Studies into the Reactions of Some Simple Cyclic Acetals with Boron Trihalides/ Lithium Aluminium Hydride and Boron Hydrochlorides.

A Thesis submitted by

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in candidature for the degree of

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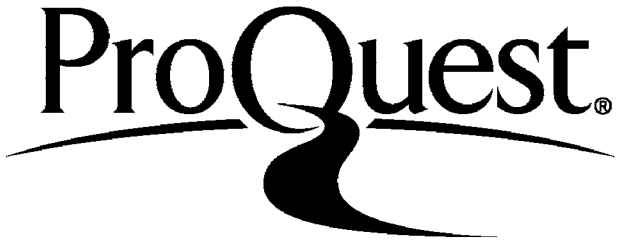

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KEITH RUTTER: Studies into the Reactions of Some Simple Cyclic Acetals with Boron Trihalides/Lithium Aluminium Hydride and Boron Hydrochlorides.

ABSTRACT

1. The use of 2-n-propyl-1,3-dioxane as a model substrate has enabled the following conclusions to be drawn with respect to the reaction between cyclic acetals and boron trichloride (or boron tribromide)/lithium aluminium hydride which gave hydroxyether products.

(a) The stoichiometry of the reaction is 3:1 with respect to the acetal/boron trihalide ratio.

(b) An α-haloether- containing complex is the substrate which is reduced by the lithium aluminium hydride to an ether function.

2. The use of a number of substituted dioxolanes, dioxanes, dioxepanes and dioxocanes has enabled the following conclusions to be drawn about the substituent effects upon the cleavage reaction.

(a) Substituents at C_2 effect the facility of cleavage, thus electron withdrawing groups at C_2 retard cleavage and vice versa.

(b) Substituents at C_4 (or C_5) effect the direction of ring cleavage, thus electron withdrawing groups at C_4 (or C_5) upon the dioxolane favour cleavage of the C_2 - O bond farther from the substituent.

(c) For a given C_2 substituent in a variety of ring sizes the facility of cleavage has been shown to be as follows dioxolane $\sim$ dioxane $<$ dioxepane $\sim$ dioxocane

3. The following reactions have been carried out using boron trichloride/lithium aluminium hydride as the active reagent.

(a) (±)-cis-4-Hydroxymethyl-2-propyl-1,3-dioxane → DL-1-O-butyl butan-1,3,4-triol + DL-3-O-butyl butan-1,3,4-triol.

(b) (±)-cis-4-n-Butoxymethyl-2-propyl-1,3-dioxolane → DL-3,4-di-O-butyl butan-1,3,4-triol + DL-1,4-di-O-butyl butan-1,3,4-triol.

(c) 1,3-O-Butylidene-DL-erythritol → 1-O-butyl-DL-erythritol + 2-O-butyl-DL-erythritol.

(d) 2,4-Di-O-butyl-1,3-O-butylidene-DL-erythritol → 1,2,3-tri-O-butyl-DL-erythritol.

(e) 1,3:2,4-Di-O-butylidene erythritol → 1,2-di-O-butyl-DL-erythritol.

(f) 1,3:4,6-Di-O-butylidene galactitol → 1,6-di-O-butyl galactitol + 1,4-di-O-butyl-DL-galactitol.

Rationales for each of these reactions are discussed.

4. The reactions of boron tribromide/lithium aluminium hydride with 1,3-benzodioxoles were considered, thus 1,3-benzodioxole itself was cleaved to 2-methoxy phenol while 2-phenyl-1,3-benzodioxole gave 2-benzyloxy phenol. The mechanism of the reaction is discussed.

5. The reaction of boron monohydrochloride ($BHCl_2$) with 1,3-dioxanes (which yield respective hydroxyethers) is considered and a possible mechanism discussed.

6. The E.I. mass spectra of some of the acetal cleavage products are discussed along with the C.I. mass spectra of the substrate acetals themselves.

CONTENTS

I GENERAL INTRODUCTION.

IA. Cyclic Acetals and Lewis acids.

The product obtained when 1 mole of an aldehyde is catalytically condensed with 1 mole of a diol is called a cyclic acetal. The most common catalysts in contemporary use are mineral acids, Lewis acids and acidic resins. The simplest cyclic acetals are those obtained from formaldehyde (generally as paraldehyde) and the appropriate diol, when the shown progenitive compounds are given, (Table IA-1.).

Diol	Cyclic acetal
Ethan- 1,2- diol	1,3- dioxolane
Propan- 1,3- diol	1,3- dioxane[1]
Butan- 1,4- diol	1,3- dioxepane[2]
Pentan- 1,5- diol	1,3- dioxocane[3]

Table IA-1.

By using other aldehydes and suitably substituted diols the respective parent compounds can be modified to give a large range of homologues.

The mechanism of the above acetalation reaction involves initial and reversible formation of a hemi-acetal, via nucleophilic attack of one of the diol's oxygens upon the protonated aldehyde. Loss of 1 mole of water then yields a resonant stabilised oxocarbonium species which is then further attacked by the other hydroxyl group to give a cyclic acetal[4] (fig. IA-1).

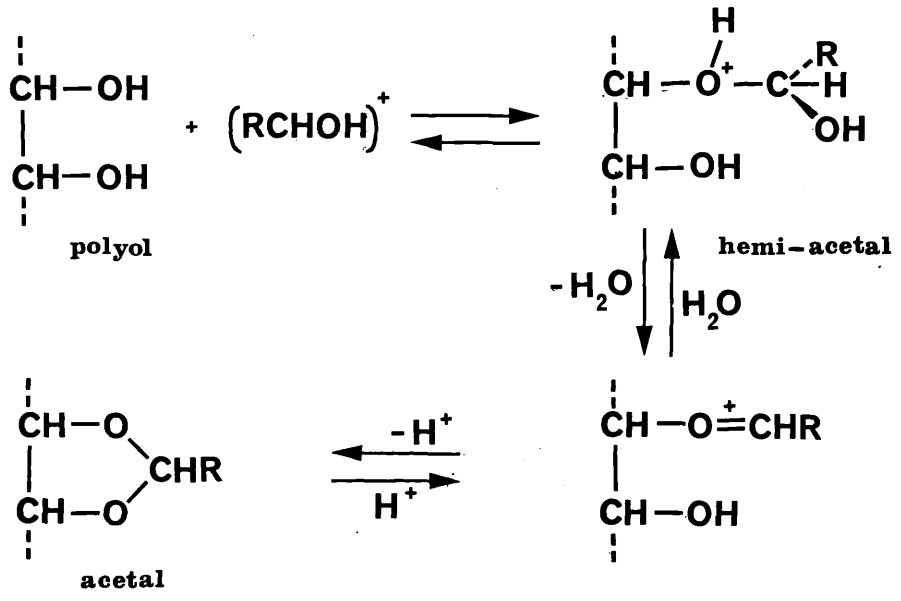


Fig. IA - 1.

When the acetalation reaction of a polyol is considered the situation becomes much more complex, as here the question arises as to which of the many possible structural isomers will be formed and also in what relative proportions they will be present at any one time as the reaction proceeds.

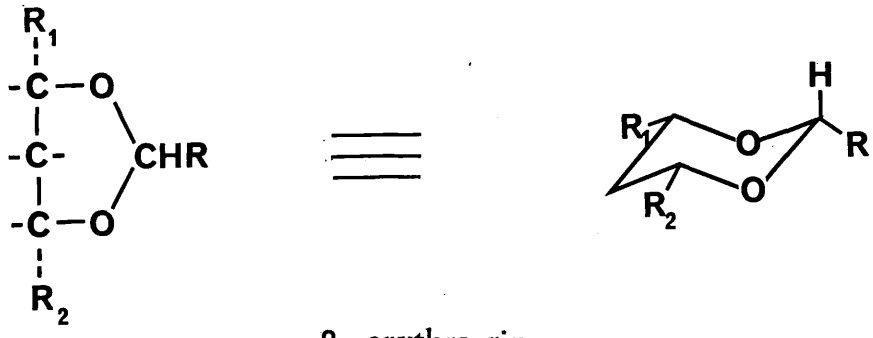
Extensive study into these problems culminated in results published by Hann and Hudson[5] which were extended and modified by the later work of Barker and Bourne.[6] This took the form of an empirically based set of rules, based upon the contemporary literature, which enabled them to make the following general predictions about the thermodynamic equilibrium products of any reaction between contiguous hydroxyl groups and an aldehyde.

(a) β -Erythro rings are the most stable as they allow large groups to be equatorially disposed at positions 2, 4 and 6.

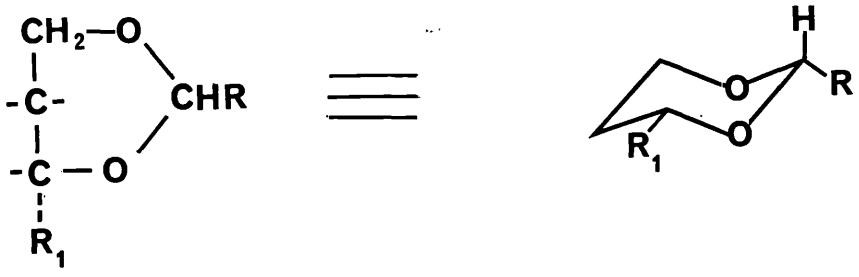
(b) The second preference is for β -rings in which one of the primary hydroxyl groups of the polyol is involved in acetal formation.

(c) Next are the α, α-threo, β-threo and γ-threo rings.

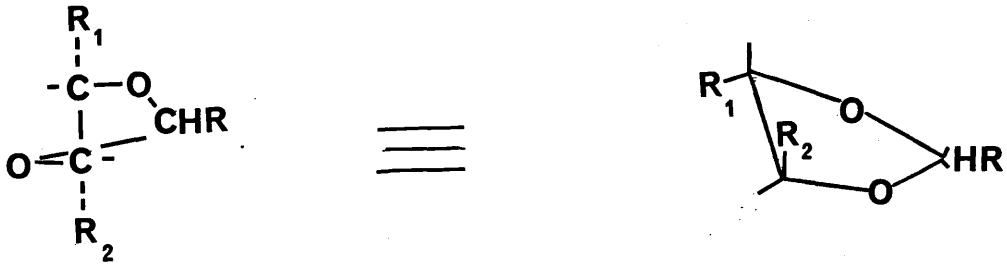
Where α, β and γ are 5, 6 and 7-membered rings respectively whilst threo and erythro refer to the relative stereochemistry of the bonding hydroxy groups: those on the same side of the carbon chain in the Fischer projection formulae are erythro whilst those on opposite sides are threo,[7] (fig. IA -2).



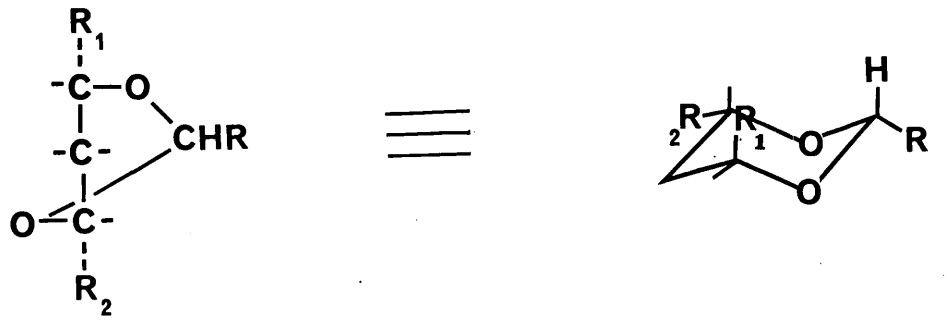
β-erythro ring



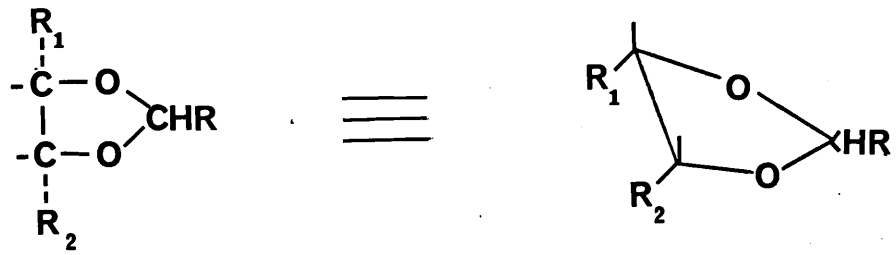
β-ring



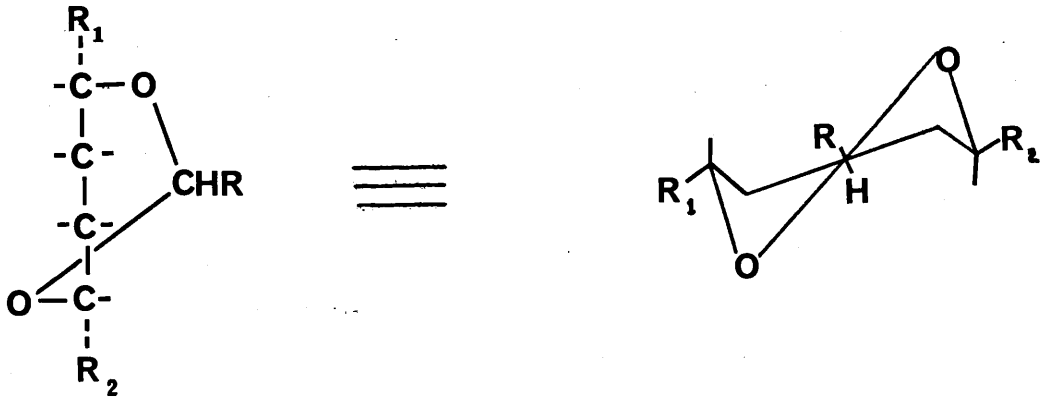
α-threo ring



β-threo ring



α- erythro ring



γ- threo ring

Fig. 1A - 2.

The increased stereochemical sensitivity of modern physical techniques and the independent and resulting growth in understanding of the stereochemistry of the acetalation reaction, have resulted in further modifications to the Barker and Bourne rules.[8] This is because previously they did not preferentially distinguish between the stabilities of the two possible dioxanes which could result from an axial or equatorial disposition of hydroxyl groups. Whereas now in the light of the "Gauche effect" it is possible to say that a given β-ring in a chair conformation, with an axial hydroxyl group, capable of intramolecular hydrogen bonding with the acetal ring oxygens, and which also has a gauche C-O bond dipole interaction with these oxygens, is more favoured than a β-ring with an equatorially disposed hydroxyl group which has a trans C-O dipole interaction and cannot from hydrogen bonds.

The "Gauche effect" mentioned above refers to a generalization made by Phillips[9] which states that the conformer of a compound in solution which is substituted with highly electronegative substituents and which has the maximum number of gauche interactions between adjacent electron pairs and/or bonds, will be the preferred conformer. If the substituents are hydroxyl groups they can of course be further stabilised by intramolecular hydrogen bonding.

If one now considers the products produced under kinetic control then the situation changes, as here the main criterion for product formation is a low activation energy which results in a rapid build-up of one or more thermodynamically unstable acetals. As the reaction progresses their concentrations slowly diminish to give a complementary increase in the concentration of the acetal with the lowest free energy. The mechanism of this very complex interchange is not really understood.

A group of cyclic acetals which do not have these complex stereochemical influences upon their formation are the 1,3-benzodioxoles. They cannot generally be prepared by the direct condensation of an aldehyde with an appropriate catechol derivative because of the formation and predominance of polymers in this reaction. Hence the main method of preparation involves treatment of the aromatic diol with a base followed by addition of a 1,1-dihaloalkane,[10] (fig. IA - 3).

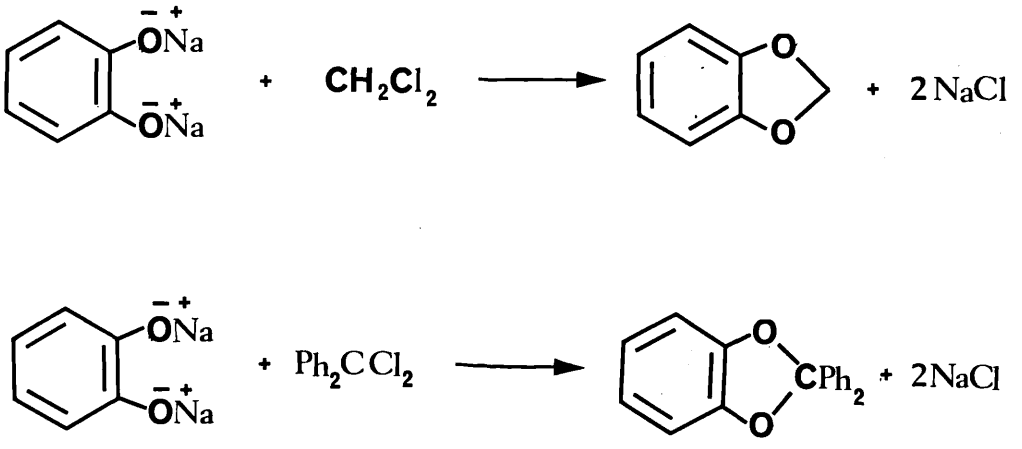


Fig. IA - 3.

The diphenylmethylene acetal shown was introduced by Robinson[11] as a superior alternative to the methylenedioxy function used in the protection of the hydroxyl groups of the catechol system during synthesis. Its main advantage is that it is easily removed by catalytic hydrolysis whereas the methylene acetal demands far more vigorous treatment, such as the use of hydrogen iodide or boron halides.[12]

The cyclic acetals are also widely used for the protection of 1,2 and 1,3 diol systems in steroid, glyceride and carbohydrate chemistry. They are easily introduced by a variety of methods and are generally stable towards most oxidising, reducing and basic conditions.[6]

The cyclic acetals also find wide industrial application in such as the pharmaceutical industry (as solvents for cosmetics), in the manufacture of pesticides[13] (especially the 2-substituted dioxanes and dioxepanes), drugs (such as the 2,2-dialkyl-4-hydroxymethyl-1,3-dioxolanes) and also in the production of many resins and polymers for use in paints and plastics.[14]

One of the main reasons for the wide usage of cyclic acetals as protecting groups in organic synthesis is the fact that they are easily removed under acidic conditions. The mechanism of the acid hydrolysis of cyclic acetals has been looked into by many workers and was generally thought to involve rapid and reversible protonation of one of the acetal's oxygen atoms followed by rate determining rupture of the C-O bond to give a resonant stabilised oxocarbonium transition state, i.e. specific acid catalysis by an A-1 mechanism.[15]

Recent work has shown however that while the A-1 mechanism may be relevant to the acid hydrolysis of acyclic acetals, the rate determining step for the cyclic acetals probably involves the bimolecular attack of water upon an oxocarbonium species,[16] (fig. IA-4).

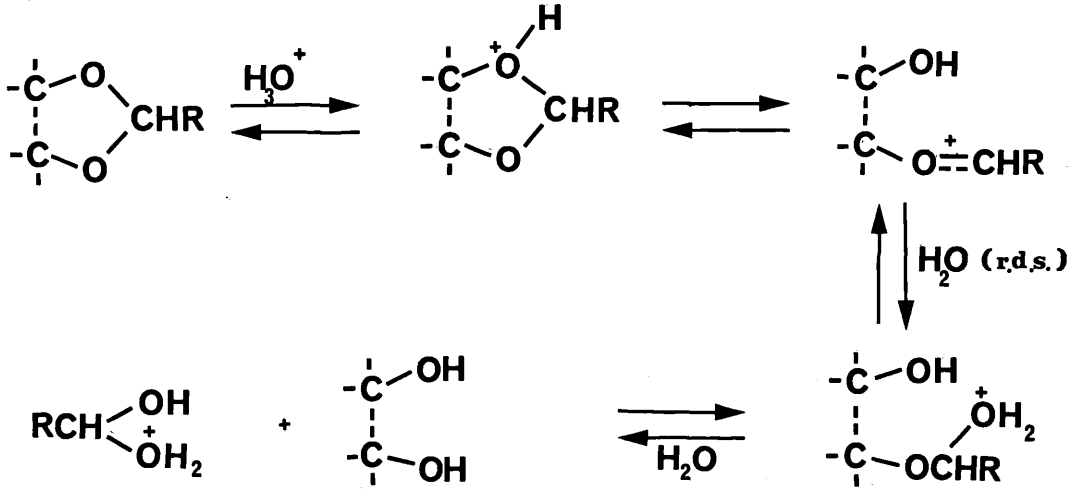


Fig. IA - 4.

