this reagent and 2:4-O-methylene-D-glucitol was recovered in 85% yield (exp. 39d). Tetrahydrofuran, instead of the more usual diethyl ether, was chosen as the solvent as its higher boiling point allowed the reaction mixture to be refluxed at a higher temperature. The reaction of the reducing agent on the boron groups is uncertain but it may behave similarly to sodium borohydride:[59]

$$3(RO)_2BCl + 3NaBH_4 \longrightarrow 2B_2H_6\uparrow + 2B(OR)_3 + 3NaCl \quad \text{(Equ.47)}$$

It was hoped that hydrolysis would remove the boron, to give a methyl ether derivative of the hexitol.

3. Reaction of lithium aluminium hydride

The best results were obtained from the following method. The product from the reaction of excess boron trichloride with the methylene acetal was dissolved in tetrahydrofuran and the solution added to the slurry of lithium aluminium hydride in the same solvent. The reaction was then refluxed for thirty minutes. The excess reducing agent was destroyed by addition of water and the resulting suspension of solid in the solvent was acidified with hydrochloric acid. The organic solvent was evaporated off, the alumina removed by centrifuging and ionic products on an ion exchange resin. Boric acid was removed by treatment with acidified methanol and the neutralised residue was extracted with pyridine. This extract yielded an oily product, which was investigated by paper chromatography.

Tri-O-methylene-D-mannitol (exp.39a) yielded a mixture

of products, but no hexitol. This suggests that reduction of an intermediate, such as α-chloromethyl ether, has occurred, because, if this were not so, subsequent hydrolysis would yield the hexitol.

2:4-O-Methylene-D-glucitol (exp. 39b) was treated first with excess boron trichloride and then with the reducing meagent, but no attempt was made to remove the boric acid. A pyridine extract yielded a heavier residue than expected and this probably contained the organic products and boric acid. The hexitol products were separated by acetylation, chloroform extraction of the acetates and deacetylation. This gave a low yield of an oil (0.4 g. from 2.0 g. of starting material). Paper chromatography showed the presence of a small amount of hexitol and of a second product, which had the same R_g value as 2:4-O-methylene-D-glucitol, but which stained the silver nitrate spray more rapidly. The mixture was eluted on a celite column. The hexitol was isolated and shown to be glucitol (0.2% yield). The remaining product, or products, came off the column in one fraction and this was concentrated to give a partially crystalline oil (19.8% yield, calculated as $C_7H_{16}O_6$). This was

examined by paper chromatography and, in the solvent (a), two compounds were detected; one had the same R_g value as 2:4-O-methylene-D-glucitol, but stained the silver nitrate spray more rapidly, and the other had a lower R_g value (R_g:1.59). Solvent (f) usually separates hexitols and their mono- and di- substituted derivatives more effectively than the previous solvent and in this, a small amount of unchanged acetal, as well as a greater amount of a slower moving compound, was detected. These results suggest that the oil may contain three compounds. Acid hydrolysis gave some hexitol and this shows the presence of a compound, such as an acetal, readily hydrolysed by these conditions. The presence of methylene acetal was confirmed by a chromotropic acid determination of the formaldehyde, liberated during the hydrolysis. This gave a value for the amount of acetal of 5%. Reaction with boron trichloride gave a high yield of hexitol and this would be expected if the other products are ethers. A Zeisel determination showed the oil to have a methoxyl content of 11.8% (monomethyl-D-glucitol has a methoxyl content of 15.8%).

These results are explained by the reaction shown in Fig. III, p78.

The detection of unchanged acetal suggests that not all the rings were attacked and this agrees with the results found in the reaction of excess boron trichloride and aqueous methanol on this compound (exp.19); here, too, unchanged acetal was isolated. Two methyl ethers, 2-O-methyl- and 4-O-methyl-D-glucitol, can be formed in the above reaction, and, unless one ring oxygen is preferentially attacked, a mixture would be expected. If a model of the acetal molecule is made, it is seen that the two ether oxygens are equally accessible for attack by boron trichloride. The results of chromatography suggest that two similar compounds were formed.

These results show that a methyl ether is formed by the reduction of the product from the reaction of excess boron trichloride with a methylene acetal. It was decided to make no attempt to separate the mixture of products from the above reaction but instead to carry out the reaction on 2:5-O-methylene-D-mannitol. This acetal had been found to be converted quantitatively into mannitol, on reaction with excess boron trichloride and aqueous methanol, and so the products of the reduction

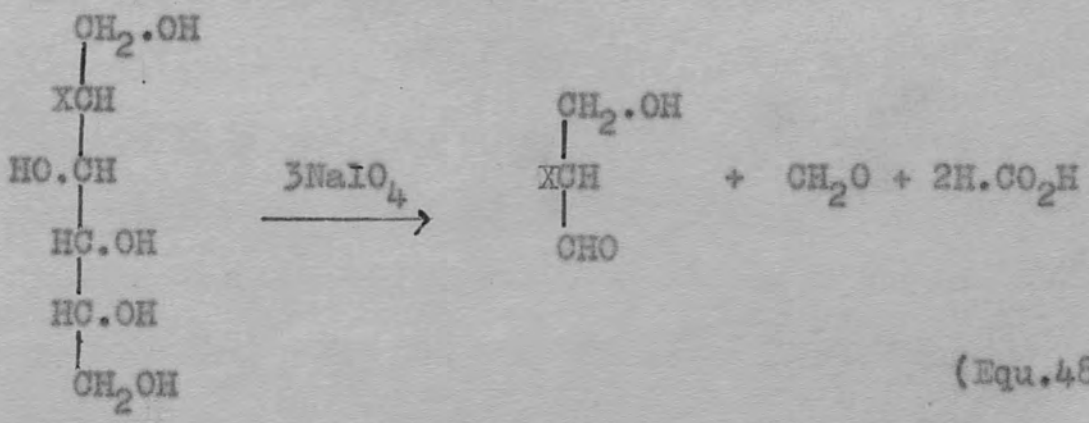
should contain no unchanged acetal. Also, the two reduced products, 2-O-methyl- and 5-O-methyl-D-mannitol, are, from the symmetry of the mannitol molecule, the same compound. The products should, therefore, be a less complex mixture than in the above reaction.

2:5-O-Methylene-D-mannitol was treated with excess boron trichloride and then with lithium aluminium hydride (exp. 39c). The organic product was isolated as an oil and was investigated by paper chromatography. This showed the presence of a small amount of hexitol and a second product, with a higher R_m value. These were separated by elution with aqueous ethanol on a carbon-celite column. One fraction yielded mannitol (1.1% yield) and the second product was isolated as an oil (A) (59%, calculated as $C_7H_{16}O_6$).

(A) was examined by paper chromatography and appeared to be a single compound. The absence of unchanged acetal was confirmed by carrying out a chromotropic acid determination of the methylene acetal content. This gave a value of 0.1%, which is within the limits of error of the determination. The R_m value of (A), in solvent (f),

was less than that of the monomethylene acetal and, on ionophoresis in a borate buffer, it had a higher M_m value. This suggests that it forms a more stable borate complex than the acetal and that it may therefore be a monosubstituted hexitol. It was shown to be a derivative of mannitol by reaction with boron trichloride and aqueous methanol, which yielded mannitol.

The position of the substituent in the mannitol molecule was investigated by periodate oxidation of (A). One molecular proportion of this (calculated as $C_7H_{16}O_6$) was found to consume 3.00 molecular proportions of periodate, with the production of 1.02 molecules proportions of formaldehyde and 1.90 of formic acid. The only monomethyl hexitol which gives values similar to these is 2(5)-O-methyl-D-mannitol:



(Equ.48)

The value obtained for the formic acid is less than the theoretical value of 2.00, but previous work has shown that the formic acid determination by titration with standard alkali, in the presence of an indicator, often gives a low value for the acid content[60]. This may be because some of the formic acid reacts with products containing alcohol groups, to give formate esters. These would hydrolyse slowly during the titration and so not all the formic acid would be estimated.

These results suggest that (A) is a 2-O-substituted mannitol and its carbon and hydrogen content agree with those calculated for a mono-methyl ether. Zeisel analysis confirmed the presence of a methyl ether, but variable values were obtained for the methoxyl content and these were all higher than that calculated for the monomethyl ether. The oil was converted into the crystalline acetate, m.p. 102-102.5°, and this was analysed. The carbon and hydrogen content agreed with those calculated for penta-O-acetyl-O-methyl-D-mannitol and the methoxyl content was also close to the calculated value.

As the methoxyl content of (A) does not agree with the calculated value for 2(5)-O-methyl-D-mannitol, it was

decided to synthesize this compound by another method and to compare the properties of (A) with the known compound. No reference has been found to the preparation of this compound, although the other mono-methyl ethers of mannitol have been reported. 3(4)-O-Methyl-D-mannitol, m.p. 133-134°[61], has been prepared by the reduction of 4-O-methyl-D-mannose and its structure has been proved by referance to this compound. The acetate, m.p. 85-86°, is also known. 1(6)-O-Methyl-D-mannitol, m.p. 119°, has been prepared by the reduction of 1-O-methyl-D-fructose[62]. Its structure was proved by comparison with an authentic specimen prepared from 5:6-anhydro-1:2-3:4-di-O-isopropylidene-D-mannitol (unpublished work). Preparation of the acetate was not recorded.

2-O-Methyl-D-mannose, however, is known[63]. It was prepared by the following series of reactions:

D-Mannosedibenzylmercaptal $\xrightarrow{\text{acetone}}$ di-O-isopropylidene derivative

$\xrightarrow[\text{methylation}]{\text{exhaustive}}$ mono-O-methyl ether $\xrightarrow[\text{ii) } HgCl_2]{\text{i) acid hydrolysis}}$

mono-O-methyl-D-mannose(m.p. 136-137°)

On treatment with phenyl hydrazine, a hydrazone, containing a methoxyl group, and an osazone, containing no methoxyl group and identical with glucosazone, were obtained. This suggests that the mannose is substituted in the 2-position and that the methoxyl group is lost during osazone formation.

The Parnas-Klimek test for the presence of cis glycol groups (these form an insoluble copper complex with the reagent)[64] was positive for mannose, which contains such a group, but was negative for the ether. This is understandable if the ether is substituted in the 2-position.

Professor E. Pacsu very kindly sent us a specimen of 2-O-methyl-D-mannosedibenzylmercaptal. This was treated (exp. 40) with mercuric chloride, to remove the mercaptal groups, and the oily product shown to contain a small amount of mannose, but chiefly a compound with a higher R_m value. Both products were detected by the silver nitrate and p-anisidine hydrochloride sprays, but triphenyl tetrazolium chloride spray was reduced only by the mannose. This suggests that the main product may contain a substituent adjacent to the reducing group,

that is on the 2-position. The hexoses were reduced to the corresponding hexitols by an aqueous solution of potassium borohydride[65]. Paper chromatography showed that no reducing sugars remained. The hexitols were separated on a carbon-celite column.

2-O-Methyl-D-mannitol was thus obtained as a syrup. The rates of elution on paper of this compound and of (A) were compared in several solvents. These were found to be identical in solvent (a), solvent (f) and solvent (b). The two compounds also migrated at the same rate on ionophoresis in borate and molybdate buffers. 1:3:4:5:6-Penta-O-acetyl-2-O-methyl-D-mannitol was prepared and this had the same m.p. as the acetate of (A) and this was not depressed when the two compounds were mixed. Further evidence that the two acetates were different samples of the same compound was obtained by comparison of their infra-red absorption spectra by Dr. R. L. Williams. [redacted]. These were found to be identical over the range 5000 cm.$^{-1}$-666.7 cm.$^{-1}$. Peaks at 2836 cm.$^{-1}$ were correlated with the carbon-hydrogen stretching frequency of the methoxyl group. Justification for this correlation was found by examining the spectra of anisole and methyl

2-naphthyl ether; these both had absorption peaks at 2837 cm.$^{-1}$. Other workers have investigated a series of methyl ethers and shown the spectra of these to contain characteristic shoulders, on the side of the carbon-hydrogen absorption bands, in the range 2815-2832 cm.$^{-1}$. These were correlated with the vibrations of the methoxyl group[66]. In the spectrum of 4-hydroxymethyl-2:2-dimethyldioxolan, absorption at 2820 cm.$^{-1}$ and 2841 cm.$^{-1}$ may be due to the methoxyl group vibrations.[67]

The spectrum of (A) was also investigated. An absorption peak was found at 2843 cm.$^{-1}$ and this suggests the presence of the methoxyl group. A band at 3425 cm.$^{-1}$-3257 cm.$^{-1}$ probably arises from the vibrations of alcohol groups[68] and the broadness may be caused by intermolecular hydrogen bonding[69].

These results suggest that the acetate of (A) and 1:3:4:5:6-penta-O-acetyl-2-O-methyl-D-mannitol are two samples of the same compound. Further, as the acetate of (A) and the penta-acetate were both obtained by acetylation of (A) and of 2-O-methyl-D-mannitol, it follows that these ethers are also identical. The infra-red spectrum of (A) suggests that it is a methyl ether

but the results of a Zeisel determination gave a value between that calculated for a mono- and a di-O-methyl ether of mannitol. High results have been reported for hexa-O-methyl-D-mannitol. E. von Rudloff has investigated this reaction and shown that mannitol and glucitol give apparent methoxyl contents of 11.8% and 12.7%, owing to the production of volatile ethyl and vinyl iodides[70]. As methyl ethers yield the alcohol during the reaction with hydrogen iodide, this may undergo further reaction so that, in the final titration, iodine from ethyl and vinyl iodides, as well as from methyl iodide, is detected. If all this iodine is assumed to be derived from methyl iodide, a high result will be obtained. This may account for the values obtained for (A) and these may not conflict with the postulated structure.

These results also substantiate the structure of the mono-O-methyl-D-mannose of Pacsu. The evidence presented for this structure showed it to be a mono-O-methyl ether, but the evidence for the position of the substituent was not conclusive. On the other hand, (A) has been shown, by periodate oxidation, to contain a substituent at the 2-position in the mannitol molecule but the evidence that it is a mono-O-methyl ether is

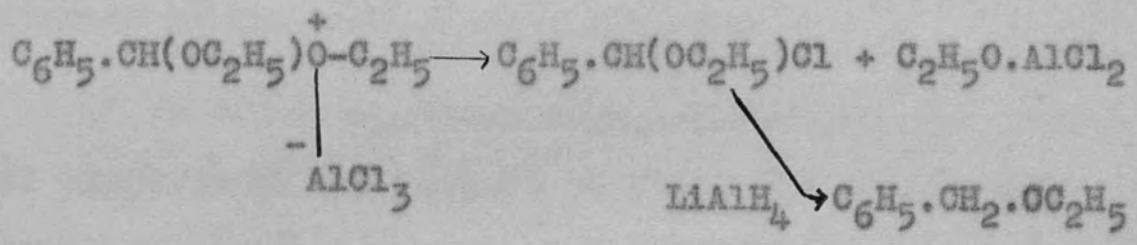
less well-founded. As the hexitol, derived from the mono-O-methyl-D-mannose, and (A) are identical, the postulated structures of the mannose derivative and of (A) are confirmed.

STRUCTURE OF THE PRODUCT OF THE REACTION OF EXCESS BORON TRICHLORIDE WITH CYCLIC METHYLENE ACETALS

The isolation of 2-O-methyl-D-mannitol (in 59% yield) from the reduction by lithium aluminium hydride of the product from the reaction of excess boron trichloride with 2:5-O-methylene-D-mannitol can be explained by the reactions shown in Fig. III, p. 78. The small amount of mannitol (1.1%) isolated may arise from the action of traces of atmospheric moisture on the intermediate product before reduction, or from impurity in the sample of cyclic acetal.

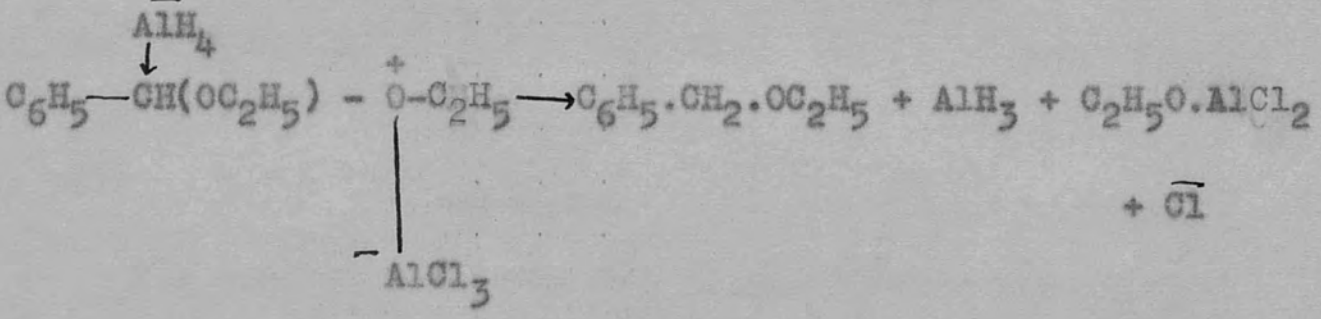
This reaction can be compared with the reduction of non-cyclic acetals and ketals and some activated ethers by a mixture of aluminium chloride and lithium aluminium hydride. Reduction occurs readily, although the compounds are unaffected by lithium aluminium hydride alone[71,72]. Two mechanisms have been suggested for the reduction of the

diethyl acetal of benzaldehyde. It may occur through the formation of an α-chloroether, known to be readily reduced to the ether (analogous to Fig. III a):



(Equ.49a)

Alternatively, reduction could be caused by the attack of the nucleophilic aluminohydride ion on the complex, which contains a positively charged centre:



(Equ.49b)

An analogous mechanism can be written for the boron trichloride reaction (Fig. IIIb). This seems a less probable mechanism as boron trichloride is considerably more reactive than aluminium chloride and the complex would be expected to undergo fission before it was attacked by the nucleophilic reagent.

In order to obtain more information, the infra-red spectrum of the product of the reaction of boron trichloride with a cyclic methylene acetal was examined and interpreted by Dr. R. L. Williams. [redacted].

The 1:1 complex of p-dioxan and boron trichloride was prepared as a reference compound[73] (exp.41). This is a very stable complex and reacts with pyridine and hydroxylic solvents to yield p-dioxan. It only decomposes, to yield products other than p-dioxan, when heated above its melting point (78° *in vacuo*).

The spectra of dioxan and of the complex were recorded and strong absorption at 789 $cm.^{-1}$ and 761 $cm.^{-1}$, found only in the spectrum of the complex, was correlated with the stretching vibration of the boron-chlorine bonds. The assymetric stretching vibrations of these bonds in

boron trichloride give rise to absorption peaks at 995 cm.$^{-1}$ (due to ~~10~~ ^{10}B-Cl) and at 954 cm.$^{-1}$ (due to ~~11~~ ^{11}B-Cl)[74]. The lower frequency found in the co-ordination compound is caused by the increased electron density on the boron atom in this molecule. This decreases its electron-accepting powers and so the back co-ordination of the chlorine atoms is less than in boron trichloride. The resulting reduction in the double bond character of the boron-chlorine bonds in the co-ordinated compound will cause the absorption to be at a lower frequency.

If ring opening occurs in the reaction of the acetal with boron trichloride, dichloroboronites or chloroboronates are expected as products. The infra-red spectra of compounds of this type have been investigated[75]. Absorption of methyl dichloroboronite at 997 cm.$^{-1}$ and 960 cm.$^{-1}$ was correlated with assymetric boron-chlorine vibration; methyl chloroboronate absorbed radiation at 630 cm.$^{-1}$ and this was correlated with the boron-chlorine vibration.

The spectra of tri-O-methylene-D-mannitol and of its product with boron trichloride were recorded. Absorption in the latter spectrum at 663 cm.$^{-1}$ was thought to be caused

by the boron-chlorine vibration. This frequency is considerably lower than that in the spectrum of the p-dioxan-boron trichloride complex and this would imply that if a complex is also formed in the reaction of the acetal, the latter complex is more stable than that from p-dioxan. This is unlikely and it is more probable that ring opening has occurred and the frequency at which absorption occurs is in fact close to the absorption of methyl chloroboronate.

To conclude, the infra-red absorption spectrum of the product of the reaction of excess boron trichloride with tri-O-methylene-D-mannitol suggests that ring opening has occurred and that chloroboronates are formed. The reaction of boron trichloride with a cyclic methylene acetal therefore involves the formation of an α-chloromethyl ether, which does not undergo further reaction with the reagent. The chlorine can be replaced by an atom or group to yield a polyol substituted in one of the positions originally linked in the ring (Fig. III a) p. 78.

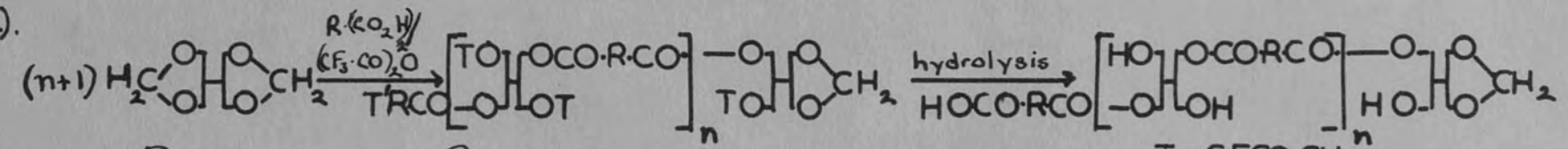
REACTION OF A MIXTURE OF CARBOXYLIC ACID AND TRIFLUOROACETIC ANHYDRIDE WITH CYCLIC ACETALS AND KETALS OF POLYOLS

PRODUCTION OF POLYMERIC PRODUCTS

The reactions of a mixture of a mono-carboxylic acid and trifluoroacetic anhydride with cyclic acetals and ketals of D-glucitol and D-mannitol have been discussed in the Introduction p.28. The methylene acetals are considerably less reactive than ketals or other acetals and yield a different type of product. The rings are probably opened to give acyl and trifluoroacetoxymethyl groups linked to the oxygens originally linked in the ring. Hydrolysis removes the trifluoroacetoxymethyl groups and partially-substituted esters of the hexitol are isolated. Benzylidene acetals and isopropylidene ketals, on the other hand, yield products containing acyl groups linked to both oxygens originally in the ring and the benzylidene and isopropylidene residues are broken off in the initial reaction and not in the subsequent hydrolysis.

FIG. II

a).

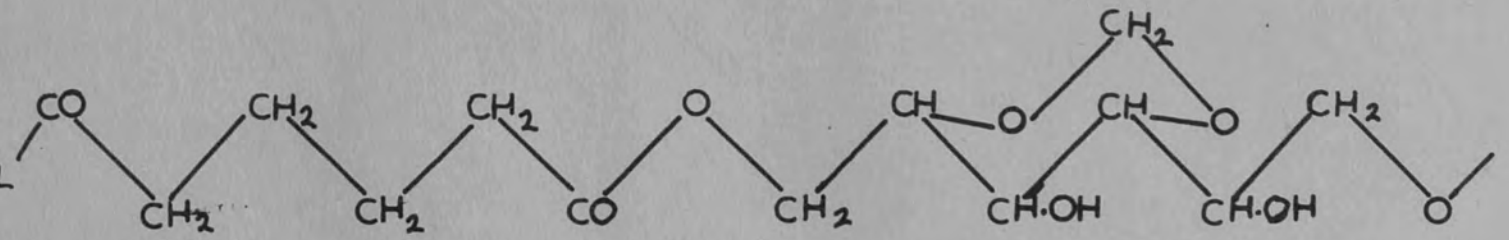


GENERAL POLYMERIZATION REACTION

T - $CF_3CO_2CH_2$·
T' - CF_3CO_2CO·

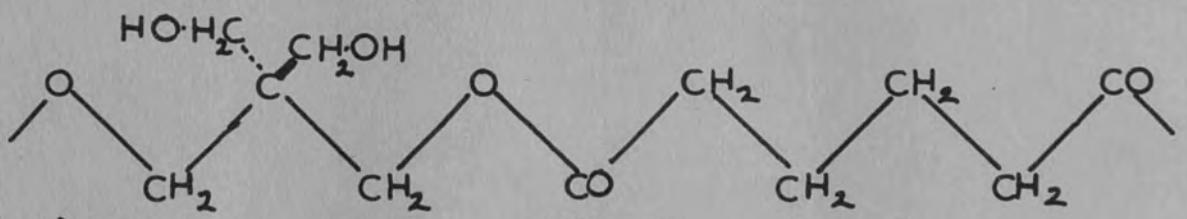
b).

POLYMER FROM
1:3-2:4-5:6-TRI-O-
METHYLENE-D-GLUCITOL



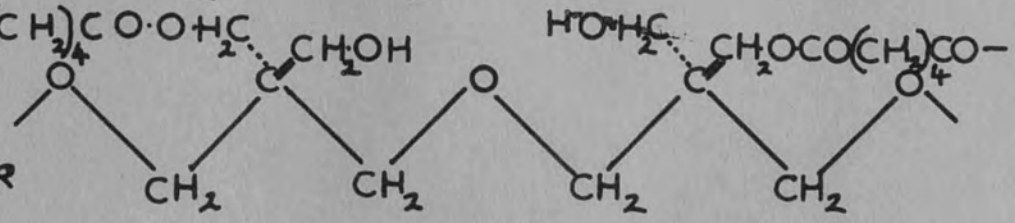
c).

POLYMER FROM
DI-O-METHYLENE
PENTAERYTHRITOL

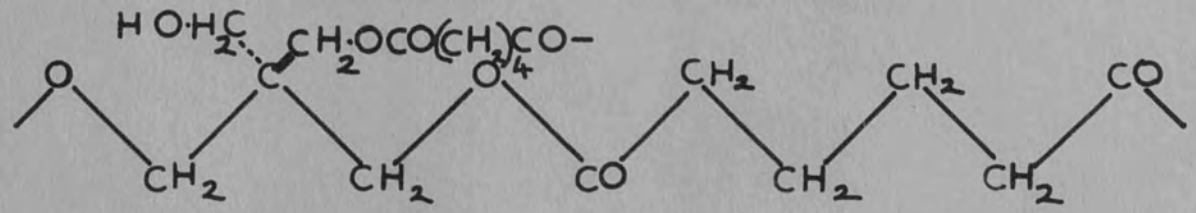


(i).

POSSIBLE BRANCHING
UNITS IN THIS POLYMER



(ii).



The reactions of a di-carboxylic acid and trifluoroacetic anhydride with cyclic acetals and ketals have not been investigated, but a di-ester of the acid would be the predicted product. If the polyol derivative contains no reactive group other than two methylene rings, the reaction product, after hydrolysis, would be expected to be a linear poly-ester, containing free alcohol groups (Fig. IV a). There is also the possibility that an intramolecular reaction may occur, but, as the cyclic product would contain at least eight cyclic atoms, this is unlikely. The presence of molecules with more than two reactive centres would lead to branching in the poly-ester chain and probably to a cross-linked product. If the reactive group is a single benzylidene acetal or isopropylidene ketal ring, a linear poly-ester could again be formed, but it would contain no free alcohol groups.

These postulated reactions are typical condensation polymerisations. Although no product is eliminated in the formation of the ester links, the linear molecules are built up by simple ring opening reactions at a constant rate, unlike a true addition polymerisation, which is a

rapid radical- or ion-initiated chain reaction. The chain-length of a condensation polymer depends on the duration of the reaction and can be controlled by addition of mono-valent "chain stoppers" or excess of one of the reagents.