Meanwhile, the direction of cleavage in the acid hydrolysis of substituted dioxanes has been theoretically shown to be influenced by the electronic nature of substituents at positions 4, 6 and to a lesser extent, position 5 on the ring. Thus an +I substituent at position 4 promotes protonation at O_3, thereby facilitating cleavage of the C_2 -O_1 bond.[17]

Acidic hydrolysis typifies one of the main reaction categories of the cyclic acetals: that of electrophilic attack upon one of the acetal ring oxygens which subsequently results in a substrate species susceptible to nucleophilic attack at one of the C - O bonds. Other examples of this are acetolysis[18] and Lewis acid cleavage.[19] The latter of which is of particular relevance to this thesis.

A Lewis acid can broadly be defined "as an electron pair acceptor" and hence includes the trihalides, trihydrides and trialkyls of the Group IIIb elements. Of particular interest to this thesis are the trihalides of aluminium and especially of boron.

In the molecule MX_3 (where M = boron or aluminium and X = hydrogen, halogen or alkyl), the root parameter for the incipient Lewis acidity is the incomplete octet of the central atom M. The relative facility with which a particular MX_3 coordinates with a given electron pair donor (or Lewis base) is dependent upon a complex interplay of many factors. which may broadly be grouped under the nature of M, the nature of X and to some extent the nature of the base.

It is generally found that the acceptor ability of the trihalides and trihydrides in Group IIIb decreases in the order B>Al >Ga>In,[20] although there are deviations from this sequence as shown by the greater acceptor power of trimethylaluminium over trimethyl boron.[21]

One solution to the electron deficiency problem - that of dimerisation or polymerisation via alkyl, halide or hydride bridges - is readily adopted by the heavier elements of Group IIIb but does not occur to any great extent in the chemistry of boron, although

the multicentre type bonds in diborane and the higher boranes are a unique alternative in which the electron deficiency is carried by the molecule as a whole.[22,23] The net result of this reluctance shown by the boron compounds to dimerise or polymerise is that they form a large number of coordination compounds with Lewis bases - such as amines, phosphines, sulphides and ethers - in which the boron achieves its maximum coordination and approximately sp^3 hybridization.[24]

The trihalides of boron illustrate well the complexity of Lewis acidity in that their relative acceptor strengths are the inverse of what one would expect on simple electronegativity grounds: the expected order is $BF_3 > BCl_3 > BBr_3 > BI_3$.[25]

An early attempt at rationalizing this experimental observation made the assumption that on coordination all of the halogen to boron π-bonding, present in the uncoordinated halide, is lost on formation of the adduct. Hence boron trifluoride is destabilised to a greater extent than the other halides, on coordination, because it contains the greatest amount of π-bonding.[26] Cotton[25] called this destabilisation "reorganization energy."

The above rationale is now considered to be an oversimplification, however, as it has been shown that π-bonding does remain in the Lewis salt[27] and that it probably competes with the " σ " lone pair of the donor (which subsequently forms the σ-bond) for the vacant p_z orbital of boron. Hence, as the order of remnant π-bonding is thought to be in the order F > Cl > Br > I then the trifluoride possesses the weakest boron to donor bond.[28]

Because of the large steric and electronic changes that occur in both substrates on formation of a Lewis complex the reaction is open to analysis by many physical techniques, such as nuclear magnetic resonance (n.m.r.) studies,[29,30] infra-red (I.R.) studies,[21] mass spectral studies[28] and gas phase calorimetry.[31]

It is also the bond modification undergone by the donor molecule (that the physical techniques monitor) that is responsible for the wide application that the boron trihalides find in many branches of synthetic and industrial chemistry, as the polarised Lewis complex is far more sensitive to nucleophilic attack than the uncoordinated species. The nucleophilic attack can be either intramolecular (by way of a halide ion leaving the boron) or intermolecularly by a variety of species.

The facility with which intramolecular attack occurs increases from the donor-boron trifluoride system to the donor-boron triiodide system, due to the increasing leaving group tendencies shown as one goes from the fluoride to the iodide, due in turn to the increasing polarisability and decreasing strength of the respective boron-halide bonds in the heavier halides.[32]

Thus, boron trifluoride either neat or in the form of one of its many coordination compounds, is an extremely useful initiator or catalyst[33] for a wide variety of reactions, especially Friedel-Crafts type reactions, including: alkylations, acylations[34], addition processes[35], anomerisations[36] and polymerisation reactions. For example the ethylation of benzene by ethyl fluoride proceeds as shown in figure IA - 5.[37]

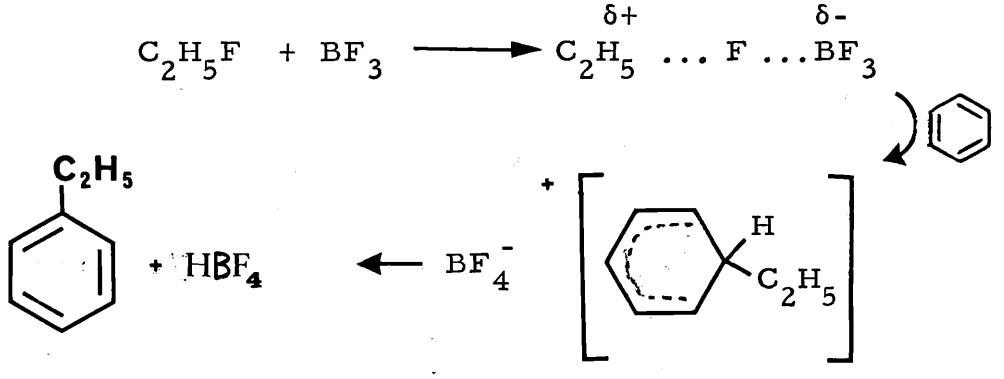


Fig. IA - 5.

Meanwhile, the other trihalides as well as acting as Friedel-Crafts "catalysts", also give numerous reactions which are directly preceded by the formation of the coordination complexes.[38] Of particular reference to this thesis are the reactions given by alcohols and especially ethers.

For instance in the former case dichloroboronites, chloroboronates and borates are produced when either 1, 2 or 3 moles of a primary or secondary alcohol reacts with one mole of the boron trichloride, the mechanism of the reaction probably involves a 4-centre transition state, (fig. IA - 6).

$$BCl_3 + ROH \longrightarrow ROBCl_2 + HCl$$
$$BCl_3 + 2ROH \longrightarrow (RO)_2BCl + 2HCl$$
$$BCl_3 + 3ROH \longrightarrow (RO)_3B + 3HCl$$

Mechanism

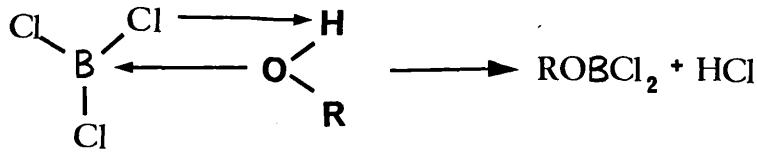


Fig. IA - 6

With tertiary alcohols, however, boron trichloride gives boric acid and the relevant alkyl or aryl chloride. The reaction goes via three main pathways, (fig. IA - 7).

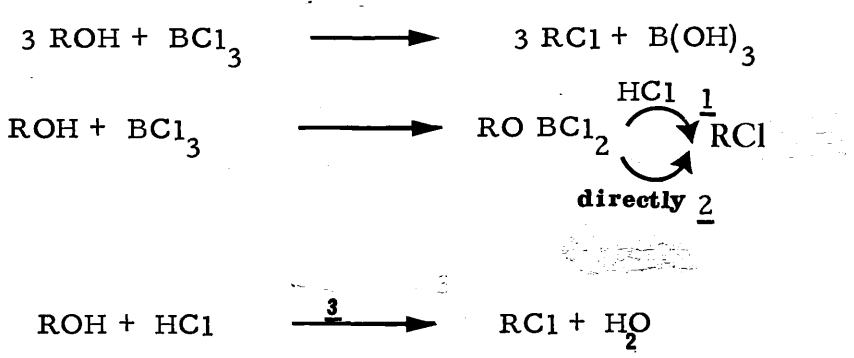


Fig. IA - 7.

The greater nucleophilic power of the heavier halide ions, increasing from chloride to iodide, is demonstrated in the fact that boron triiodide gives alkyl iodides even with primary alcohols. While boron tribromide gives both alkyl bromides and alkyl borates. with secondary alcohols, reaffirming its intermediary position.[39]

The relative inertness of the Lewis bonded boron trifluoride is again demonstrated when the base is an ether (alicyclic or cyclic), when the adducts formed (generally of 1:1 stoichiometry) are sometimes stable enough to be distilled unchanged or else they dissociate liberating boron trifluoride and the free ether on heating.[40]

When the higher molecular weight trihalides react with ethers, however, their propensity to further reaction results in the cleavage of one of the C - O bonds of the ether to give an alkyl halide.[38]

This tendency to alkyl halide formation increases as one goes from boron trichloride to boron triiodide as indeed was seen in the reaction of alcohols.

Thus the initially formed 1:1 complex between diethyl ether and boron trichloride only degrades on melting[41] while the analogous boron tribromide and boron triiodide systems go straight to the alkyl halide without giving an isolatable complex (fig. IA - 8).[42]

$$Et_2O \cdot BCl_3 \xrightarrow{heat} Et\ O\ BCl_2 + EtCl$$

$$3\ R_2O + BX_3 \longrightarrow (RO)_3B + 3\ RX$$

$$(RO)_3B + 3H_2O \longrightarrow 3\ ROH + H_3BO_3$$

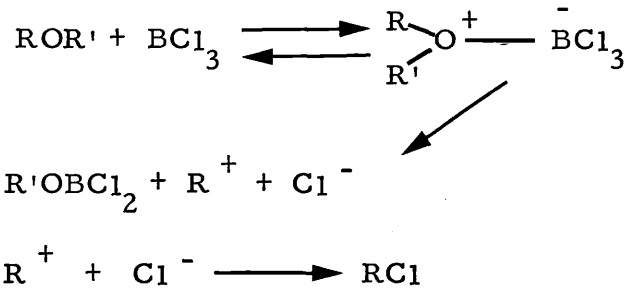
(where X = Br or I)

Fig. IA - 8.

As shown treatment of the borate with water gives the relevant alcohol.

Asymmetric alicyclic ethers can in theory give one of two alkyl halides but it is generally found that the C-O bond that is broken is the one that is attached to the more electronegative carbon.[43] Also the ease with which fission occurs is greater than for the symmetric ethers, such that heating is not required even with boron trichloride.

The mechanism of the reaction probably involves an Sn_1 type generation of a carbonium ion which is then quenched by a halide ion from the boron trihalide, (fig. IA - 9).



(where R is the better +I group)

Fig. IA - 9.

This ability of boron trichloride and boron tribromide to cleave mixed ethers has been widely applied in synthetic chemistry and has resulted in a complementary increase in the use of ethers as protecting groups for alcohols and phenols.[44,45,46]

Cyclic ethers containing one oxygen undergo ready ring cleavage with the trichloride and tribromide. Ethylene oxide and oxetane are cleaved even at -80°, when the molar ratio is 1:1, while with excess ether polymers are the main products, (fig. IA-10).[47,48]

a) 1:1 Molar ratio.

Ethylene oxide

b) With excess ether.

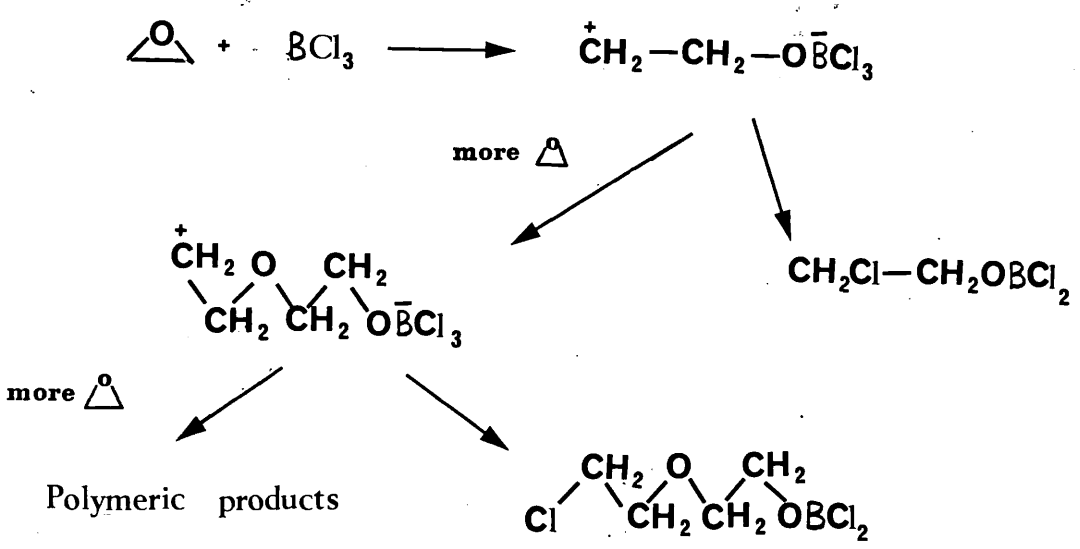


Fig. IA - 10.

Tetrahydrofuran and tetrahydropyran however are a little less reactive in that their 1:1 complexes can be isolated at low temperatures. Although they do decompose on warming, undergoing cleavage and dimerisation reactions in a similar fashion to the three and four membered rings.

In the above reactions dimerisation and polymerisation of the cyclic ethers are the results of nucleophilic attack by an unbonded ether oxygen upon the shown carbonium ion (fig. IA - 10b) and the polymerisation is terminated by the competing nucleophilic attack of the halide ion. In cyclic acetals however the second (unbonded) oxygen can act as an "internal nucleophile" and so assist in the monomolecular cleavage of the cyclic acetal-boron trihalide complex as well as stabilizing the resulting carbonium ion. The overall result of this is that cyclic acetals undergo

cleavage reactions with a much greater facility than the cyclic ethers.

This point is well demonstrated by the polymerisation of 1, 3-dioxolane with boron trifluoride which is thought to involve either a monomolecular or a bimolecular opening of the 1, 3-dioxolane-boron trifluoride complex, (fig. IA - 11).[50]

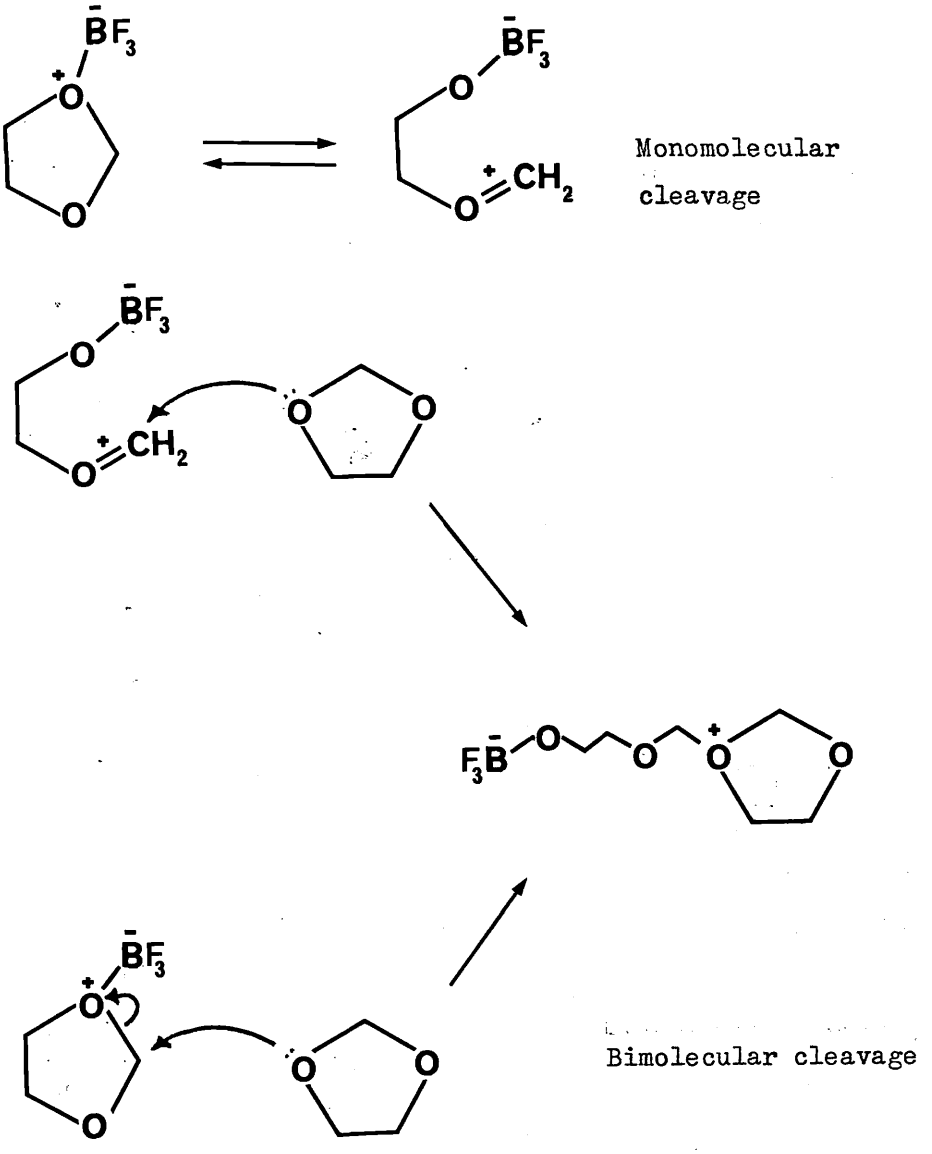


Fig. IA - 11.

If however, the halide ion in the 1, 3-dioxolane-boron trihalide complex had been an active nucleophile, then it would tend to quench the polymerisation of the acetal as was the case in the cyclic ethers. This infact is the case with boron trichloride and boron tribromide, when rate determining, unimolecular ring cleavage occurs to give a resonant stabilised oxocarbonium ion, (fig. IA - 12). The next step is thought to be attack of the halide ion upon the oxocarbonium species to give an α-haloether.

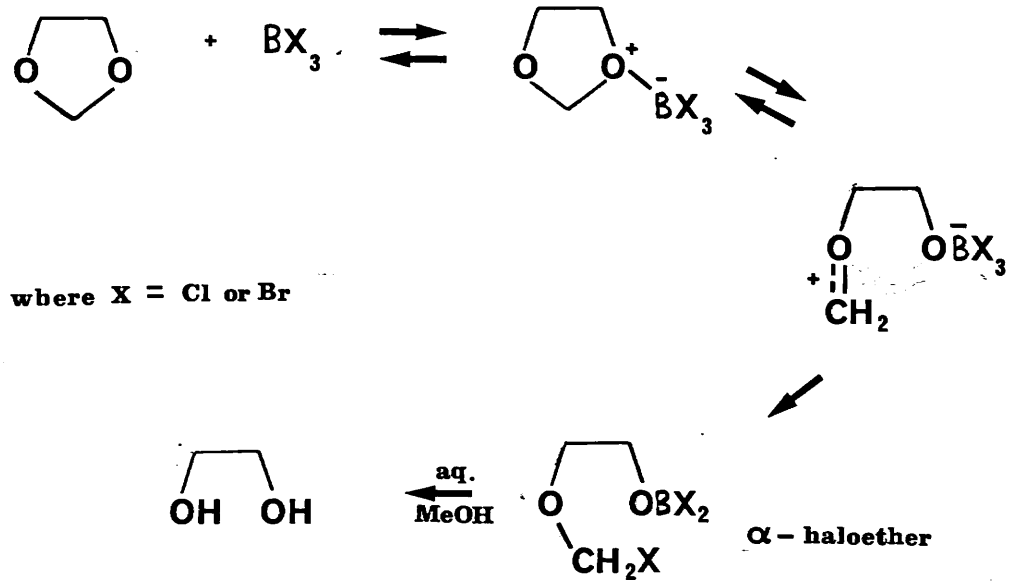


Fig. IA - 12.

The above rationale formed the basis for the procedure used by Bonner and Saville to remove protecting acetal or ketal groups from a large number of polyol systems, i. e. treatment of the acetal with boron trichloride followed by methanolysis yields the parent polyol.[51]

They also pointed out that by a suitable choice of other nucleophilic species, notably methoxide, acetate and hydride ions, then the α-haloether can be modified in a variety of ways, (fig. IA-13)[52]

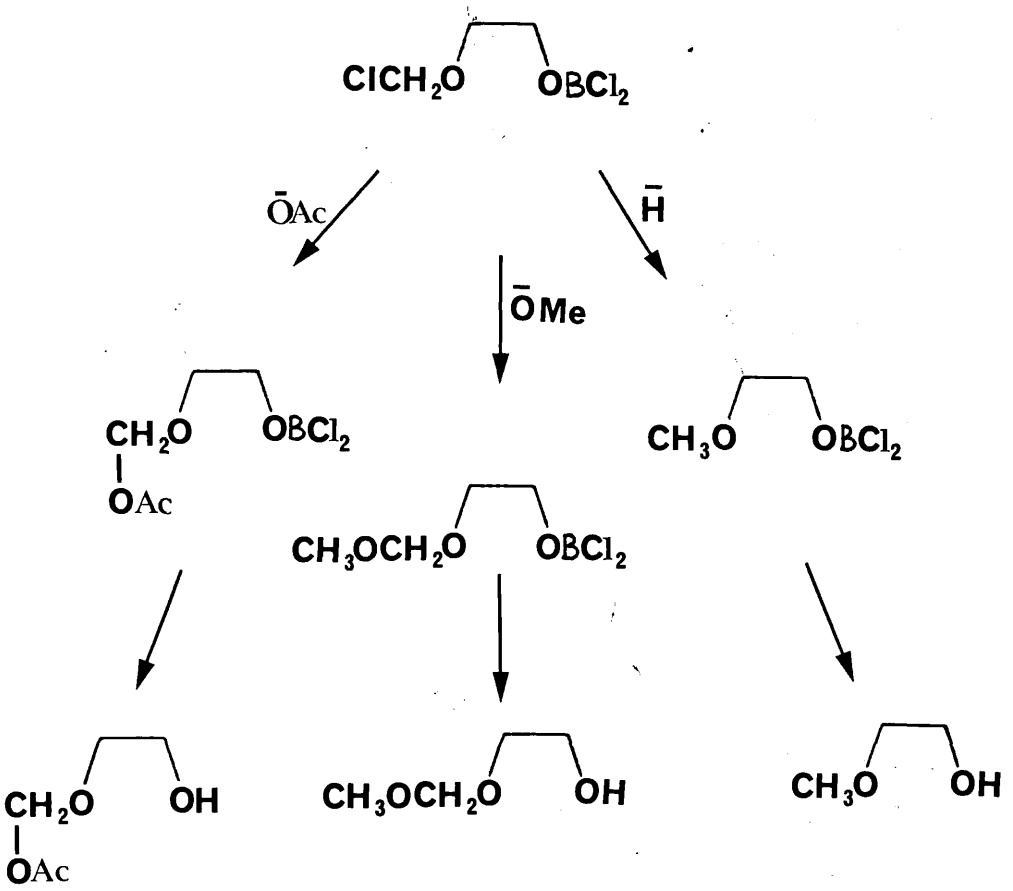


Fig. IA - 13.

It is the last of these reactions that has been examined in greater detail in this thesis.

IB. Hydrogenolysis of cyclic acetals.

A number of reagents will effect cleavage of cyclic acetals in a variety of different ways. Some of these ways are given in Table IB - 1.

Reagent	Mode of fission
N. N. Dibromo benzenesulphonamide[53] or ozone[54]	- oxidative fission
n-Butyl lithium[55, 56]	- cyclo elimination to olefins
Photochemical hydride abstraction, (acetone initiated)[57]	- to give esters
Diisobutyl aluminium,[91] decaborane[92] or "mixed hydrides" (e.g. $LiAlH_4$ + BF_3, $LiAlH_4$ + $AlCl_3$)[67, 68, 73, 74] or borane-tetrahydrofuran[80, 83]	- reductive fission

Table IB - 1.

Of the two "mixed hydride" reagents the lithium aluminium hydride/aluminium trichloride combination has received more attention in the past few years and consequently it is the better understood of the two systems.

Thus the stoichiometry of the $LiAlH_4/AlCl_3$ reaction in ethereal solution is as shown in Figure IB - 1.

$$3\ LiAlH_4 + AlCl_3 \longrightarrow 3LiCl + 4\ AlH_3$$ [58, 59]

$$LiAlH_4 + AlCl_3 \longrightarrow LiCl + 2AlH_2Cl$$ [59]

$$LiAlH_4 + 3AlCl_3 \longrightarrow LiCl + 4AlHCl_2$$ [59]

Fig. IB - 1.

The lithium chloride produced above is only precipitated in the first reaction, presumably due to formation of a soluble complex between it and the aluminium chlorohydride species in the second and third reactions.[59]

The nature of the aluminium chlorohydrides has been

conclusively demonstrated by Ashby and Prather[59] in their infra-red studies into ethereal solutions of the reaction mixtures and also by isolation and characterisation of the triethylamine adducts of AlH_3, AlH_2Cl, and $AlHCl_2$.

They suggested that the reaction proceeds via a reversible and sequential hydride displacement of chloride from the aluminium trichloride[60] (Fig. IB - 2).

$$AlCl_3 \longrightarrow AlCl_2H \rightleftharpoons AlH_2Cl \rightleftharpoons AlH_3$$

Fig. IB - 2

The Lewis acidity in the above sequence decreases as one goes from aluminium trichloride to the trihydride whereas the reducing ability - or relative hydride donor ability - increases in the same direction. This sliding-scale relationship of their properties is sufficient to produce differences in overall reaction type for a particular substrate. For example with triphenyl ethylene oxide two reaction pathways are possible depending upon whether $AlHCl_2$ or AlH_3 is used,[62] (fig. IB - 3).

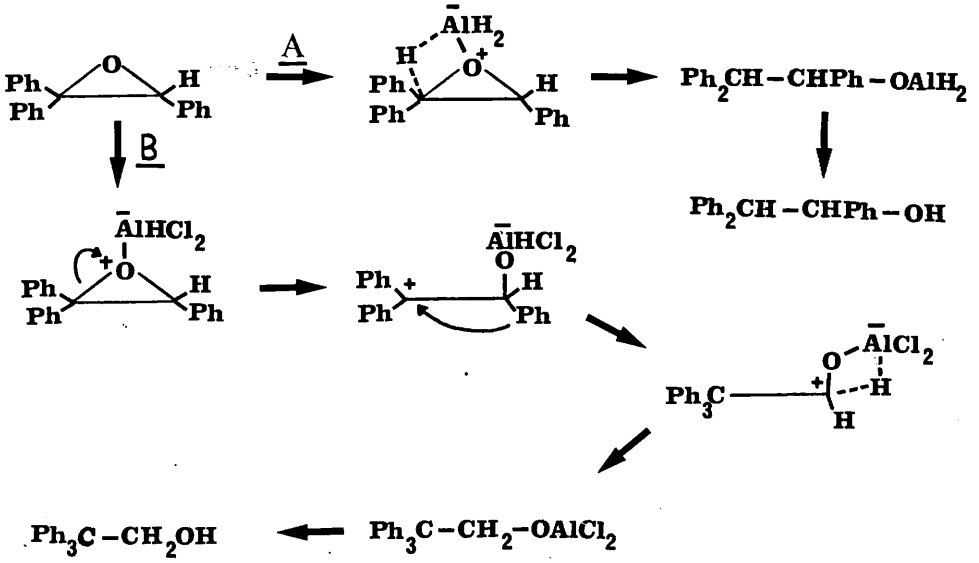


Fig. IB - 3.

In pathway B the stronger Lewis acidity of $AlHCl_2$ promotes the C-O bond cleavage and formation of the carbonium ion - as testified by the phenyl migration - while the greater hydride donor ability of AlH_3 favours pathway A.

The 4-centre-type hydride donation[63] that occurs above is also thought to persist in the hydrogenolysis of 1,3-dioxolanes and 1,3-dioxanes by the aluminium chlorohydrides. This implies that the same molecule that is bonding to the acetal oxygen is also supplying the hydride ion, a thesis which is supported by Ahmad and Logani[64] in their work on the hydrogenolysis of steroidal cyclic acetals with aluminium dihydromonochloride. Davis and Brown[65] have also shown that aluminium monochlorodihydride has only one replaceable hydrogen in its hydrogenolysis of 1,3-dioxolanes: they cite the formation of the shown complex as the main reason for the chlorohydrides' inability to Lewis bond intermolecularly with a second molecule of dioxolane and hence its second hydrogen is redundant, (fig. IB - 4).

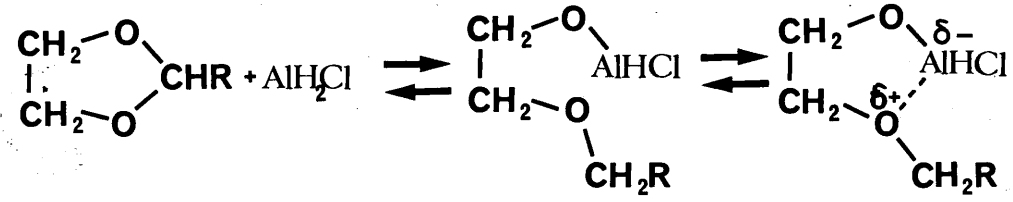


Fig. IB - 4.

Supporting this rationale is the fact that in cases where further Lewis bonding is unfavourable such as in the analogous 1,3-oxothiolanes, a second molecule can be hydrogenolysed. This is because the oxygen of a second molecule of dioxolane or oxothiolane competes more successfully for the aluminium species than the sulphur.[66]

The generally accepted mechanistic interpretation for the reaction between a cyclic acetal and the aluminium chlorohydrides arose mainly from work carried out using simple 1, 3-dioxolanes and 1, 3-dioxanes as "model" substrates. Consequently the early work lays greater emphasis upon the electrochemical aspects of the mechanism than the stereochemistry.

Hence Leggetter and Brown[1] concluded from their experiments that substituents at position 2 upon the 1, 3-dioxolanes are largely responsible for the rate of cleavage - and to a lesser extent those at positions 4 or 5 - while the particular C-O bond that breaks is dictated by the electronic nature of the substituents at positions 4 or 5, (fig. IB - 5).

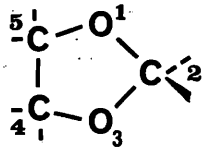


Fig. IB - 5.

More specifically they found that +I substituents at C_2 accelerate and -I groups retard hydrogenolysis. While +I substituents at C_4 or C_5 facilitate cleavage of the C_2-O bond further from the substituent while -I groups promote cleavage at the nearer C_2-O bond. They also found that 1, 3-dioxolanes cleave faster than the corresponding 1, 3-dioxanes.

The situation becomes more complex with an increase in the number of substituents, as steric factors become increasingly more relevant to the reaction pathway. For instance in 2, 2, 4, 4-tetra-alkyl-1, 3-dioxolane[67] non-bonded interactions between substituents in the transition state dominate the competing electronic stabilising properties of the substituents to such a degree that cleavage occurs almost totally at C_2-O_3, (fig. IB - 6).

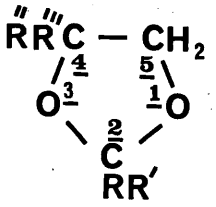


Fig. IB - 6.

It was the experimental observation of the above electronic and steric substituent effects which indicated that an oxocarbonium-type species is involved in the transition state to ring cleavage. Thus Brown[68] envisaged rapid and reversible association of the Lewis acid with the acetal or ketal, followed by slow rate-determining cleavage of the ring giving an oxocarbonium ion which is then rapidly and irreversibly reduced, by 4-centre intramolecular hydride transfer.

The stereochemistry of the transition state demands that for cleavage to occur, say at C_2-O_3, then maximum mutual planarity is favoured for the O_1 equatorial lone-pair, the C_2-O bond and the C_2-O_3 bond: this is because in this conformation maximum assistance to bond cleavage can be given by O_1. Watts[69] expresses the above arrangement as that conformation in which the plane containing C_5-O_1-C_2 is essentially perpendicular to the plane containing C_4-O_3-C_2.

Once cleavage -C_2-O_3- has begun the C_2-O_1 bond begins to rotate in such a manner that the less bulky C_2 substituent moves towards the acetal ring and to such a degree that the nascent C_2 p-orbital can achieve maximum overlap with the O_1 p-orbital hence yielding the oxocarbonium species.[70,71]

The 2, 4-dialkyl-1, 3-dioxolanes present an interesting situation in that they appear to be near the balance point between the opposing steric and electronic directive effects.[72] For instance cis-2, 4-dimethyl-1, 3-dioxolane gives predominantly the electronically directed product (A) while the respective trans isomer gives an approximately 2:1 product mixture favouring the sterically directed cleavage product (B), (fig. IB - 7).

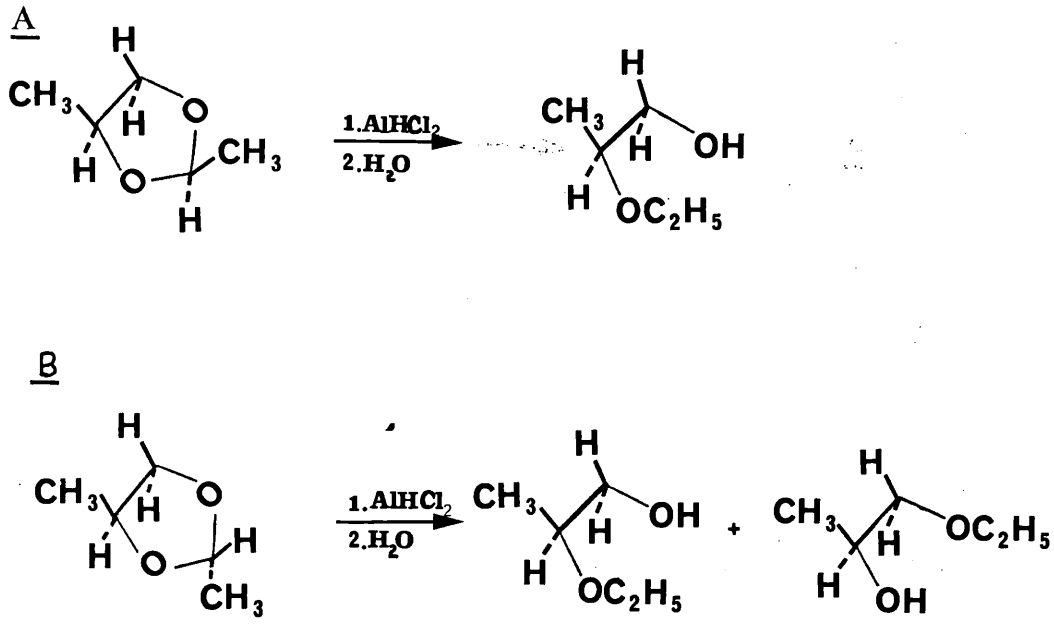


Fig. IB - 7.

A possible explanation for this may be found in Brown's[65] rationalization for the observation that AlH_2Cl only has one replaceable hydrogen in cyclic acetal hydrogenolysis. He envisaged a complex of the type shown, in which the aluminium bonds with both oxygens of the cleaved acetal, (fig. IB - 8).

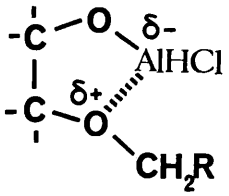


Fig. IB - 8.

If one presumes that the aforementioned conformation of the transition state is present and also that transfer of the hydride is via a 4-centre mechanism, then as this transference is progressing, the aluminium is regaining its Lewis acidity and hence is increasingly able to bond with O_1 (fig. IB - 9).

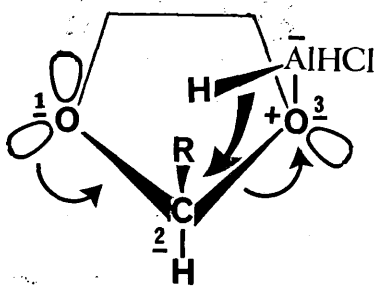
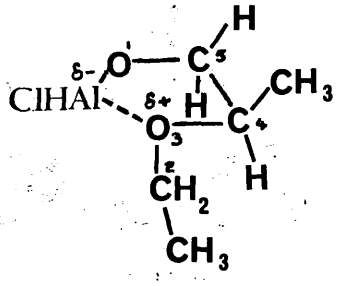


Fig. IB - 9.

Models show that in the cis isomer cleavage of the C_2-O_3 bond and formation of an Al-O_1 bond can occur with a minimum of steric interaction between the equatorially disposed methyl groups on carbons 2 and 4. Hence cleavage to the more stabilized oxocarbonium species can take place unhampered by steric effects.

Meanwhile in the trans isomer, cleavage at the C_2-O_3 bond and formation at the Al-O_1 bond is hindered by interaction between the C_4 methyl group and the O_3 substituents which are forced on to eclipsed positions on the shown five membered ring, (fig. IB - 10).

Cis-isomer complex



Trans-isomer complex

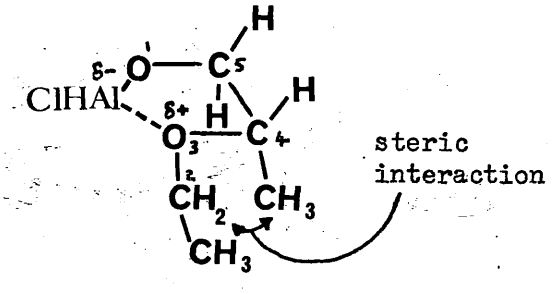


Fig. 1B - 10.

Hence formation of the immediate product from the more electronically favoured oxocarbonium ion is sterically hindered while cleavage at C_2-O_1 and formation of Al-O_3 goes via the less electronically favoured at the two oxocarbonium ions but does not have the same steric congestion in the postulated

five membered ring. Experiment shows that of the two opposing effects the steric influence dominates in trans 2, 4-dimethyl-1, 3-dioxolane and becomes progessively more dominant as the size of the substituents increases.[72]

It has also been shown experimentally that the cis isomers of 2, 4-dialkyl-1, 3-dioxolanes cleave at a faster rate than the corresponding trans isomers. This again is probably due to the steric congestion that exists, in the transition state to bond cleavage, of the trans isomers relative to that in the cis. Hence the higher activation energy of the former causes the cis to cleave faster.

In the carbohydrate field Bhattacharjee and Gorin[73,74] used aluminium chlorohydrides to prepare a number of O-alkyl derivatives, not readily obtained by other methods, from certain hexofuranoside and hexopyranoside acetals. From their experimental work they have made a number of generalisations, regarding the effects upon the direction of cleavage, of the electronic and steric idiosyncracies of the monsaccharide environment.

(a) 5, 6-0-Linked or 3, 5-0-linked acetals and ketals react faster than 1, 2-0-linked acetals or ketals.

(b) Dioxolanes react faster than dioxanes.

(c) The relative reactivities of the substrates studied are, 0-isopropylidene > 0-cyclohexylidene > 0-benzylidene > 0-ethylidene > 0-methylene.

(d) 0-Methylene acetals and 5, 6-0-linked rings in the 1, 2:5, 6-disubstitued glucofuranose compounds give the electrochemically directed product i.e. the 6-0-alkyl product.

(e) In pyranosides, methyl-4, 6-0- benzylidene-α-D-galactopyranoside gives mainly the 6-0-benzyl product while the methyl 4, 6-0-benzylidene-α-D-glucopyranoside and mannopyranoside give both the 4-0-benzyl and 6-0-benzyl ethers in an approximately 3:2 ratio.

In more recent work Liptak et al[75] have demonstrated that in substituted 4,6-O- linked hexopyranoside acetals the major directing influence is the bulkiness of the 3-O-alkyl sustituents which shield O_4 from attack by the aluminium species and hence promote cleavage to the 4-O-alkyl product. This is emphatically demonstrated with benzyl-2,3-di-O-benzyl-4,6-O-benzylidene-β-D-galactopyranoside which yields 92% of the 4-O-benzyl product whereas phenyl-4,6-O-benzylidene-2,3-O-methyl-β-D-galactopyranoside gives the 6-O-benzyl derivative as the main product.[76]

They also suggest that when the aglycon moiety becomes very bulky - as say in a disaccharide or in a free rotating benzyl group - then it can also shield the O_4 from attack and consequently favour the 4-O-alkyl product, although if the substituent is small or cannot readily rotate near the O_4 then it has no effect on the bond cleavage.