The synthetic fibres, nylon 6.6 (prepared from adipic acid and hexa-methylene diamine), nylon 6 (from ω-caprolactam) and terylene (from terephthalic acid and glycol) are prepared by polycondensations. These polymers necessarily contain no free functional groups, such as alcohols, as these would react during the polymerisation reaction to give a cross-linked product, which could not be drawn into a fibre.[76] The presence of alcohol groups is desirable and enables the fibre to absorb water, which is held by hydrogen bonding, and also causes it to have a high dye uptake and reduced static; though the synthetic materials have, in comparison with cotton or linen, the advantage of drying rapidly, they have the concomitant disadvantage of being less comfortable and warm to wear, and less easy to dye. Free alcohol groups can be introduced into the polymer molecule, although the production cost is increased, by blocking the groups during polymerisation and later

liberating them. The postulated reaction of a di-O-methylene polyol, however, should yield a poly-ester containing free alcohol groups, so it was decided to investigate this type of reaction. (Trifluoroacetic anhydride has been used to prepare a polymer from p-hydroxybenzoic acid. The product would be expected to be a linear poly-ester, but its properties suggest that it may contain cross-links).[77]

The reaction between dibasic adipic acid and methylene acetals containing only two reactive rings has been carried out. Tri-O-methylene-D-glucitol was chosen because, in its reaction with acetic acid and trifluoroacetic anhydride, the βC ring has been shown to be stable to the reagent.[32] Although the reactions of di-O-methylene pentaerythritol with this type of reagent had not been previously investigated, it seemed probable that both rings would react and it also has been used.

Equimolar proportions of acetal and acid were treated with excess trifluoroacetic anhydride, which also acted as solvent ~~(exp.43)~~. The reaction was left at room temperature for a few hours and, after the volatile

products had been removed, the residue was treated with an aqueous solution of sodium bicarbonate. The insoluble product was filtered off but it was found that, if it had been in contact with the alkaline solution for only a few hours, it decomposed in the presence of moisture, liberating formaldehyde. This suggests that the hydrolysis of the trifluoroacetoxymethyl groups was incomplete and that these were hydrolysed later to give formaldehyde and trifluoroacetic acid, which catalysed the hydrolysis of the adipyl ester groups. If the product was left in an aqueous solution of sodium bicarbonate for a few days, the insoluble residue was found to be stable.

The product from the tri-O-methylene-D-glucitol reaction is a colourless, brittle solid, melting at 130-150° (exp. 43) to a viscous liquid, which can be drawn into brittle threads. The solid becomes swollen in some solvents and dissolves completely in pyridine. Alkaline hydrolysis yielded 2:4-O-methylene-D-glucitol in 33% yield and the only other hexitol detected by chromatography was a trace of D-glucitol; adipic acid was identified as its S-benzyl-

iso-thiouronium salt in 52% yield. The physical properties of the solid are typical of a linear polymer and the hydrolysis products suggest that the linear molecules are made up of alternate 2:4-O-methylene-D-glucitol and adipic acid units linked by ester groups. British Nylon Spinners Ltd. have investigated the infra-red absorption spectrum of the polymer for us and confirm the presence of alcohol, carboxylic ester (but not trifluoroacetate) and cyclic ether groups. The carboxylate ion is also present, presumably as the end group in some of the molecules, and the carboxylic acid group was detected in the acid-treated polymer. If the absorption coefficients of the carboxylic ester and carboxylate ion are the same, the ratio of the two absorptions gives the relative number of the two kinds of group in a molecule of the polymer. A value of ten ester groups to one carboxylate ion is obtained but, as a molecule may contain two, one or no carboxylate end groups, an average chain length of the molecules cannot be calculated unless the proportions of the different types of molecule are known.

The reaction has therefore yielded the type of

product predicted from the results of the reaction of mono-carboxylic acids and trifluoroacetic anhydride with tri-O-methylene-D-glucitol. Only the position of the ester links in the D-glucitol molecule is uncertain but, from the nature of the products of the mono-carboxylic acid reactions, these are probably in the 1:6-positions of the hexitol (Fig. IV b). p.100

The viscosity of solutions of the polymer in pyridine were measured and values for the specific viscosity, η_{sp}, and relative viscosity, η_r, were obtained for solutions of different concentrations. These values are functions of the concentrations of the solutions and the quantities, η_{sp}/c, and $\ln\eta_r/c$ approach the same limiting value for a solution of infinite dilution; this is called the intrinsic viscosity, $[\eta]$, and can be determined graphically, giving a value for this polymer of 0.165. The intrinsic viscosity is related to the weight average molecular weight, M, by the empirical expression:[78]

$$[\eta] = K_1 M + K_0$$

The values for the constants K_1 and K_0 are usually calculated from measurements of the viscosity of a similar polymer of known molecular weight, in the same solvent

and at the same temperature. No reference could be found for the constants of a poly-ester dissolved in pyridine, so the values used by Flory in the molecular weight determination of polydecamethylene glycol adipates in chlorobenzene at 25° were substituted:[79]

$$[\eta] = 2.12 \times 10^{-5} M + 0.060$$

$$\therefore \quad M = \frac{[\eta] - 0.060}{2.12 \times 10^{-5}}$$

$$= 4,960.$$

(These authors use different concentration units, so that the numerical values of their constants are not the same as those used here). This result gives an indication of the weight average molecular weight of the polymer and suggests that, if the repeating unit in a chain is a 2:4-O-methylene-D-glucitol adipate ester residue, $C_{13}H_{20}O_8$ (m.wt.304), the chains contain an average of sixteen units.

British Nylon Spinners Ltd. also showed that the polymer, from its X-ray diagram (Fig.XIV), is highly crystalline and found that it has a moisture regain of 6.4%, compared to 4.5% for nylon 6.6. Both these properties may be due to the relatively low molecular weight and the corresponding high proportion of polar end-groups in the polymer. The softening point is 88°, compared

to 265° for nylon 6.6 and 220° for nylon 6. The polymer therefore has too low a molecular weight to give a useful fibre but a modification of the reaction conditions should give a product of the required molecular weight (1200). Its relatively high water uptake may also be due to the presence of the alcohol groups and, if a product of higher molecular weight retained this property, it should provide useful fibres.

Di-U-methylene pentaerythritol reacted with adipic acid and trifluoroacetic anhydride (exp. 44) to give a colourless, rubbery solid which does not dissolve completely in any of the common organic solvents; on heating, it does not melt but begins to char at about 300°. These properties are very different from those of the polymer obtained from tri-O-methylene-D-glucitol and are typical of a cross-linked polymer. Alkaline hydrolysis yielded pentaerythritol and adipic acid, isolated in 50% and 68% yield respectively. Viscosity measurements could not be carried out because no solvent could be found which completely dissolved the polymer; pyridine which had been in contact with the polymer had the same viscosity as the pure solvent.

The hydrolysis results suggest that the polymer is built up of alternate pentaerythritol and adipic acid residues, linked by ester groups (Fig. IV c). p.100 Branching must occur at some positions in the chain and a unit must be present which can react to give a tri- or tetra-ester. Any dipentaerythritol in the technical pentaerythritol, used in the preparation of di-O-methylene pentaerythritol, would give rise to di-O-methylene dipentaerythritol in the reaction with formaldehyde and this would be expected to react with adipic acid and trifluoroacetic anhydride to give a tetra-ester (Fig. IV c(i)). Dipentaerythritol residues could therefore cause branching in the polymer and, to test this idea, pentaerythritol has been purified by a standard method (exp. 45). The technical product, m.p. 253-264°, was treated with benzaldehyde in the presence of acid, and di-O-benzylidene pentaerythritol recrystallised to constant melting point. Dipentaerythritol, if present, would also yield a di-O-benzylidene derivative, but this is readily hydrolysed by moisture[2] and di-O-benzylidene pentaerythritol would be freed from dipentaerythritol during recrystallisation. The purified acetal was hydrolysed to pentaerythritol, m.p. 268-269°.

A test for the presence of traces of dipentaerythritol has been reported[80]: the sample is treated with nitric acid and the aldehydic oxidation product of dipentaerythritol, $O(CH_2.CHO)_2$, detected by its reaction with Schiff's reagent. Both technical and purified samples of pentaerythritol have been found to give positive results for this test, which suggests that they both contain dipentaerythritol. However, the validity of the test seems doubtful as pentaerythritol itself would be expected to be oxidised to an aldehydic compound under these conditions[81]. The purified sample was therefore assumed to contain no dipentaerythritol.

Di-O-methylene pentaerythritol was then prepared from the purified pentaerythritol and was found to have the same m.p. as the acetal prepared from technical pentaerythritol. It was treated with adipic acid and trifluoroacetic anhydride (exp. 46) and again the product was a rubbery, colourless compound which showed no sign of melting below 300°. This suggests that the original sample of acetal also contained no di-O-methylene dipentaerythritol and may well have been purified from it during recrystallisation, as in the purification of the

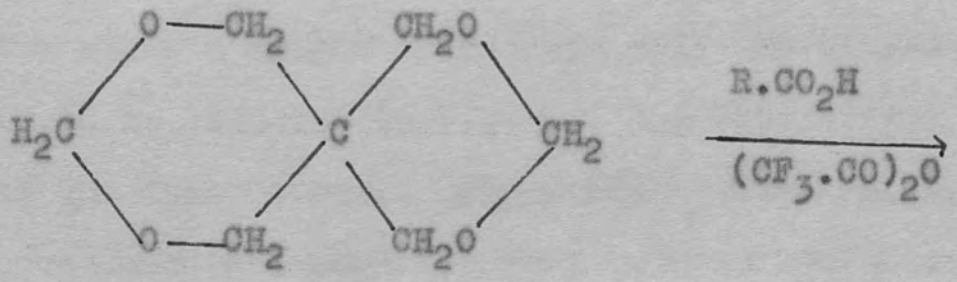
di-O-benzylidene acetal.

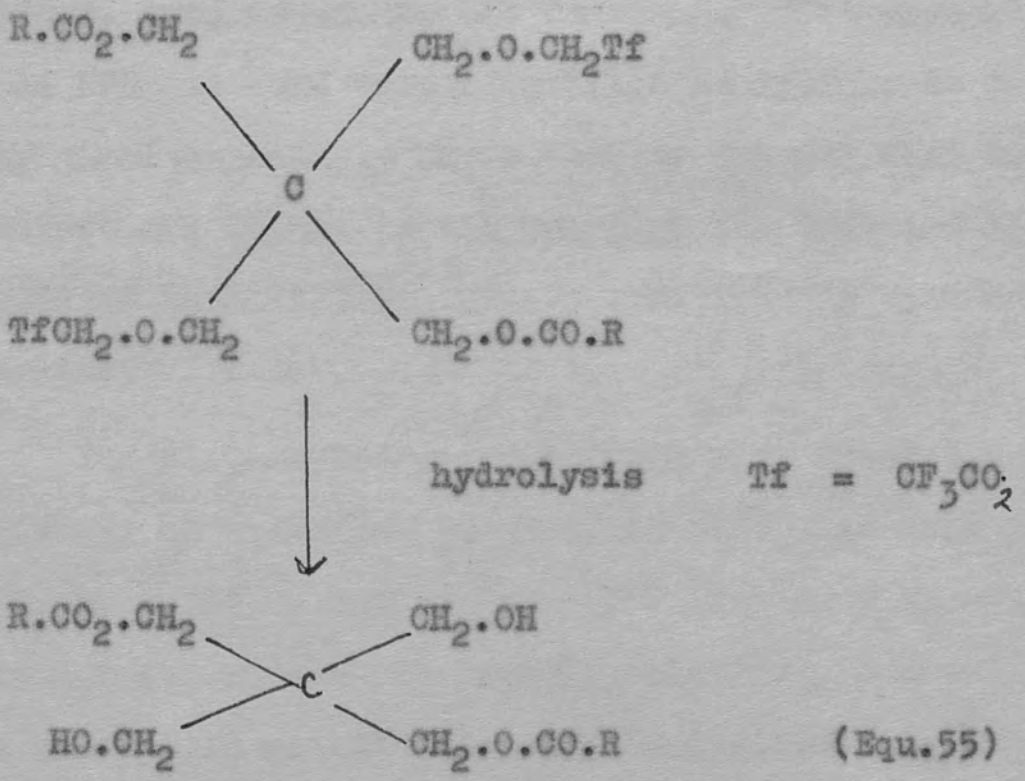
The cross-linking in the polymer therefore cannot be explained by the presence of dipentaerythritol residues. Another possible explanation is that a third or even a fourth adipate ester group is introduced into some pentaerythritol chain units (Fig. IV c(ii) p.100) either by displacement of trifluoroacetoxymethyl residues, which would then no longer be efficient blocking groups, or by further esterification during the removal of these groups by hydrolysis. To gain more information about the properties of these six-membered acetal rings, their reactions with mono-carboxylic acids and trifluoroacetic anhydride have been investigated.

REACTION OF THIS REAGENT WITH THE CYCLIC ACETALS AND KETALS OF PENTAERYTHRITOL

If it behaves similarly to the methylene acetals of D-glucitol, di-O-methylene pentaerythritol will react with a mixture of equimolar proportions of a mono-carboxylic acid and trifluoroacetic anhydride to give di-O-acyl-di-O-

trifluoroacetoxymethyl pentaerythritol, which, on hydrolysis, will give di-O-acyl pentaerythritol:





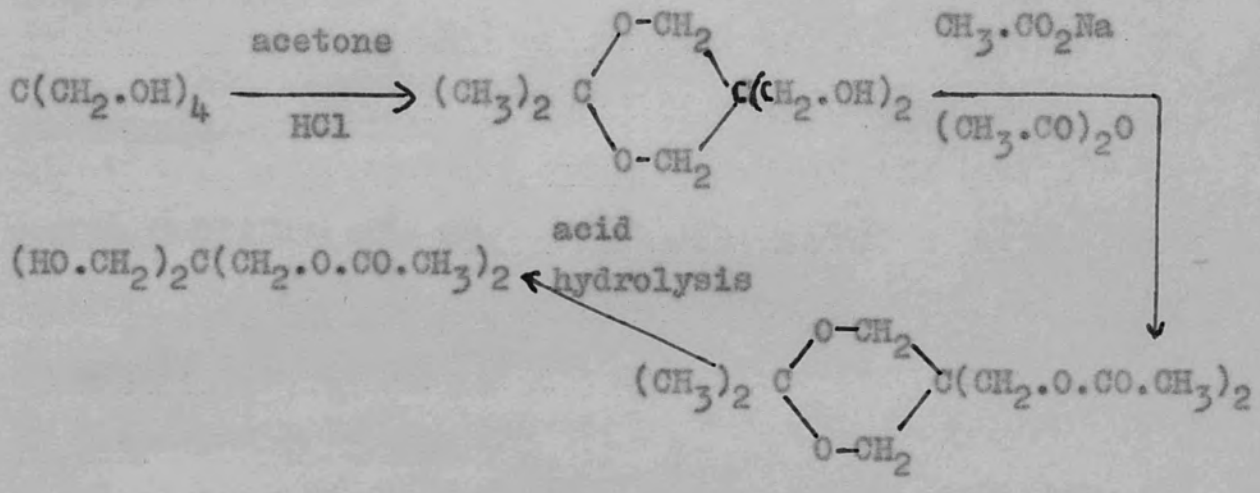
(Equ.55)

Benzoic acid and trifluoroacetic anhydride would therefore be expected to react with the acetal to give di-O-benzoyl pentaerythritol, a known, crystalline compound[82]. The reaction, (exp.47) in fact, yielded an oil which could not be crystallised and also in too great a weight to contain only the dibenzoate (0.66 g. compared to 0.52 g., the theoretical yield of the di-benzoate). The product could not be investigated by chromatography because benzoates are not detected by the ester spray. It was refluxed with aqueous sodium hydroxide solution, but, after several hours, some insoluble oil remained. Pentaerythritol and benzoic acid were identified as hydrolysis products by chromatography. These results suggest that benzoate esters are formed in the reaction but that the final product is a mixture, possibly containing some unreacted acetal.

The di-O-methylene acetal was also treated with a mixture of equimolar proportions of acetic acid and trifluoroacetic anhydride (exp. 48), followed by hydrolysis in aqueous sodium bicarbonate solution. A low yield of a chloroform-soluble oil was obtained and the oil was shown by chromatography to contain at least two esters.

Pentaerythritol was detected in the aqueous layer and this suggests that hydrolysis of the acetate, as well as the trifluoroacetate groups, had occurred in the aqueous solution (pH 9).

The known compound, di-O-acetyl pentaerythritol[82], was then prepared (exp. 49) so that its stability to alkaline hydrolysis and its R_f values in various solvents could be compared to those of the product from di-O-methylene pentaerythritol. The reactions used were:



(Equ.56)

Mono-O-isopropylidene pentaerythritol is prepared even in the presence of excess acetone as the di-ketal is formed only under anhydrous conditions. The acetate of the mono-ketal was shown by chromatography to contain a trace of tetra-

acetate but the product of acid hydrolysis of this compound contained at least three esters besides the tetra-acetate, and also some pentaerythritol. No iso-propylidene derivatives were detected, which suggests that hydrolysis was complete.

Orthner and Freyss[82] report that, on standing, pentaerythritol was deposited from the oily product, identified as the di-acetate, and they suggest that it is formed, together with the tetra-acetate, by spontaneous disproportionation:

Di-acetate → mono-acetate and tri-acetate → tetra-acetate and pentaerythritol.

To see if this mixture of products had been formed by disproportionation, the mixture was purified from tetra-acetate, by separation on paper. The remaining esters were investigated by chromatography at various time intervals after the separation, to see whether the tetra-acetate had been reformed (exp. 49c); none was detected. Samples were then treated with aqueous solutions of different pH and the chloroform-soluble products investigated by chromatography, to see whether the

tetra-acetate was formed under these conditions. None was found after treatment with dilute acid or with dilute alkali, pH 7-8, but at pH 9 and pH 10 some was formed. This suggests that alkali-catalysed disproportionation can occur. Intramolecular acyl migrations in partially-esterified polyols are known to be catalysed by traces of alkali and probably involve an orthoacyl intermediate[83]. Intramolecular migration in partially-substituted pentaerythritol esters would not yield a different ester, but it is possible that an intermolecular reaction may also occur under alkaline conditions. The reaction product from di-O-methylene pentaerythritol had been treated with an aqueous solution of pH 9 and the product from the hydrolysis of di-O-acetyl-isopropylidene pentaerythritol with solid silver carbonate, so that the mixtures of esters obtained from both these reactions may have been formed by disproportionation of the di-ester in the presence of traces of alkali.

The reaction of di-O-methylene pentaerythritol with acetic acid and trifluoroacetic anhydride was therefore repeated (exp. 50), but the hydrolysis was carried out in an aqueous buffer at pH 7.0. Trifluoroacetoxymethyl groups should be hydrolysed in neutral conditions[33], but

disproportionation of the acetate groups should not occur. Greater weight of chloroform-soluble material was isolated than in the first experiment and this was shown by chromatography again to be a mixture of three esters, including the tetra-acetate, and a trace of a fourth; no pentaerythritol could be detected in the aqueous layer. It is unlikely that di-O-acetyl-O-methylene pentaerythritol is present as this should have a higher R_f than the tetra-acetate in the solvent (g) and so be detected, but mono-O-acetyl-O-methylene pentaerythritol may be a component of the mixture. The R_f values in solvent (a) of two of the esters (0.79 and 0.87) correspond closely to the values for two of the products from di-O-acetyl-O-isopropylidene pentaerythritol (0.81 and 0.89) and these are probably the di- and tri-esters. The trace of ester, R_f 0.64, may correspond to the product of the latter reaction, R_f 0.67, and is probably the mono-ester

As it is unlikely that the mixture of esters arose during hydrolysis at pH 7.0, it must have been formed during the reaction of acetic acid and trifluoroacetic anhydride with the acetal. One explanation is that the trifluoroacetoxymethyl groups are displaced by acetyl groups yielding di-, tri-, and tetra-esters, but not mono-esters. An analogous reaction is not found with the

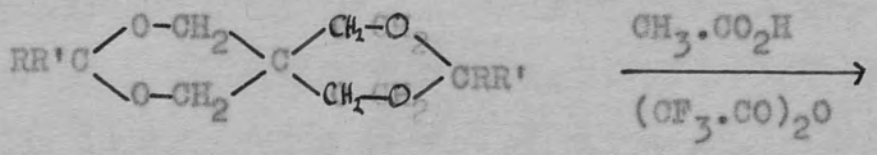
methylene acetals of D-glucitol, but, in the products from these reactions, the trifluoroacetoxymethyl groups are linked to oxygens derived from secondary alcohols, while in the pentaerythritol derivatives they are linked to oxygens derived from primary alcohols. This may account for the different course of the reactions.

These results suggest that the reaction of any carboxylic acid and trifluoroacetic anhydride with di-O-methylene pentaerythritol will yield a mixture of the corresponding esters. They explain the production of an oil in the reaction of benzoic acid and trifluoroacetic anhydride with the acetal; this is probably a mixture of benzoate esters. The production of a cross-linked polymer in the reaction with adipic acid is also explained, as tri- and tetra-adipate esters of pentaerythritol are probably present, acting as branching points in the chains (Fig. III c(ii)).

p.100

It then seemed of interest to investigate the reactions of benzylidene acetals and isopropylidene ketals of pentaerythritol with acetic acid and trifluoroacetic anhydride and to compare them to the reactions of the corresponding acetals and ketals of D-glucitol and D-mannitol.

If the reactions are similar, the pentaerythritol derivatives will be converted into the crystalline tetra-acetate (p.32).



$$C(CH_2.O.CO.CH_3)_4 + RR'C(Tf_2)_2$$

$$Tf = CF_3.CO_2^-$$

(Equ.57)

Di-O-benzylidene pentaerythritol was treated with a mixture of equimolar proportions of acetic acid and trifluoroacetic anhydride (exp. 51) and an intensely orange solution was formed. The product was an oil, which showed no signs of crystallising. Chromatography showed the presence of the tetra-acetate and smaller amounts of three other esters and hydrolysis with dilute hydrochloric acid liberated benzaldehyde. This suggests that one of the three esters may be di-O-acetyl-O-benzylidene pentaerythritol and this was prepared by acetylation of mono-O-benzylidene pentaerythritol (exp. 52). The product contained a small

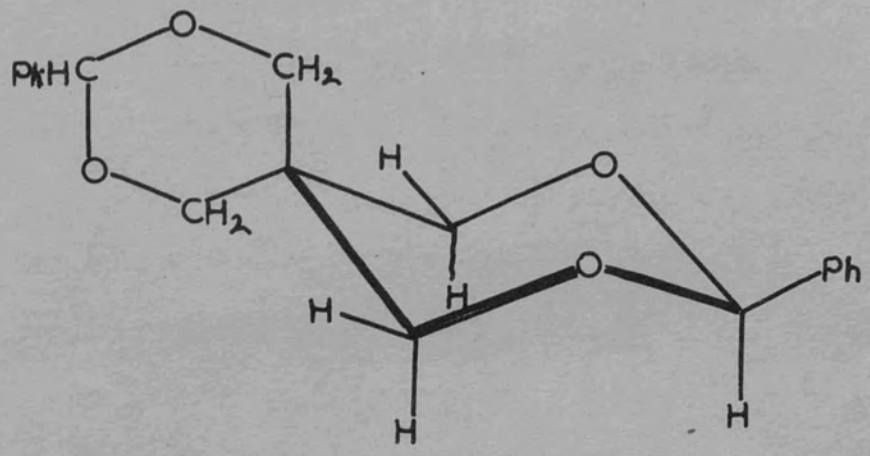
amount of a second ester, probably the mono-acetate, and it was purified by elution with solvent (g) on a cellulose column. The synthesis of di-O-acetyl-O-benzylidene pentaerythritol has not been previously reported and this preparation yielded it as an oil. It was found to have the same R_f value as one of the products from the reaction of di-O-benzylidene pentaerythritol.

Di-O-benzylidene pentaerythritol was then treated with trifluoroacetic anhydride and excess acetic acid (exp. 53). This reagent has been found to open methylene rings with the production of acetate and acetoxymethyl groups[31]. The reaction mixture was nearly colourless and yielded an oil, which was shown by chromatography to contain a similar mixture of esters to those found in the previous experiment. The tetra-acetate and di-O-acetyl-O-benzylidene pentaerythritol were present in considerably higher proportions than the other two products and an attempt was made to separate these two esters on a cellulose column, but was unsuccessful.

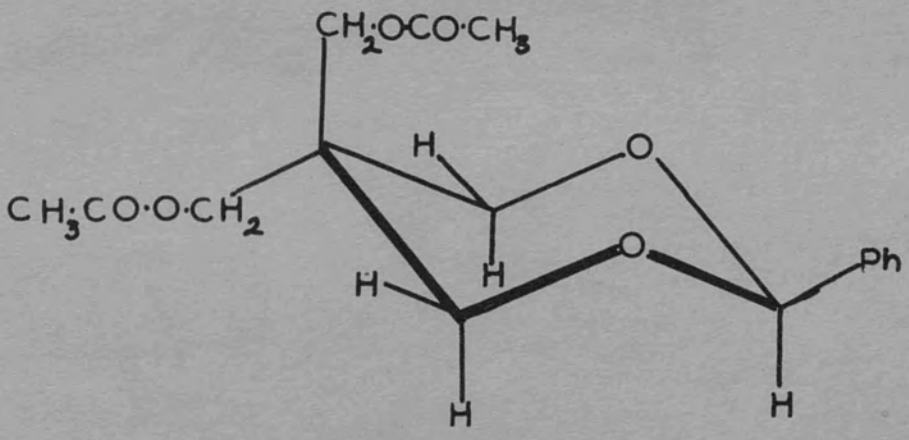
Mono-O-benzylidene pentaerythritol was also treated with trifluoroacetic anhydride and excess acetic acid (exp. 54) and yielded a similar mixture of esters.

These results show that one acetal ring in di-O-benzylidene pentaerythritol is readily opened, to give di-O-acetyl-O-benzylidene pentaerythritol, but that not all of this product undergoes further reaction to give the tetra-acetate. This stability of the benzylidene ring is surprising, as no products containing unopened rings have been isolated from the reaction of the benzylidene acetals of D-glucitol and D-mannitol with trifluoroacetic anhydride and acetic acid or with the acetolysis reagent. From a model of di-O-benzylidene pentaerythritol (Fig. V), it can be seen that there is no steric hinderance to the approach of the reagent, unless very bulky, to any of the four ring oxygens. When reaction occurs at one ring, the two primary alcohol residues are released as acetates. These are free to rotate about the bond to the quarternary carbon, which is still linked in the unreacted ring. From a model of di-O-acetyl-O-benzylidene pentaerythritol (Fig. V), it can be seen that these acetoxymethyl groups, particularly the one in the axial position, hinder further attack on the acetal ring and this could account for its stability. The same situation probably arises in the reaction of mono-O-benzylidene pentaerythritol. Free

FIG. V



DI-O-BENZYLIDENE PENTAERYTHRITOL



DI-O-ACETYL-O-BENZYLIDENE PENTAERYTHRITOL

alcohol groups are known to be more rapidly acetylated than those linked in a benzylidene acetal[32], so di-O-acetyl-O-benzylidene is probably again formed initially. In the corresponding hexitol derivatives, none of the cyclic carbon atoms is quarternary and steric hinderance to attack may not occur in these reactions. The nature of the other products of the benzylidene acetal reactions is less certain, but the product with the low R_f value in solvent (g) was detected by the hydroxylamine and 2:4-dinitrophenylhydrazine sprays and it may be mono-O-acetyl-O-benzylidene pentaerythritol. The fast-moving product (R_f 0.78, 0.82, 0.84) was also detected by both sprays and may be benzylidene diacetate, although it would not be expected to be formed in the reaction of di-O-benzylidene pentaerythritol with a mixture of equimolar proportions of acid and anhydride.

Mono-O-isopropylidene pentaerythritol was treated with a mixture of equimolar proportions of acetic acid and trifluoroacetic anhydride (exp. 55) and a dark-coloured reaction mixture was formed. The product was a dark oil, considerably heavier than the theoretical weight of tetra-acetate. The tetra-acetate was isolated, after several treatments with decolourizing charcoal, in 13.5% yield.

The ketal reacted with the anhydride and excess acetic acid (exp. 56) to give a yellow solution and yielded the tetra-acetate in 25.1% yield, and also a colourless oil, which could not be crystallised. Chromatography showed the presence of only traces of esters, other than the tetra-acetate, in these reaction products and the non-crystalline product was probably formed from the isopropylidene residues perhaps by formation and polymerisation of a vinyl ester (see p.65). The ketals of D-mannitol have also been found to give these dark oils and mannitol hexa-acetate in low yield (21%)[32].