The same workers have also demonstrated that in 2,3-O-linked[77] and 3,4-O-linked[78] pyranosides the direction of cleavage is a function of the configuration of the acetal carbon. So in 2,3-O-benzylidene pyranosides the exo-isomer gives a product bearing an axial hydroxyl group at C_2 and an equatorial O-benzyl group at C_3 due to the aluminium species attacking mainly at the equatorial oxygen and so yields a product with a C_3 equatorial hydroxyl function and a C_2 axial O-benzyl group.

The use of borane as a hydrogenolytic cleavage reagent is relatively recent although the sodium borohydride catalysed cleavage of epoxides[79] by the borane-tetrahydrofuran complex is well documented. Fleming and Bolker[80] have successfully cleaved a number of acetals and ketals using excess of a molar solution of the borane-tetrahydrofuran complex[81,82] in tetrahydrofuran at or slightly above room temperature.

Their results have shown that the effect of the acetals substituents upon the rate and direction of cleavage parallel those

in the aluminium chlorohydrides' reaction, although at present only the electrochemical aspects have been examined. Consequently they have postulated that an oxocarbonium species is present in the transition state of the cleavage process, (fig. IB - 11).

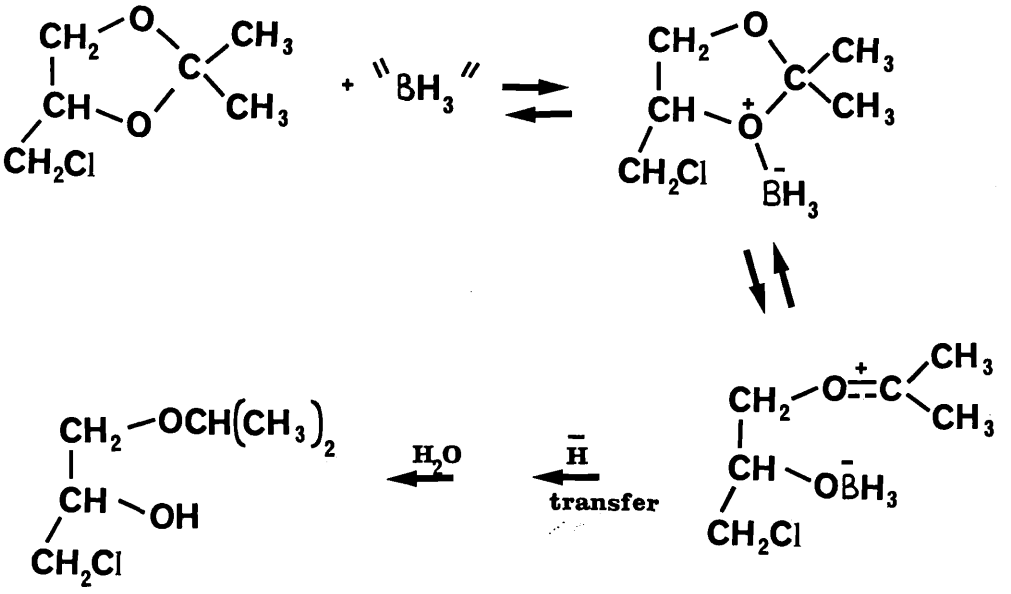


Fig. IB - 11.

The nature of the reacting boron species is not quite clear. Kinetic experiments upon the reaction, when excess borane is used, have indicated a third-order dependence upon the borane and hence complexes of the following type are thought to be involved[83]: B_2H_6, $H_3B\text{-}H\text{-}BH_2\text{-}THF$ and $BH_3\text{-}THF$, (fig. IB - 12).

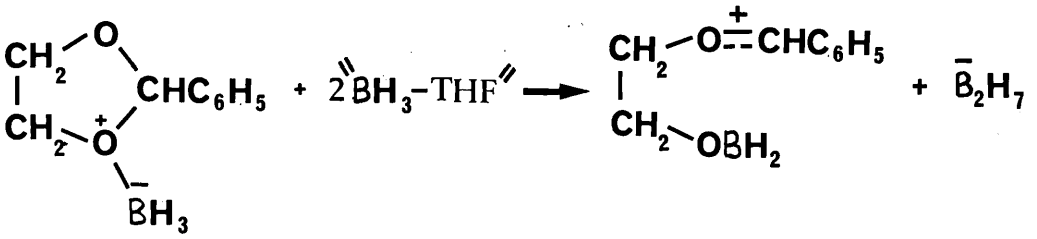


Fig. IB - 12.

Meanwhile, when excess acetal is used one mole of the borane reagent is sufficient to cleave three moles of acetal, suggesting that some sort of polyalkoxyboron species is involved in the mechanism.

Just as the chloride ion in aluminium trichloride can be displaced by hydride ions to yield the aluminium chlorohydrides, so boron forms the analogous boron hydrochlorides. They are conveniently prepared by a number of procedures the most common of which are shown below.

(a) From hydrogen chloride and borane,[84] (fig. IB - 13).

$$BH_3 + HCl \longrightarrow BH_2Cl + H_2$$

$$BH_3 + 2HCl \longrightarrow BHCl_2 + 2H_2$$

(b) From diborane and boron trichloride[85],

$$B_2H_6 + BCl_3 + 3R_2O \longrightarrow 3H_2BCl{:}OR_2$$

$$B_2H_6 + 4BCl_3 + 6R_2O \longrightarrow 6H\,BCl_2{:}OR_2$$

(c) From boron trichloride and borohydrides,[86,87]

$$BCl_3 + NaBH_4 + 2R_2O \longrightarrow NaCl + 2H_2BClOR_2$$

$$3BCl_3 + NaBH_4 + 4R_2O \longrightarrow NaCl + 4RHBCl_2{:}OR_2$$

Fig. IB - 13.

Their main synthetic use is in the hydroboration[88-91] of olefins to give the relevant alkyl chloroboranes, which are useful

intermediates for many reactions.

In the light of the success of 92-4 borane and the aluminium chlorohydrides as reductive cleavage reagents, it was decided to examine the possible use of boron hydrochlorides in a similar manner. So their reactions with a number of 1, 3-dioxolanes and dioxanes have been looked at.

Also in this thesis the reaction of acetals with boron trichloride and lithium aluminium hydride - first used by Bonner and Saville[52] in this laboratory - has been looked at in greater detail.

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II. THE REACTION OF SIMPLE CYCLIC ACETALS WITH BORON TRICHLORIDE/LITHIUM ALUMINIUM HYDRIDE

IIA. Introduction.

The hydrogenolysis of cyclic acetals using aluminium chlorohydrides[1] depends upon initial and reversible Lewis-coordination of the cleavage reagent with one of the acetal's oxygens. This results in a polarization of the acetal particularly at the $O\text{-}C_2\text{-}O$ moiety and a related propensity to rate-controlling cleavage of the $C_2\text{-}O$ bond farther from the bonding Lewis acid. The cleavage is consummated by the facile donation of a hydride ion from the aluminium into the nascent oxocarbonium species at C_2, probably via a 4-centre transition state.[2]

Obviously if boron trichloride is the reacting Lewis-acid hydride donation cannot take place, although Bonner and Saville[3] suggest that analogous donation of a chloride ion occurs to yield an α-chloroether. The halide is then displaced by a hydride ion from lithium aluminium hydride to yield an ether function as shown in figure IIA - 1.

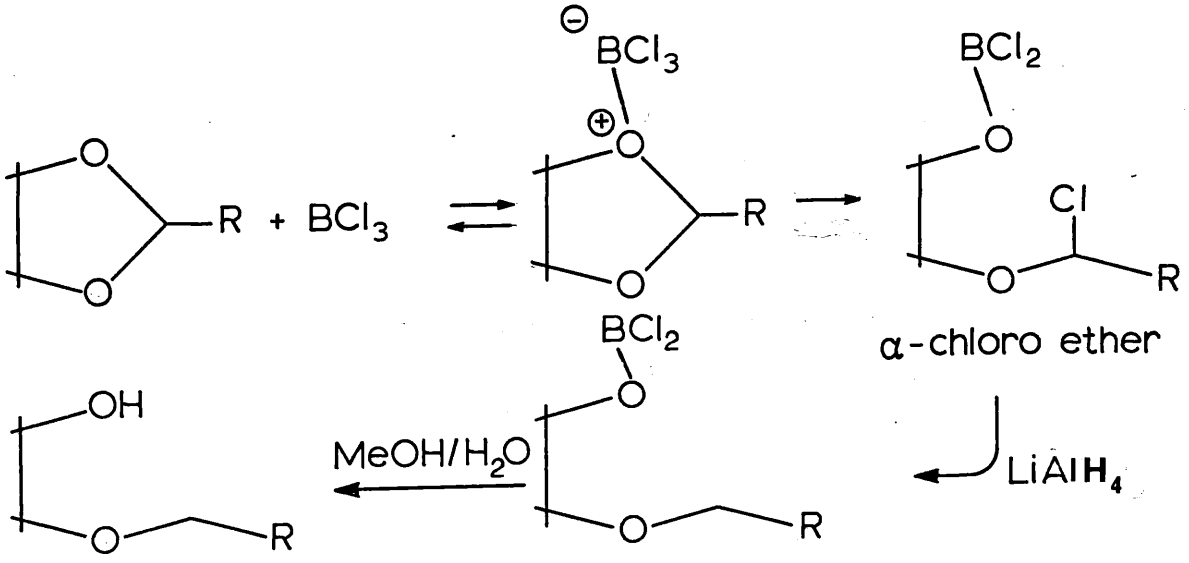


Fig. IIA - 1.

The main differences between the boron trichloride / lithium aluminium hydride system and the aluminium chlorohydrides or borane are as follows.

1) Boron trichloride is a much stronger Lewis acid especially when compared to the aluminium chlorohydrides.

2) The hydride donation is probably an intramolecular process in the borane and chlorohydride systems whereas it must occur intermolecularly with the boron trichloride/lithium aluminium hydride combination.

Work by Deters et al[5] has demonstrated that the rate of exchange of boron trichloride from one Lewis base site to another, in its reaction with ethers, is slower than that of similar but weaker Lewis acids such as boron trifluoride or aluminium trichloride. The most probable reason for this slower exchange rate is the greater strength of the boron trichloride-ether bond.

Given then that the initial formation of the Lewis complex is a fast process in all of the cases considered - as they are all strong Lewis acids - it seems plausible to expect equimolar amounts of any one of them plus a cyclic acetal to exist mainly in the coordinated state. If this is true then one can also expect that the polarisation of the $O\text{-}C_2\text{-}O$ moiety will be greater when complexed to boron trichloride than say with aluminium dichlorohydride. Hence the facility to bond cleavage will be greater in the boron trichloride complex and so one might expect acetals that are not readily hydrogenolysed by the aluminium chlorohydrides[1] or borane[4] - such as 1,3-dioxolane and 2-chloromethyl-1, 3-dioxolane - to undergo cleavage with the boron trichloride system. This possibility is examined in section IIC - ii(a) of this thesis.

Also the question of whether an α-chloroether really is formed from the boron trichloride and a cyclic acetal is considered. This essentially involves differentiating between a mechanism

in which ring cleavage occurs prior to addition of the lithium aluminium hydride (fig. IIA - 2a) and one in which the hydride ion actually brings about ring cleavage (fig. IIA - 2b).

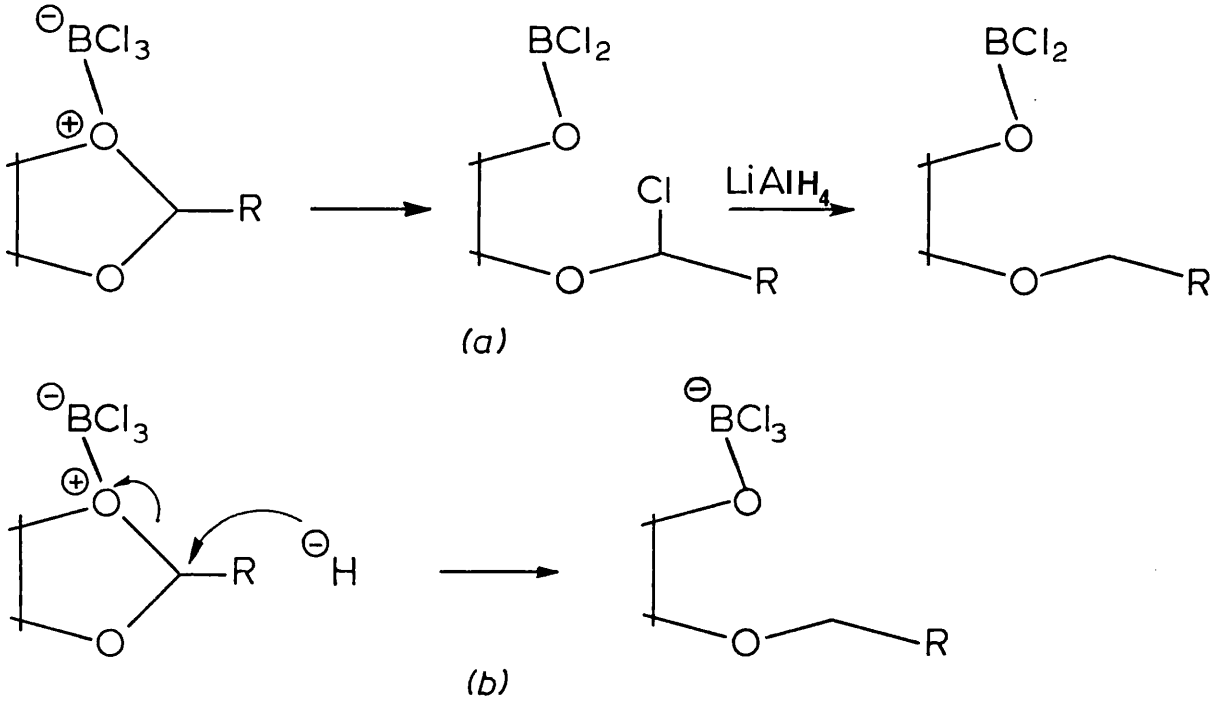


Fig. IIA - 2.

The following points are also discussed.

1) The effect of C_2 substituents upon the relative ease of acetal cleavage.

2) The effect of C_4 (or C_5) substituents upon the direction of cleavage.

3) The effect of varying ring size upon the relative ease of cleavage.

4) Whether, if the α-chloroether is present, halide transfer is an intermolecular or an intramolecular process.

Thus the aim of the following section is to illuminate the "boron trichloride/lithium aluminium hydride plus cyclic acetal"

reaction generally and perhaps to gain insight into the reaction mechanism. The basic model used is that previously suggested by Bonner and Saville.[3]

IIB. Reactions of boron trichloride/lithium aluminium hydride with 2-n-propyl-1, 3-dioxane.

i) Introduction.

It was decided that 2-n-propyl-1, 3-dioxane would be a good model compound to work with. This is because it is easily prepared and purified and the electron donating character (+ I) of the 2-n-propyl group would by analogy with the aluminium chlorohydride reactions, make for facile cleavage. Also the proton magnetic resonance (p.m.r.) spectrum of 2-n-propyl-1, 3-dioxane possesses a characteristic and easily identifiable signal due to the acetal proton (triplet, ca. 4.5 δ) thereby allowing the electronic environment of the O-C_2-O function to be monitored in a qualitative fashion.

ii) Results and discussion.

(a) General reaction procedure, work-up and analysis.

2-n-Propyl-1, 3-dioxane (0.01 mol.) was slowly added to an ice-cool solution of boron trichloride (0.01 mol.) in dry methylene chloride. After stirring for 10 minutes an ethereal suspension of lithium aluminium hydride (0.01 mol.) was added to the pale green solution and the resulting mixture stirred at room temperature until effervescence had ceased: this generally took about half an hour. All subsequent reactions were carried out using this general procedure unless otherwise stated.

Work-up was then carried out in the following way. The reaction mixture was poured into ice-cooled aqueous methanol and brought to neutrality by the addition of 4N sodium hydroxide. After filtering off the insoluble inorganic material most of the

methanol was removed under vacuum, then more methanol was added and this was also removed. This process was repeated twice more to ensure that any residual boric acid was removed as its volatile trimethyl ester.

Finally chloroform was added to the cloudy syrup remaining, the last traces of inorganic material removed by centrifugation and the resulting solution was dried over anhydrous sodium. sulphate along with the chloroform washings of the inorganic material.

Analysis of this crude work-up solution using gas liquid chromatography (g.l.c.) showed the absence of any 2-n-propyl-1, 3-dioxane while the presence of one main product plus a small amount of a more polar side product was indicated.

Removal of the chloroform under vacuum gave a pale green oil, the infra-red spectrum of which indicated a hydroxyl function in the molecule while the 60 MHz p.m.r. spectrum showed the presence of a butoxy function. Meanwhile the acetal proton triplet of 2-n-propyl-1, 3-dioxane was absent.

The cleavage product expected from the above reaction was 3-n-butoxy-propan-1-ol; a sample of this compound was then prepared by an independent route so that a comparison could be made between it and the product given by the boron trichloride/lithium aluminium hydride combination. Hence when the infra-red and p.m.r. spectra of the two compounds, as well as their g.l.c. retention times, were shown to be identical it was concluded that the product isolated from the 2-n-propyl-1, 3-dioxane reaction was indeed 3-n-butoxy-propan-1-ol.

Meanwhile the polar side product was shown to be propan-1, 3-diol by comparison with the g.l.c. retention time of a reference sample of this compound.

This experiment demonstrated that hydrogenolysis of the 2-n-propyl-1, 3-dioxane was possible under the described conditions using the boron trichloride/lithium aluminium hydride combination (fig. IIB - 1).

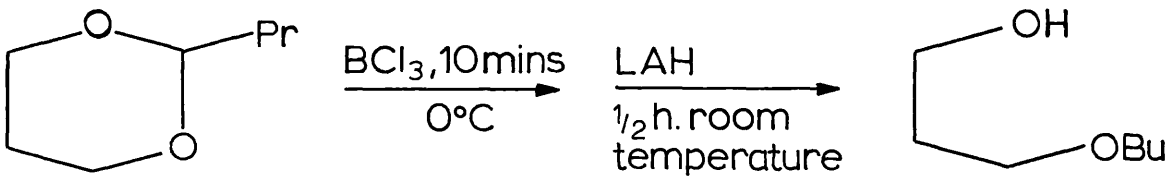


Fig. IIB - 1.

(b) Stoichiometry of the reaction.

By repeating the above reaction with varying amounts of 2-n-propyl-1, 3-dioxane - i.e. 1, 2, 3, 4 or 5 mole equivalents of dioxane per mole equivalent of boron trichloride - it was found that complete hydrogenolysis was still possible with a 3:1:1 mole ratio of acetal to trichloride to hydride. With 4 or 5 moles of acetal however residual substrate was still present in the worked-up product mixture.

Thus the hydrogenolysis of the 2-n-propyl-1, 3-dioxane occurs in a 3:1 molar stoichiometry with respect to the boron trichloride and whatever the resulting complex is it can be reduced by 1 mole equivalent of lithium aluminium hydride to give, on work-up, 3 molesof 3-n-butoxy propan-1-ol.

Bonner and Saville[3] envisaged that the boron trichloride/ lithium aluminium hydride cleavage of cyclic acetals occurred via an α-chloroether intermediate and, in the light of the observed 3:1 stoichiometry, it does not seem too great a step to suggest that all three of the chlorine atoms in boron trichloride are donated (as chloride ions) to give a complex of the type shown in figure IIB -2 and that this complex is reduced by the lithium aluminium hydride.

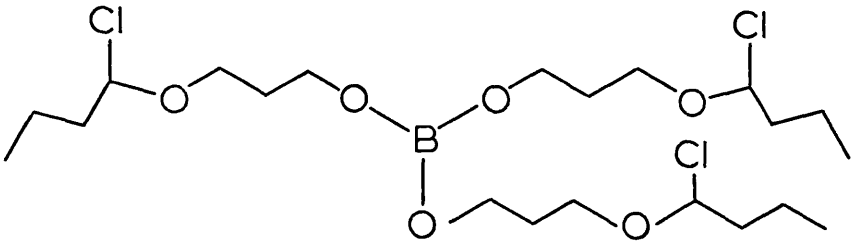


Fig. IIB - 2.

The modified reaction pathway would therefore be as shown in figure IIB - 3.

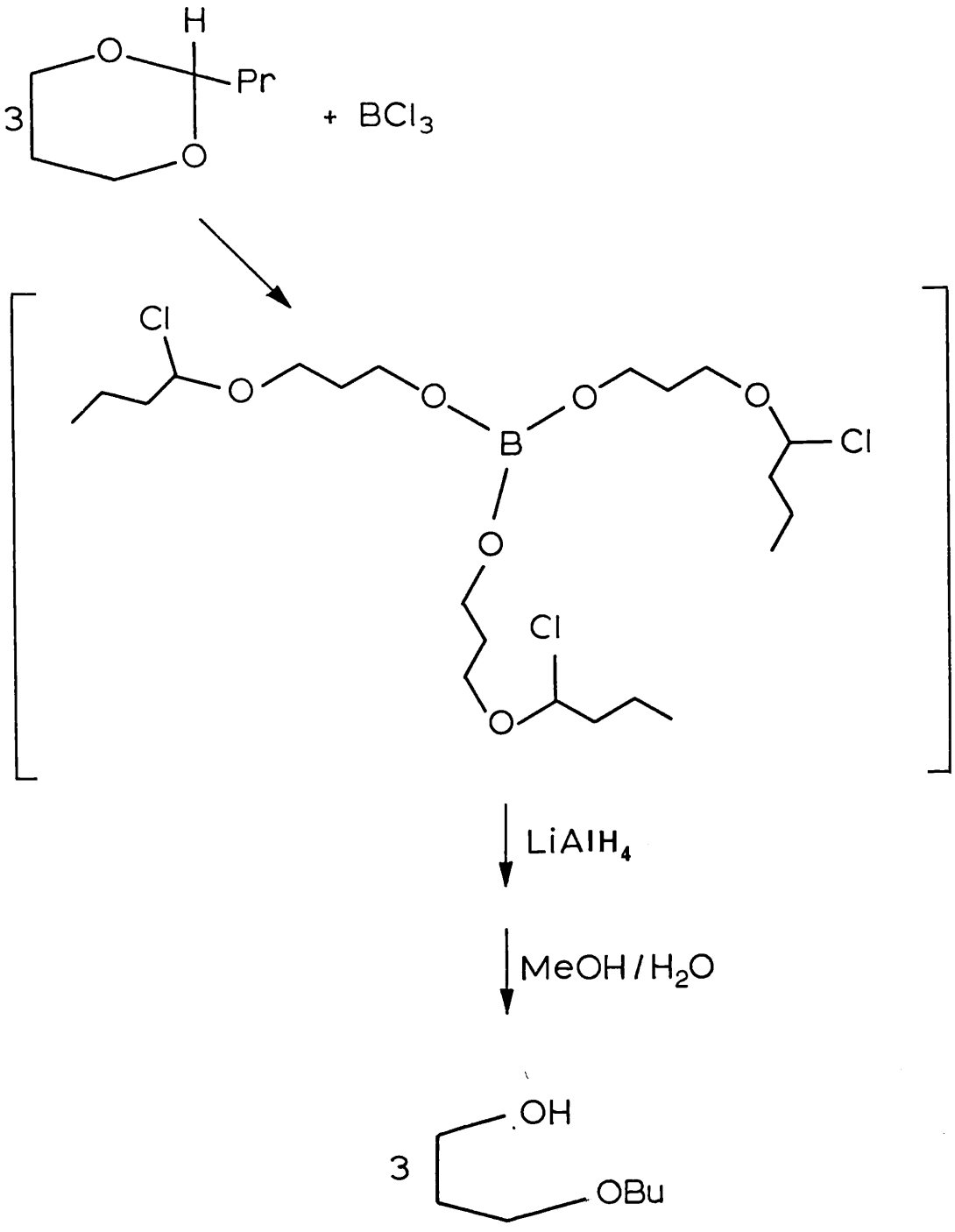


Fig. IIB - 3.

An immediate point of interest in the above scheme is the apparent ability of boron trichloride to form a Lewis-complex with a third molecule of the 1, 3-dioxane when already bonded to two other acetal molecules: a situation which does not occur when the Lewis base is an acyclic ether.[6] For instance the chloroboronate formed from boron trichloride and diethyl ether does not react further (fig. IIB-4a).

(a)

$$Et_2O + BCl_3 \rightleftharpoons Et_2O.BCl_2 \xrightarrow{heat} EtOBCl_2 + EtCl$$

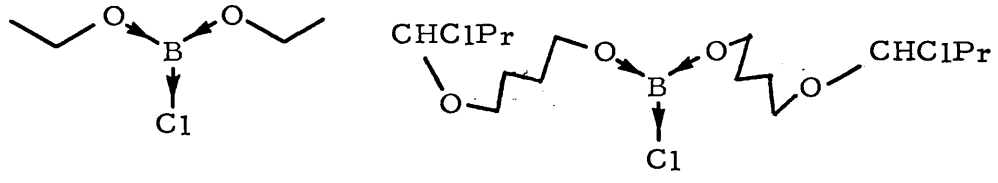
$$EtOBCl_2 + Et_2O \rightleftharpoons Et_2OBCl_2OEt$$

$$Et_2OBCl_2OEt \longrightarrow (EtO)_2BCl + EtCl$$

$$(EtO)_2BCl + Et_2O \not\longrightarrow \text{No Reaction}$$

Diethylchloroboronate

(b)



where OEt $> OCH_2CH_2OCHClPr$ in + I character (←).

Fig. IIB - 4.

The most probable reason for the greater reactivity shown by the dioxanes is probably due to the ease with which ring cleavage occurs. Thus because of this cleavage the charge build-up upon the boron - due to the formation of the Lewis complex - is removed in a far more facile manner when the dioxane is the attacking base (i.e. by formation of the α-chloroether) than when the acyclic ether is the base. It is for this reason that attack of a second and third

molecule of dioxane upon the boron is not as electronically unfavourable as the analogous reactions of the acyclic ether. Also even though the 1, 3-dioxanes and acyclic ethers are approximately equal in basicity the resulting substituents in the dichloroborinate and dialkylchloroboronate given by the dioxanes are probably of lower electron donating power (+ I) than those given by the acyclic ethers (fig. IIB - 4b) due to the -I inductive effect of the unbonded oxygen in the cleaved dioxane: thus the Lewis acidity of the boron in the respective dichloroborinates and dialkylchloroboronates will be higher for the dioxane derivatives than the acyclic ether compounds.

A necessary conclusion of the above reasoning is that a 1, 3-dioxane should form a complex and undergo cleavage when either an alkyldichloroborinate or a dialkyl chloroboronate is the acting Lewis acid. Experiments were then carried out to see if this assumption was correct.

Propan-2-ol (0.0085 mol.) was slowly added to a stirred solution of boron trichloride (0.0085 mol.) in methylene chloride at $0^{o}C$. After stirring the resultant solution for 20 minutes, to allow the hydrogen chloride to escape, 2-n-propyl-1, 3-dioxane (0.017 mol.) was added. After stirring for 5 minutes an ethereal suspension of lithium aluminium hydride was added and after the usual procedure the worked-up product mixture was analysed upon the gas liquid chromatograph.

This showed that very little substrate remained, and that again the main product was 3-n-butoxy-propan-1-ol. Similar results were given when 1 mole equivalent of the dioxane was added to a solution containing 1 mole equivalent of boron trichloride plus 2 mole equivalents of propan-2-ol or 1 mole equivalent of ethan-1, 2-diol. Thus the 3:1 stoichiometry was further corroborated (fig. IIB - 5).

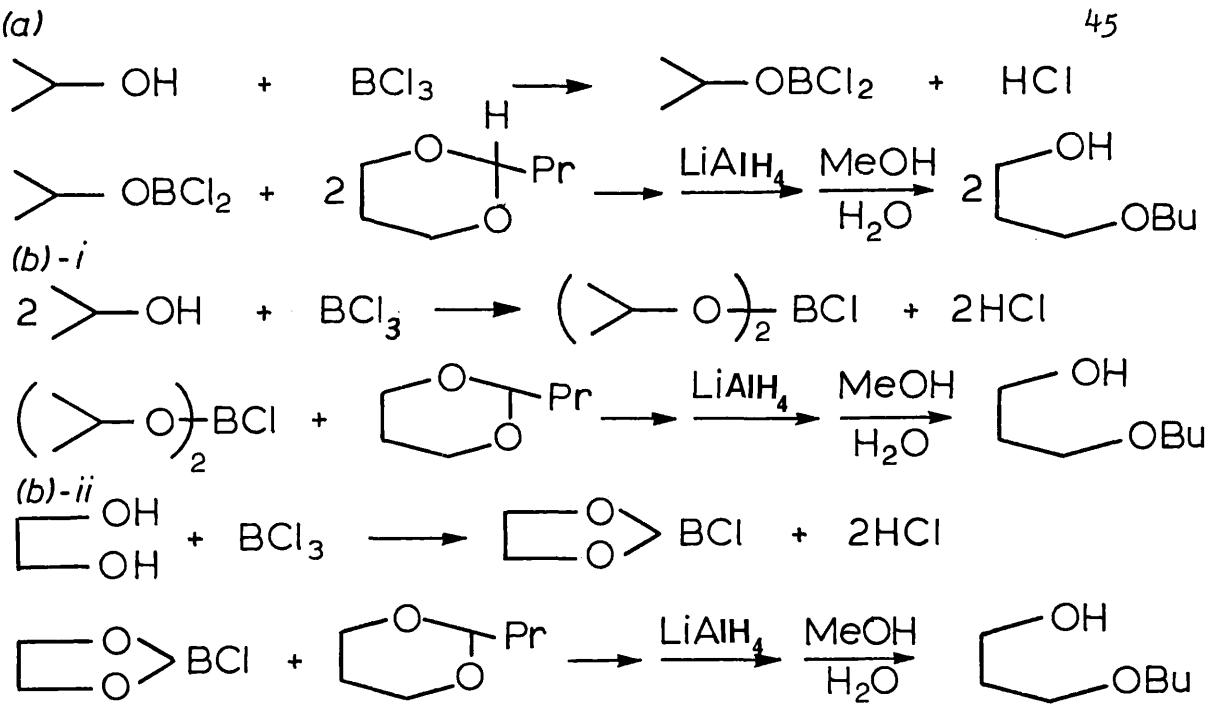


Fig. IIB - 5.

A valid criticism of the above experiment is that residual hydrogen chloride in the reaction mixture may have aided in the cleavage of the dioxane. In order to see if this was the case gaseous hydrogen chloride (0.02 mol.) was bubbled into a methylene dichloride solution of 2-n-propyl-1, 3-dioxane (0.013 mol.) and the reaction mixture stirred at 0^{o} for 10 minutes. After this time the solution was treated with lithium aluminium hydride (0.013 mol.) in the usual way. After work-up a g.l.c. of the product showed that no reaction had occurred in the sense that the main product was 2-n-propyl-1, 3-dioxane, although a small amount of propan-1, 3-diol was present. The yield of dioxane however (92%) was large enough to imply that the presence of residual hydrogen chloride would not make any difference to the cleavage reactions mentioned above. Under more extreme conditions hydrogen chloride will bring about the cleavage of a dioxane although the nature of the conditions and products are very different from those considered here, as demonstrated by Bartok and Molnar.[7]

(c) Evidence for α-chloroether.

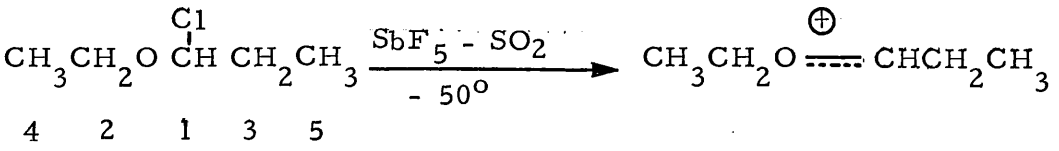
Implicit within the previous discussion is the assumption that the 1,3-dioxane ring opens prior to the addition of the lithium aluminium hydride, due to the formation of an α-chloroether. Experiments were then carried out to test this assumption.

Thus a 3:1 mixture of 2-n-propyl-1,3-dioxane and boron trichloride was prepared in ice-cooled carbon tetrachloride. At regular intervals a sample of the reaction mixture was withdrawn and its p.m.r. spectrum taken thereby affording a means of monitoring any changes that occurred in the reaction mixture.

The first spectrum - taken 2 minutes after the addition of the acetal - showed a slight downfield shift of the multiplet due to the propyl chain's methylene protons (1.4 — 1.9δ) while the multiplet centred at 3.9δ in the free acetal shows a loss of coupling character and an homogenisation that would be associated with a change from a cyclic to a linear array of the C_4 and C_6 methylene protons. The most informative features of the spectrum however were a triplet, integrating to one proton, at 5.75δ (J = 5.5 Hz) and the disappearance of the acetal protons triplet from 4.5δ.

Also significant was the fact that very little change had occurred between the time when the first spectrum was taken and 24 h. later when the final spectrum was run. This suggests that the complex is formed within the first two minutes after the addition of the acetal.

Olah and Sommer[8] in their work on stable carbonium ions looked at the proton magnetic resonance spectra of a number of α-chloroethers. They cite a triplet at around 5.85δ as belonging to the C_1 proton on the α-chloroether, which is in good agreement with the 5.75δ observed above (fig. IIB - 6).



$\delta H_1 = 5.9$ at -20°

$J_{1,3} = 5.5$ Hz

Fig. IIB - 6.

When the same experiment was repeated with a 6:1 acetal to boron trichloride ratio then the acetal proton triplet was seen to be present at 4.5δ along with the "α-chloroether" triplet at 5.75δ and the multiplet at 1.4δ, belonging to the n-propyl groups methylene protons.

A spectrum was also taken of the 3:1 reaction mixture in carbon tetrachloride 30 minutes after the addition of an ethereal lithium aluminium hydride suspension: this showed the presence of a butyl group but the absence of both the acetal triplet and the triplet at 5.75δ. G.l.c. analysis of the products from this reaction again showed that 3-n-butoxy propan-1-ol was the main product. If the 3:1 reaction mixture is worked-up without addition of the lithium aluminimum hydride then the main product is propan-1, 3-diol which also tends to support the view that ring cleavage occurs prior to the addition of the hydride.

The not unreasonable assumption made during the above experiments was that the use of carbon tetrachloride as a solvent system would not have any significant effect upon the reaction pathway that is followed when methylene dichloride is the solvent, i.e. that the proton magnetic resonance spectra are a faithful

representation of what occurred in the initial cleavage reactions.

It was then decided to try and isolate the product given from the 3:1 reaction mixture. This was carried out by removing the methylene dichloride under reduced pressure over a period of about 1 h. at room temperature. When all of the solvent had been removed - and collected in cold traps immersed in liquid air - a pale green syrup remained in the flask. A p.m.r. spectrum of this syrup was the same as that given previously by the 3:1 acetal/boron trichloride in CCl_4 so that no appreciable decomposition had occurred on removing the solvent. An infra-red spectrum of the syrup showed the presence of a large B-O[9] stretch at 1340 cm^{-1} while the B-Cl stretch at 900 cm^{-1} was notably absent, a peak at 670 cm^{-1} and 750 cm^{-1} does occur in the C-Cl stretch region however.

The presence of residual methylene dichloride may have been responsible for the C-Cl stretch in the above infra-red spectrum so the experiment was repeated using diethyl ether as the solvent, when a similar spectrum was given indicating that the peak was produced by the complex.

If any boron trichloride had condensed over with the methylene dichloride during the isolation of the complex, it could easily be converted to the equivalent amount of hydrogen chloride by washing the methylene chloride with water: the resulting hydrochloric acid solution was then titrated against 0.1N sodium hydroxide thereby giving an estimation of the amount of boron trichloride removed. With an initial amount of 0.86 g of boron trichloride - where 0.83 g was necessary for theoretical combination with the acetal - 0.06 g was estimated to be present in the methylene dichloride. This again suggests that the boron trichloride has been modified to a considerable degree in the reaction and that the product formed is more than just a simple association complex.

In conclusion then the following statements may be made

about the reaction between 3 mole equivalents of 2-n-propyl-1, 3-dioxane and 1 mole equivalent of boron trichloride.

1) The product formed involves considerable modification to both substrates and as a single product is given on treatment with lithium aluminium hydride or water this suggests that the three dioxane molecules have been modified in the same way.

2) Infra-red and proton magnetic resonance data suggest that this modification includes ring opening and formation of an α-chloroether prior to the addition of the hydride.

3) Infra-red data definitely shows that there are no B-Cl bonds in the product while at least one B-O bond is present.

It was then decided to extrapolate the results, obtained by using 2-n-propyl-1, 3-dioxane as a model substrate, to other simple acetals in the hope that further insight into the reaction pathway would be obtained.

IIC. Reactions of boron trichloride/lithium aluminium hydride with simple dioxolanes, dioxanes, dioxepanes and dioxocanes.

i) Introduction.

The original motivation behind using the boron trichloride/lithium aluminium hydride combination as a hydrogenolysis reagent was that it may effect cleavage of acetals not readily hydrogenolysed by borane or the aluminium chlorohydrides, namely those containing a hydrogen or electron withdrawing (-I) group at C_2.

The results from the previous section (IIB) had indicated that the boron trichloride/lithium aluminium hydride combination could be used with confidence for a 1, 3-dioxane with an electron donating (+ I) group at C_2. The following section discusses the results given when various 1, 3-dioxolanes, 1, 3-dioxanes, 1, 3-dioxepanes and 1, 3-dioxocanes substituted at C_2 with either H, n-Pr or CH_2Cl- were used as substrates.

Experimental evidence for the participation of an

oxocarbonium ion as intermediate to α-chloroether formation is discussed as well as the mode of transfer of the chloride ion.

ii) Results and discussion.

(a) Simple cleavage reactions.

The same experimental procedure that had been used to hydrogenolyse the 2-n-propyl-1, 3-dioxane was used in all cases. Hence a 3:1 mixture of the acetal and boron trichloride in methylene chloride was treated with an ethereal suspension of lithium aluminium hydride.

After work-up the product mixtures were analysed using gas liquid chromatography which allowed the retention times of the products to be compared with independently prepared reference materials. The infra-red and 60 MHz proton magnetic resonance spectra of the products were also compared with those of the reference samples.

As can be seen in Table IIC - 1 good yields of the respective hydroxyethers were given in all cases and recovery was always greater than 80%. Residual substrate was present in only two of the product mixtures - those of 2-chloromethyl-1, 3-dioxolane and 2-chloromethyl-1, 3-dioxane- and the amount of this was reduced by the use of a 1:1 mixture of acetal and boron trichloride. The only other observed products, the respective polyols, were present in all of the product mixtures to within about 5% of the total yield. This proportion could be lowered by increasing the amount of lithium aluminium hydride from 1 mole equivalent to 2 mole equivalents - based on the amount of boron trichloride present - and also by extending the time the hydride was in contact with the α-chloroether complex from 0.5 h. to 1 h., although it was never possible to remove it completely.

Substrate	Product	Yield of Substrate (%) ++	Yield of Product(%) ++
2-n-Propyl-1, 3 -dioxolane	2-n-butoxy ethan-1-ol	0	>95
1, 3-Dioxolane	2-methoxy ethan-1-ol	<1	90-5
		x 40	60
		+ 78	16
2-Chloromethyl -1, 3-dioxolane	2-(2-chloroethoxy) -ethan-1-ol	33	67
		xx 86	14
2-n-Propyl-1, 3-dioxane	3-n-butoxy propan-1-ol	0	>95
1, 3-Dioxane	3-methoxy propan-1-ol	<1	90-5
2-Chloromethyl -1, 3-dioxane	3-(2-chloroethoxy) -propan-1-ol	44	49
2-n-Propyl-1, 3-dioxepane	4-n-butoxy butan-1-ol	0	>95
1, 3-Dioxepane	4-methoxy butan-1-ol	0	95
2-Chloromethyl-1, 3-dioxepane	4-(2-chloroethoxy) -butan-1-ol	<1	95
2-n-Propyl-1, 3-dioxocane	5-n-butoxy pentan-1-ol	0	98
1, 3-Dioxocane	5-methoxy pentan-1-ol	0	95
2-Chloromethyl -1, 3-dioxocane	5-(2-chloromethyl) -pentan-1-ol	<1	95

xx Yield with AlH_2Cl after 48 h. at room temperature in ref. 1 at 80% recovery.

x Yield with AlH_2Cl after 44 h. at room temperature in ref.1 at 55% recovery.