As no di-O-acetyl-O-isopropylidene pentaerythritol was detected among the products, this suggests that, if this compound is formed in the reaction of the mono-ketal, ring-opening can then readily occur without hinderance by the two acetoxymethyl groups. It is more probable that the ring opening reaction and acetylation of the alcohol groups occur at similar rates and the acetate of the mono-ketal is then unlikely to be formed.

To conclude, a mixture of a carboxylic acid and trifluoroacetic anhydride causes ring opening of cyclic acetals and ketals of pentaerythritol. Only in the

reaction of the isopropylidene ketal are the products analogous to those formed in the reaction of the corresponding hexitol derivative. Neither the methylene nor the benzylidene acetals yield the products predicted from the results of the hexitol reactions. This may be due to the differences in the relative positions of, and in the substituents in, the 1:3-dioxo-rings in the two types of polyol derivatives.

EXPERIMENTAL

GENERAL TECHNIQUES AND PREPARATION OF POLYOL DERIVATIVES

Experiment I. Paper chromatography[84].

Many of the reaction products have been investigated by descending development with a suitable solvent on Whatman No. I paper. After the developed chromatogram has been dried, it is sprayed with a reagent which gives contrasting colours with the eluted products and with the paper. The positions of the compounds are recorded as R_f values, the distance travelled by the compound from the base line/distance between solvent front and base line, or as R_x values, distance travelled by the compound/distance travelled by a standard, X.

i) Solvents:

Solvent (a).- water-saturated n-butanol. This is prepared by shaking the two liquids together for a few hours, cooling them to 0° and then syphoning off the organic layer.

Solvent (b).-ethyl acetate, acetic acid, water (9:2:2, by volume).

Solvent (c).- acetone, water(4:I by volume).

Solvent (d).-ethanol, ammonia (d,0·888), water(80:4:16, by volume).

Solvent (e).-mesityl oxide,water, 85% formic acid. The oxide (225 ml.), water (225 ml.) and acid (108 ml.) are shaken together and the organic layer syphoned off.

Solvent (f).-n-butanol, pyridine, water, saturated aqueous solution of boric acid(6:4:2:I by volume).

Solvent (g).-petroleum ether (b.p. 60-80°) saturated with dimethyl sulphoxide[85]. This solvent differs from the preceding solvents in that the stationary phase is not water, but dimethyl sulphoxide. Only compounds soluble in petroleum ether are eluted from the base-line, and in this work it has been found that only fully-substituted polyols are eluted. Although these compounds are eluted together near the solvent front in

the solvents with an aqueous stationary phase, in this solvent they move at different rates and can be distinguished.

ii). Sprays:

Silver nitrate reagent[86] - The paper is dipped in a solution of silver nitrate in acetone (2·5 ml. of a saturated aqueous solution in 500 ml. of acetone) and, when it is dry, sprayed with an ethanolic sodium hydroxide solution (10 g. of sodium hydroxide dissolved in a small volume of water and made up to 500 ml. with ethanol). The reagent is reduced by reducing sugars and compounds containing vicinal alcohol groups or compounds which are converted to these under the alkaline conditions of the spray. When all the spots have appeared, the papers are dipped in aqueous ammonia and washed with water.

Periodate reagent[87] - The paper is sprayed with a 2% aqueous solution of sodium metaperiodate and allowed to dry at room temperature. It is then sprayed with a 0·5% aqueous solution of potassium permanganate. Compounds containing vicinal alcohol groups are oxidized by the periodate to carbonyl compounds, which reduce the permanganate and appear as brown spots on a pink background. As the paper dries, it also reduces the permanganate and this may be prevented by placing the paper between glass plates. When all the spots have appeared, the paper is washed with water to remove unreacted permanganate and, if the brown spots are faint, the dry paper is dipped in a benzidine reagent (I·0g. benzidine, 8·0g. trichloroacetic acid, 20g. acetic acid, 12 ml. water, 160ml. ethanol) and the positions of the polyols are shown by dark blue spots.

Phenol red, borate spray[88] - A 0·5N aqueous solution of sodium borate is mixed with a 0·2% ethanolic solution of phenol red and with methanol (1:2:7, by volume). Five drops of a 2N aqueous solution of sodium hydroxide are added to neutralize

the acidity of the paper. Any acidic compound or compound which can form a borate complex and so become acidic is detected as a yellow spot on a pink background. It is a useful spray for the detection of pentaerythritol.

Potassium dichromate spray - The paper is sprayed with a solution of potassium dichromate in 3N aqueous sulphuric acid (0·4g. in 100 ml.) and placed between glass plates. Any compound containing free alcohol groups, isolated or vicinal, is detected as a white spot on a yellow background. The paper is soon oxidized also and the spots disappear. A similar spray has been used by J.L.Frahn and J.A. Mills[89].

p-Anisidine hydrochloride spray[90].- The paper is sprayed with a 2% solution of p-anisidine hydrochloride in n-butanol and dried at 110°. Reducing sugars are decomposed by the strong acid to furfuraldehyde derivatives and detected by characteristic colours.

Triphenyl tetrazolium chloride spray[91] - A freshly prepared mixture of equal volumes of a 2% aqueous solution of triphenyl tetrazolium chloride and an aqueous N/I sodium hydroxide solution is sprayed on the paper. This is then kept at 40° in a water-saturated atmosphere for 20 min, and, after the excess reagent has been washed off, is dried at 25°. Reducing sugars containing unsubstituted alcohol groups adjacent to the reducing groups are detected.

Hydroxylamine spray[92] - The paper is sprayed with a freshly prepared mixture of equal volumes of a methanolic solution of hydroxylamine hydrochloride (6·95 g./100ml.) and a methanolic solution of potassium hydroxide (6·17g./100 ml.) and is dried at a temperature and for a time depending on the reactivity of the esters. Mannitol hexa-acetate reacts with hydroxylamine in 10 min. at room temperature or in 3 min. at 80-90°, but pentaerythritol tetra-acetate must be heated to 110° for 10 min. The paper is then sprayed with a mixture

of equal volumes of aqueous ferric chloride solution and aqueous N/2 hydrochloric acid. Acetates, lactones and amides appear as purple spots on a yellow background, but benzoates are not detected.

2:4-Dinitrophenylhydrazine spray[93 ~~101~~] - The paper is sprayed with a saturated solution of 2:4-dinitrophenylhydrazine in aqueous 2N hydrochloric acid and dried at 50°. Benzaldehyde appears in the cold and benzylidene acetals appear on heating as orange spots on a yellow background. Isopropylidene ketals liberate acetone in the presence of the acid but the yellow colour this gives with the reagent is not easy to detect against the yellow background.

Ninhydrin spray[94 ~~102~~] - The paper is sprayed with an ethanolic solution of ninhydrin (0·2g./100 ml. of solution + 5% v:v $H{\cdot}CO_2H$) and is heated at 100-120° for 5 min. This reagent detects amino acids and amides as purple spots. It will also detect carboxylic acids which have been eluted as their ammonium salts in solvent (d); the paper is dried at 80°, at which temperature the salts are converted into the amides.

Bromophenol blue spray[95 ~~103~~] The paper is sprayed with an aqueous solution of bromophenol blue (0·05g./100 ml.) and acids are detected as yellow spots on a blue background.

Experiment 2. Paper ionophoresis[96 ~~104~~].

This has been carried out on Whatman No. 3 paper, and the technique of A.B. Foster has been used. The borate buffer (p_H 9.8) is prepared by dissolving boric acid (29·77g) and sodium hydroxide (16·00 g.) in water (4 litres). In this buffer, polyols containing free alcohol groups in the required positions in their molecules form negatively charged borate complexes of varying stabilities and, under the influence of an electromotive force, migrate towards the cathode. The dried paper is sprayed with the periodate reagent, as the silver nitrate spray reacts very slowly with the borate complexes of the polyols.

Experiment 3. Column chromatography[97 ~~105~~].

The column is packed with a solid and the mixture then eluted down it with a suitable solvent. Measured volumes of eluent are collected in an automatic fraction collector and the presence of polyol derivatives in each tube is detected by paper chromatography.

Charcoal-celite column - A mixture of equal volumes of charcoal and celite is placed in hydrochloric acid for a few hours and then washed free from acid. It is then placed in ethanol and finally washed free from this with the same volume of water used in the removal of acid. The column is prepared by packing the greater length of it with this mixture, with narrow sections of washed celite above and below this. It is then washed with several litres of water. The rate of elution of compounds on this column depends on the strength of their adsorption on charcoal and on their solubility in the eluting solvent. The column is first eluted with water and hexitols are eluted more rapidly than their derivatives. If these are strongly adsorbed, the percentage of ethanol in the solvent is gradually increased to give a gradient elution[84(p.41)].

Celite column[98 ~~106~~] - The celite is treated with hydrochloric acid, washed with water and dried at 110°. It is mixed with 3/4 of its weight of stationary phase, usually water, and then slurried with the eluting solvent. The column is prepared from this slurry and washed with the solvent, before the mixture to be separated, dissolved in the solvent, is placed on it. The relative rates of elution of different compounds are the same as on paper in the same solvent.

Cellulose column - This has been used with solvent (g). The column is prepared from a slurry of cellulose (Whatman Standard Grade) in acetone and then washed with solvent (g). To introduce the dimethyl sulphoxide stationary phase onto the cellulose, the column is then washed with a 20% solution of dimethyl sulphoxide in benzene and finally again with solvent (g). Azobenzene is

eluted down the column to test the packing and, if this is satisfactory, the mixture is then placed on the column. The order of elution is the same as on paper in the same solvent.

Experiment 4. Ion exchange resins.

These have been used to remove ionic material from aqueous solutions of hexitols and their water-soluble derivatives. The washed resins may either be placed in a column and the mixture eluted down this with water or they can be added directly to the aqueous solution of the mixture and then filtered off. Biodeminrolit, a mixture of equivalent amounts of Zeo-Karb 225 (a polystyrene resin containing sulphonic acid groups) and De-acidite FF (a polystyrene resin containing quaternary ammonium groups), has been used to remove cations and anions. It has not been used in the carbonate form, but no loss of polyol on the resin has been detected. Amberlite IR-120 (H), similar to Zeo-Karb 225, has been used to remove cations.

Experiment 5. Preparation of cyclic acetals and ketals and other derivatives of polyols.

a). 1:3-2:4-5:6-Tri-O-methylene-D-glucitol[3a].

D-Glucitol (50 g.), 37% aqueous solution of formaldehyde (75 ml., 3·1 mol.) and hydrochloric acid (d 1·18, 50 ml., 2·0 mol.) were mixed and kept at 50° for 4 days. The solid soon dissolved and crystals then began to separate. The reaction mixture was cooled to 0° for 8 hr. and the crystals (37·8g.) filtered off and washed with water. They were recrystallized from water to give tri-O-methylene-D-glucitol (33·5g., 55·9%), m.p. 204-205°, $[\alpha]_D^{22}$ -28·8(c 1·04 in $CHCl_3$). Three recrystallizations raised the m.p. to 206-210° but the sample, m.p. 204-205°, was used in experiments. Bourne et al.[32] give m.p. 208-210° and $[\alpha]_D^{16}$ -27·5 (c 2·31 in $CHCl_3$).

b). 1:3-2:5-4:6-Tri-O-methylene-D-mannitol[4].

D-Mannitol(50g.) was mixed with 37% aqueous formaldehyde

(100 ml., 4·0 mol.) and hydrochloric acid(d 1·18, 100 ml., 4·2 mol.) a nd treated as above. The crude product (59·0g.) was recrystallized from 50% aqueous ethanol to give tri-O-methylene-D-mannitol , m.p.230-232°, $[\alpha]_D^{27}$ -96·5(c0·6I in $CHCl_3$). Fletcher et al.[5] give m.p.230-232° and $[\alpha]_D^{20}$ -103·9 (c 0·77 in $CHCl_3$).

c). I:6-Di-O-acetyl-3:5-di-O-acetoxymethyl-2:4-O-methylene-D-glucitol.

The acetolysis mixture was prepared by mixing acetic anhydride (14 ml.) and acetic acid (6 ml.) , cooling this in ice and then adding sulphuric acid (d 1·84, 0·2 ml.). Powdered tri-O-methylene-D-glucitol (1·0g.) was then added to the stirred mixture at 0° and, when the acetal had dissolved (about 2 hr.), the reaction mixture was filtered into ice water. The precipitated solid (0·23g.) was filtered off and recrystallized from ethanol to give the ester, (0·12 g.,6·2%), m.p.IIO-III° and $[\alpha]_D^{24}$ +29·9 (c I.I7 in $CHCl_3$). Bourne et al.[32] give m.p.IIO-III° and $[\alpha]_D^{14}$ +26·9 (c 2·3I in $CHCl_3$). (The conditions and proportions of reagents given in this preparation are those used by Ness et al.[4] in the acetolysis of tri-O-methylene-D-mannitol. The method given for the tri-O-methylene-D-glucitol reaction[3a] yielded an impure product containing unreacted acetal.)

d) Methyl α-D-glucoside was prepared from D-glucose according to a standard method,[99] ~~107~~. The glucoside was obtained in 22·3% yield and had m.p. 163-165°. Heilbron and Bunbury[100] give m.p. 166°.

e) 2:4-O-Methylene-D-glucitol.

Acetolysis of tri-O-methylene-D-glucitol (10g.) was carried out as in exp. 5c using 46 ml. of acetic anhydride, 20 ml. of acetic acid and 0·6ml. sulphuric acid (d 1·84).

The reaction mixture was poured into ice water and, after 2 hr., the solid initially precipitated had nearly all redissolved. The solution was extracted with chloroform and the extracts washed

with aqueous sodium bicarbonate solution and water, and dried over $MgSO_4$. The extract was evaporated down to give an oil(19·2g.) which crystallized. It was dissolved in dry chloroform (200 ml.) and 20 ml. of a M/5 methanolic sodium methoxide solution was added. The reaction mixture was cooled to 0° and a solid was soon precipitated. After 26 hr. at 0°, this was filtered off (6·06 g., m.p. 150-155°). It was crystallized from aqueous ethanol to yield 2:4-O-methylene-D-glucitol(4·05g., 45·5%), m.p. and mixed m.p. 161-162°, $[\alpha]_D^{20}$ -9·0(c 0·83 in H_2O). Bourne et al.[31] give m.p. 163-164° and $[\alpha]_D^{21}$ -9·9 (c I.00 in H_2O).

f) 2:5-O-Methylene-D-mannitol[4].

Acetolysis of tri-O-methylene-D-mannitol (10g.) was carried out with an acetolysis mixture prepared by the addition of sulphuric acid (d,I.84, 1.0 ml.) to an ice-cold mixture of acetic anhydride (70 ml.) and acetic acid (30 ml.). The reaction mixture was stirred at 0° for about 15 min. before it solidified to a crystalline mass. This was broken up and poured into 800 ml. of ice water. After 22 hr. at 0°, the solid was filtered off, washed and dried. The filtrate was extracted with chloroform and the washed and dried extract concentrated to give a crystalline residue, which was combined with the precipitated solid (20·2g.). The solid was dissolved in dry chloroform (200 ml.) and cooled to 0°. 20 Ml. of a solution of sodium methoxide (containing 0·I g of sodium) was added and a solid soon precipitated. After 24 hr. at 0°, the solid (6·3g.), m.p. 178-179°, was filtered off and recrystallized from ethanol. 2:5-O-Methylene-D-mannitol was obtained (2·9g., 32·6%), m.p. 178-179°, $[\alpha]_D^{20}$ -51·2 (cI·2 in H_2O). A chromatogram showed the presence of a trace of hexitol. Ness et al.[4] give m.p. 173-174° and $[\alpha]_D^{20}$-5I·4 (cI·2 in H_2O).

g). D-Glucitol hexa-acetate was prepared from D-glucitol by a standard method (ref. 99, p. 114). The hexa-acetate was obtained in 43.2% yield and had m.p. 97-99°. Lomar et al.[101] give m.p. 99°.

h). D-Mannitol hexa-acetate was prepared from D-mannitol by a standard method (ref. 99, p. 114). The hexa-acetate was obtained in 84.8% yield and had m.p. 120-121°. Bourne et al.[32] give m.p. 122°.

i). 1:3:5:6-Tetra-O-acetyl-2:4-O-methylene-D-glucitol was prepared from 2:4-O-methylene-D-glucitol by a standard method (ref. 99, p. 114). The tetra-acetate was obtained in 35.2% yield and had m.p. 150-152°. Bourne et al.[32] give m.p. 150-151°.

j). 1:5:6-Tri-O-benzoyl-2:4-O-methylene-D-glucitol was prepared from 2:4-O-methylene-D-glucitol by a standard method[3b]. The tribenzoate. was obtained in 9.2% yield and had m.p. 152-154°. Bourne et al.[3b] give 154°.

k). 1:6-Di-O-toluene-p-sulphonyl-2:4-O-methylene-D-glucitol was prepared from 2:4-O-methylene-D-glucitol by a standard method[3b]. The sulphonate was obtained in 18% yield and had m.p. 129-130°. Bourne et al.[3b] give m.p. 129-130°.

l). Di-O-methylene pentaerythritol[102].

Pentaerythritol (49.5 g.) was treated with 37% aqueous solution of formaldehyde (85 ml., 2.9 mol.) and hydrochloric acid (d, 1.18, 45 ml., 1.4 mol.). The reaction mixture was refluxed for 5 hr. and the solid soon dissolved. It was left at room temperature overnight and then neutralised with solid sodium carbonate, to give a pH of 8. After the water had been evaporated off, the residue was extracted with ether, giving an oil smelling of formaldehyde. This was extracted with petroleum ether (b.p. 60-80°) to give the acetal (32.5 g., 55.8%), m.p. 48.5-49°. (Found: C, 52.4; H, 7.5%. Calc. for $C_7H_{12}O_4$: C, 52.5; H, 7.6%).

~~Calc. for $C_7H_{12}O_4$: C,52·5;H,7·6%~~). Skrabal et al.[18] give m.p.50°.

m). Di-O-benzylidene pentaerythritol.

See exp. 45.

n). Mono-O-isopropylidene pentaerythritol.

See exp. 49.

o). Pentaerythritol tetra-acetate was prepared from pentaerythritol by a standard method[82].

The tetra-acetate was obtained in 43·2% yield and had m.p. 78-80°. (Found: C,5I·4;H,6.8%. Calc. for $C_{13}H_{20}O_8$: C,5I·3;H,6·6%). Orthner et al.[82] give m.p.83°.

p). Samples obtained from other workers in these laboratories:-

I:3-2:5-4:6-Tri-O-ethylidene-D-mannitol, m.p. 165-170° (174-176°).

Chromatograms showed the presence of traces of hexitol and partially substituted hexitols.[7]

Tri-O-benzylidene-D-mannitol, m.p. 2II-215°(223-224°). Chromatograms showed the presence of no hexitols or their derivatives detected by the silver nitrate spray[103].

I:2-3:4-5:6-Tri-O-isopropylidene-D-mannitol, m.p.64-65° (69-70°).

Chromatograms showed the presence of a trace of hexitol.[8]

I:2-3:4-5:6-Tri-O-cyclohexylidene-D-mannitol,m.p.77° (83-85°). Chromatograms showed the presence of a trace of hexitol.[9]

1:2-5:6-Bis-O-(I':I':I-trifluoroisopropylidene)-D-mannitol,[104] Chromatograms showed the sample to contain only one compound, (R_m:6·I), detected by the periodate spray.

Mono-O-benzylidene pentaerythritol[105](from Dr.M. Ruszkiewicz) m.p.133·5°.

REACTIONS OF ACETIC ANHYDRIDE AND METHYL IODIDE WITH TRI-O-METHYLENE HEXITOLS, IN THE PRESENCE OF ALUMINIUM CHLORIDE

Experiment 6 Purification of reagents and solvents.

Aluminium chloride was not purified but was ground to a fine powder before use.

Acetic anhydride was purified by a standard method[106] and had b.p.139°/760 mm., n_D^{20} 1·3893. Walton et al.[106] give b.p. 139·3°/740 mm. and n_D^{25} 1·3885.

Methyl iodide was used without further purification.

Nitrobenzene was purified by a standard method and had b.p. 206-2II°/760 mm. and n_D^{20} I·5530. Weissberger[116] gives b.p. 2I0·8°/760 mm. a nd n_D^{20} I·5536. sym-Tetrachloroethane was purified by a standard method and had b.p.146°/760 mm. and n_D^{21} I·493. Weissberger[116] gives b.p.146·2°/760 mm. and n_D^{15} I·497.

All reactions are carried out under anhydrous conditions with dry reagents and solvents.

If the standard properties of the products are not given, they will be found in Experiment 5.

Experiment 7 Reaction of acetic anhydride and aluminium chloride with 1:3-2:4-5:6-tri-O-methylene-D-glucitol.

a) 1:3-2:4-5:6-Tri-O-methylene-D-glucitol (I·00 g.) and anhydride (I·0 ml., 2·4 mol.) were dissolved in nitrobenzene (20 ml.) and the solution stirred in a dry apparatus, cooled in ice water. Aluminium chloride (2·60 g., 4·2 mol., calculated as $AlCl_3$), dissolved in nitrobenzene (30 ml.), was added dropwise to the reaction mixture. The resulting solution was poured onto ice and, after four hours, the organic layer was separated, washed with 2N hydrochloric acid and 5% aqueous sodium

bicarbonate solution and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure to yield an oil. This was extracted with ethanol and a white solid (0·20 g.), m.p. 149-156°, precipitated from this. Recrystallization from ethanol gave 2:4-O-methylene-D-glucitol (0·03 g., 3·4%), m.p. and mixed m.p. 160-1°.

b). 1:3-2:4-5:6-Tri-O-methylene-D-glucitol (1·00 g.) was dissolved in nitrobenzene (20 ml.) and aluminium chloride (5·52 g., 9 mol.) in nitrobenzene (30 ml.) was added dropwise to the stirred reaction mixture at room temperature. The mixture became black. The products were hydrolysed as in (a) and the organic and aqueous layers separated. The nitrobenzene was washed with aqueous sodium bicarbonate solution and concentrated to yield a brown powder (1·50 g.), which gave no crystalline products. The aqueous layer was neutralized, filtered free from the precipitated alumina and evaporated to dryness. The residue was extracted with pyridine and after removal of the solvent, under reduced pressure, an oil was obtained. This was acetylated with acetic anhydride (2·6 ml.) in pyridine (12 ml.). The reaction mixture was left at room temperature for 15 hr. and then poured into water. The precipitated solid (0·47 g., 28·5%), m.p. 145-148°, was recrystallised from ethanol to give 1:3:5:6-tetra-O-acetyl-2:4-O-methylene-D-glucitol, m.p. 151-152°, (Found = C, 49·5; H, 6·3%. Calc. for $C_{15}H_{22}O_{10}$ = C, 49·7; H, 6·1%.) Periodate oxidation by a spectro-photometric method (see exp. 35) on the deacetylated compound was carried out:

Time (min.)	D	% Periodate reacted (from calibration curve Fig VIIa(i)) p. 174.	Mols of periodate reacted/mol. of polyol.
30	0·484	68·8	1·19
90	0·491	70·0	1·14
150	0·487	69·5	1·16

100% $NaIO_4$-D= 0·660; 100% KIO_3- D= 0·100

This gives a periodate uptake of I·I6 mol./mol. of acetate. (2:4-O-Methylene-D-glucitol consumes I·00 mol. of periodate/mol.)

A chloroform extract of the acetylation filtrate gave, on evaporation, an oil (0·I0 g.), which gave a white solid, m.p. I37-I45°, after treatment with ethanol.

Experiment 8 Reaction of acetic anhydride and aluminium chloride with I:3-2:5-4:6-tri-O-methylene-D-mannitol.

I:3-2:5-4:6-Tri-O-methylene-D-mannitol (I·00 g.) and aluminium chloride (5·52g., 9 mol.) were dissolved in nitrobenzene (60 ml.) and acetic anhydride (I·0 ml., 2·4 mol.) in nitrobenzene (I0 ml.) was added to the stirred reaction mixture at room temperature. The mixture became black and the products were worked up as in exp. 7 (b). The nitrobenzene layer yielded no crystalline products. The aqueous layer was extracted with pyridine and the extract yielded an oil. An aqueous solution of this was examined by paper chromatography using the solvent (a) and the silver nitrate spray. Two products were detected, $R_{mannitol}$ = I·0 and $R_{mannitol}$ = 2·7. Ethanol extraction of the oil yielded mannitol (0·06 g.), m.p. and mixed m.p. I60-I63°. The mannitol and the oil, obtained by the evaporation of the ethanolic mother liquors, were acetylated with acetic anhydride (2·6 ml.) in pyridine (I2 ml.). The reaction mixture was left at room temperature for I5 hr. and then poured into water. The precipitated solid (0·63 g.) was filtered off and recrystallized from ethanol to give D-mannitol hexa-acetate (0·22 g., II·I%), m.p. and mixed m.p. II8-I20°. A chloroform extract of the acetylation filtrate gave, on evaporation, a solid (0·I9 g.), m.p. I30-I35°. Reacetylation and recrystallisation from ethanol gave 2:4:5:6-tetra-O-acetyl-I:3-O-methylene-D-mannitol (0·I2 g., 7·2%), m.p. and mixed m.p. I39°-I4I°; Fletcher et al[119] give m.p. I43-I44°.

Experiment 9. Reaction of methyl iodide and aluminium chloride with I:3-2:4-5:6-tri-O-methylene-D-glucitol.

a). I:3-2:4-5:6-Tri-O-methylene-D-glucitol (I:00 g.) was dissolved in nitrobenzene (30 ml.) and aluminium chloride (0·62 g., I mol.), in nitrobenzene (20 ml.) was added. Methyl iodide (0·8 ml., 2·8 mol.) in nitrobenzene (I0 ml.) was added dropwise to the stirred reaction mixture, cooled in ice water. The products were hydrolysed and worked up as in exp. 7(b) and the nitrobenzene layer gave an oil, on evaporation of the solvent. This was extracted with ethanol to yield I:3-2:4-5:6-tri-O-methylene-D-glucitol (0·04g., 4%), m.p. and mixed m.p. 205-207°. The neutralized aqueous layer yielded I:3-2:4-5:6-tri-O-methylene-D-glucitol (0·24g., 24%), m.p. a nd mixed m.p. 205-207°, $[\alpha]_D^{19}$ - 2I·4 (c I·I7 in $CHCl_3$). The mother liquors gave a small quantity of solid, m.p. I95-200°, presumably impure I:3-2:4-5:6-tri-O-methylene-D-glucitol.

b). I:3-2:4-5:6-Tri-O-methylene-D-glucitol (5.00 g.) and aluminium chloride (6·70 g., 2·2 mol.) were dissolved in nitrobenzene (I50 ml.). Methyl iodide (3·0 ml., 2·2 mol.), in nitrobenzene (25 ml.), was added at room temperature to the stirred reaction, which was then stirred at 55° for 15 min. The products were hydrolysed and worked up as in exp. 7(b). The nitrobenzene layer yielded a solid (I·3 g.), which gave no crystalline products. The aqueous layer yielded an oil, which was acetylated with acetic anhydride (II·0 ml.) in pyridine (30 ml.). After 15 hr. at room temperature, the reaction mixture was poured into water and the precipitated solid (0·47 g.), m.p. I48°, filtered off. This was crystallized from ethanol to give I:3:5:6-tetra-O-acetyl-2:4-O-methylene-D-glucitol (0·I5 g., 5·6%), m.p. and mixed up m.p. I5I-I52°. (Found: C,50·0; H,6·3; OMe,0°/$_o$; N-alkali uptake II·06 ml./g. Calc. for $C_{15}H_{22}O_{10}$: C,49·7;H,6·I;OMe,0°/$_o$; N -alkali uptake II·04 ml./g.) A chloroform extract of the

acetylation filtrate gave, on evaporation, a second product (1·59 g.), m.p. 115–116°. Five recrystallizations from ethanol raised the melting point to a constant value of 120–122°. (Found: C, 49·1; H, 6·4; OMe, 0%; N-alkali uptake, 10·2 ml./g. Calc. for $C_{12}H_{18}O_8$: C, 49·7; H, 6·2%; N-alkali uptake, 6·2 ml./g. $C_{13}H_{20}O_9$ requires C, 48·7; H, 6·3%; N-alkali uptake, 9·37 ml./g.)