\+ Yield with BH_3 after 24 h. at 57° in ref. 4.

++ Total isolated yield was ca. 85% in each case.

Note: All product mixtures contained ca. 5% diol.

Table IIC - 1.

The increased reactivity of the boron trichloride/lithium aluminium hydride combination over borane or the aluminium chlorohydrides is well illustrated by comparison of the reactions of the three reagents with 2-chloromethyl-1,3-dioxolane and 1,3-dioxolane (Table IIC - 1). Thus while hydrogenolysis of 1,3-dioxolane requires 44 h. for a 60% yield of 2-methoxy-ethan-1-ol with aluminium dihydrochloride[1] at room temperature, almost complete conversion of the acetal is given after a total reaction time of 35 minutes with the boron trichloride/lithium aluminium hydride.

The main reason for this greater reactivity is probably the greater Lewis acidity of the boron trichloride which causes greater polarisation of the $O\text{-}C_2\text{-}O$ moiety thereby enhancing cleavage of the $C_2\text{-}OB$ bond. The difference in Lewis acidity between boron trichloride and the aluminium chlorohydrides or borane is also enhanced by the fact that the latter two reagents are used in Lewis base solvents.

The overall reaction may be represented as shown in figure IIC - 1.

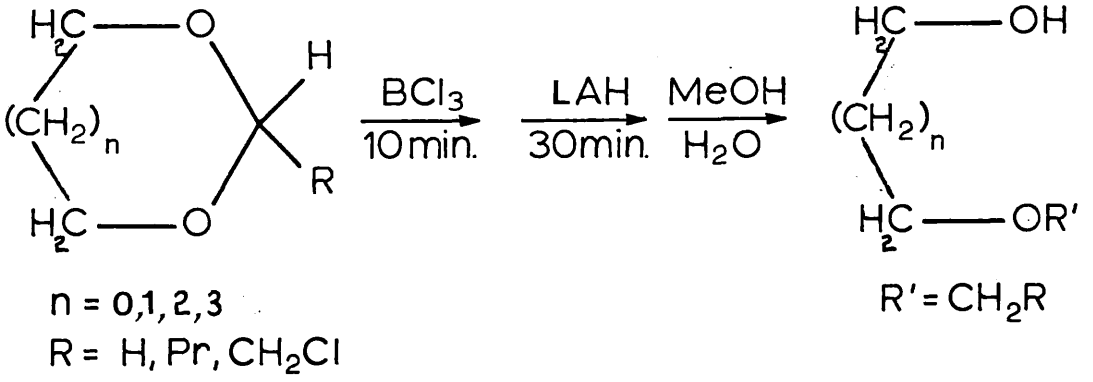


Fig. IIC - 1.

(b) Preparation of substrates.

1, 3-Dioxolane and 1, 3-dioxane were prepared by the method of Leggetter and Brown[1] in which the appropriate diol was heated with a slight excess of paraformaldehyde in the presence of anhydrous magnesium sulphate. Concentrated hydrochloric acid was the catalyst used and the reaction mixture was heated at such a rate that the cyclic acetal was distilled over.

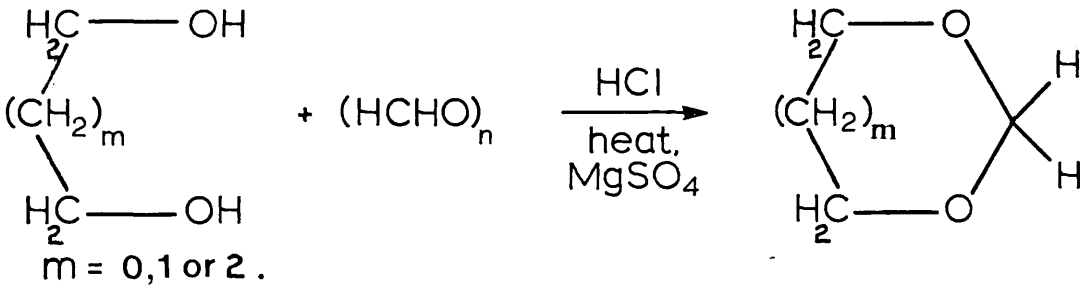


Fig. IIC - 2.

The 1, 3-dioxepane was prepared by a slightly different procedure in that the butan-1, 4-diol, paraformaldehyde and magnesium sulphate were refluxed together in the presence of concentrated hydrochloric acid for 3 h. and then the acetal was given on distillation.

Attempts at the preparation of 1, 3-dioxocane directly from pentan-1, 5-diol and paraformaldehyde resulted in low yields of the monomer and quite substantial amounts of the dimer and higher polymers.

Success was achieved when the method of Anteunis and Becu[10] was used in which the mixed acetal shown in figure IIC - 3a is first formed by the p-toluenesulphonic acid catalysed condensation of paraformaldehyde with ethanol and pentan-1, 5-diol using benzene as the solvent.

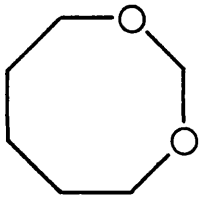
Reduced pressure pyrolysis of the mixed acetal gives 1, 3-dioxocane in good yield without any appreciable polymerisation, possibly via the mechanism outlined in figure IIC - 3b.

(a) $HOCH_2(CH_2)_3CH_2OH + (HCHO)_n \xrightarrow{\text{in EtOH}}$

$EtO\,CH_2O\,CH_2\,(CH_2)_3CH_2OCH_2OEt$

mixed acetal

Reduced pressure pyrolysis



(b)

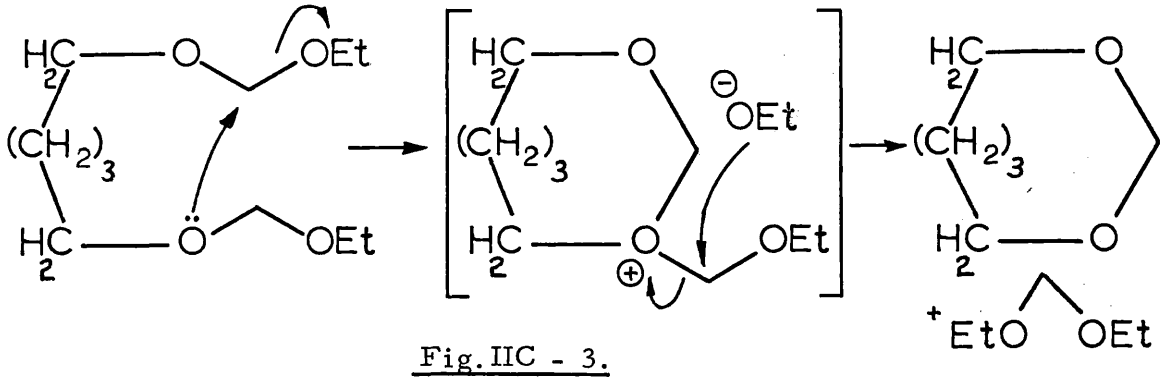


Fig. IIC - 3.

The 2-n-propyl substituted acetals were all prepared by the p-toluenesulphonic acid catalysed condensation of butyraldehyde with the appropriate diol, using toluene as a solvent. The water produced during the reaction was azeotropically removed using a modified Dean and Stark assembly (fig. IIC - 4).

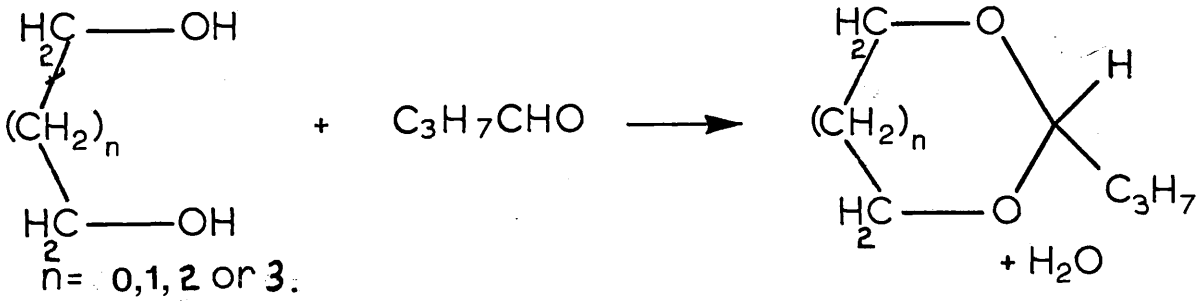


Fig IIC - 4.

Meanwhile the 2-chloromethyl derivatives were given when an equimolar mixture of 1, 1-diethoxy-2-chloroethane was heated with the appropriate diol using p-toluenesulphonic acid as the catalyst. The reactants were heated until the theoretical amount of ethanol had been distilled over (fig. IIC - 5).

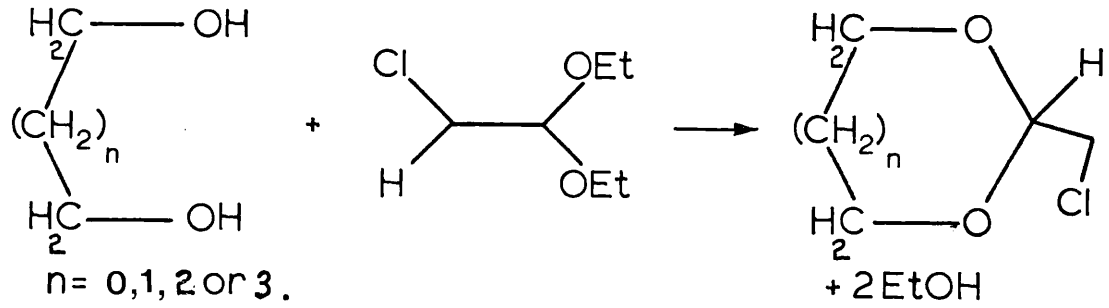


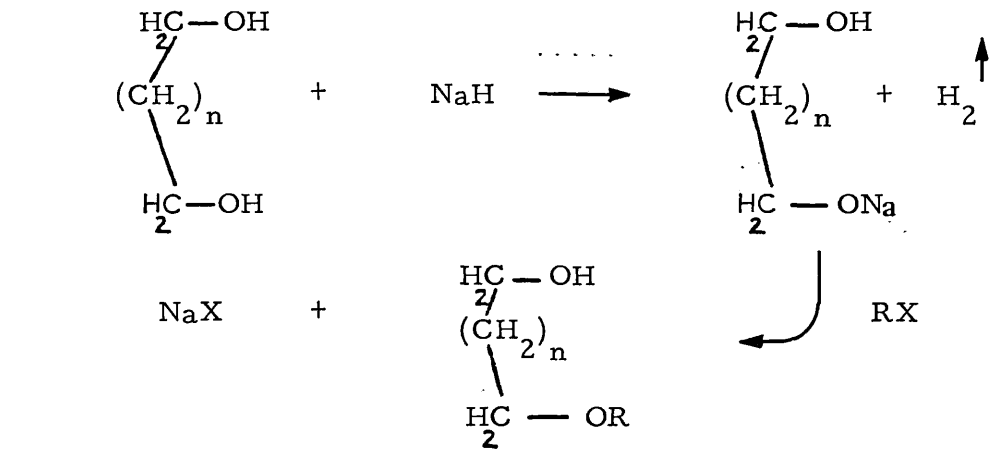
Fig. IIC - 5.

All of the cyclic acetals mentioned above were purified by distillation and dried over anhydrous sodium carbonate 24 h. prior to a cleavage reaction.

(c) Preparation of reference compounds.

The general method of structure proof used in the aforementioned series of experiments was to compare the product from the particular hydrogenolysis reaction under consideration with an independently prepared sample of the expected product.

The methoxy and n-butoxy derivatives of ethan-1, 2-diol, butan-1, 4-diol and pentan-1, 5-diol were prepared by treating the monosodium salt of the diol with either methyl iodide or n-butyl bromide respectively, using dry dimethyl formamide (D.M.F.) as the solvent (fig. IIC - 6).



n = 0, 2 or 3.

RX = MeI or n-BuBr

Fig. IIC - 6.

For 3-methoxy propan-1-ol[11] a slightly different procedure was used in which 3-chloro propan-1-ol was added to a refluxing solution of sodium methoxide in methanol. The same procedure was used to prepare 3-n-butoxy propan-1-ol (fig. IIC - 7).

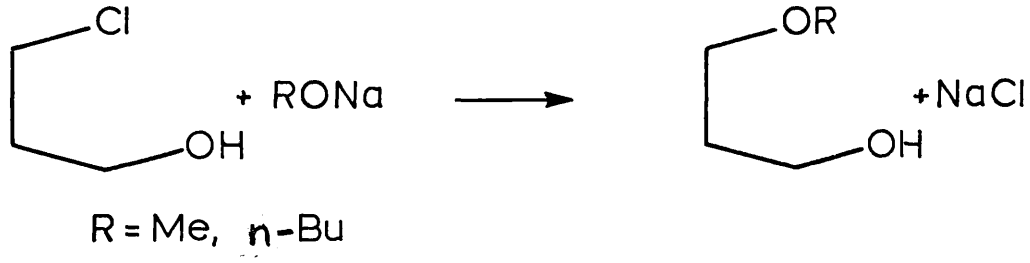


Fig. IIC - 7.

(d) Structure proofs for the products given by the 2-chloromethyl substituted acetals.

The product given from the cleavage of 2-chloromethyl-1, 3-dioxolane was shown to be 2-(2-chloroethoxy)-ethan-1-ol by comparing the b.p. and the I.R. spectra of the isolated product with those given

by an authentic sample of 2-(2-chloroethoxy)-ethan-1-ol prepared by the method outlined by Leggetter and Brown.[1]

The product given by cleavage of 2-chloromethyl-1, 3-dioxane was shown to be 3-(2-chloroethoxy)- propan-1-ol by a number of physico-chemical techniques: thus the I.R. spectrum of the product showed the presence of OH and C-Cl stretch, the C.I. mass spectrum showed that its molecular weight was 138 while the E.I. fragmentation pattern and 60 MHz p.m.r. spectrum of the product agreed with that expected from 3-(2-chloroethoxy)-propan-1-ol. Finally elemental analysis confirmed that the empirical formula was $C_5H_{11}ClO_2$.

A similar combination of techniques was used to show that the products given by 2-chloromethyl-1, 3-dioxepane and 2-chloromethyl-1, 3-dioxocane were 4-(2-chloroethoxy)-butan-1-ol and 5-(2-chloroethoxy)-pentan-1-ol respectively.

IID. Evidence for participation of an oxocarbonium ion in the reaction pathway.

i) Introduction.

In the following sections experimental evidence is considered that was designed to test the supposition held by this thesis that an oxocarbonium ion is the substrate to α-chloroether formation.

The mode of transfer of the chloride ion is also considered.

ii) Results and discussion.

(a) Substitutents at C_2 on the 1, 3-dioxolane ring.

Formation of the α-chloroether can occur in two main ways. The first of these involves nucleophilic attack of a chloride ion upon an oxocarbonium species given on fission of the C_2-OB bond, while in the second the C_2-OB bond is broken because of nucleophilic attack of a chloride ion at C_2 (fig. IID - 1).

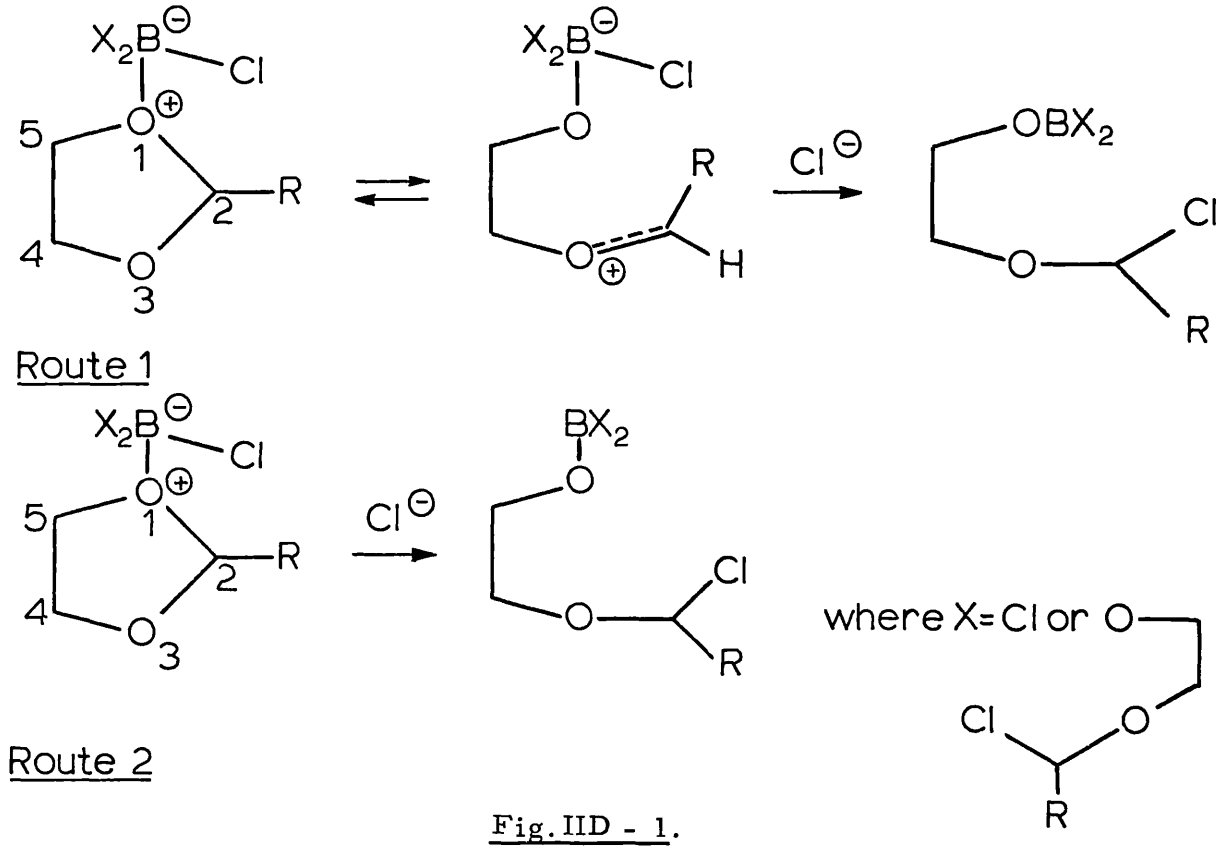
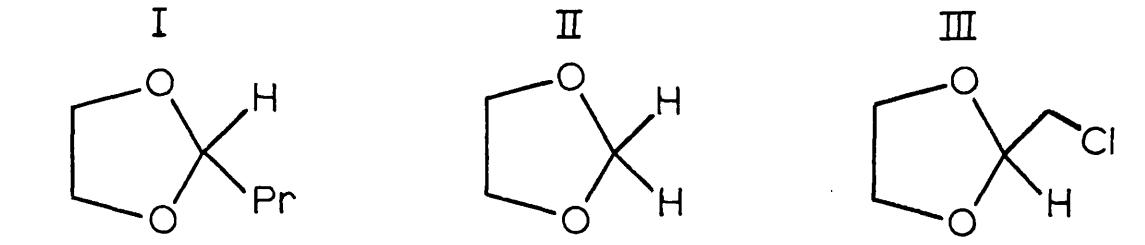


Fig. IID - 1.

Thus as far as route 1 is concerned the presence of a +I group at C_2 would stabilize the oxocarbonium species thereby facilitating ring cleavage and the subsequent formation of an α-chloroether. Similarly a -I group at C_2 would tend to retard α-chloroether formation.

However, if nucleophilic attack of the chloride ion is the initiating step to ring cleavage then one would expect the electronic nature of the C_2 substituent to have the reverse effect on the ease of cleavage. This is because a +I group at C_2 would produce a less attractive site for nucleophilic attack than would a -I group, and so the cleavage process would be less likely to occur in the former case. Hence route 1 would predict that the relative ease of α-chloroether formation and therefore hydrogenolysis of compounds I, II and III (figure IID - 2) would be in the order I > II > III while route 2 would predict the reverse order. Thus by placing two of the shown compounds in the presence of a deficient amount of boron trichloride it was hoped that a qualitative estimation of their relative reactivities could be made.