Experiment 10 Reaction of acetic anhydride and aluminium chloride with 1:6-di-O-acetyl-3:5-di-O-acetoxymethyl-2:4-O-methylene-D-glucitol.

The acetate (0·90 g.) and acetic anhydride (0·9 ml., 4·6 mol.) were dissolved in nitrobenzene (20 ml.). The solution was cooled in ice water and a solution of aluminium chloride (2·51 g., 8·8 mol.) in nitrobenzene (30 ml.) was added dropwise to the stirred reaction mixture, cooled in ice. The products were then hydrolysed as in exp. 7(a). The nitrobenzene layer yielded an oil which, on extraction with ethanol, gave a solid (0·20 g.), m.p. 158°. This was extracted and recrystallized from ethanol to give 2:4-O-methylene-D-glucitol (0·09 g., 21·8%) m.p. and mixed m.p. 161–162°, $[\alpha]_D^{24}$ -12·0°, ~~12·0°~~ (c 1·30 in H_2O)

Experiment 11 Reaction of aluminium chloride with acetates, followed by changes in optical rotation.

a). 1:6-di-O-acetyl-3:5-di-O-acetoxymethyl-2:4-O-methylene-D-glucitol

$[\alpha]_D^{21}$ +26·2 (c 0·94 in $C_6H_5NO_2$)

" +$AlCl_3$ (5·3 mol.) 7 min. after mixing $[\alpha]_D^{21}$ -2·7

195 min. " " $[\alpha]_D^{21}$ -8·0 (constant)

(acetate, c 0·75 in $C_6H_5NO_2$)

($AlCl_3$, c 1·25 in $C_6H_5NO_2$)

b) D-mannitol hexa-acetate $[\alpha]_D^{20}$ +14·1 (c 0·99 in $C_6H_5NO_2$)
" $AlCl_3$ (7·7 mol.) 20 min. after mixing $[\alpha]_D^{20}$ 0 (constant)
(acetate, c 0·80 in $C_6H_5NO_2$)
($AlCl_3$, c 1·89 in $C_6H_5NO_2$)

Experiment I2 Reaction of aluminium chloride with methyl α-D-glucoside.

The glucoside (1·00g.) was partially dissolved in nitrobenzene (30 ml.) and aluminium chloride (4·17 g., 6 mol.) in nitrobenzene (20 ml.) added. The glucoside then dissolved completely and the reaction was stirred at room temperature for 20 min. and then at 50° for 15 min. The products were hydrolysed and worked up as in exp. 7(b). The water-soluble products were investigated by paper chromatography in solvent (a). Silver nitrate and aniline hydrogen phthalate sprays detected glucose and the former spray detected some methyl α-D-glucoside.

Experiment I3 Reaction of aluminium chloride with 2:3:4;6-tetra-O-methyl-D-glucose.

The ether (0·60g.) was dissolved in nitrobenzene (20 ml.) and aluminium chloride (1·47g., 4·3 mol.) in nitrobenzene (20 ml.) was added. The solution was stirred at room temperature for 10 min. and at 55° for 15 min. The products were hydrolysed and worked up as in exp. 7(b). and the nitrobenzene and aqueous layers were investigated by chromatography in solvent (a). The aniline hydrogen phthalate spray detected only unreacted tetra-O-methyl-D-glucose.

Experiment I4 Reaction of aluminium chloride with tri-O-methylene-D-hexitols.

a). 1:3-2:4-5:6-Tri-O-methylene-D-glucitol (1·00g.) was dissolved in nitrobenzene (20 ml.) and aluminium chloride (1·35 g., 2·2 mol.) in nitrobenzene (35 ml.) was added. The solution was left at room temperature for 10 min. and then kept at 55° for 15 min., when it darkened. The products were hydrolysed and isolated

as in exp. 7(b). The nitrobenzene layer yielded a brown powder (I·2 g.), which gave no crystalline products. The aqueous layer yielded a white solid (0·50 g.), m.p.I70-I80°. Recrystallisation from ethanol gave I:3-2:4-5:6-tri-O-methylene-D-glucitol (0·3I g., 3I%), m.p. and mixed m.p. 202-204°.

b) I:3-2:4-5:6-Tri-methylene-D-glucitol (I·00g.) was dissolved in nitrobenzene (30 ml.) and aluminium chloride (5.52 g., 9·I mol.) in nitrobenzene (35 ml.), added. The reaction mixture was stirred at room temperature for 30 min., becoming deep orange, and worked up as in exp. 7(b). The nitrobenzene layer yielded I:3-2:4-5:6-tri-O-methylene-D-glucitol (0·0I g., I%), m.p. and mixed m.p. 200-204°. The a queous layer yielded 2:4-O-methylene-D-glucitol, (0·57 g., 64·2%), m.p. and mixed m.p. I59-I60°.

c) I:3-2:5-4:6-Tri-O-methylene-D-mannitol (I·00g.) was dissolved in nitrobenzene (25 ml.) and the aluminium chloride (2·67 g., 4 mol.), in nitrobenzene (30 ml.), added. The reaction was stirred at room temperature for 30 min. and became deep orange. The alumina, nitrobenzene and neutralized aqueous layers were separated by centrifuging at 3000 r.p.m. for 15 min. The nitrobenzene layer yielded a brown solid (0·50 g.), which yielded no crystalline products. The aqueous layer, after evaporation of the water and pyridine extraction, gave impure mannitol (0·04 g.), m.p. I50-I60°, showing no further depression with mannitol. Acetylation of the mother liquors with acetic anhydride (2·6 ml.) in pyridine in the usual way yielded a crystalline solid (0·I0 g.), m.p.I28-I33°. Recrystallization from ethanol gave 2:4:5:6-tetra-O-acetyl-I:3-O-methylene-D-mannitol, m.p. and mixed m.p. I38-I40°. Fletcher et al[119,127] give m.p. I43-I44°.

Experiment I5 Investigation of the alumina precipitated in the hydrolysis of the above reactions.

The precipitated alumina was dissolved in concentrated hydrochloric acid and the solution centrifuged to remove suspended solid. It was then eluted with water on a charcoal-celite column and the eluent collected in 25 ml. fractions. These were concentrated and the contents analysed by paper chromatography. Fractions 2I-90 had pH less than 3·0, and fractions 47-70 contained mannitol and salts. No other products were detected.

REACTIONS OF BORON TRICHLORIDE WITH CYCLIC ACETALS AND KETALS AND OTHER DERIVATIVES OF POLYOLS.

Experiment I6 Purification of reagents and solvents.
All apparatus in contact with BCl_3 was cleaned with cleaning a cid, to remove any grease, and dried thoroughly before use. Because of its rapid hydrolysis with traces of water, BCl_3 was exposed for the shortest time possible to the atmosphere, unless the container was fitted with a silica gel drying tube. As BCl_3 boils at I2·5°/760 mm[107] it was handled by cooling to -80°, in a bath of solid carbon dioxide and acetone, and at this temperature it behaves as a comparatively involatile liquid.

The BCl_3 was obtained from B.D.H. in sealed ampoules, containing 50 g. or 25 g. samples. These were cooled, opened and the contents poured into a I00 ml. flask, in a cooling bath. This flask was immediately connected to a length of glass tubing, the other end of which passed into a second flask, in a cooling bath. This flask was also fitted with a silica gel drying tube, so that the pressure in the apparatus was atmospheric. The distillation flask was removed from the cooling bath and allowed to warm up to room temperature. The BCl_3 then distilled through the glass tubing and condensed in the cooled receiving flask. Any impurities, involatile at room temperature, remained in the distillation flask. Clean, dry test tubes, which had been drawn out in a hot flame to form constrictions near the mouths, were placed in the cooling bath. These had previously been weighed and were closed with well-fitting corks, covered with cellophane, to prevent the entry of much atmospheric moisture. The corks were then removed and the BCl_3 poured from the receiving flask into the tubes. This was carried out as quickly as possible and the corks replaced. The tubes were sealed off by applying a small flame to the constriction. The ampoules, obtained in this way, and the residual pieces of glass were reweighed to give the

weight of BCl_3 in each ampoule. When the reagent was required, the ampoule was cooled and then broken open and the contents poured into the cooled reaction flask.

Dichloromethane was purified by a standard method[116] and had b.p.39-39·5°/765 mm.. It was stored in a dark bottle over calcium chloride.

Commercial methanol was used without further purification. The standard properties of the products, if not given, will be found in exp. 5.

REACTION OF BORON TRICHLORIDE WITH SOME POLYOL DERIVATIVES, FOLLOWED BY TREATMENT WITH AQUEOUS METHANOL

Experiment I7 with I:3-2:4-5:6-tri-O-methylene-D-glucitol.

The acetal (0·8I g.) was dissolved in dichloromethane (40 ml.) and added dropwise in 30 min. to boron trichloride (3·0I g., 6·9 mol.) in the same solvent (30 ml.), at -80°. The reaction flask was allowed to warm to room temperature and then connected, through a trap at -80°, to a water pump; this removed the solvent and excess boron trichloride. The flask was finally heated to 40° on a water bath, to remove traces of solvent. The residue was a brown glassy material (I·69g.). Commercial methanol was added and the glass dissolved. The solvent was evaporated off, removing boron as volatile methyl borate, to give an oily residue (I·I0g.). This was tested for boron (as boric acid) by placing a spot of the acid solution on turmeric paper and heating this; a red colour showed the presence of boric acid. Methanol was repeatedly added and distilled off until this test was negative. The product was examined by paper chromatography in solvent (C) and this showed the presence of hexitol, R glucitol:I·0, a second product, R_g:I·45, and a third, R_g:I·90 (2:4-O-methylene-D-glucitol, R_g:I·36). The oil was acetylated by refluxing for 30 min. with sodium acetate (6·4g., excess used to neutralize hydrochloric

acid) and acetic amhydride (20 ml.). The reaction mixture was poured into water and the precipitated solid filtered off. This was shown to be glucitol hexa-acetate (0·76g.), m.p. 94-97°, mixed m.p. 95-96°. A chloroform extract of the filtrate gave impure glucitol hexa-acetate (0·35g.), m.p. 92-93°. This was recrystallized from ethanol to give the pure ester (0·22g.), m.p. 93-97° a nd mixed m.p. 95-96°(total yield 60·8%). The mother liquors yielded a crystalline solid (0·10g.), m.p. 90-150°. Deacetylation was effected by the addition of a drop of 0·2N sodium methoxide in methanol to a chloroform solution, and paper chromatography in solvent (c) showed the presence of hexitol, R_g:1·00, and a second compound, R_g:1·27 (2:4-O-methylene-D-glucitol, R_g:1·25).

Experiment 18 with 1:3-2:5-4:6-tri-O-methylene-D-mannitol. The acetal (0·91g.) was dissolved in dichloromethane (50 ml.) and added dropwise in 30 min. to boron trichloride (3·06 g., 6·2 mol.) in dichloromethane (30 ml.) at -80°. The reaction was worked up as in exp. 17 to give a glass (1·95g.). Boric acid was removed with methanol and a white solid (0·96g.) was obtained. This was examined by paper chromatography in solvent (c), which showed the presence of hexitol, Rmannitol:1·00, a second product, R_m:1·44, and possibly a third, R_m:1·72 (2:5-O-methylene-D-mannitol, R_m:1·30). Crystallization from 90% methanol gave impure mannitol (0·45g.), m.p. 156-159°. A second crystallization gave mannitol (0·26g.), m.p. and mixed m.p.159-160°. The mother liquors were concentrated and the residue acetylated with sodium acetate (0·4g.) and acetic anhydride (4.0 ml.) in the usual way. A chloroform extract of the hydrolysed reaction was washed with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulphate and concentrated to give a solid (0·26g.). This was crystallized from ethanol to give mannitol hexa-acetate (0·06g.), m.p. 116-117° and mixed m.p. 118-120° (total yield of mannitol, 52·8%). Reacetylation

of the mother liquors from this gave a crystalline solid (0·0Ig.), m.p. I37-I38°. Deacetylation of this was carried out as in exp.I7 and paper chromatography, in solvent(c), showed the presence of hexitol, R_m:I·00, and a second product, R_m:I·43 (2:5-O-methylene-D-mannitol, R_m:I·28, I:3-O-methylene-D-mannitol, R_m:I·40).

Experiment I9 with 2:4-O-methylene-D-glucitol.

a). The acetal (0·II g.) was suspended in dichloromethane (20 ml.) and cooled to -75°. The boron trichloride (0·86 g., 13 mol.) was added and the reaction worked up as in exp.I7 to give a glass (0·27 g.). Boric acid was removed with methanol and a chromatogram of the product run in solvent (a). This showed the presence of hexitol, R glucitol:090, and a second product, R_g:2·3(2:4-O-methylene-D-glucitol, R_g:2·I). Distillation of the methanol gave an oil which was acetylated with sodium acetate (0·20 g.) and acetic anhydride (20·0 ml.). A chloroform extract of the hydrolysed mixture gave an oil (0·27 g.), which crystallized from ethanol to give glucitol hexa-acetate (0·I5 g., 6I·0%), m.p. 95-98° and mixed m.p.97°. The mother liquors yielded I:3:5:6-tetra-O-acetyl-2:4-O-methylene-D-glucitol (0·004 g.), m.p. and mixed m.p.I48-I49°.

b). The acetal (0·2I g.) was sealed with boron trichloride (2·2 g., I7 mol.) in a test tube and left at room temperature for 48 hr. It was worked up in the usual way and a chromatogram showed the presence of some unchanged acetal.

Experiment 20 with 2:5-O-methylene-D-mannitol.

The acetal (0·I0 g.) was suspended in dichloromethane (2·0 ml.) a nd boron trichloride (I.08g., 15·5 mol.) was added and the reaction worked up as in exp.17 to yield a glass (0·23g.). This was treated with methanol to give a solid residue (0·09 g.). A chromatogram of this in solvent (a) showed the presence of hexitol, R ma nnitol:I·00. Crystallization from 90% methanol gave

mannitol (0·08g., 94·0%), m.p. and mixed m.p. I69-I70°.
The residue from the mother liquors was acetylated and yielded mannitol hexa-acetate (0·04g.), m.p. and mixed m.p. I22-I24°.
Experiment 2I with di-O-methylene pentaerythritol.
The acetal (0·I4g.) was dissolved in dichloromethane (I0 ml.) and cooled to -80°. Boron trichloride (2·94g., 28 mol.) was added a nd the reaction was worked up as in exp. 17 to give a colourless product (0·24g.). This was treated with methanol and the involatile residue was washed with chloroform, giving pentaerythritol (0·09 g., 76·5%), m.p. and mixed m.p. 258-260°. A chromatogram of the products, in neutral solution, was run in solvent (a). This showed the presence of pentaerythritol.
Experiment 22 with I:3-2:5-4:6-tri-O-ethylidene-D-mannitol.
The acetal (0·50g.) was dissolved in dichloromethane (40 ml.) and cooled to -40°. Boron trichloride (I·57g., 7 mol.) was added and the reaction worked up as in exp.17 to give a brown product (0·85g.). This was treated with methanol and a chromatogram of the products run in solvent (c). This showed the presence of hexitol, $R_{mannitol}$:I·0, and a second product, R_m:I·2-I·5 (the starting material contains an impurity, R_m:I·23). Distillation of the methanol gave a discoloured solid (0·44g.), which was only partially soluble in water. The suspension was extracted with chloroform. The aqueous layer was concentrated and gave a solid residue (0·35g.). This was crystallized from 90% methanol to give mannitol containing a small amount of impurity (0·20g., 66·6%), softening at 152° and melting at 162°, mixed m.p. I60-I62°.
Acetylation of the mother liquors gave mannitol hexa-acetate (0·08g.), m.p. and mixed m.p. II4-II6°. The mother liquors from this gave a second acetate (0·0Ig.), m.p. II2-II3°, which depressed the m.p. of mannitol hexa-acetate, giving a mixed m.p. I05-II5°. The chloroform extract yielded a dark oil (0·IIg.) and a chromatogram of this showed it to contain no products staining the silver nitrate spray.

Experiment 23 with tri-O-benzylidene-D-mannitol.
The acetal (0·76g.) was dissolved in dichloromethane (40 ml.) and boron trichloride (I·4Ig., 7·I mol.) added to the cooled solution which became orange. The reaction was worked up as in exp.17 to give a residue of solid and a dark oil (I·66g.). This was treated with methanol and a chromatogram run in solvent (c). This showed the presence of hexitol, $R_{mannitol}$:I·0, and a second product, not present in unreacted acetal, R_m:I·30. Evaporation of the methanol left a solid and a pleasant-smelling oil (0·77g.). This gave a suspension in water and a chloroform extract was taken. The aqueous layer was concentrated to dryness and the solid residue (0·32g.) was crystallized from 90% methanol; crystals of mannitol (0·2Ig.), m.p. and mixed m.p. I60-I62°, were obtained. The mother liquors were acetylated to give mannitol hexa-acetate (0·I3g.), m.p. and mixed m.p. II8-I20° (total yield of mannitol, 85·4%). A chromatogram was run on the chloroform extract but no polyols could be detected. The extract had a zero optical rotation. Evaporation of the solvent gave a dark oil (0·I6g.).

Experiment 24 with di-O-benzylidene pentaerythritol.
The acetal (0·50g.) was dissolved in dichloromethane (5 ml.) and boron trichloride (I·60g., 5·9 mol.) added to the cooled solution to give a yellow colour. This was worked up in the usual way giving a residue (0·7Ig.), which was treated with methanol to give a mixture of solid and a pleasant-smelling oil (0·80g.). The solid was washed thoroughly with chloroform, and pentaerythritol was obtained (0·20g., 9I%), m.p. 264-266°. The chloroform extract was concentrated to give a yellow, pleasant-smelling oil (0·26g.). This was dissolved in ethanol (I0 ml.) and I ml. of this treated with 2:4-dinitrophenylhydrazine reagent (prepared by dissolving 2g. of reagent in methanol (30 ml.)

and water (10 ml.), adding concentrated sulphuric acid (4 ml.) and filtering) and a precipitate was formed only after standing for 15 min. at room temperature. (A 1% solution of benzaldehyde in ethanol gave an immediate precipitate under these conditions). 5 Ml. of the ethanolic solution were boiled with 10% aqueous sodium carbonate solution (20 ml.) for 2 hrs. After cooling, this was extracted with chloroform and the extract washed with N/$_1$hydrochloric acid and water. The dry extract was evaporated to give an oil (0·03g.), smelling of benzaldehyde. This was dissolved in ethanol and treated with 2:4-dinitrophenylhydrazine reagent. An orange precipitate was immediately formed and was recrystallized from ethanol to give benzaldehyde 2:4-dinitrophenylhydrazone, m.p. 236-238°. Vogel[114] gives m.p. 237°.

Experiment 25 with mono-O-benzylidene pentaerythritol.
The acetal (0·36 g.) was dissolved in dichloromethane (5 ml.) and cooled. Boron trichloride (1·89g., 10 mol.) was added and a yellow solution was formed, which was worked up to give a solid and an oil (0·68g.). This was treated with methanol and the product was a mixture of solid and pleasant-smelling oil (0·48g.). The solid was washed with chloroform to give pentaerythritol (0·20g., 91%)., m.p. 268-269° (softening at 263°) and mixed m.p. 270-271°. The chloroform washings gave a pleasant-smelling oil (0·09g.).

Experiment 26. with 1:2-3:4-5:6-tri-O-isopropylidene-D-mannitol.
The ketal (0·65g.) was dissolved in dichloromethane (30 ml.) and added to boron trichloride (1·71g., 8 mol.) in the same solvent at -70°. The reaction mixture became orange and contained a yellow solid. It was worked up to give a residue of oil and solid, which was treated with water but was only partially soluble in this. A chloroform extract was taken and chromatograms were run on samples from each layer in solvent (c). In the aqueous layer., Hexitol, $R_{mannitol}$:1·0, and a second product, R_m: 1·37, were present. No polyol was detected in the chloroform

layer. The aqueous layer was concentrated and yielded a solid (0·85g.). This was crystallized from 90% methanol to give mannitol (0·29g.), m.p. 163-164° and mixed m.p. 164-166°. Acetylation of the mother liquors gave mannitol hexa-acetate (0·09g.), m.p. 114-116° and mixed m.p. 117-118° (total yield of mannitol, 83·7%). The mother liquors from this gave a solid (0·02g.), m.p. 110-114° and mixed m.p. with mannitol hexa-acetate 90°. The chloroform extract gave a dark orange, pleasant-smelling oil.

Experiment 27 with 1:2-3:4-5:6-tri-O-cyclohexylidene-D-mannitol. The ketal (0·35g.) was dissolved in dichloromethane (30 ml.) and added dropwise to cooled boron trichloride (0·69g., 7·0 mol.) in the same solvent (20 ml.). A brown solution was formed and this was worked up to give a residue containing an orange oil and a solid (0·73 g.). Methanol was added and a chromatogram run in solvent (c). This showed the presence of hexitol, $R_{mannitol}$: 1·0, a second product, R_m:1·30, and a third, R_m:1·5. Evaporation of the methanol left a residue of solid and oil (0·34 g.), which was partially soluble in water. The oil was extracted with chloroform. The aqueous layer gave a solid residue which, on crystallization from 90% methanol, precipitated mannitol (0·07g.), m.p. 164-166° and mixed m.p. 163-165°. The residue from the mother liquors was acetylated to give mannitol hexa-acetate (0·03g.), m.p. and mixed m.p. 118-119° (total yield of mannitol, 55·0%). The chloroform layer was evaporated down to leave an orange, pleasant-smelling oil (0·16g.). A chromatogram of this showed the presence of no products sensitive to the silver nitrate spray. A sodium fusion was carried out on a small quantity and chlorine was shown to be present. The oil was heated to 200°/10mm. and a few drops distilled, but the bulk of the oil became a black resinous solid.

Experiment 28 with 1:2-5:6-bis-O-(1':1':1'-trifluoroisopropylidene)-D-mannitol.

a). The ketal (0·02g.) was cooled in a bath of acetone/carbon dioxide and boron trichloride (0·30g., 55 mol.) was added.

After the usual treatment, a colourless glass (0·02g.) was obtained. This was dissolved in methanol and a chromatogram run in solvent (a). The silver nitrate spray showed the presence of a small amount of hexitol, $R_{mannitol}$:1·0, and a second product, R_m:5·8 (the starting material was not detected by this spray).

b). The ketal (0·02g.) was weighed into a dry test tube. Boron trichloride (0·64g., 108 mol.) was added to the cooled tube which was then sealed off. After standing at room temperature for 6 days, only a few crystals remained undissolved. The tube was broken open and the excess boron trichloride evaporated off. The colourless residue was dissolved in methanol and a chromatogram run in solvent (a). The periodate spray showed the presence of hexitol, $R_{mannitol}$: 1·0, and one or more products, R_m:5·1-6·1. (The starting material was detected by this spray, R_m:6·1).

Experiment 29 with D-mannitol hexa-acetate.

The acetate (0·07 g.) was dissolved in a small volume of dichloromethane and cooled. Boron trichloride (1·19g., 70 mol.) was added to give a clear solution at room temperature. This was worked up to give a glassy residue (0·06g.), which was dissolved in methanol. Chromatograms of this in solvent (a) and in solvent (f) showed the presence of hexitol. Evaporation of the methanol gave a white solid (0·03g.). This was crystallized from 90% methanol to give mannitol (0·02g.), m.p. and mixed m.p. 169-169·5°. The mother liquors deposited more mannitol (0·006g.), m.p. 168·5-169° and mixed m.p. 169-170° (total yield of mannitol, 77%).

Experiment 30 with 1:5:6-tri-O-benzoyl-2:4-O-methylene-D-glucitol.

The benzoate (0·05g.) was dissolved in dichloromethane (10 ml.) a nd boron trichloride (1·00g., 85 mol.) was added to the cooled solution. This was worked up to give a glass (0·09g.) smelling strongly of benzoyl chloride. It was dissolved in methanol and a chromatogram run in solvent (a)., showing the presence of

hexitol and smaller amounts of other products, $R_{glucitol}$:2·2,2·7 and 5·5(2:4-O-methylene-D-glucitol,R_g:2·2). The residue from evaporation of the methanol was acetylated and the acetate crystallized from ethanol to give impure glucitol hexa-acetate, m.p. 109° and mixed m.p. 106° (measured on the micro melting point apparatus). A specimen of glucitol hexa-acetate had m.p. of 109-110°, in this apparatus.

Experiment 31 with 1:6-di-O-toluene-p-sulphonyl-2:4-O-methylene-D-glucitol.

The ester (0·06g.) was dissolved in dichloromethane (10 ml.) and boron trichloride (0·79g, 56 mol.) added to the cooled solution. This was worked up to give a glass, which dissolved in methanol, and a chromatogram was run on this solution in solvent (a). A small amount of hexitol, $R_{glucitol}$:1·0, and a second product, R_g:6·6, were detected. (The starting material was not detected by silver nitrate or periodate sprays). Evaporation of the methanol gave an oil, which did not crystallize on standing.

Experiment 32 with D-glucitol.

The glucitol (0·71g.) was suspended in dichloromethane (80 ml.) and cooled. Boron trichloride (4·5g., 9·8 mol.) was added but did not appear to cause any further solution. The reaction was worked up in the usual way, to give a white solid (0·78g.), which only partially dissolved in methanol but was soluble in water. A chromatogram showed the presence of hexitol only. Evaporation gave an oil (0·79g.) and this was acetylated to give glucitol hexa-acetate (~~(0·19g.)~~ (1·20g., 79·5%)), m.p. ~~89-92°~~ 95-98° and mixed m.p. ~~89-95°~~.

Experiment 33 with D-mannitol.

This was carried out as in the last experiment and analagous results were obtained, mannitol being recovered in 89% yield.

Experiment 34 with methyl α-D-glucoside.

The glucoside (0·02g.) was treated with boron trichloride (0·59 g., 50 mol.) and methanolysis or hydrolysis of the products was carried out in three different ways:

i). with aqueous methanol. A chromatogram showed the presence of glucose and of a second product with the same R_g value as methyl-D-glucoside.

ii). with absolute methanol. A chromatogram showed the presence of the same products as those obtained from treatment (i).

iii). with water. Only glucose was detected.

Experiment 35 Reaction of a I:I molar ratio of boron trichloride and acetal.

The acetal selected was I:3-2:5-4:6-tri-O-methylene-D-mannitol. This (0·48g.) was dissolved in dichloromethane (50 ml.) and boron trichloride (0·26 g., I mol.) added to the cooled solution. The usual treatment gave a reddish glass (0·86g.) which dissolved in methanol; a chromatogram run in solvent (c) showed the presence of hexitol, $R_{mannitol}$:I·0, and a second compound, R_m:I·2 (2:5-O-methylene-D-mannitol, R_m:I.I, I:3-O-methylene-D-mannitol, R_m:I·2). Methanol was evaporated off and an oil obtained (0·55g.). Methanol was again added and distilled off to leave an oil (0·5Ig.). This dissolved only partially in methanol and, after standing in the refrigerator, crystals were deposited. These were filtered off (A) and the filtrate evaporated down (0·36 g.). A column (length-45 cm., cross sectional area-15·9 sq. cm.) was prepared from celite (200 g.) mixed with the stationary phase, water (200 ml.), and slurried with solvent (a). The filtrate residue was dissolved in solvent (a) (I0 ml.) and dry celite (I0 g.) added to adsorb the solution. More solvent was added to give a thick slurry and this was poured onto the column. The beaker which had contained the slurry and the walls of the column were washed with small volumes of solvent and the washings drained down into the column. The column was then set up in the fraction collecting apparatus and 25 ml. fractions of eluent were collected. The products came off the column in too dilute a solution to be detected directly by chromatography. Instead, I0 fractions (250 ml.) were evaporated down together and the

residues examined by running chromatograms in solvent (c).

Fractions I-70 - no products detected by silver nitrate spray.

II-20- " crystalline deposit B.

3I-40- " crystalline deposit C

Fractions 7I-I70- product, R_m:I·2. D

Fractions I8I-336- product, R_m:I·0. E

Identification of products:

Product (A) and (E). The crystals (0·I2g.), filtered off before the column separation, were shown to be mannitol, m.p. I58-I63° and mixed m.p. I65°. The specific rotation was measured in the form of a borate, $[\alpha]_D^{17}$ +27·5(c0·60 in H_2O, with 2·5 molar proportions of boric acid and of sodium hydroxide). Under the same conditions, an authentic specimen gave $[\alpha]_D^{19}$ +29·8.

Product (B). The crystals, obtained from the evaporation of the solvent, were shown to be I:3-2:5-4:6-tri-O-methylene-D-mannitol (0·003g.), m.p. and mixed m.p. 225°.

Product (C). The crystals, obtained from evaporation of the solvent, were shown to be I:3-4:6-di-O-methylene-D-mannitol, (0·05g.), m.p. and mixed m.p. 20I-209°. A mixture with tri-O-methylene-D-mannitol melted at I90-200°. Infra-red spectra of (C) and of an authentic sample were identical, but not the same as the spectrum of 2:4-3:5-di-O-methylene-D-mannitol. (These spectra were measured for us by Dr. D.H. Whiffen at Birmingham University) (Found: C,46·2; H, 6·9%. Calc.for $C_8H_{14}O_6$: C,46·6; H,6·9%).

Product (D). Evaporation of the solvent gave an oil (0·09g.), which did not crystallize. A chromatogram was run in solvent (a), and this product had R_m:2·66(I:3-O-methylene-D-mannitol, R_m2·66, 2:5-O-methylene-D-mannitol, R_m:2·00). The oil was acetylated with acetic anhydride (0·50 ml.) in pyridine (2·0 ml.). After 48 hr. at room temperature, the solution was poured onto ice water and extracted with chloroform. The extract was washed with dilute hydrochloric acid and with I0% aqueous sodium

bicarbonate solution and dried with magnesium sulphate. The solvent was evaporated off to give an oil, which was crystallized from ethanol. This gave 2:4:5:6-tetra-O-acetyl-I:3-O-methylene-D-mannitol (0·04g.), m.p. I38-I40°. Fletcher et al[119] give I43-I44°. (Found:C,49·8;H,6·4%. Calc. for $C_{15}H_{22}O_{10}$:C,49·7; H,6·I%). Periodate uptake was measured by a spectrophotometric method[110]. The acetate (0·00640g.) was dissolved in dry chloroform and I0 drops of 0·2M sodium methoxide in methanol added. The reaction mixture was left in the refrigerator for 63 hrs. and then the chloroform was evaporated off. Water (2 ml.) was added and the solid dissolved. The solution was neutralized with a small lump of solid carbon dioxide and freeze dried. Two solutions, to act as blanks, were prepared by adding I0 drops of 0·2M sodium methoxide in methanol to two flasks, evaporating down, adding 2 ml. of water, neutralizing with solid carbon dioxide and finally freeze drying. A solution of sodium metaperiodate, 0·0I496M, was prepared and standardized against a standard arsenious oxide solution, 0·02995N. A solution of potassium iodate (AR) of the same molarity as the periodate was then prepared. 5 Ml. of periodate solution were added to the freeze dried, deacetylated compound and to one of the blanks; 5 ml. of iodate solution were added to the other blank. These three solutions, in stoppered flasks, were kept at 34° in the dark. I Ml. samples were withdrawn from the test solution at various time intervals and diluted to 250 ml. The absorption of the diluted solution was measured on a Hilger Uvispek at 2230 Å. Similarily, a I ml. sample was taken from each blank and diluted to 250 ml. and the absorption measured. (A separate experiment had shown that the relation between the optical density, D, and the percentage composition of the periodate/iodate solution is linear).

Time (min.)	D	% periodate unreacted (from calibration curve) Fig. VIIa(ii)) p.174.	Mols. of periodate reacted/ mol. of polyol.
30	0·377	5I·05	2·03
60	0·376	5I·05	2·03
90	0·355	47·00	2·24

100% $NaIO_4$-D,0·634 I00% KIO_3-D,0·I08

This gave a periodate uptake of 2·03 mol./mol. of polyol. (I:3-O-Methylene-D-mannitol consumes 2·00 mol. periodate/mol. of acetal; 2:5-O-methylene-D-mannitol consumes I·00 mol. periodate / mol. of acetal.).

ANALYSIS OF THE PRODUCT FROM THE REACTION OF BORON TRICHLORIDE WITH TRI-O-METHYLENE-D-MANNITOL.

Experiment 36

The acetal was weighed into a clean, dry test tube and this was heated in a flame and drawn out to form a narrow constriction near the open end. The tube was fitted with a cellophane-covered cork and placed in a cooling bath. Boron trichloride was added, and the tube sealed off at the constriction and reweighed, giving the weight of boron trichloride added. After several hours at room temperature, complete solution had occurred, and the tube was broken open. In the first experiments, the excess boron trichloride was evaporated off on the oil pump until the involatile residue had constant weight. In case any decomposition of the α-chloro ether, the postulated product, should occur at this low pressure, the boron trichloride was removed by evacuation on the water pump in subsequent experiments. The residue, a glassy substance, was dissolved in a measured volume of water and the empty tube reweighed, to give the weight of the residue. The solution, containing the products of hydrolysis of the glass, was left at room temperature for a few hours, because when titration was carried out immediately after hydrolysis, titration results were found to va ry). Titrations were then carried out to

estimate the total acidity of the solution and the chloride ion content.

a). Determination of the strong acid content.

Boric acid is a very weak acid but in the presence of a polyol, such as mannitol, which is formed from the acetal, it forms a strongly acid complex. Additional mannitol was added, to ensure that all the boric acid was in this form, and the total acidity, due to hydrochloric acid and to the complex, was found by titration with standard sodium hydroxide (0·1N), using phenolphthalein as indicator (column V, Table I p. 68)

b). Determination of the $\overline{Cl}$ concentration (Volhard's method).

The sample was acidified with 6N nitric acid and excess silver nitrate added. (This had been standardized against hydrochloric acid of known strength). Nitrobenzene was then added and the sample shaken to coagulate the precipitated silver chloride. The unreacted silver nitrate was titrated against ammonium thiocyanate of known strength, using ferric alum indicator. In this way, the number of equivalents of reacted silver nitrate, and so the concentration of chloride ion, could be determined. The value for this concentration was found to be influenced by the p_H of the sample. To investigate this, estimations were carried out on samples:i) at the acid p_H, attained on hydrolysis of the glass,ii) made alkaline with sodium hydroxide and boiled for 15 min.,iii) neutralized to phenolphthale in end point and left for a few minutes to reach equilibrium (column IV).

c). Determination of the boric acid content.

This could be found from the difference between the strong acid content, due to hydrochloric acid and boric acid, and the hydrochloric acid content. The latter value was given by the Volhard determination, but, as was mentioned above, was dependent on the p_H of the sample. As the acid determination was carried out on an acid sample, the value for $\overline{Cl}$ in acid conditions was used to give the boric acid concentration (column VI).

d). Determination of formaldehyde, liberated on hydrolysis.[108] The glassy residue was washed with water into a 400 ml. beaker and the acid solution neutralized with 0·1N alkali solution, using phenolphtalein as indicator. Methyl red was then added and 2N acetic acid added dropwise until the solution became just pink. An equal volume of a buffer at p_H 4·6, prepared from equal volumes of 2N sodium acetate and N/1 hydrochloric acid, was added, as the dimedone derivative is least soluble at this p_H. The dimedone solution (15 ml.), prepared by dissolving 2g. in ethanol (25 ml.) and diluting to 50 ml. with water, was added and a precipitate soon appeared. After standing for 44 hr. at room temperature, this was filtered off into a weighed sintered-glass crucible, and dried to constant weight in a desiccator. The melting point of the solid was determined and was found to be 187°, mixed with an authentic formaldehyde dimedone derivative, m.p. 188° (column IX).

The results of these analyses are set out in Table Ip.68. The weighed amounts of the reactants and the estimated amounts of the hydrolysis products are expressed in millimoles. The difference in weight of the glassy residue and the acetal is assumed to be due to the addition of boron trichloride, with no subsequent elimination, so that the increase in weight is expressed in millimoles of boron trichloride (column II).

REACTIONS OF SOME NUCLEOPHILIC REAGENTS WITH THE PRODUCT OF REACTION OF EXCESS BORON TRICHLORIDE WITH A CYCLIC METHYLENE ACETAL.

Experiment 37 Reaction of sodium acetate with the product of the reaction of excess boron trichloride with:-

a). I:3-2:5-4:6-Tri-O-methylene-D-mannitol.

The acetal (0.54g.) was treated with 13 molecular proportions of boron trichloride to give a glassy product (1·08g.). Sodium acetate (2·0g., 11 mol.), suspended in dry chloroform (10.ml.),

was added and the product dissolved with evolution of heat. The reaction mixture was refluxed on the water bath for 60 min. and then left for 60 min. at room temperature. The chloroform was evaporated off under reduced pressure, to leave a gelatinous solid. In an attempt to remove boron as methyl borate, absolute methanol (I5 ml.) was added and evaporated off. This was repeated to give a solid (0·52g.), which was extracted first with chloroform and then with pyridine. Chromatograms of these solutions were run in solvent (a) and the papers were sprayed with the silver nitrate reagent.

$CHCl_3$ extract - $R_{mannitol}$: 2·2 (faint), 4·0, 5·I, 6·3.

C_5H_5N extract - $R_{mannitol}$: I·0 (faint), 2·I (faint), 3·7, 4·7, 5·6.

(I:6-di-O-acetyl-3:4-di-O-acetoxymethyl-2:5-O-methylene-D-mannitol, R_m:6·0).

b). I:3-2:4-5:6-Tri-O-methylene-D-glucitol.

The acetal (0·50g.) was treated with 7·2 molecular proportions of boron trichloride to give a glassy residue (I·0Ig.). This was treated with II molecular proportions of sodium acetate in chloroform, as in (a).

$CHCl_3$ extract - $R_{glucitol}$: I·0 (faint), 2·I, 3·6, 4·8, 5·6.

C_5H_5N extract - $R_{glucitol}$: 0·9, I·5 (salts), 2·0, 3·2, 4·4, 5·3.

(I:6-di-O-acetyl-3:5-di-O-acetoxymethyl-2:4-O-methylene-D-glucitol, R_g:5·6)

c). 2:4-O-Methylene-D-glucitol.

The acetal (0·0Ig.) was treated with I2 molecular proportions of boron trichloride to give a glassy residue (0·29g.). This was treated with 23 molecular proportions of sodium acetate and worked up as in (a), except that the methanolic solution was acidified with dilute hydrochloric acid to p_H6, before the methanol was evaporated off. A pyridine extract was taken and investigated by paper chromatography in solvent (a).

C_5H_5N extract - $R_{glucitol}$:0·96, I·6 (with salts), 2·I. (2:4-O-methylene-D-glucitol, R_g: I·7).

Experiment 38 Reaction of sodium methoxide with the product of the reaction of excess boron trichloride with:-

a). I:3-2:5-4:6-Tri-O-methylene-D-mannitol.

The acetal (0·30g.) was treated with 8 molecular proportions of boron trichloride to give a residue (0·65g.). A solution of sodium methoxide in methanol was prepared by adding sodium (0·4g., I0 mol.) to absolute methanol (25 ml.), and this was added to the reaction product. The resulting suspension was refluxed for a few minutes and then the precipita te was filtered off and shown to be sodium chloride, containing little organic material. Dilute hydrochloric acid was added to the filtrate until this had p_H8 and the methanol and water then evaporated off. The solid residue was extracted with chloroform and then n-butanol. Chromatograms were run on these extracts in solvent (a) and the papers were sprayed with silver nitrate reagent.

$CHCl_3$ extract - $R_{mannitol}$: 2·2, 3·8, 5·5.

$n\text{-}C_4H_9OH$ extract - $R_{mannitol}$: 0·3, I·5, 2·7.
(2:4-O-methylene-D-glucitol, R_m:I·9)

b). I:3-2:4-5:6-Tri-O-methylene-D-glucitol.

The acetal (0·30g.) was treated in (a).

$CHCl_3$ extract - $R_{glucitol}$: 0·I5, 0·4, I·0, 2·5, 4·7.

$n\text{-}C_4H_9OH$ extract - $R_{glucitol}$:0·I5, 0·4, I·0, 2·5.

c). 2:4-O-Methylene-D-glucitol.

The acetal (0.I2g.) was treated with I30 molecular proportions of boron trichloride to give a product (0·37g.), which was reacted with a sodium methoxide solution, prepared by dissolving sodium (I·9g.) in absolute methanol (20 ml.). This was worked up as in (a) and a pyridine extract taken of the product. A chroma togram of this extract was run in solvent (a).

C_5H_5N extract - $R_{glucitol}$: 0·9, 2·I, 3·6.
(2:4-O-methylene-D-glucitol-R_g:2.2).

Experiment 39 Reaction of lithium aluminium hydride with the product of reaction of excess boron trichloride with:-

a). I:3-2:5-4:6-Tri-O-methylene-D-mannitol.

The acetal (2·0 g.) was treated with I7 molecular proportions of boron trichloride to give a glassy residue (4·49g.), which was dissolved in purified tetrahydrofuran (50 ml.). (This was dried over calcium chloride, then over sodium, and distilled from this through a fractionating column at atmospheric pressure. The fraction boiling at 64-65° was collected. The solvent was stored over sodium and redistilled before use). The solution was added to the reducing reagent, prepared in the usual way from lithium aluminium hydride (6·0g.) in tetrahydrofuran (200 ml.). After refluxing for 30 min., water (I00 ml.) was added to the cooled slurry which was then neutralized with hydrochloric acid. The alumina was filtered off and the concentrated filtrate extracted with chloroform and then passed down a biodeminrolit ion-exchange resin column. The eluent was concentrated and this a nd the chloroform extract were investigated by paper chromatography in solvent (a). This showed the presence in the aqueous layer of a small amount of product, $R_{mannitol}$:I·9, and rather more of products, R_m:3·3 and R_m:4·5, and in the chloroform extract of product, R_m: 4·9 (2:4-O-methylene-D-glucitol, R_m:2·0).

Experiment 39b 2:4-O-Methylene-D-glucitol.

The acetal (2.00g.) was treated with I3 molecular proportions of boron trichloride to give a glassy residue (4·96g.).

The reducing agent was prepared by adding lithium aluminium hydride (7·00g., I8 mol.) to a I litre, three-necked flask, fitted with a mercury-sealed stirrer, a condenser and a dropping funnel. The open ends of the condenser and funnel were fitted with silica gel drying tubes. Purified terahydrofuran (350 ml.) was added through the funnel to the flask, which was cooled in an ice bath, and, as soon as sufficient solvent was present, the grey slurry was stirred.

The glassy residue was dissolved in tetrahydrofuran (I50 ml.) and this solution added dropwise from the funnel to the stirred slurry, at room temperature. Effervescence occured after each addition and the mixture became warmer. The flask was then heated on a water bath, with continued stirring, so that the solvent refluxed for 45 min. After the flask had been cooled in ice, water (I00 ml.) was added cautiously to the stirred slurry, to hydrolyse the lithium aluminium hydride. The suspension was then neutralized with concentrated hydrochloric acid

and alumina was precipitated. This was removed partly (by filtration through a sintered-glass funnel and partly by centrifuging the filtrate). The solution was then passed down a biodeminrolit ion exchange resin column. The solution from this was concentrated to dryness and finally freeze dried to give an oil (9·8g.). The weight of this oil suggested that some alumina was still present, and it was acetylated, in order to separate the organic material. Acetylation was carried out by refluxing the oil with sodium acetate (8·2g.) and acetic anhydride (60 ml.) for I hr. The reaction mixture was then poured into water and this extracted with chloroform. The extract was washed with I0% aqueous sodium bicarbonate solution and with water. The dried extract was evaporated to give an oil (3·8g.), which showed no sign of crystallizing. It was deacetylated in chloroform by a 0·2M solution of sodium methoxide in methanol (6·5 ml.) and, after standing in the refrigerator for 2 days, the precipitated oil (0·40g.) was separated. A chromatogram was run in solvent (a) and this showed the presence of hexitol, $R_{glucitol}$:0·9, and of a second product, R_g:2·2, which stained the silver nitrate reagent more rapidly than 2:4-O-methylene-D-glucitol, R_g:2·3.

A column, of diameter 5 cm., was prepared from celite (240g.). This was mixed with water (I80 ml.) and slurried with solvent (a), before packing into the column. The oil was dissolved in water (6 ml.), slurried with celite (8g.), and poured onto the column. This was then eluted with solvent (a), at a flow rate of I drop/2 sec.. The eluent was collected in 50 ml. fractions and these were concentrated and the residues investigated by paper chromatography.

Fractions	I-50	no product detected	
	5I-95	Product, $R_{glucitol}$:2·2	A
	96-105	" :I·9	B
	106-I20	" :0·97, I·87	C
	I20-I55	" :I·0.	D

(2:4-O-methylene-D-glucitol, R_g:2·I)

Investigation of fractions:

Fraction A. The oil (0·40g.) partially crystallized after standing in a desiccator, but could not be crystallized from any of the usual solvents. It was investigated by chromatography in various solvents:-

i). solvent (a)

$R_{glucitol}$: (linked in streak) : I·59, staining silver nitrate reagent more slowly than glucitol.
I·79, staining silver nitrate at the same rate as glucitol.

(2:4-O-methylene-D-glucitol, R_g: I·79, staining silver nitrate more slowly than the fraction A products).

ii). solvent (f)

R_g : 2·30 (periodate spray)
: 3·20 (very faint)

(2:4-O-methylene-D-glucitol, R_g: 3·I9)

iii).ionophoresis in borate buffer, p_H 9·8, for 2 hr. and at 1200 volts.

M_g : 0·92 (periodate spray)

(2:4-O-methylene-D-glucitol, M_g : 0·73)

The product was then heated with dilute sulphuric acid in a sealed tube for 2 hr. The tube was broken open and the contents neutralized with sodium bicarbonate, evaporated to dryness and the residue extracted with pyridine. The pyridine was evaporated off and a chromatogram run on the residue, in solvent (a).

$R_{glucitol}$: I·00
: 2·I6
: 2·98 (very faint; a similar spot, R_g: 2·8, found in the products of the action of acid on glucitol).

(2:4-O-methylene-D-glucitol, R_g : 2·00.)

A boron trichloride degradation was carried out in the usual way and the products examined by chromatography.

i). solvent (a)

$R_{glucitol}$: 0·97
: 2·00 (faint)

(2:4-O-methylene-D-glucitol, R_g : 2·00.)

ii). solvent (f).

R_g : I·06 (periodate spray)
: I·85

(2:4-O-methylene-D-glucitol, R_g : 2·8I)

The product was examined for the presence of methylene acetal groups, using chromotropic acid to detect formaldehyde liberated by acid hydrolysis[I09]. The oil (0·0035g.) was dissolved in water (I0 ml.) and I ml. samples of this solution were pipetted into test tubes. I Ml. samples of water were pipetted into similar tubes, to act as blanks. 1·9 ML. of a freshly prepared chromotropic acid solution [prepared by dissolving the sodium salt of chromotropic acid (0·5g.) in water (50 ml.) and adding a mixture of 2 volumes of sulphuric acid (dl·84) to I of water (200 ml.)] were added to each tube, which was fitted with a metal cap, and the contents shaken. The tubes were then heated in a boiling water bath in subdued light for 30 min. The absorption of the contents of each tube was then compared with the absorption of aqueous sulphuric acid solution (2:I,v:v), using filter no. 606, in the EEL absorptiometer. The test solutions could not be measured directly against the blanks, as the chromotropic acid decomposes in strong light. A standard curve was drawn by taking solutions containing known amounts of 2:4-O-methylene-D-glucitol, treating these with chromotropic acid and plotting the optical density of the solutions against the moles of methylene acetal used. (Fig: VIb)p.173. From this, the amount of methylene acetal in the oil could be determined.

Wt. of sample = 0·00250g.; optical density, 9·7,
equivalent to 5·4% formal.

(This may not be a very accurate result, as there was only enough material for one determination).

Zeisel determinations were carried out on the oil and gave an average value for the methoxyl content of II·8% (mono-methyl glucitol-I5·8%).

Acetylation of the oil gave no crystalline product.

Fraction (B). When this was concentrated, it was found to contain some hexitol, so that this fraction and fraction (C) were not examined further.

Fraction (D). This yielded an oil (0·04g.) and this was examined by chromatography in solvent (a).

$R_{glucitol}$: I·00

The oil was acetylated with sodium acetate (0·9g.) and acetic anhydride (5·0 ml.) in the usual way to give an oil (0·05g.). This was dissolved in chloroform and filtered through an asbestos filter (Ford's sterimat), to remove traces of celite. The filtrate was concentrated and crystallized from ethanol, to give glucitol hexa-acetate (0·0Ig., 0·2%), m.p. and mixed m.p96·5-97·0° (Found: C,50·3;H, 6·07% Calc. for $C_{18}H_{26}O_{I2}$: C,49·8; H,6·07%).

Experiment 39(c)

2:5-O-Methylene-D-mannitol.

The acetal (2·9I g.) was treated with I8 molecular proportions of boron trichloride, to give a glassy residue (6·25g.). The reducing agent was prepared as in (b) from lithium aluminium hydride (6·00 g.), suspended in sodium-dried diethyl ether (200 ml.). The glassy residue, which was insoluble in ether, was dissolved in tetrahydrofuran (I00 ml.) and added slowly to the stirred slurry, at room temperature. After refluxing for 60 min., the stirred reaction mixture was cooled in ice, and water (I50 ml.)) added cautiously. It was then acidified to p_H4 with concentrated hydrochloric acid. The organic solvents were evaporated off under reduced pressure on the water bath and the aqueous residue concentrated. This was then centrifuged at 3000 r.p.m., to separate the precipitated alumina, and the supernatant liquid was passed down a biodeminrolit ion-exchange resin column. The

eluent was concentrated to dryness by freeze drying and the turmeric test showed the presence of boric acid. This was removed by repeatedly refluxing with methanol, acidified with dilute hydrochloric acid, and then evaporating to dryness. The neutralized residue was extracted with pyridine and this was concentrated to give a dark oil (I·98 g.), which was investigated by paper chromatography, using solvent (f) and the periodate spray. This showed the presence of hexitol, $R_{mannitol}$: I·0, and a second product, R_m:I·4, (2:5-O-methylene-D-mannitol, R_m:2·0). A column (diam. 4·5 cm., length 49·0 cm.) was prepared from equal volumes of charcoal and celite and the oily product, dissolved in a small volume of water, was run onto the top of the column. This was first eluted with water, the percentage of ethanol increasing continuously from 0-I0%. The rate of flow of solvent from the column was 3 drops/sec. and it was collected in 25 ml. fractions. The contents of each tube was investigated by paper chromatography in solvent (a).

Fractions I - 39	no product detected.	
40 - 5I	product, $R_{mannitol}$: I·0	B
52 - 54	product, $R_{mannitol}$: I·0, 2·2.	
55 -100	product, R_m : 2·6	A
IOI -I50	no product detected.	

Investigation of fractions:

Fraction A. The concentrated solution was filtered through an asbestos filter, (Ford's sterimat), to remove any fine particles of celite, and evaporated to dryness, to give a colourless oil (I·70g.).(Found: C,43·4; H,8·2; OMe, 26·5, 2I·8%. $C_7H_{16}O_6$ requires C,42·9; H,8·2; OMe,I5·8%). Unsuccessful attempts were made to crystallize this from various solvents and the oil still showed no sign of crystal formation on prolonged drying in a phosphorus pentoxide vacuum desiccator. It was examined by chromatography.

i). solvent (a)

$R_{mannitol}$: 2·0 (silver nitrate spray)

(2:5-O-methylene-D-mannitol, R_m : 2·2, staining the silver nitrate spray slower than the oil.)

ii). solvent (f)

R_m : I·8 (periodate spray)

(2:5O-methylene-D-mannitol, R_m : 2·8).

iii). ionophoresis in borate buffer, p_H 9·8, for 3 hr., at 1200 volts.

M_m : 0·74 (periodate spray)

(2:5-O-methylene-D-mannitol, M_m : 0·58).

A boron trichloride degradation was carried out on (A),(0·008g.), in the usual way and the products were investigated by chromatography.

i). solvent (a)

R_m : 0·97 (Silver nitrate spray).

R_m : I·9, very faint

(2:5-O-methylene-D-mannitol, R_m : I·9)

ii). ionophoresis in borate buffer, p_H 9·8, for 3 hr. at 1200 volts.

M_m : 0·97 (periodate spray)

The residue was crystallized from 90% methanol to give crystals of mannitol, m.p. and mixed m.p. I68-I68·5°.

The presence of methylene acetal groups in (A) was tested by treating it with acid, and/so hydrolysing any methylene acetal groups to formaldehyde, which would then be detected by chromotropic acid, as in exp. 39(b).

Weight of (A), 0·0I00I g., optical density, 0·8, equivalent to 0·I% formal. (Fig. VIb) p.173.

The periodate oxidation uptake and the oxidation products of (A) were investigated.

i) Periodate uptake (mols. of periodate reacting with I mol. of polyol)[110]. (A) was weighed in a capillary tube and this placed in a flask, to which I0 ml. of sodium periodate solution (0·0I5 M), standardized against a standard arsenious oxide solution, was added. The reaction flask was placed in a thermostat at 35° and, when the oil had completely dissolved, I ml. samples were withdrawn. These were diluted to 250 ml. and the optical density of these diluted solutions measured at 2230 Å, on the Hilger Uvispek. Under the same conditions, I ml. samples of the sodium periodate solution and a potassium iodate solution (0·0I5 M) were diluted and the optical densities measured. A graph, relating the % of sodium periodate to the optical density, D, was drawn (this had previously been shown to be linear). The % of unreacted sodium periodate in the test solutions, corresponding to the measured optical density, was then read off from the graph. (Fig. VII b(i) and (ii) p.174)

Wt.of (A)	Molarity of $NaIO_4$ and KIO_3	Time (min.)	D	% $NaIO_4$ unreacted	Mols.of IO_4 / mol. of polyol
0·00684g.	0·0I523	35	0·265	35·5	2·82
		64	0·25I	33·0	2·93
		95	0·250	32·8	2·94
		I25	0·250	32·8	2·94
0·00334g.	0·0I532	30	0·458	66·7	3·00
		70	0·455	66·2	3·04
		90	0·451	65·5	3·II
		300	0·456	66·3	3·03

I00% $NaIO_4$ - D,0·632; I00% KIO_3 - D,0·063 (0·0I523 M)
I00% $NaIO_4$ - D,0·64I; I00% KIO_3 - D,0·094 (0·0I532 M)

Average value for periodate uptake, 3·00 mols. / mol. of diol (calculated as $C_7H_{16}O_6$).

ii) Determination of formaldehyde, produced in oxidation[111]. Erythritol was used as a standard in this experiment[~~110~~ 112]. A known weight of this was dissolved in 10 ml. of sodium periodate solution (0·015M) and the reaction flask placed in a thermostat at 35°, in the dark. After 60 min., when oxidation was complete, samples were withdrawn by pipette and diluted with water, to give solutions of various concentration. 1 Ml. of each of these solutions was pipetted into a test tube, to which was then added 0·25 ml. of a 20% aqueous sodium sulphite solution, to reduce the unreacted periodate. 9 Ml. of a freshly prepared chromotropic acid solution (see exp. 39(b)) were added and the tubes closed with metal caps and heated in a boiling water bath in the dark for 30 min. After cooling, 0·5 ml. of a half-saturated solution of thiourea in water was added and the tubes shaken, to remove any iodine. The optical density of the solutions was then measured on the EEL spectrometer, using the filter no. 606. The instrument was set at a zero reading, using an identical cell, containing an aqueous sulphuric acid solution (sulphuric acid (d1·84) : water, 2:1, v:v). Blanks were prepared from 1 ml. of the sodium periodate solution, diluted to the same concentrations used in the test measurements. These were treated exactly as above and the optical densities measured against the same aqueous sulphuric acid. 1 Mole of erythritol was assumed to liberate 2 moles of formaldehyde on oxidation and a standard graph was drawn, plotting the optical density of each solution against its formaldehyde content. (Fig. VIa) p.173.