2-n-propyl - 1, 3-dioxolane

1, 3 - dioxolane

2-chloromethyl -1, 3 - dioxolane

Fig. IID-2.

In the first reaction 2-n-propyl-1, 3-dioxolane (0. 0097 mol.) and 1, 3-dioxolane (0. 0097 mol.) were added to a solution of boron trichloride (0. 00195 mol.) in methylene dichloride and the resulting solution was stirred for 10 minutes at 0°. The reaction mixture was then treated with an ethereal solution of lithium aluminium hydride in the usual way and after work-up a sample of the product mixture was analysed using gas liquid chromatography. A comparison of the relative amounts of 2-n-butoxy ethan-1-ol and 2-methoxy ethan-1-ol present in this mixture could then be made. A similar procedure was repeated using 2-chloromethyl- 1, 3-dioxolane and 1, 3-dioxolane as the competing substrates.

Compound mixture	Products			Relative amounts of products (mole %)
I + II	2-n-butoxy ethan-1-ol	+	2-methoxy ethan-1-ol	~100: very small
II + III	2-methoxy ethan-1-ol	+	2-(2-chloroethoxy) -ethan-1-ol	95.2: 4.8

Table IID - 1

Table IID - 1 shows that the relative product ratios are in the sequence I > II > III which, according to the discussion above, is that which would be expected if route 1 were the relevant reaction pathway.

The assumption has been made in the above discussion that the isolated hydroxyether ratios are a direct translation of the α-chloroether ratios that existed in the system before the addition of the lithium aluminium hydride. On a qualitative basis this does not appear to be an unreasonable assumption as any change in the conditions, such as the nature of the solvent system, is common to both substrates and occurs after the formation of the respective α-chloroether.

(b) Substituents at C_4 on the 1, 3-dioxolane ring.

If the conclusions from the preceding experiments are correct then this implies that the electronic nature of substituents at positions 4 or 5 on the 1, 3-dioxolane ring can influence the direction of bond cleavage, in the sense that one of the two possible oxocarbonium ions would be electronically preferred. Thus a +I group would favour cleavage of the C_2-O bond farther from it while a -I group would favour cleavage of the nearer C_2-O bond (fig. IID - 3).

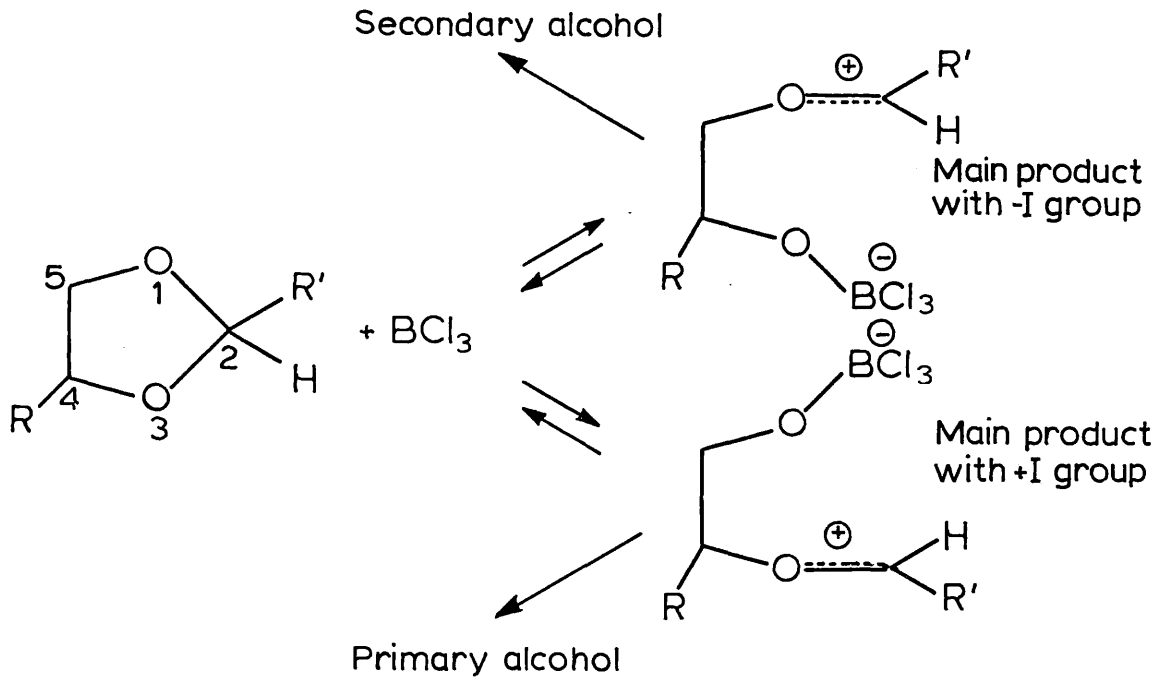
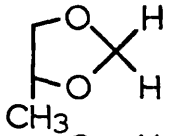
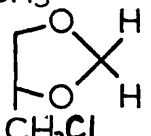
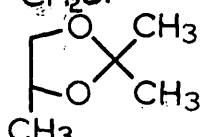
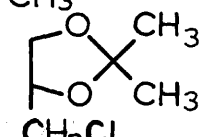


Fig. IID - 3.

The substrates shown in Table IID - 2 were then prepared and treated with boron trichloride/lithium aluminium hydride in the usual way. After work-up the product mixtures were analysed using gas liquid chromatography and were shown to consist of the respective hydroxyether isomers plus small amounts of the diols: in no case was there any residual substrate observed.

	Reaction Substrate	Products		Yield(%)	Reaction time* (mins)
		Primary Alcohol (%)	Secondary Alcohol (%)		
1		95	5	95	10
2		7	93	90	10
3		44	56	92	2
4		5	95	87	2

* "Reaction time" denotes time in contact with BCl_3

Table IID - 2.

It can be seen in reactions 1, 2 and 4 that the cleavage has been directed in a manner that would be expected from a mechanism in which oxocarbonium ion stability played a dominant role. Hence the +I methyl group in 4-methyl -1, 3-dioxolane (1) gives predominant cleavage at C_2-O_1, while the -I chloromethyl functions of 4-chloromethyl-1, 3-dioxolane (2) and 4-chloromethyl-2, 2-dimethyl-1, 3-dioxolane (4) favour cleavage of the C_2-O_3 bond.

The results from reaction 3 do not follow this simple trend however, as there is no single dominant product because cleavage of C_2-O_1 and C_2-O_3 has occurred to approximately the same degree. It must be admitted that there is no clear explanation for this observed product ratio, all that can be said is that it is the net result of a complex interplay between the slightly different basicities of O_1 and O_3 ($O_3 > O_1$ due to the C_4 methyl substituent), the different oxocarbonium ion stabilities (also due to the C_4 substituent) and the stereochemistry present in the transition states to the cleavage reactions.

Leggetter and Brown[1, 12] have shown that the stereochemistry present in the transition state is important in deciding the direction of cleavage of highly substituted dioxolanes. In particular 2, 2, 4, 4-tetramethyl-1, 3-dioxolane gave only 6% primary alcohol and 94% of the tertiary alcohol, due to the steric congestion present in the oxocarbonium ion given upon cleavage of C_2-O_1 which would have been the electronically favoured oxocarbonium ion (fig. IID - 4).

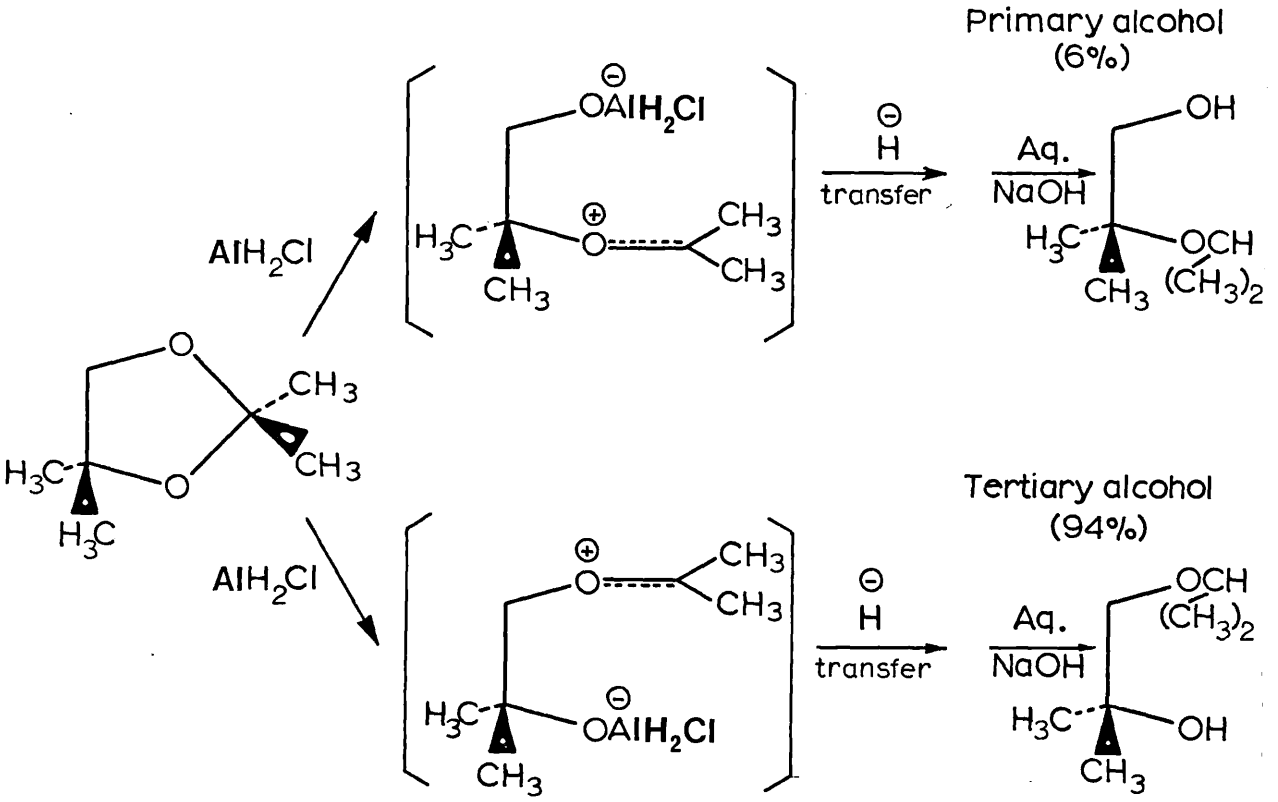


Fig. IID - 4.

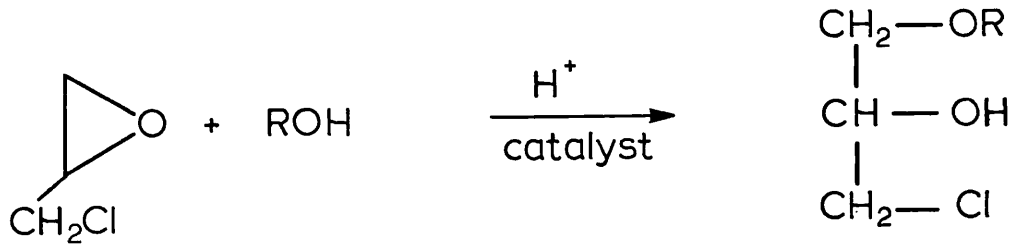
The same workers also showed that 2, 2, 4-trimethyl-1, 3-dioxolane gave "normal" electronically directed cleavage with aluminium dihydrochloride. In the light of the fact that the boron (in boron trichloride) may still attack the dioxolane when already bonded to two molecules of cleaved acetal (p.40) whereas the aluminium species works to a 1:1 stoichiometry, it is not surprising then that steric factors come into play earlier in the boron trichloride/lithium aluminium hydride reaction (for a given series of substrates) than they do in the aluminium dihydrochloride reactions.

What is important however, is that these experiments show that the cleavage reactions are not necessarily directed by simple electronic factors but that they may be the result of a far more complex interplay of many factors.

The main methods of structure proof for the products used in the above experiments were as follows. First by repeating the hydrogenolysis reactions with aluminium dihydrochloride[1] and

comparing the retention times of the known products from these reactions with those given by the boron trichloride/lithium aluminium hydride reactions. This was essentially conclusive proof as the relative proportions of each isomer given by the aluminium dihydrochloride are well documented and so makes identification of individual isomers possible.

By way of confirmation one of the isomers of each pair was synthesised by an independent route. Hence 1-chloro-3-methoxy propan-2-ol and 1-chloro-3-isopropoxy propan-2-ol[13] were prepared by treating 3-chloro-1, 2-epoxypropane with the appropriate alcohol, in the presence of sulphuric acid as catalyst (fig. IID - 5).



Probable mechanism

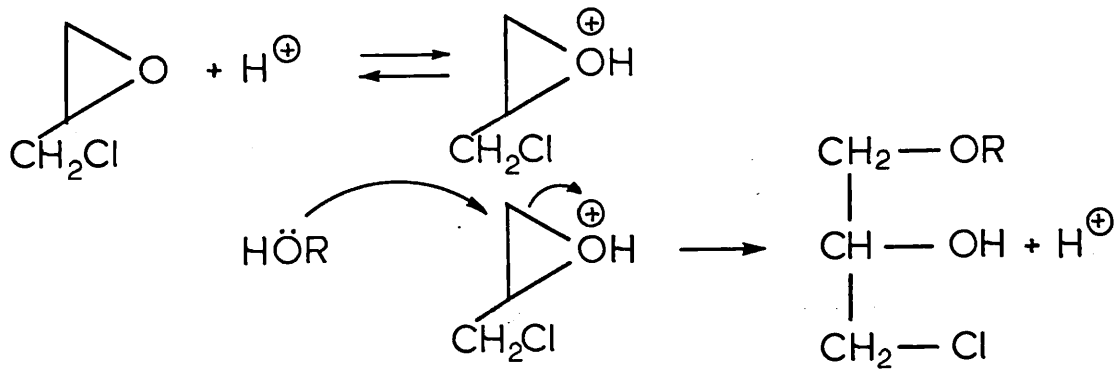


Fig. IID - 5.

1-Methoxy-propan-2-ol was prepared from 1,2-epoxy propane and sodium methoxide[14] (fig. IID - 6) while 1-isopropoxy propan-2-ol[15] was given from the sodium hydroxide catalysed addition of propan-2-ol to 1,2-epoxypropane.

$$2\,MeOH + 2Na \longrightarrow 2MeO^{\ominus}\,Na^{\oplus} + H_2$$

Probable mechanism

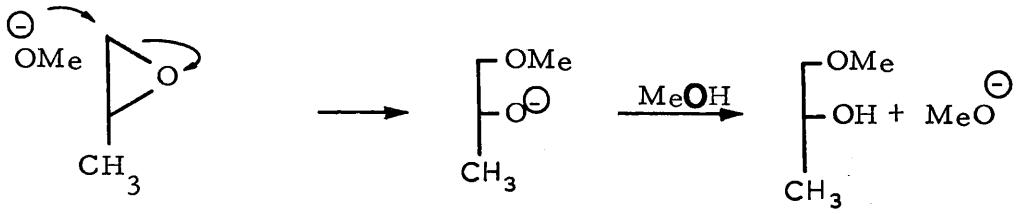


Fig. IID - 6.

(c) Donation of the chloride ion.

At this stage it was confidently assumed that an oxocarbonium ion was the species attacked by a chloride ion to give an α-chloroether. However the mechanism of the attack was uncertain.

Davis and Brown[2] were able to show that hydride donation during the hydrogenolysis of 1,3-dioxolanes by aluminium dihydrochloride occurs via a 4-centre transition state in a necessarily intramolecular reaction. The way they did this was to use a number of 2-(2-alkylvinyl)-1,3-dioxolanes as the substrate for hydrogenolysis.

These on treatment with aluminium dihydrochloride gave one product in every case, by addition of the hydride ion to C_2 on the dioxolane ring. However figure IID - 7 shows that there are two possible reaction sites in the oxocarbonium species given from a 2-(2 alkylvinyl)-1,3-dioxolane, and so they concluded that the exclusive modification of the α-site implied an intramolecular process proceeding via a 4-centre transition state.

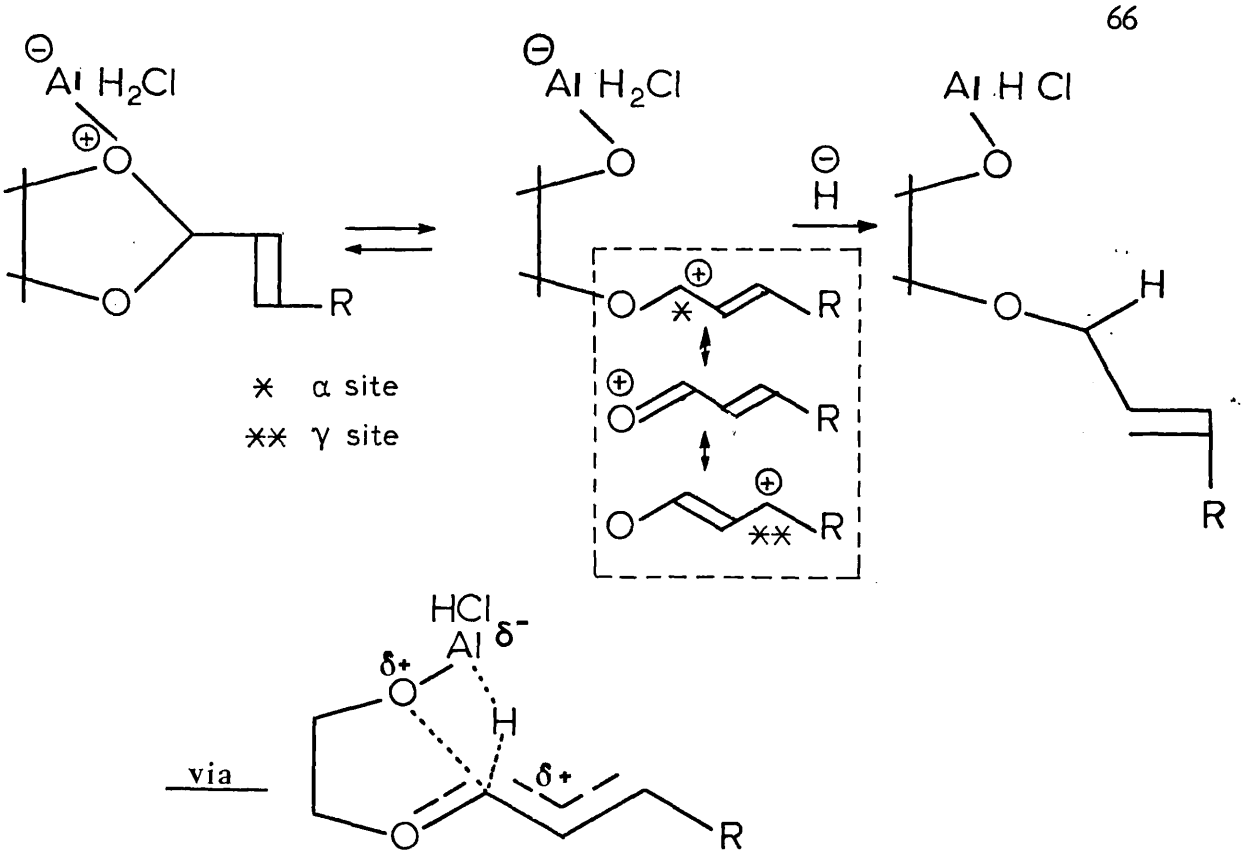


Fig. IID - 7.

It was decided to try an analogous reaction using the boron trichloride/lithium aluminium hydride combination upon 2-vinyl-1, 3-dioxolane and 2-(prop-1-enyl)-1, 3-dioxolane when the same choice of reaction sites would be available to the chloride ion. Also as allyl chlorides would not undergo appreciable reduction by the lithium aluminium hydride under the prevailing conditions, one would expect any γ-chlorination product to be translated to the final work-up mixture (fig. IID - 8).