A known weight of (A) was treated in the same way and the moles of formaldehyde, corresponding to the measured optical density, read from the standard graph.

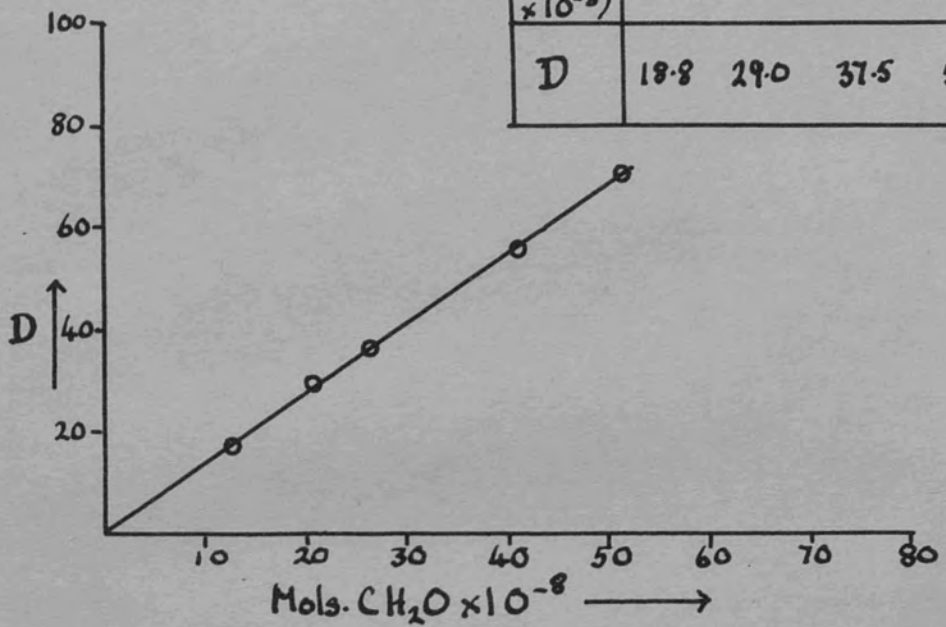
Wt. of (A)	Optical density, D. (100×dilution)	Formaldehyde (mols.)
0·00309 g.	23·8	$16·5 \times 10^{-6}$
0.00303 g.	21.1	$14·8 \times 10^{-6}$

This gives a value of 1.07 and 0.96 mols. of formaldehyde, produced per mol. of polyol (calculated as $C_7H_{16}O_6$), on

FIG. VI

a).

CH_2O (mols. $\times 10^{-8}$)	13·2	20·6	26·4	41·1	57·4
D	18·8	29·0	37·5	57·8	71·9



b).

CH_2O (mols $\times 10^{-8}$)	10·3	20·6	51·4
D	14·4	29·6	71·9

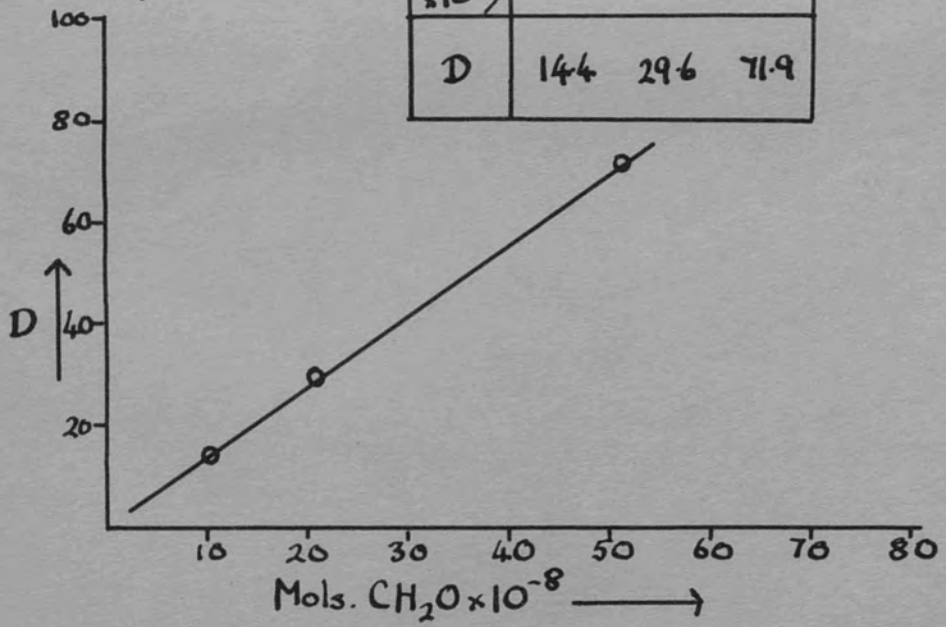
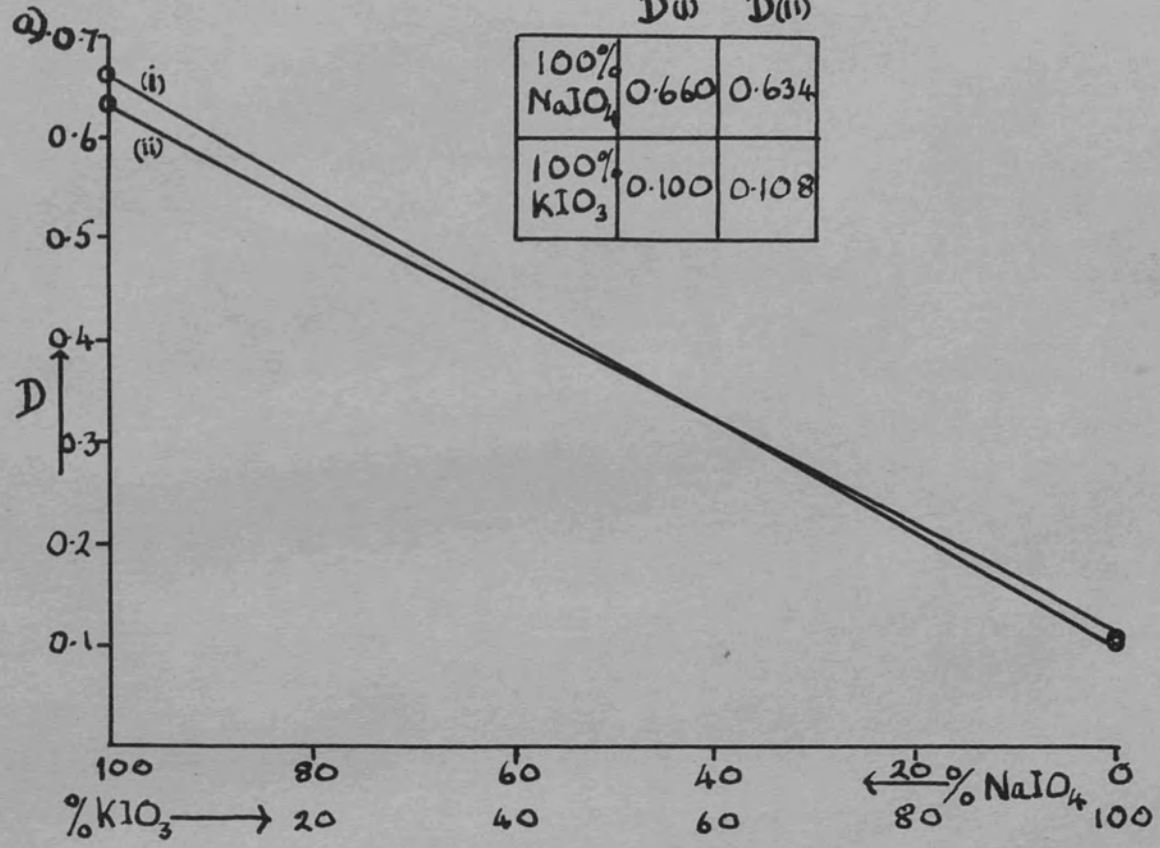


FIG. VII

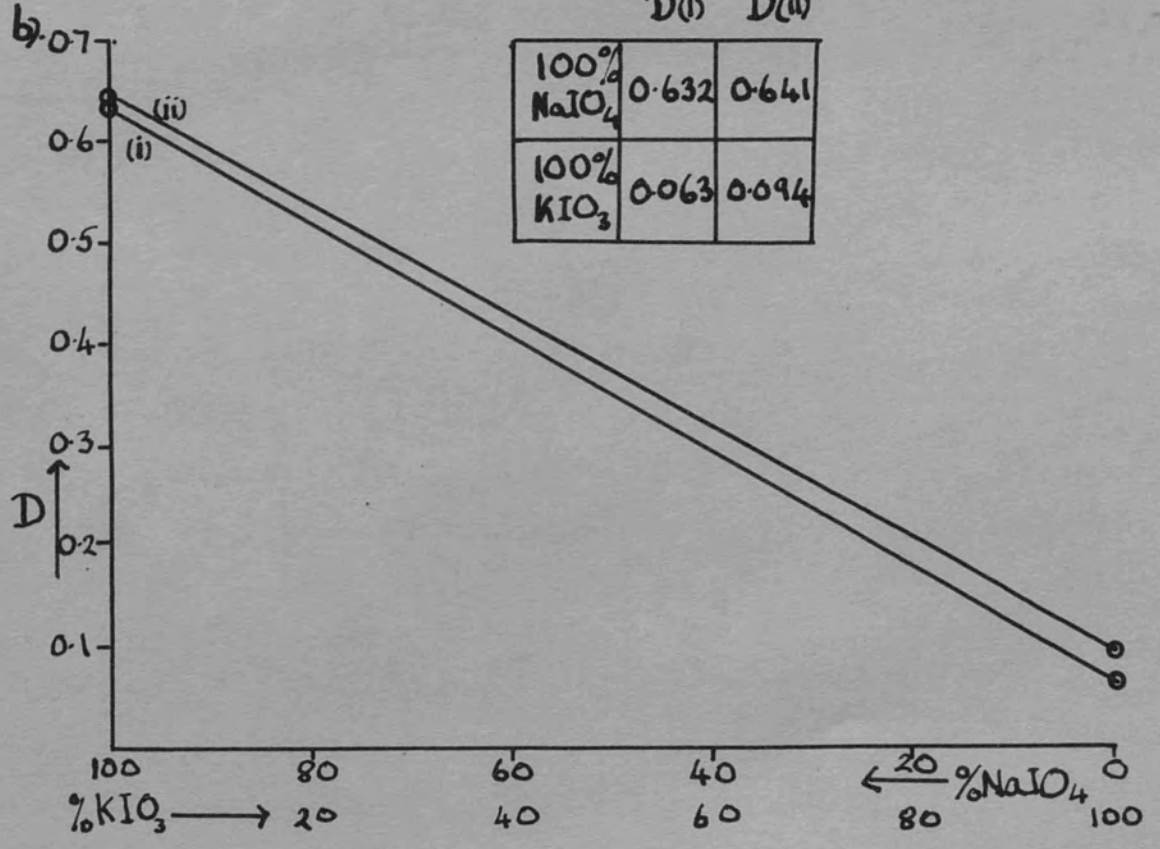
a)

	D(i)	D(ii)
100% $NaIO_4$	0·660	0·634
100% KIO_3	0·100	0·108



b)

	D(i)	D(ii)
100% $NaIO_4$	0·632	0·641
100% KIO_3	0·063	0·094



periodate oxidation.

iii) Determination of formic acid, produced in oxidation of (A). A known weight of (A) was oxidized as above with sodium periodate solution and, after known reaction times, 2 ml. samples were withdrawn and diluted with water. Ethylene glycol (0·5 ml.) was added to each, to remove unreacted periodate. After standing in the dark for 30 min., the samples were titrated with standard sodium hydroxide solution, using methyl red as indicator. Blanks were made up from 2 ml. of sodium periodate solution and treated as above. These became alkaline on the addition of I drop of the hydroxide solution.

Wt. of (A)	Time (min.)	Vol: of NaOH solution (ml.)	Mols. of acid/ mol. of polyol.
0·00614 g.	200	I·I75 (0·00964N)	I·8I
0·00534 g.	240	I·035 (0·00962N)	I·83
	I440	I·075 (")	I·90.

(A) (0·I03g.) was acetylated by refluxing with sodium acetate (0·I0g.) and acetic anhydride (2·0 ml.) for 60 min. The reaction mixture was poured into water and, after hydrolysis of the anhydride, was extracted with chloroform. The extract was washed with I0% aqueous sodium bicarbonate solution, and with water and dried over anhydrous magnesium sulphate. The chloroform was evaporated off to give a semi-crystalline oil (0·22g.). This was crystallized from aqueous ethanol to give the acetate of (A) (0·I2g.)., m.p. I02-I02·5°, unchanged by further crystallization. (Found: C,50·I;H,6·4;OMe,8·0%. $C_{I7}H_{26}O_{II}$ requires C,50·3;H,6·5;OMe,7·6%).

Fraction B. The solution was concentrated, filtered through an asbestos filter and evaporated to give a white crystalline solid (0·07g.,I·I%), m.p. I60-I6I°. This was recrystallized from 90% methanol to give mannitol (0·03g.), m.p. and mixed m.p. I68-I69° (Found: C,39·6;H,7·8%. Calc. for $C_6H_{I4}O_6$; C,39·5; H,7·7%).

Experiment 39 (d) Reaction of lithium aluminium hydride with a methylene acetal (2:4-O-methylene-D-glucitol tetra-acetate).

The reducing agent was prepared as before, mixing the hydride (I·36g.) with dried, distilled tetrahydrofuran (I00 ml.), to give a slurry. The acetate (0·73g.) was dissolved in tetrahydrofuran (20 ml.) and the solution added to the stirred slurry at room temperature. The mixture was refluxed for 45 min. and then cooled in ice, and water (I0 ml.) added cautiously. The suspension was neutralized with dilute hydrochloric acid and the alumina separated by filtration and centrifuging at 3000r.p.m. The concentrated solution was passed down a biodeminrolit ion-exchange column and the eluent concentrated to give white solid (0·34g.), m.p. I6I-I62°. This was investigated by paper chromatography in solvent (a) and was shown to contain hexitol, $R_{glucitol}$:I·0 (very small amount), and a second product, R_g:2·6(2:4-O-methylene-D-glucitol, R_g:2·6). The solid was crystallized from aqueous ethanol, to give 2:4-O-methylene-D-mannitol,(0·34g.,85%), m.p. and mixed m.p. I64-I65°, $[\alpha]_D^{21}$ -9·5 (c I·0 in H_2O).

Experiment 40

a) Preparation of I:3:4:5:6-penta-O-acetyl-2-O-methyl-D-mannitol. Prof. E. Pacsu, of Princeton, New Jersey, very kindly provided a sample of 2-O-methyl-D-mannose dibenzylmercaptal. The mercaptal (0·65g.) was demercaptalized by dissolving in acetone (I6 ml.), adding water(8 ml.), warming at 54° for a few minutes a nd finally adding mercuric chloride (I·25 g.) in acetone (2 ml.). A fine white precipitate was formed and the mixture was refluxed for 45 min.. The solid was filtered off and the filtrate reheated, but no further precipitation occured and the reaction was assumed to have ended. The acid solution was concentrated to about a quarter of its original volume and hydrogen sulphide bubbled through it. The black mercuric sulphide was

separated by centrifuging at 6000 r.p.m. and the supernatant liquid and washings again treated with hydrogen sulphide, There was no further precipitation and the dissolved gas was removed by heating the solution under reduced pressure, until the lead acetate test for hydrogen sulphide was negative. The solution was neutralized with silver carbonate, filtered from silver chloride, concentrated, and treated with hydrogen sulphide to precipitate any dissolved silver. As the silver sulphide was not easily filtered off, charcoal was added and a clear filtrate was obtained. This was concentrated to give an oil, which was investigated by chromatography.

i). Solvent (a)

$R_{mannose}$	:0·97	(p-anisidine hydrochloride spray)
	:I·9	
R_m	:0·97	(triphenyl tetrazolium chloride spray)
	: -	
R_m	:I·0	(silver nitrate spray)
	:I·9	

(2-O-methyl-D-mannosedibenzylmercaptal, R_m:5·0)

ii). ionophoresis in borate buffer, p_H 9·8, for 3 hr. at 1200 volts.

M_m	:0·34	(silver nitrate spray)
	:0· 93	

The oil was then reduced to a mixture of the corresponding polyols. It was dissolved in water (5 ml.) and the solution neutralized with sodium bicarbonate. An aqueous solution of potassium borohydride (0·I6g. in 7·5 ml. of water) was added and gas was evolved, the p_H of the reaction mixture rising to I0. After standing at room temperature overnight, the gas evolution had stopped and the ion exchange resin, analar IR-I20(H), added, to decompose the excess borohydride. Sodium bicarbonate was

added to raise the p_H from 2 to 5. The resin was filtered off and the filtrate and washings concentrated, under reduced pressure, to give a white solid. Absolute methanol was added to this and distilled off. After this had been repeated, the turmeric test for boric acid was negative. The residue was an oil (0·17g.) and chromatography of this in solvent (a) showed the presence of hexitol, $R_{mannitol}$:0·92, and a second product, R_m: 1·84. No reducing sugar was detected by the p-anisidine hydrochloride spray.

The products were separated on a charcoal/celite column (diam. 2 cm., length 39 cm.). The column was eluted first with water (300 ml.) and then with 2% aqueous ethanol. This was found to give a better separation than the gradient elution used in exp. 39c. The solvent flowed from the column at the rate of 1 drop/ 6 sec., and 10 ml. fractions were collected. The fractions were investigated by paper chromatography in solvent (a).

Fractions 1 - 11 no product detected.
12 - 17 product, $R_{mannitol}$: 1·0.
18 - 20 no product detected.
21 - 56 product, R_m : 1·9
57 - no product detected.

Fractions 21 - 56 were concentrated, filtered through an asbestos filter and evaporated down to give an oil (0·09 g.). This was acetylated in the usual way with sodium acetate (0·1g.) and a cetic anhydride (2·0 ml.) to give 1:3:4:5:6-penta-O-acetyl-2-O-methyl-D-mannitol (0·06g.), m.p. 102-102·5°, after two crystallizations from aqueous ethanol.

b). Comparison of the product (A) from exp.39c and 2-O-methyl-D-mannitol.

i) By paper chromatography.

i). Solvent (a)

(A), $R_{mannitol}$: 1·50 (silver nitrate spray)

2-O-Methyl-D-mannitol, R_m : 1·50

(2:5-O-methylene-D-mannitol, R_m : 1·60)

ii). solvent (f)

(A), R_m : 2·00 (periodate spray)

2-O-methyl-D-mannitol, R_m : 1·97

(2:5-O-methylene-D-mannitol, R_m : 2·83)

iii). solvent (b)

(A), R_m : 1·90 (silver nitrate spray)

2-O-methyl-D-mannitol, R_m : 1·87

iv). ionophoresis in borate buffer, p_H 9·8, for 3 hr. at 1200 volts.

(A), M_m : 0·86 (periodate spray)

2-O-methyl-D-mannitol, M_m : 0·85

(2:5-O-methylene-D-mannitol, M_m 0·65)

v). ionophoresis in molybdate buffer, p_H 5, for 3 hr. at 500 volts.

(A), M_m : 1·00 (silver nitrate spray)

2-O-methyl-D-mannitol, M_m : 1·00

ii) By investigating the acetates.

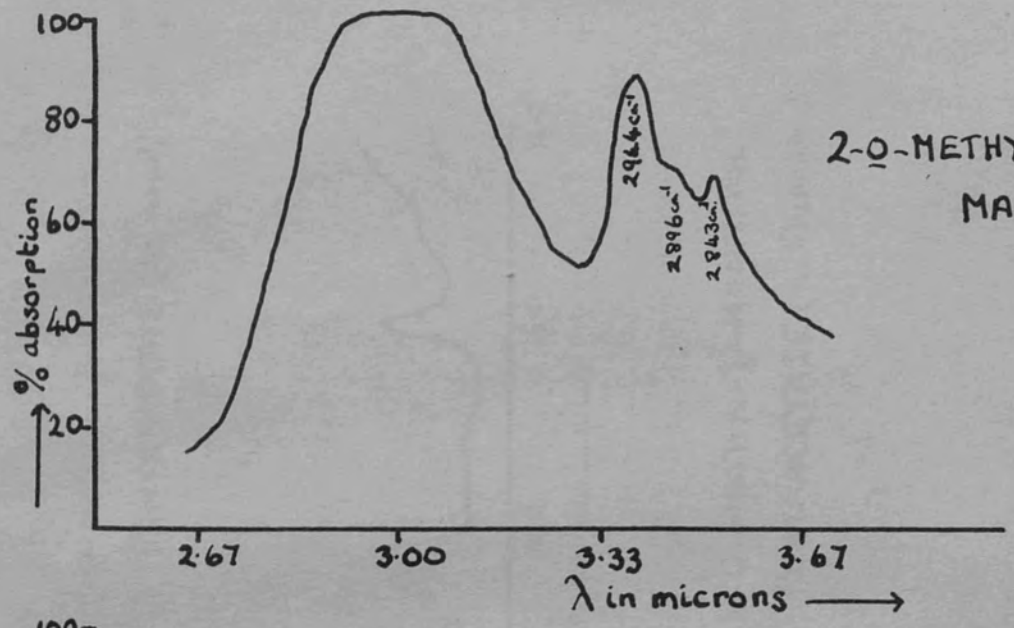
(A) acetate, m.p. 102-102·5°.

1:3:4:5:6-penta-O-acetyl-2-O-methyl-D-mannitol, m.p. 102-102·5°.

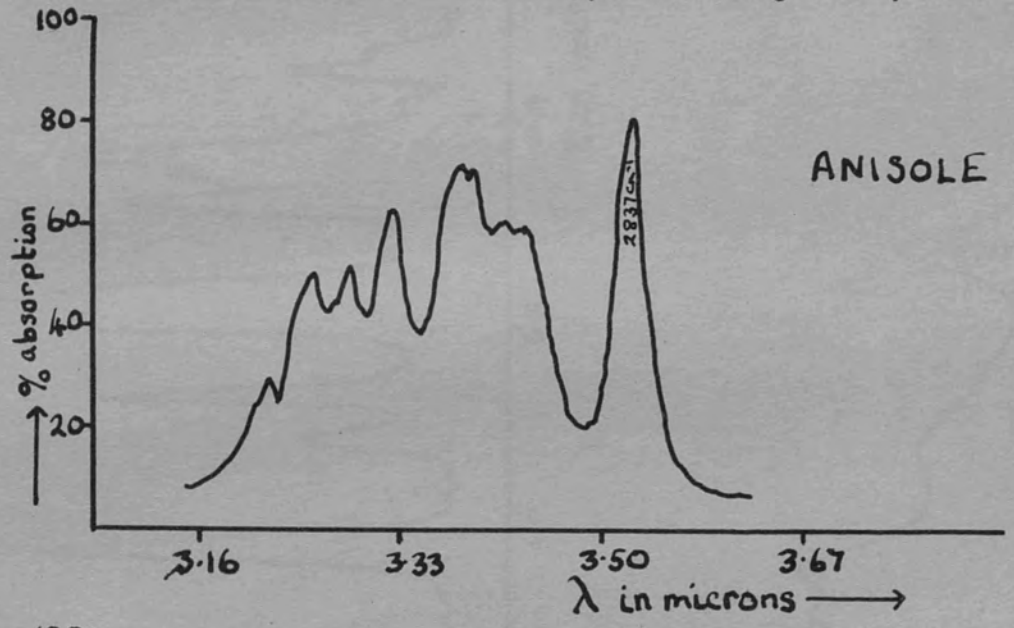
Mixed m.p. 101·5-102·5°.

The infra-red spectra of the two acetates (Fig.IX) were measured by Dr.R.L. Williams [redacted]. He used a sodium chloride prism spectrometer for the range, 5000cm.$^{-1}$ 666·7cm.$^{-1}$, a nd a diffraction grating spectrometer (third order spectrum) for the fine spectrum, 3158 cm.$^{-1}$-2727 cm.$^{-1}$. The samples were prepared in nujol mulls. The spectra of the two acetates were identical over the range, 5000 cm.$^{-1}$ -666·7 cm.$^{-1}$ The absorption was next investigated in greater detail in the region, 3158 cm.$^{-1}$ - 2727 cm.$^{-1}$, to locate the symmetrical CH stretching frequency of

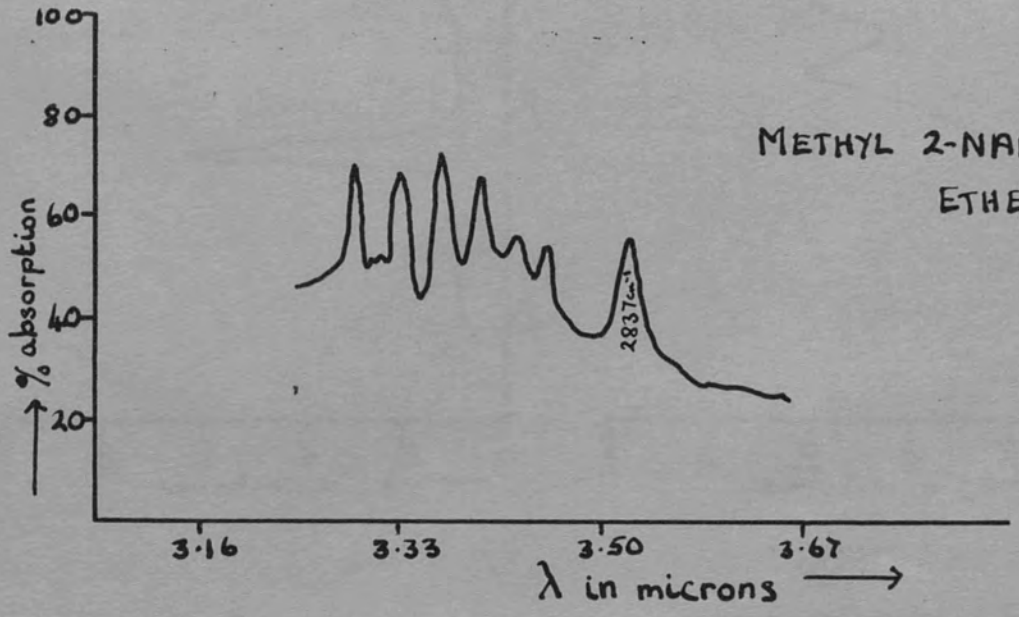
FIG. VIII



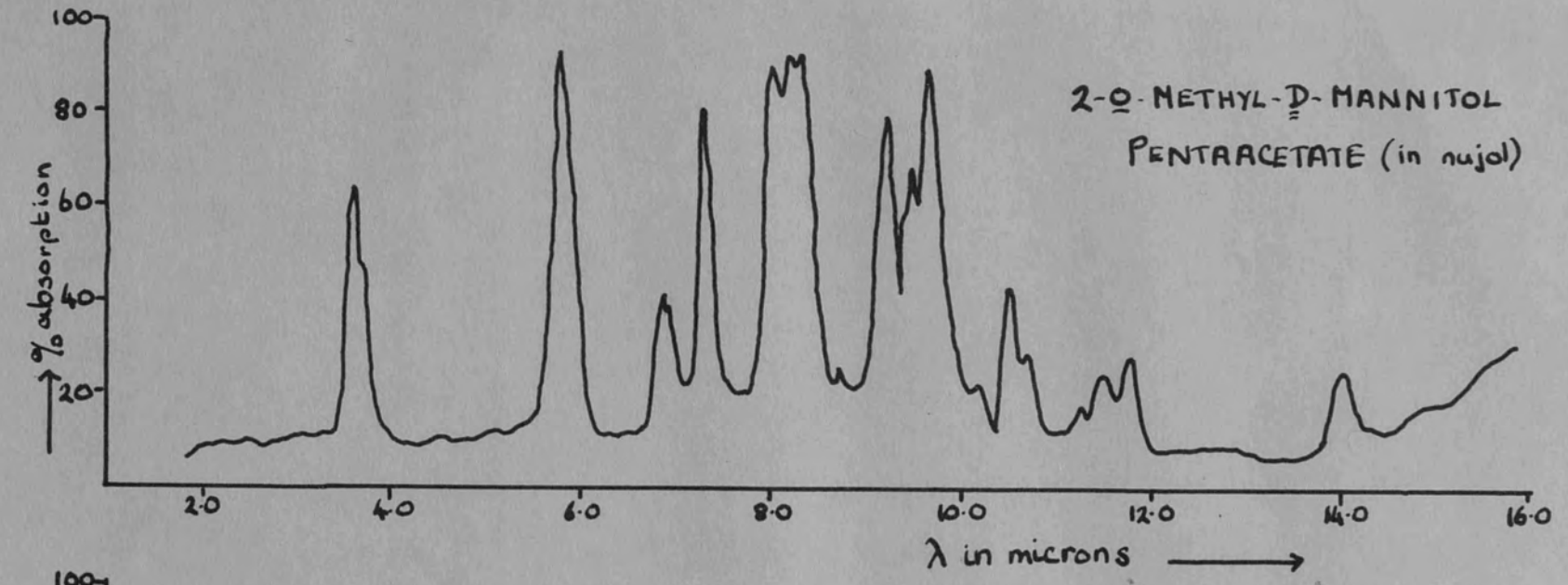
2-O-METHYL-D-MANNITOL



ANISOLE



METHYL 2-NAPHTHYL ETHER.


2-O-METHYL-D-MANNITOL
PENTAACETATE (in nujol)
% absorption
100
80
60
40
20
2·0
4·0
6·0
8·0
10·0
12·0
14·0
16·0
λ in microns

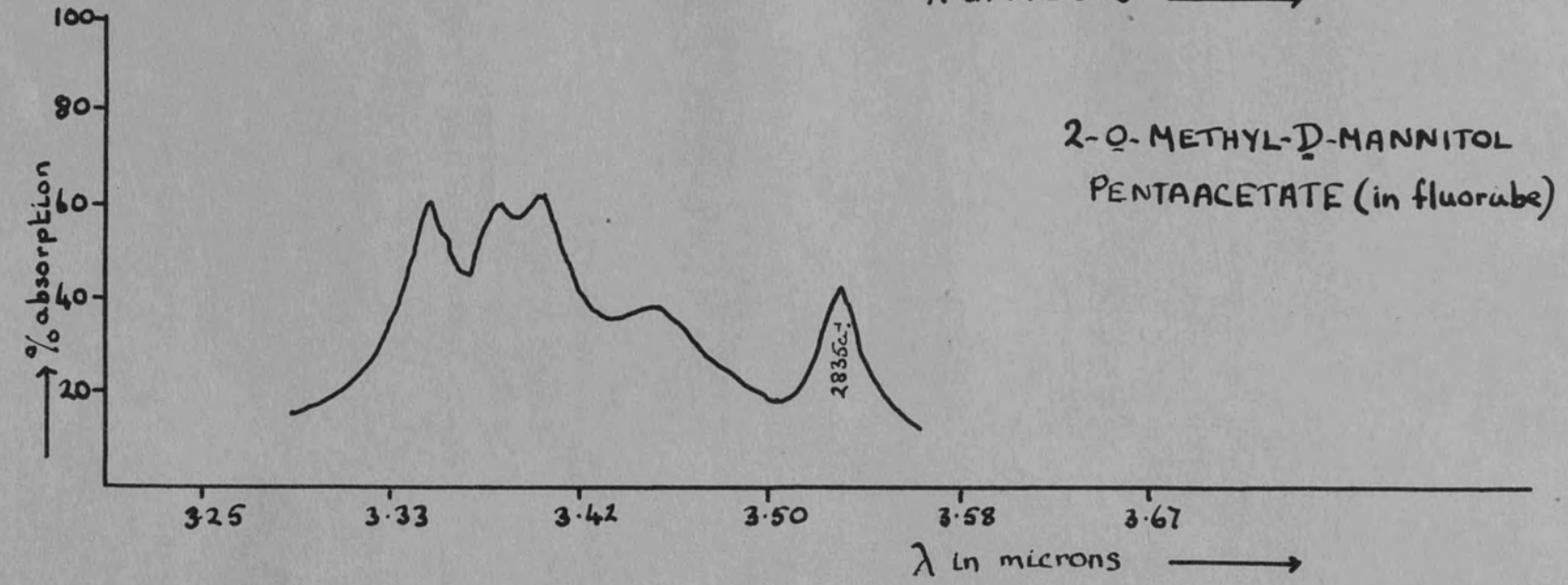

2-O-METHYL-D-MANNITOL
PENTAACETATE (in fluorube)
% absorption
100
80
60
40
20
2836 cm⁻¹
3·25
3·33
3·42
3·50
3·58
3·67
λ in microns

FIG IX

the methoxyl group. Previous work on anisole and methyl 2-napthyl ether had shown the peak at 2837 cm.$^{-I}$ (Fig.VIII) to be characteristic of the methoxyl group and it was assumed to be caused by the CH stretching vibrations. In the acetates, a peak was found at 2837 cm.$^{-I}$ and 2835 cm.$^{-I}$ respectively, confirming the presence of a methoxyl group.

The spectrum of the unacetylated compound (A) was also examined (Fig.VIII). This showed a broad band, 3425 cm.$^{-I}$ - 3257 cm.$^{-I}$ ~~3257 cm.$^{-I}$~~, characteristic of hydroxyl groups and a peak at 2843 cm.$^{-I}$ probably due to the CH vibration of the methoxyl group.

INVESTIGATION INTO THE STRUCTURE OF THE PRODUCT OF THE REACTION OF EXCESS BORON TRICHLORIDE WITH A CYCLIC METHYLENE ACETAL, USING INFRA-RED SPECTROSCOPY.

Experiment 4I.

The reaction was carried out under anhydrous conditions, to avoid the formation of any boric acid which would interfere with measurement of the spectrum of the product. I:3-2:5-4:6-Tri-O-methylene-D-mannitol (0·02g.) was weighed into a dry tube, fitted with a B10 socket. The tube was then drawn out to form a constriction near the mouth and was left in a desiccator overnight. It was fitted to a B10 cone, which formed the vertical arm of a T-joint. One horizontal arm of this led, through a tap, T_1, to a phosphorus pentoxide drying tube, and the second arm was bent, at a short distance from the T-joint, to lead vertically downwards, through a second tap, T_2, to a B10 cone carrying a tube. Tap T_2 was closed and the tube, containing the acetal, was cooled in a bath of acetone/carbon dioxide. Boron trichloride (I·99g., I80 mol.) was placed in the tube, under T_2, and this tap was then opened. The reagent distilled over into the cold tube, containing the acetal, and the cooling bath was removed.

Not all the acetal had dissolved at this low temperature, but as the tube warmed up, the solid dissolved in the boron trichloride and at room temperature the excess trichloride evaporated off. Both taps, T_1 and T_2, were closed and the tube which had contained the trichloride was replaced by one with a side arm, which was connected, through a trap at -70°, to the water pump. T_2 was opened and the apparatus evacuated at room temperature for 60 min. The tube, containing the product (0·06g.), was sealed off at the constriction. A sample of the complex formed between p-dioxan, and boron trichloride was also prepared[73]. The dioxan (7·2g.) purified by distilling from sodium, was dissolved in dichloromethane (10 ml.) and cooled to 70°. The boron trichloride (2·3 g., 0·25 mol.) was added, heat was given out, and a solid separated. After 15 min. the reaction was allowed to warm to room temperature and the solid dissolved. After 60 min., volatile matter was removed, first on the water pump and then at 2 mm. on the oil pump, at room temperature. The residue was a white crystalline solid (3·74g.). This was recrystallized from dichloromethane/petroleum ether (b.p. 60-80°), under anhydrous conditions. The complex decomposed at 80° under reduced pressure, to give a blue liquid but was stable for some weeks at room temperature and atmospheric pressure.

Dr. R.L. Williams [redacted] measured the infra-red spectra of these compounds, using a sodium chloride prism spectrometer. The dioxan-boron trichloride complex spectrum (measured in carbon disulphide) showed strong absorption at 789 $cm.^{-1}$ and at 761 $cm.^{-1}$ Neither of these bands is present in the dioxan spectrum and are thought to be due to the BCl stretching vibration (Fig.X). The trimethylene mannitol/boron trichloride product, in carbon disulphide, absorbed at 663 $cm.^{-1}$ This band was not found in the spectrum of the acetal itself, and was correlated with the BCl vibration (Fig.XI).

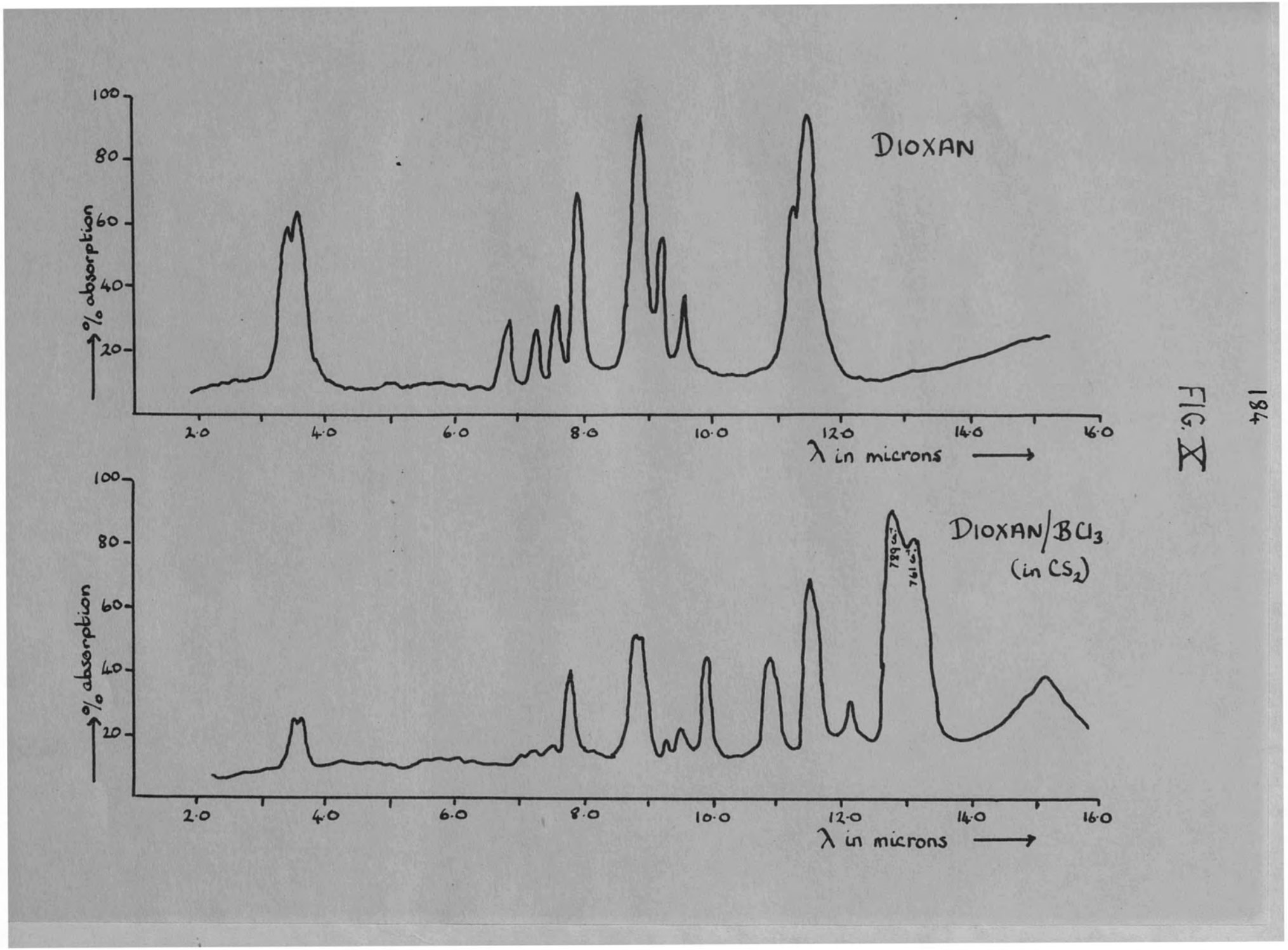

DIOXAN
% absorption
100
80
60
40
20
2·0
4·0
6·0
8·0
10·0
12·0
14·0
16·0
λ in microns
DIOXAN/BCl3
(in CS2)
789 cm⁻¹
761 cm⁻¹

FIG X

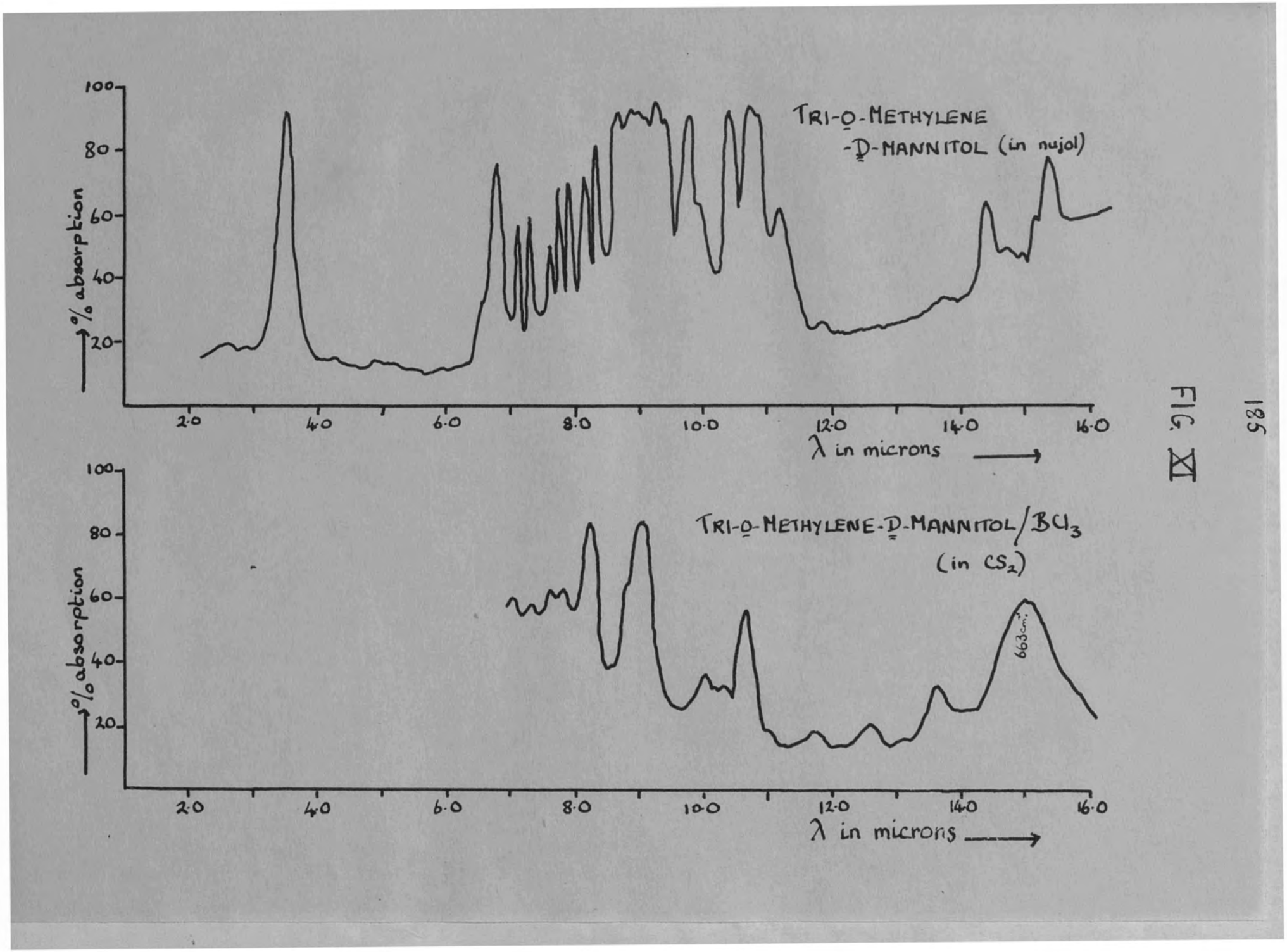

TRI-O-METHYLENE
-D-MANNITOL (in nujol)
% absorption
100
80
60
40
20
2·0
4·0
6·0
8·0
10·0
12·0
14·0
16·0
λ in microns
TRI-O-METHYLENE-D-MANNITOL/BCl3
(in CS2)
663cm-1

FIG. IX

REACTIONS OF A MIXTURE OF CARBOXYLIC ACID AND TRIFLUOROACETIC ANHYDRIDE WITH CYCLIC ACETALS AND KETALS OF POLYOLS

Experiment 42. Purification of reagents.

Preparation of trifluoroacetic anhydride[77].

Trifluoroacetic acid (II8.2 g.) was added to phosphorus pentoxide (I03.0 g.) contained in a flask cooled in ice water. The flask was then closed with a silica-gel drying tube. When the vigorous reaction had ceased, the flask was connected to a distillation apparatus and heated on an electric mantle. The fraction distilling at 38-42° (9I.0g.) was collected under anhydrous conditions. To avoid hydrolysis, the anhydride was stored in a stoppered flask in a desiccator.

Preparation of anhydrous acetic acid.

The freezing point of analar acetic acid was measured by supercooling the liquid acid to I4° and then causing solidification by touching the container with a lump of solid carbon dioxide. A thermometer, immersed in the acid, gave a constant reading of I5.7° during the solidification. As the presence of 0.I% of water in the acid causes a freezing point depression of 0.2°, this depression of 0.9° below the freezing point of the pure acid (I6.6°) corresponds to 0.45% of water. The acid was purified by a standard method[II3], to give a sample with freezing point I6.5°. Benzoic and adipic acids were dried in a phosphorus pentoxide vacuum desiccator.

The reactions were carried out under anhydrous conditions and in apparatus fitted with silica-gel drying tubes. The standard properties of the products, if not given, will be found in exp. 5.

Experiment 43. Reaction of trifluoroacetic anhydride/adipic acid with I:3-2:4-5:6-tri-O-methylene-D-glucitol.

The acetal (2.00g.) and the acid (I.34g., I.0 mol.) were

weighed into a flask and the anhydride (7·6 ml., 6·0 mol.) was added. The solids rapidly dissolved, with the evolution of heat, to give a viscous, discoloured solution. After 3 hr. at room temperature, the volatile products were evaporated off at 40° under reduced pressure on the water pump. Anhydrous carbon tetrachloride was added and then evaporated off, to remove any traces of volatile products. This was repeated twice to give a viscous, transparent residue, (6·46 g.). 10% aqueous sodium bicarbonate solution (75 ml.) was added to this and the mixture left at room temperature for 72 hr., to ensure complete hydrolysis of the trifluoroacetoxymethyl groups. The insoluble residue was filtered off and washed carefully with water. After drying in a vacuum desiccator, the product was a colourless, brittle solid (2.13g.), softening to a viscous liquid over the range 110-120°. A second specimen melted over the range 130-150°. (Found: C,47·6;H,6·7%;N-alkali uptake, 5·51 ml./g. $C_{13}H_{20}O_8$ requires C,51·3; H,6·6%; N-alkali uptake,6·57 ml./g.). The molten liquid could be drawn into threads, which became brittle on cooling. The solid became swollen and dissolved in pyridine, became swollen in chloroform and benzene without dissolving completely, and did not appear to swell in water.

i). Investigation of the products of alkaline hydrolysis.
The solid (0.49g.) was hydrolysed by refluxing with N/10 sodium hydroxide solution (30 ml.). It soon dissolved completely and, after 30 min., the solution was cooled and acid added to give a p_H of 8. The solution was concentrated to dryness and the solid residue extracted with boiling pyridine (A). The insoluble residue was dissolved in water and acid added to give a p_H of 4. The solution was again evaporated to dryness and the residue extracted with pyridine (B). The extract (A) was concentrated to give a brown solid which was shown by chromatography to contain 2:4-O-methylene-D-glucitol and a trace of glucitol. An ethanol extract of this yielded 2:4-O-methylene-D-glucitol(0·10g.,33%),

m.p. and mixed m.p. 161-162°, $[\alpha]_D^{18}$ -11·7 (c0·64 in H_2O). The extract (B) yielded a brown solid. This was dissolved in water and the solution made alkaline (p_H9) and evaporated to dryness, to remove the pyridine. A paper chromatogram, run in solvent (d), was sprayed with ninhydrin and a compound running level with adipic acid, was detected (R_f:0·51,0·74). An S-benzyl-isothiouronium salt (0·15g., 52%) was prepared in the usual way[114]. This had m.p. 160° and a mixture with the adipic acid derivative had the same m.p.

ii). Viscosity measurements on a solution of the product in pyridine.

Three solutions of different concentration, c(g./100 ml.), were prepared. Known weights of the solid were taken but, as the pyridine solutions were filtered to remove any insoluble residue, the concentrations were checked by titration against standard alkali.

The densities of the solutions were measured at 25.4°, using a Weld specific gravity bottle. The weight of solution filling the bottle was determined and the volume of the bottle calculated from the weight of water it contained at this temperature. The density of water was taken as 0·9969 g./ ml. at 25·4°[115].

The viscosities were measured using an Ostwald viscometer[78]. Before each measurement, this was filled with cleaning acid and then rinsed thoroughly with distilled water, followed by acetone. The apparatus was dried by drawing a current of dry air through it at room temperature. The viscometer was placed in a thermostat at 25·4° and the rates of flow of water, pyridine and the solutions were compared by measuring the time taken by the meniscus of the liquid to fall between two marks on the vertical capillary tube. The viscosities are related to these times by the expression:

$\eta = C\rho t$ where η is the viscosity, measured in poises.
ρ is the density, measured in g./ml.
t is the time, measured in sec.

C, the calibration constant of the instrument, is determined by measuring the rate of flow of a liquid of accurately known viscosity and density. Water was used in this experiment. Its viscosity at 25·4° was calculated from the expression:[116]

$$\log\left(\frac{\eta_T}{\eta_{20}}\right) = \frac{1{\cdot}2348(20-T) - 0{\cdot}001467(T-20)^2}{T + 96}$$

($\eta_{20} = 0{\cdot}1002$ poise)

$= 0{\cdot}\not{0}08824$ poise

The viscosities of the solutions are recorded as their specific viscosities (η_{sp}) and relative viscosities (η_r):

$$\eta_{sp} = \frac{\eta - \eta_0}{\eta_0} = \eta_r - 1$$

where η is viscosity of solution

where η_0 is viscosity of solvent.

The intrinsic viscosity of the polymer, $[\eta]$, is determined by plotting the graph of η_{sp}/c against c and measuring the intercept of the straight line with the η_{sp}/c axis. Alternatively, it can be found from the gradient of the graph of $\log \eta_r$ against c.

$$[\eta] = \lim_{c \to 0} (\eta_{sp}/c) = \lim_{c \to 0} (\ln \eta_r / c)$$

From the graphs (Fig.XII), an average value of 0·165 is obtained for the intrinsic viscosity.

iii). A more detailed examination of the physical properties of this polymer has been carried out by British Nylon Spinners Ltd., Pontypool, Mon.

The infra-red absorption spectrum was examined over the range 4000-650 $cm.^{-1}$, using a Perkin-Elmer spectrometer with a sodium chloride prism. The sample was heated to 100° between sodium chloride plates and these were pressed together, to give a film of suitable thickness. The spectrum shows strong absorption from alcoholic hydroxyls at 3450 $cm.^{-1}$ and 1075 $cm.^{-1}$, and from

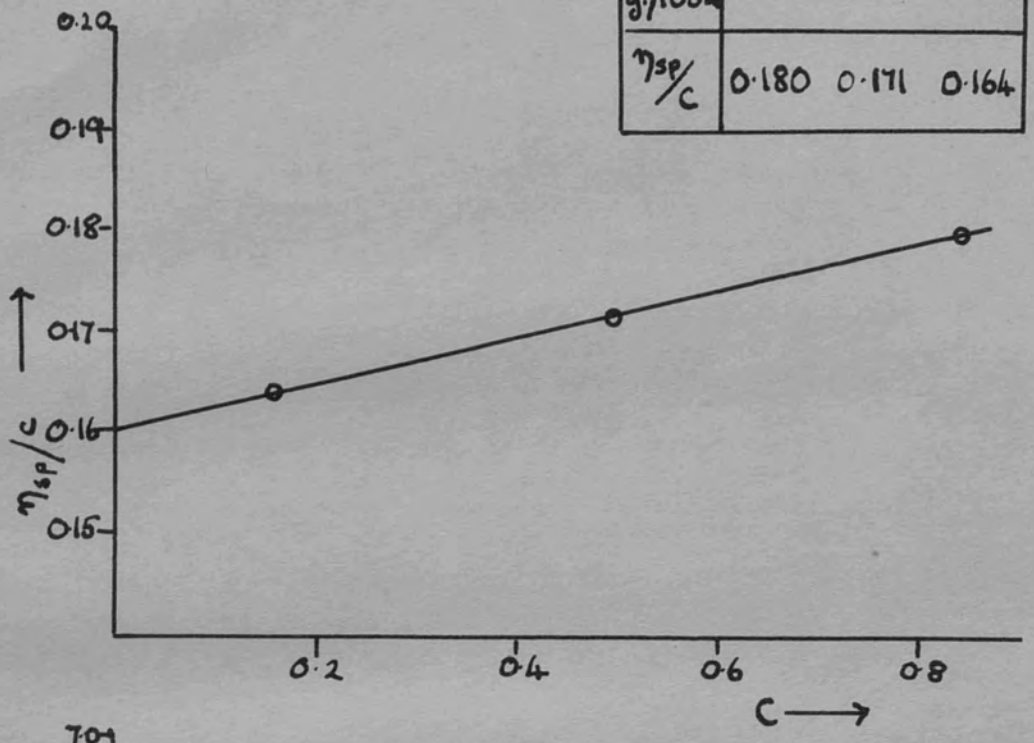
TABLE II

	c, concentration in g./100 mL.	t (sec)	ρ (g./mL.)	$\eta \times 10^2$ (poises)	η_{sp}	η_r
H_2O	-	225·4	(0·9969)	(8·824)	-	-
C_5H_5N	-	229·6	0·9782	8·818	-	-
A	0·8405	262·3	0·9812	10·15	0·1510	1·1510
B	0.4946	248·4	0·9806	9·564	0·08457	1·0846
C	0·1602	235·1	0·9801	9·050	0·02630	1·0263

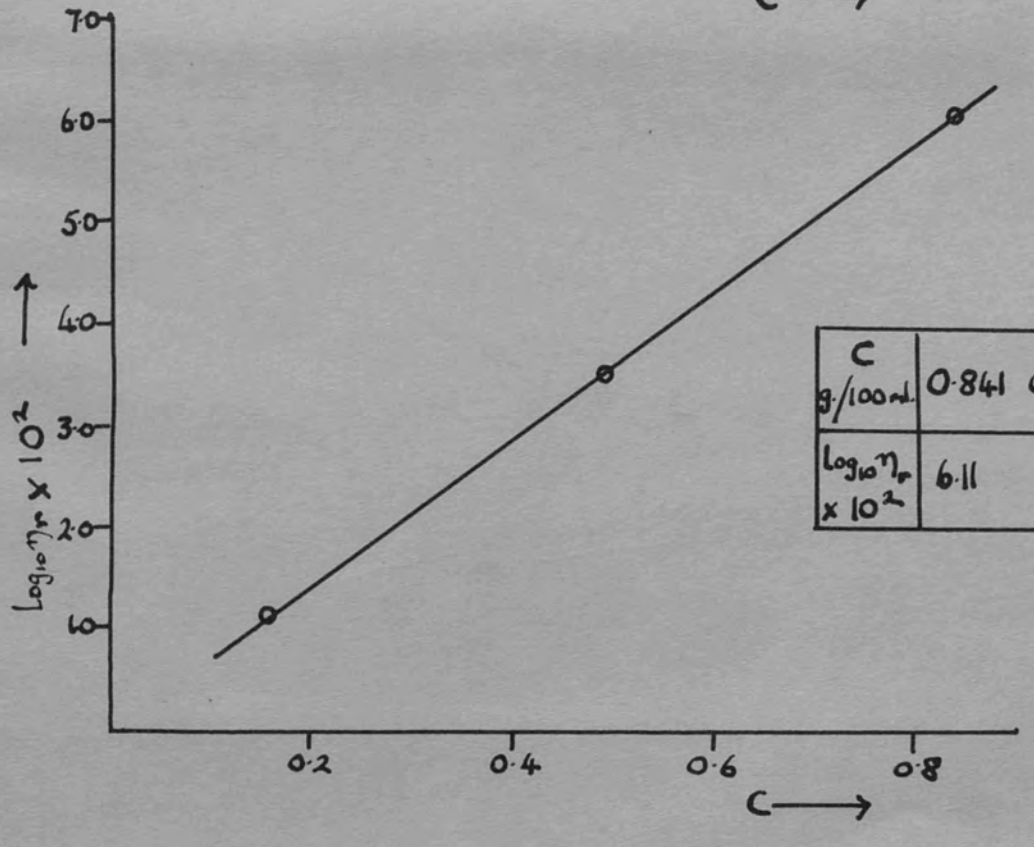
FIG XIV

FIG. XII

C g./100 ml.	0.841	0.495	0.160
η_{sp}/C	0.180	0.171	0.164



C g./100 ml.	0.841	0.495	0.160
$\log_{10}\eta_r \times 10^2$	6.11	3.54	1.12



aliphatic ester groups at I726 cm.$^{-I}$ and in the region I250 cm.$^{-I}$ and II80 cm.$^{-I}$. No absorption characteristic of fluorinated esters could be detected. The weak band at 2770 cm.$^{-I}$ and the band at I030 cm.$^{-I}$ indicate the presence of cyclic ether groups. The medium band at I565 cm.$^{-I}$ suggests the presence of carboxylate ion, which also is known to give rise to absorption at I375 cm.$^{-I}$. A second sample was boiled with N/I aqueous hydrochloric acid for one minute and then dried in an air oven at 90°. The spectrum was investigated and the band at I565 cm.$^{-I}$ found to have disappeared. No change in intensity could be detected in the I375 cm.$^{-I}$ region, but this may be because there is a high level of absorption in this region. The carbonyl stretch of the carboxyl group is present as a shoulder around I700 cm.$^{-I}$, on the side of the ester carbonyl band. A very weak broad absorption of acid hydroxyls is detectable in the region 2500-3500 cm.$^{-I}$ (Fig.XIII).

An X-ray diagram was obtained from a powered specimen of the polymer and a print is included (Fig.XIV) p.190.

The moisture regain of the polymer was measured and shown to be 6·4% compared to 4·5% for 6.6. nylon.

The softening point was determined by the penetrometer method and found to be 88°, compared to 265° for 6.6. nylon and 220° for 6 nylon. There was insufficient material for microspinning, but brittle fibres could be drawn from the melt.

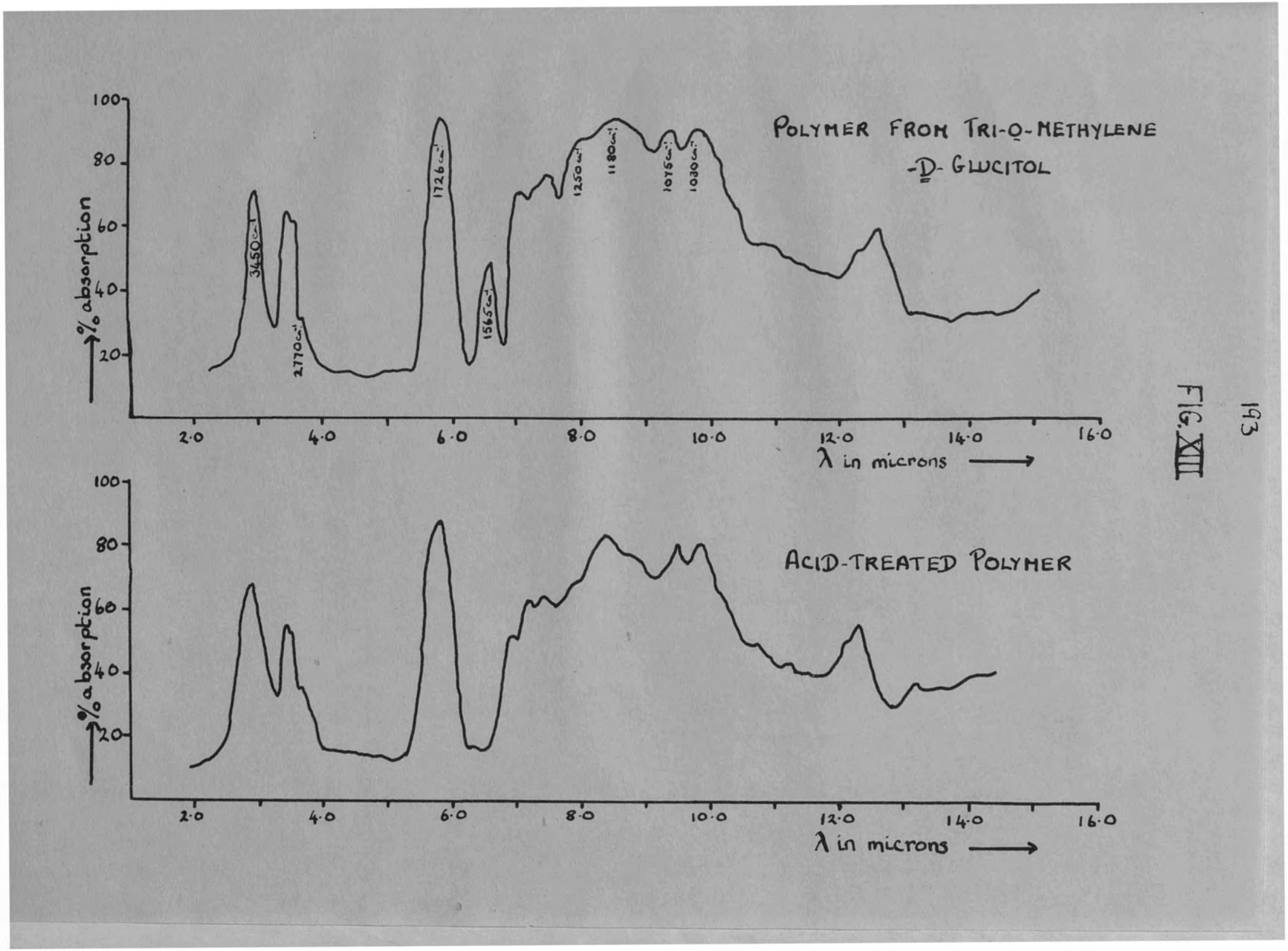

POLYMER FROM TRI-O-METHYLENE
-D- GLUCITOL
% absorption
100
80
60
40
20
3450 cm⁻¹
2770 cm⁻¹
1726 cm⁻¹
1565 cm⁻¹
1250 cm⁻¹
1180 cm⁻¹
1075 cm⁻¹
1030 cm⁻¹
2·0
4·0
6·0
8·0
10·0
12·0
14·0
16·0
λ in microns
ACID-TREATED POLYMER
% absorption
100
80
60
40
20
2·0
4·0
6·0
8·0
10·0
12·0
14·0
16·0
λ in microns

FIG. XIII

Experiment 44 Reaction of trifluoroacetic anhydride/adipic acid with di-O-methylene pentaerythritol.

The acetal (0·50g.) and the acid (0·46g., I·0 mol.) were treated with the anhydride (2·6 ml., 6·3 mol.) and the solids soon dissolved, giving a viscous solution. After 3 hr. at room temperature, the volatile products were evaporated off under reduced pressure. Anhydrous carbon tetrachloride was added and evaporated off three times to give a colourless, glassy residue. An aqueous solution of sodium bicarbonate, $p_H 8$, was added to this and, after four days, the insoluble residue was filtered off, washed with water and dried in a phosphorus pentoxide desiccator. The product was a rubbery solid (0·54g.), which showed no signs of melting but darkened at about 300°. (Found: C,52·9; H,7·5I%; N-alkali uptake, 7·09 ml./g. $C_{II}H_{I8}O_6$ requires C,53·6;H,7·5I%; N-alkali uptake, 8·I3 ml./g.). It became swollen in pyridine but did not appear to dissolve and pyridine which had been in contact with the product had the same viscosity as the pure solvent.

Investigation of the products of alkaline hydrolysis.

The solid (0·I3g.) was hydrolysed by boiling with N/I0 aqueous sodium hydroxide solution. The alkaline solution was concentrated to dryness and extracted with boiling pyridine (A). The insoluble residue was dissolved in water, acidified, concentrated to dryness and the residue extracted with absolute methanol (B). The extract (A) was investigated by paper chromatography and shown to contain pentaerythritol. The extract was concentrated and the residue (0·07 g.) was acetylated, yielding tetra-O-acetyl pentaerythritol (0·08g., 50%), m.p. 78-79° and mixed m.p.79-80°. Extract (B) was investigated by paper chromatography and shown to contain adipic acid. An S-benzyl-isothiouronium salt (0·06g., 68%) was prepared[114] and had melting point I6I-I62°; a mixture with the corresponding adipic acid derivative had the same melting point.

Experiment 45. Purification of pentaerythritol through its benzylidene derivative[117].

Technical pentaerythritol, m.p. 253-264°, (5·0g.) was dissolved in warm water (66 ml.). Hydrochloric acid (d, I·I80, II ml., 3·6 mol.) was added and then a solution of benzaldehyde (7·5 ml., 2·0 mol.) in ethanol (66 ml.) was added slowly to the shaken reaction mixture. A fine solid soon separated and the mixture was stirred for 5 hr. at room temperature and then left in the refrigerator overnight. The solid was filtered off and washed with a 50% aqueous solution of ethanol (400 ml.) and then with water (400 ml.). The dry solid (8·7g.) had m.p. I58·5-I60°. It was recrystallized twice from acetone to give colourless, plate-like crystals (I·76g., I5%), m.p. I63-I64°.

(Found: C,73·0; H,6·6% g. Calc. for $C_{I9}H_{20}O_4$: C,73·0; H,6·5%).

The acetal (I·5g.) was hydrolysed by refluxing for I hr. with hydrochloric acid (d I·I8, 0·2 ml.) in water (I5 ml.). The solid dissolved and an oily layer of benzaldehyde was formed. This was extracted with ether and the colourless crystals were recrystallized from water, and pentaerythritol (0·32g., 50%) was obtained and had m.p. 268-269°.

Samples of technical and purified pentaerythritol gave a colour with the fuchsin-sulphurous acid (Schiff's) reagent[80]. The samples were heated with nitric acid (d I·I3) for a short time and, after cooling, the reaction mixtures were neutralized with $CaCO_3$ and filtered. The filtrates were treated with equal volumes of Schiff's reagent.

Experiment 46. Reaction of trifluoroacetic anhydride/adipic acid with di-O-methylene pentaerythritol, prepared from purified pentaerythritol.

The reaction was carried out as in exp.44, but again gave a rubbery product which had no melting point but charred at about 300°.

Experiment 47. Reaction of trifluoracetic anhydride/benzoic acid with di-O-methylene pentaerythritol.

The acid (I·I7 g., 6·0 mol.) was weighed into a flask and the anhydride (I·4 ml., 6·3 mol.) was added. The acid soon dissolved at room temperature and the acetal (0·25 g.) was added. After 68 hr. at room temperature, the colourless solution was concentrated in the usual way to give an oil (I·65g.). This was dissolved in acetone and poured into an aqueous solution of sodium bicarbonate (p_H8). After a few days, the acetone was evaporated off under reduced pressure and the aqueous residue extracted with chloroform. This extract yielded an oil (0·66g.), which did not crystallize. A sample of the product (0·I2g.) was refluxed for 3 hr. with a I0% aqueous solution of sodium hydroxide but did not completely dissolve. The neutralized solution was extracted with chloroform to give an oil (0·03g.). The aqueous layer was evaporated to dryness and extracted with pyridine. The extract was investigated by paper chromatography and shown to contain pentaerythritol. Similarily, the pyridine-insoluble residue was shown to contain benzoic acid (R_f:0·80 in solvent (d)).

Experiment 48. Reaction of trifluoroacetic anhydride/acetic acid with di-O-methylene pentaerythritol.

The acid (0·22 ml.,6·0 mol.) and the anhydride (0·55 ml., 6·3 mol.) were mixed and the acetal (0·I0 g.) was added. It dissolved rapidly and the solution was left at room temperature for 3 hr. Volatile products were removed to give an oil (0·3I g.). This was treated with an aqueous solution of sodium bicarbonate (p_H9) and, after a few hours, this was extracted with chloroform. The extract yielded an oil (0·02 g.). This was investigated by paper chromatography, using the hydroxylamine spray:

i) Solvent (a)

R_f : 0·82

(tetra-O-acetyl pentaerythritol, R_f : 0·98)

ii) Solvent (g)

Base line spot.

R_f : 0·49

(tetra-O-acetyl pentaerthritol, R_f : 0·6I)

The aqueous layer was concentrated and the presence of pentaerythritol detected on a paper chromatogram.

Experiment 49. Preparation of di-O-acetyl pentaerythritol.

a). Mono-O-isopropylidene pentaerthritol[118].

Pentaerythritol (I0.0g.) was dissolved in warm water (53 ml.) and hydrochloric acid (d I·I8, 5·0 ml.) and AR acetone (202 ml., 38 mol.) were added. The solution was stirred at room temperature for I5 min. and then under reflux for 30 min. After 24 hr. at room temperature, the solution was treated with a 25% aqueous solution of sodium hydroxide, to give a p_H of 8. It was concentrated under reduced pressure, first at 50° and finally at 70°. (The product sublimes at higher temperatures). The residue was dried in a desiccator and then ground to a fine powder and placed in the cup of a Soxhlet apparatus. It was extracted for 6 hr. with petroleum ether (b.p. 40-60°) and then for I2 hr. with diethyl ether. The former extract yielded a small quantity of a discoloured, crystalline solid, m.p. I00-II0°, and the ether extract yielded the mono-ketal, a colourless, crystalline solid (3·60g., 27·8%), m.p. I26·5-I27·5°.

(Found: C,54·4; H,9·3%. Calc. for $C_8H_{I6}O_4$: C,54·5; H,9·2%).

Rapoport[118] gives m.p. I26-I27°. The products were investigated by paper chromatography in solvent (g):

	2:4-dinitrophenyl-hydrazine spray	Potassium dichromate spray.
Pet. ether extract -	Base line spot	Base line spot
	R_f : 0·I9	-
Ether extract -	Base line spot	Base line spot

b). Di-O-acetyl-mono-O-isopropylidene pentaerythritol[82].

The ketal (0.83 g.) was dissolved in warm chloroform (I6.6 ml.)

and sodium acetate (0·83 g., 2·I mol.) and acetic anhydride (3·75 ml., 8·6 mol.) were added. The mixture was refluxed for I hr. and then left at room temperature overnight. The undissolved sodium acetate was filtered off and the filtrate evaporated down to give a semi-crystalline oil, which was extracted with petroleum ether (b.p. 60-80°). Crystals of the diacetate (0·94g., 76·7%), m.p. 45-46°, separated from the concentrated extract. (Found: C,55·5; H,7·7%. Calc. for $C_{I2}H_{20}O_6$: C,55·4; H.7·7%). Orthner & Freyss[82] give m.p. 48-49°. A chromatogram run in solvent (g) showed a trace of product eluted at the same rate as the tetra-acetate and the main product running ahead of this, $R_{\text{tetra-acetate}}$:I·80.

c). Di-O-acetyl pentaerythritol[82].

The ketal ester (0·70 g.) was shaken with N/20 aqueous hydrochloric acid for I5 min. and the solid soon dissolved. After standing for I hr. at room temperature, the solution was neutralized with silver carbonate to give a p_H of 6·4. The insoluble solid was filtered off and the filtrate concentrated under reduced pressure and treated with hydrogen sulphide. The solution became black but silver sulphide was not precipitated at this p_H, so charcoal was added and the mixture shaken and then filtered to give a clear filtrate. This was concentrated on the water bath under reduced pressure and finally freeze dried. An ether extract of the residue yielded a colourless oil (0·5I g.) which later precipitated a solid. The product was investigated by paper chromatography:

(i) Solvent (a)

	Hydroxylamine Spray		Potassium dichromate spray
R_f :	-		0·47
R_f :	0·67		0·70
R_f :	0·8I)	linked in	0·80
R_f :	0·89)	streak	-
(tetra-O-acetyl pentaerythritol, R_f:0.94)			(pentaerythritol, R_f: 0.46)

(ii). Solvent (g)

	Hydroxylamine Spray	2:4-dinitrophenyl-hydrazine spray
Base line spot	—	—
R_f :	0·27	

(tetra-O-acetyl pentaerythritol, R_f, 0·27)

The products were separated from tetra-O-acetyl pentaerythritol by elution on Whatman No. 3 paper with solvent (g). After elution, the base line was cut out and eluted with chloroform, which was concentrated to give an oil. Chromatograms were run on this at various time intervals after the separation but no tetra-acetate was detected with the hydroxylamine spray.

(i). Solvent (a)

R_f : 0·68
: 0·8I
: 0·89

(tetra-O-acetyl pentaerythritol, R_f : 0·94)

(ii). Solvent (g)

Base line spot

Samples were then left in contact for several hours with aqueous solutions of different p_H and extracted with chloroform. The extracts were investigated by paper chromatography in solvent (g):

Aqueous solution	Chromatogram results
N/20 HCl	No tetra-acetate
I%$NaHCO_3$(p_H7-8)	"
IO%$NaHCO_3$ (p_H9)	Trace of tetra-acetate
$NaHCO_3/Na_2CO_3$(p_H IO)	Tetra-acetate detected

Experiment 50. Reaction of trifluoroacetic anhydride/acetic acid with di-O-methylene pentaerythritol.

The reaction was carried out as before except that hydrolysis was in an aqueous buffer (80 ml.) at p_H7·0. (This was prepared by mixing M/I5 aqueous solutions of Na_2HPO_4 (60 ml.) and of KH_2PO_4 (40 ml.)). The suspension of the product in the buffer was shaken for 2 hr. and left at room temperature overnight. It was then extracted with chloroform and this yielded an oil (0·04 g.) (A). The aqueous layer was freeze dried and the residue extracted with chloroform, to give an oil (0·09 g.) (B). The residue was finally extracted with pyridine (C). These extracts were investigated by paper chromatography, using the hydroxylamine spray:

(i). Solvent (a)

Extract:	A		B	C
R_f:	-		0·64 (faint)	0·64 (faint)
R_f:	0·79	linked	0·79	0·76
R_f:	0·87	linked	-	-

(tetra-O-acetyl pentaerythritol, R_f: 0·94)

(pentaerythritol, detected with dichromate spray, R_f: 0·45)

(ii). Solvent (g)

Extract:	A	B
	Base line spot	Base line spot
	$R_{tetra\text{-}acetate}$:I·0	-

Experiment 5I. Reaction of trifluoroacetic anhydride/acetic acid with di-O-benzylidene pentaerythritol.

The acid (0.37 ml., 20 mol.) and the anhydride (0·90 ml., 20 mol.) were mixed and the acetal (0·I0 g.) added. This soon dissolved to give an intensely orange solution. After 24 hr. at room

temperature, the volatile products were removed to give a dark oil (0·20g.). This was hydrolysed as in exp. 50 and a chloroform extract yielded a yellow oil (0·13g.). This was investigated by paper chromatography, using the hydroxylamine spray:

(i) Solvent (a)

$R_{tetra\text{-}acetate}$: 1·00

(ii) Solvent (g)

Base line spot

R_f : 0·52

: 0·68 } linked

: 0·84 }

(tetra-O-acetyl pentaerythritol, R_f: 0·51)

A sample of the product was refluxed with a dilute aqueous solution of hydrochloric acid. A chloroform extract gave an oil smelling of benzaldehyde, which gave an immediate orange precipitate with the 2:4-dinitrophenylhydrazine reagent (see exp. 24).

Experiment 52 Preparation of di-O-acetyl-mono-O-benzylidene pentaerythritol.

The acetal (0·10g.) was acetylated by the method used in the preparation of the acetate of mono-O-isopropylidene pentaerythritol (exp. 49(b)). The petroleum ether extract yielded a colourless oil (0·11 g.), which was examined by chromatography in solvent (g):

	Hydroxylamine spray	2:4-dinitrophenyl-hydrazine spray
R_f :	0·05	0·06
R_f :	0·66	0·66
	(tetra-O-acetyl pentaerythritol, R_f: 0·53)	(di-O-benzylidene pentaerythritol, R_f: 0.75)

The slow-moving product is probably the mono-ester, and the di-ester was separated from this by elution with solvent (g) on a cellulose column (diam. I·5 cm, length 2I cm). 5 Ml. fractions were collected and the product was detected in fractions 8-20. These fractions were concentrated and the discoloured residue was extracted with petroleum ether. This yielded an oil (0·I0 g.) which did not crystallize, although it appeared chromatographically pure. (Found: C,62·2; H,7·I%. $C_{I6}H_{20}O_6$ requires C,62·3; H,6·5%).

Experiment 53. Reaction of trifluoroacetic anhydride/excess acetic acid with di-O-benzylidene pentaerythritol.

The acid (I·90 ml., I00 mol.) was mixed with the anhydride (0·45 ml., I0 mol.) and the acetal (0·Ig.) added. This dissolved to give a colourless solution which, after standing at room temperature for 24 hr., had deepened to yellow. This was shaken with the aqueous buffer (exp. 50), p_H7·0, for 4 hr. and a chloroform extract yielded an oil (0.I4 g.). This was examined by chromatography in solvent (g).

	Hydroxylamine Spray	2:4-dinitrophenyl-hydrazine spray
	Base line spot	-
R_f :	0·5I	-
:	0·7I } linked in streak	0·70
:	0·82 }	-
	(tetra-O-acetyl pentaerythritol, R_f: 0·5I)	(di-O-acetyl-O-benzylidene pentaerythritol, R_f: 0·7I)

An attempt was made to separate the products on a cellulose column, eluted with solvent (g). A chromatogram run on the collected fractions showed that the faster-moving products had been eluted as a mixture, although they had been separated from the base line product and from the trace of product, R_f: 0·82.

Experiment 54. Reaction of trifluoroacetic anhydride/ excess acetic acid with mono-O-benzylidene pentaerythritol

The acid (1·90 ml., 100 mol.) and the anhydride (0·45 ml., 10 mol.) were mixed and the acetal (0·07g.) added. It dissolved to give a colourless solution after 20 hr. at room temperature and the reaction mixture was worked up as in exp. 53 to give an oil (0·11g.). This was examined by chromatography in solvent (g):

	Hydroxylamine Spray	2:4-dinitrophenyl-hydrazine spray
R_f :	0·05	0·05
R_f :	0·52	-
R_f :	0·62	0·62
R_f :	0·78 (faint)	0·76
	(tetra-O-acetyl pentaerythritol, R_f : 0·53)	(di-O-acetyl-O-benzylidene pentaerythritol, R_f: 0·62)

Experiment 55. Reaction of trifluoroacetic anhydride/acetic acid with mono-O-isopropylidene pentaerythritol.

The acid (0·37 ml., 20 mol.) and the anhydride (1·0 ml., 20 mol.) were mixed and the ketal (0·06g.) added. It rapidly dissolved to give a yellow solution which had deepened to dark red after 26 hr. at room temperature. This was worked up as in exp. 53 and yielded a dark oil (0·14g.), which partly crystallized. This was investigated by chromatography in solvent (g):

	Hydroxylamine Spray	2:4-dinitrophenyl-hydrazine, spray
	Base line spot	—
	R_f : 1·00 (tetra-acetate)	—

The oil was dissolved in ethanol and the solution boiled with decolourizing charcoal but, after three treatments, the

filtrate was still yellow. It was concentrated to dryness and extracted with petroleum ether. Crystals of tetra-O-acetyl pentaerythritol (0·0I4g., I3·5%), m.p. 78-79° and mixed m.p.79·5-80°, were deposited from the concentrated extract.

Experiment 56. Reaction of trifluoroacetic anhydride/ excess acetic acid with mono-O-isopropylidene pentaerythritol.

The acid (I·90 ml., I00 mol.) and the anhydride (0·50 ml., II mol.) were mixed and the ketal (0·06 g.) added. It dissolved to give a colourless solution, which had deepened to yellow after standing at room temperature for I7 hr. It was worked up as in exp. 53 to give a partly crystalline, colourless oil (0·I4g.). This was investigated by chromatography in solvent (g), using the hydroxylamine spray:

Base line spot

R_f : 0·49

: 0·78 (very faint)

(tetra-O-acetyl pentaerythritol, R_f: 0·49)

The oil was extracted with petroleum ether and the concentrated extract deposited fine crystals of tetra-O-acetyl pentaerythritol (0·026g., 25·I%), m.p. and mixed m.p. 75-77°. The mother liquors were concentrated and yielded an oil, containing crystals.

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REPRINTED FROM CHEMISTRY AND INDUSTRY, 1958, p. 630

BORON TRICHLORIDE AS A DEGRADATIVE REAGENT FOR CARBOHYDRATES AND THEIR DERIVATIVES

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In a study of the interaction of Lewis acids with cyclic acetals and ketals of hexitols it has been found that boron trichloride[1] is a valuable reagent for degrading these derivatives to the parent hexitols. In addition, it is effective in demethylation and deacylation of sugar derivatives and in degrading those polysaccharide derivatives which can be brought into solution with this reagent. Demethylation and deacylation usually do not proceed quite to completion in a single treatment but the main product from aldose derivatives is always the parent sugar and the method provides a simple and convenient means of identifying the latter, e.g. 2:3:4:6-tetra-*O*-methyl-glucose, 2:3:6-tri-*O*-methyl-glucose, methyl cellulose, cellulose acetate and amylopectin acetate each give glucose as the main product. Acetals and ketals always regenerate the original sugar or hexitol in high yield.

The possibility of stereochemical changes occurring in the sugar derivatives during reaction is under investigation but results to date indicate that glucose, mannose, galactose and arabinose are essentially unaffected. Fructose and sorbose, however, appear to be almost completely converted to a derivative, which has a much higher R_F value (solvent, butanol: ethanol: water=4:1:5) than either of these ketoses. The disaccharides, lactose, maltose, and sucrose are attacked to only a very slight extent by boron trichloride, probably due to their low solubility in the reagent but in these cases, boron tribromide[2] has been successfully employed to produce the constituent hexoses. From sucrose, only the glucose constituent has been identified, the fructose portion apparently undergoing further reaction, as referred to above.

The experimental procedure is based on that first reported by Gerrard.[1] Redistilled boron trichloride (0·3–0·5 g.) is introduced into a small tube which is sealed off and weighed; the tube is then cooled to −70° prior to opening. About 10 mgm. of the sugar derivative is added to 1–2 c.c. of dry dichloromethane and the contents of the sealed tube added. In some experiments, the dichloromethane was omitted and excess boron trichloride used. The mixture is kept at −70° for 30 minutes, allowed to attain room temperature and then to evaporate overnight under anhydrous conditions before working up. Any remaining solvent and boron trichloride are drawn off under vacuum and about 5 c.c. of aqueous methanol is added to decompose the residue. The methanol is removed under vacuum at room temperature and the solid product investigated by paper chromatography and ionophoresis. An alternative method of treating the residue after removal of the dichloromethane and excess boron trichloride is to shake with an aqueous suspension of silver carbonate.

Larger quantities have been treated in this way, giving products which can be isolated, purified and identified, e.g. mannitol can be obtained in 63% yield from 1:3–2:5–4:6-tri-*O*-methylene-D-mannitol by following the above procedure.

A detailed examination of selected reactions is now being made.

Received March 21, 1958

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