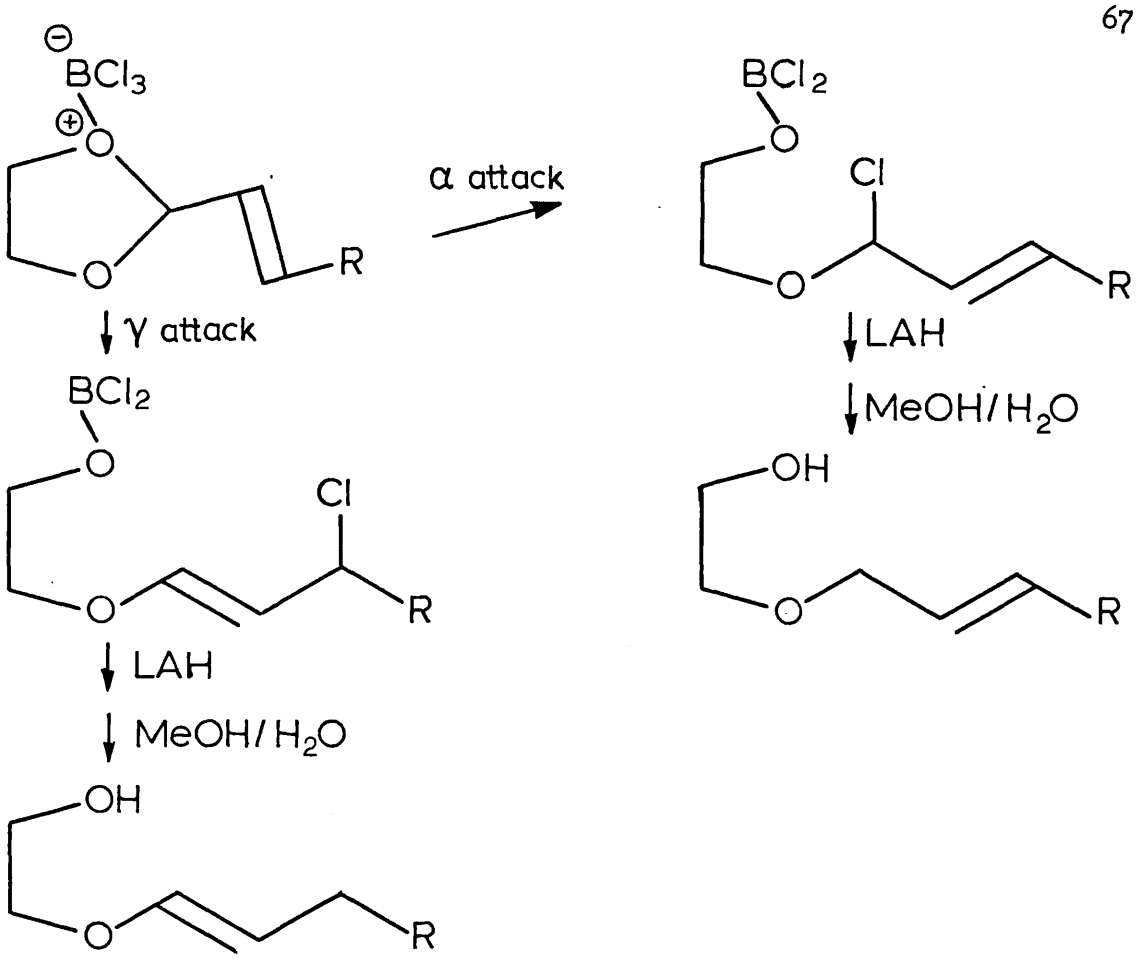


Fig. IID - 8.

A 3:1 mixture of 2-vinyl-1, 3-dioxolane and boron trichloride was stirred together for 10 minutes and then treated with an ethereal suspension of lithium aluminium hydride. The product mixture given on work-up was analysed via gas liquid chromatography as was the product isolated when the same procedure was repeated using 2-(prop-1-enyl)-1, 3-dioxolane as substrate.

In both cases only one main component was present in the work-up material and the small amount of impurity present was shown to be ethan-1, 2-diol on the basis of its retention time. Similarly the main products were shown to be 2-allyloxy ethan-1-ol and 2-(but-2-enyloxy) ethan-1-ol respectively, by comparison of their p.m.r. spectra and g.l.c. retention times with independently prepared reference samples of the same compounds (Table IID - 3).

Substrate	Product	Yield
2-Vinyl-1,3-dioxolane	2-allyloxy ethan-1-ol	81%
2-(Prop-1-enyl)-1,3-dioxolane	2-(but-2-enyloxy) -ethan-1-ol	77%

Table IID - 3.

The conclusion drawn from this experiment must be that the chloride ion is transferred via an intramolecular process probably involving a 4-centre transition state. A second interesting feature in the mechanism of chloride donation is that in order to achieve maximum coplanarity with the nascent oxocarbonium ion, the chloride has to approach from the top of the molecule, which implies that the boron has to be bonded to the axially - or pseudo axially - disposed lone pair of the oxygen in the transition state. A further implication of this aspect of the mechanism will be discussed in the next section (fig. IID - 9).

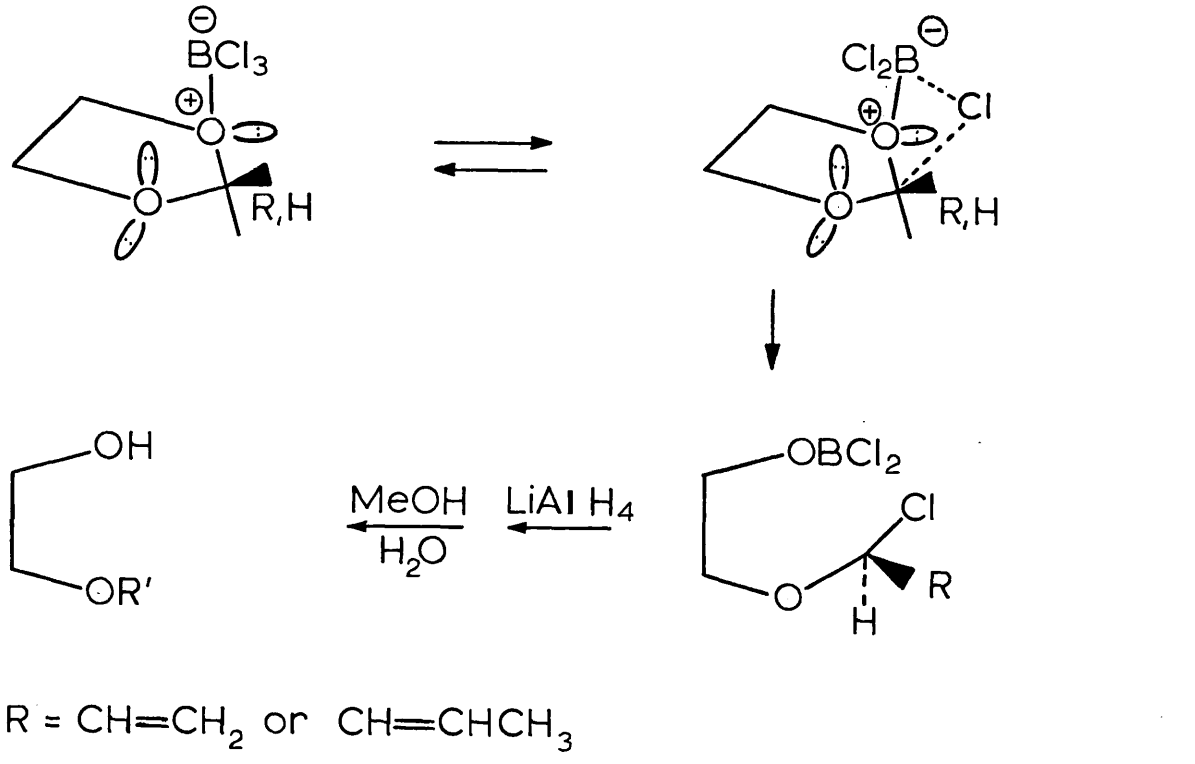


Fig. IID - 9.

The two dioxolanes used in the above experiments were prepared from ethan-1, 2-diol and the appropriate aldehydes using p-toluenesulphonic acid as the catalyst.[2] The water produced in the reaction was removed as its toluene azeotrope (fig. IID - 10).

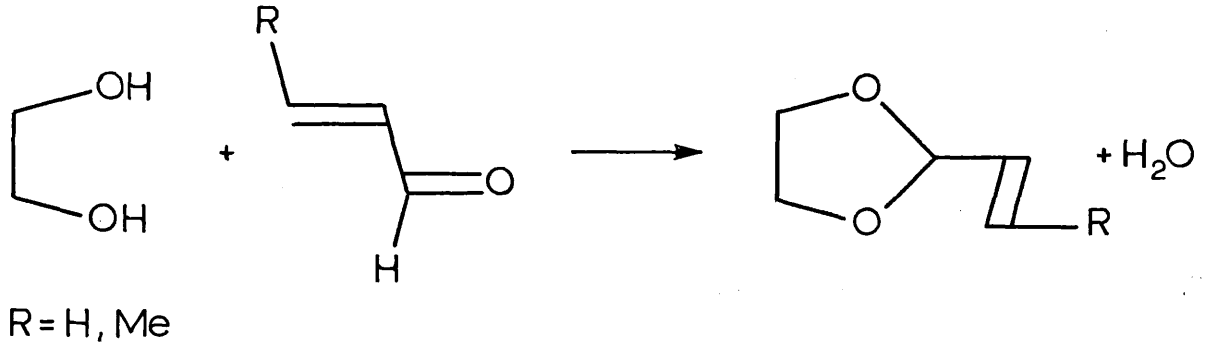


Fig. IID - 10.

The reference product 2-allyloxy ethan-1-ol was prepared from the monosodium salt of ethan-1, 2-diol and allyl bromide using 1, 2-dimethoxy ethane as the solvent. A similar procedure was used to prepare trans-2-(but-2-enyloxy)-ethan-1-ol in which 1-chloro-but-2-ene was the halide used (fig. IID - 11).

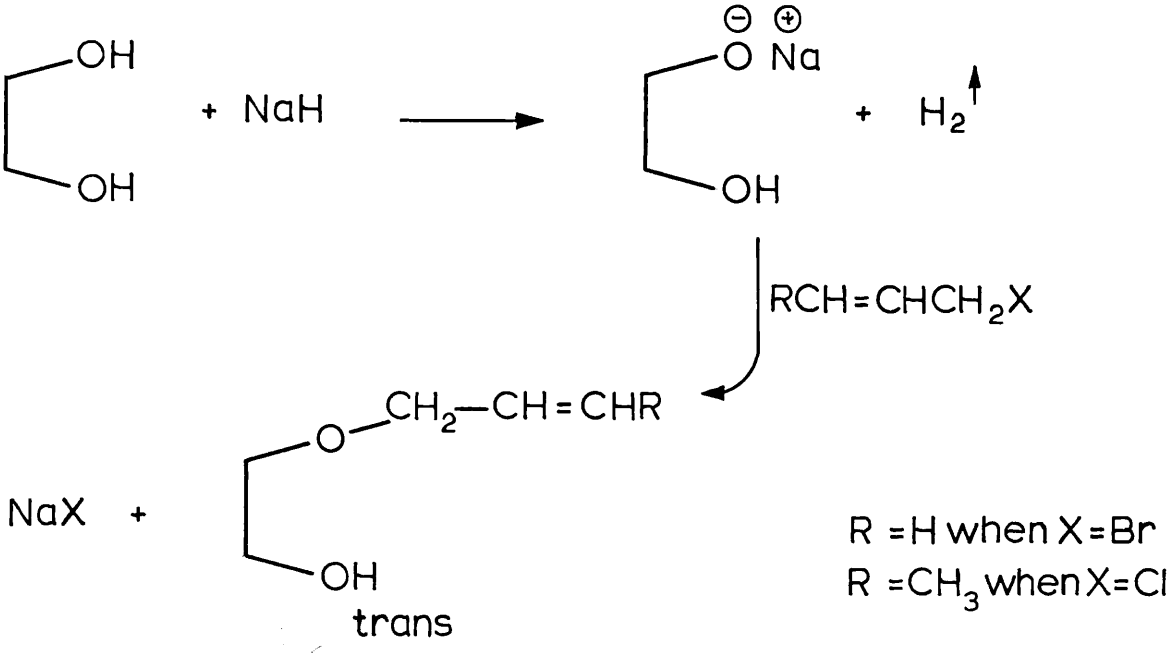


Fig. IID - 11.

(d) Effect of ring size.

The conclusion reached after sections IID - a, b and c is that an oxocarbonium ion is the substrate to α-chloroether formation in the reaction between boron trichloride and a cyclic acetal. Bearing in mind the substituent effects discussed in these sections it follows that any factor which can retard or accelerate the formation of the oxocarbonium species will have a similar effect upon the amount of α-chloroether available for reduction by the lithium aluminium hydride. One such factor is the size of the acetal ring, which largely determines the conformational itinerary of the acetal and therefore dictates the

degree of difficulty with which the molecule can attain the correct geometry necessary for oxocarbonium ion formation.[16] To recap, this demands that the plane containing C_5-O_1-C_2 should be perpendicular to the C_4-O_3-C_2 plane, hence allowing maximum electronic assistance by O_1 (say) in the breaking of the C_2-O_3 bond (fig. IID - 12).

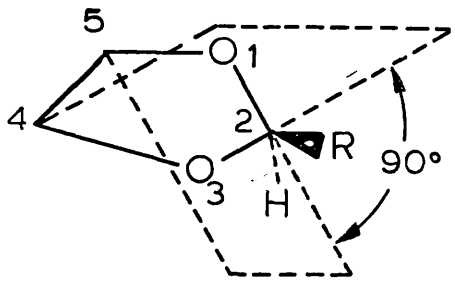


Fig. IID - 12.

In order to investigate the effects of ring size upon the relative ease of cleavage a series of experiments were performed in which two acetals of different ring size were placed in competition for a deficient amount of boron trichloride. Thus any difference in the relative amounts of the α-chloroethers produced would be reflected in the ratio of the hydroxyethers present in the final work-up mixture, after treatment with lithium aluminium hydride. The 2-propyl derivatives of 5, 6, 7 and 8 membered cyclic acetals were the particular substrates used, prepared as described in section IIC - iib.

In the first experiment a mixture of 2-propyl-1, 3-dioxolane (0.04 mol.) and 2-propyl-1, 3-dioxane (0.04 mol.) was added to a stirred ice-cooled solution of boron trichloride (0.01 mol.) in methylene chloride. After 10 minutes the reaction mixture was treated with ethereal lithium aluminium hydride in the usual way and after work-up, the relative proportions of 2-butoxy ethan-1-ol and 3-butoxy propan-1-ol were estimated by gas liquid chromatography.

A similar procedure was then repeated for the following pairs of compounds: 2-propyl-1, 3-dioxane plus 2-propyl-1, 3-dioxepane and 2-propyl-1, 3-dioxepane plus 2-propyl-1, 3-dioxocane. The relative proportions of cleavage products are shown in Table IID - 4, where it can be seen that the overall reactivity of the acetals used is in the sequence, dioxolane ~ dioxane < dioxepane ~ dioxocane, i. e. 5 ~ 6 < 7 ~ 8.

Substrates (as ring size)	Product ratio
5 + 6	1 : 1.2
6 + 7	1 : 30
7 + 8	1 : 1

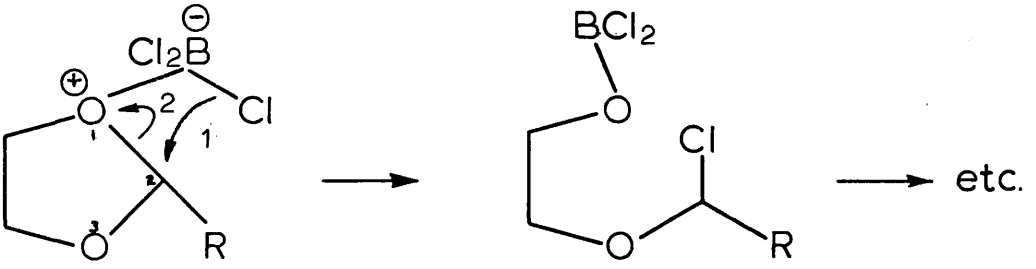
Table IID - 4.

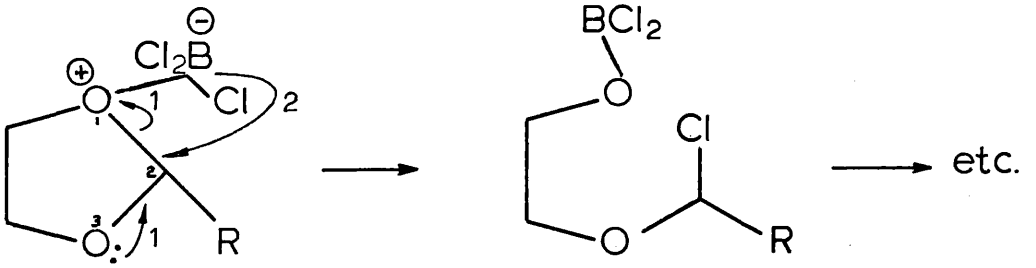
Now if ease of attainment of the transition state - to oxocarbonium ion formation - was the only relevant criterion to consider then one would expect the order of reactivity to be 5<6~7~8. This is because the conformational demands of the transition state involve a greater degree of strain in the dioxolane system than in the other acetals and consequently its attainment requires a higher activation energy. It seemed then that there was some other relevant factor (or factors) operating which was more important in 2-propyl-1, 3-dioxane than in the other acetals and that this factor (or factors) was responsible for the disparity between the observed and expected results.

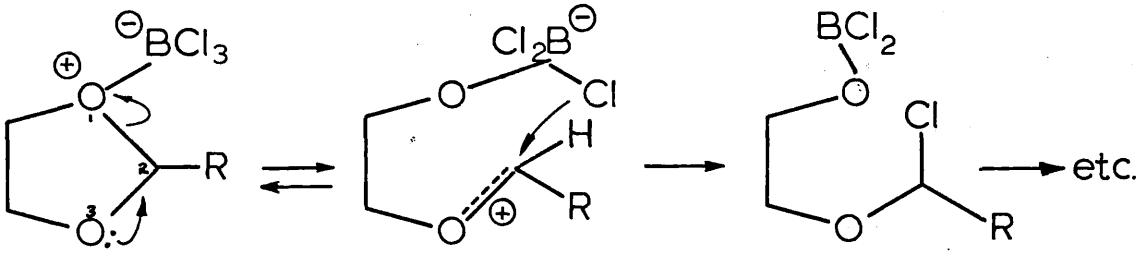
A possible explanation for the lower reactivity of the dioxane system may be gleaned if the formation of the α-chloroether from the trichloride-acetal complex is considered as two very closely related events, the initial formation of the oxocarbonium species and the intramolecular donation of the chloride ion. They must be considered as such because experiment has shown that the oxocarbonium ion

"concept" is more relevant than the chloride-initiated-cleavage model, in which the chloride nucleophile is dominating the, say, O_3 nucleophile. However the idea of an autonomous oxocarbonium species undergoing attack by the chloride ion (i.e. in which the O_3 nucleophile completely dominates) is not really feasible in the solvent system used (fig. IID-13).

Chloride dominates







O_3 dominates

Fig. IID - 13.

Consider then a molecule of the Lewis acid, which still therefore possesses at least one chlorine atom, bonded to the axial lone pair (Section IID - ii) of say O_1. The dioxane is in the chair form with the n-propyl function equatorially disposed and hence the requisite geometry for oxocarbonium formation is present. Now as C_2 - O_1 begins to break the C_2 - O_3 bond rotates in such a manner as to move the acetal proton into the ring[17] thereby allowing maximum overlap between a lone pair of electrons upon O_3 and C_2. It is this movement of the acetal proton which is of interest because molecular models show that interaction between this proton and the C_5 proton must occur. This interaction is made more likely by the fact that donation of the chloride ion into the nascent oxocarbonium species demands that C_2 and O_1 remain in virtually status quo positions, so that the interaction cannot be relieved by the ring uncurling. Therefore even though the initial geometrical requirements for the transition state to oxocarbonium ion formation are easily met, the added requirements necessary for chloride ion transfer mean that the overall formation of the α-chloroether is less favourable than if the two events had been completely autonomous. Meanwhile in the 1, 3-dioxolane there is no such hindrance to the rotation of the acetal proton but the initial requirements are not so readily given. For the 1, 3-dioxepane both processes can occur with relatively little hindrance while the molecule is in the shown (fig. IID - 14) stable configuration and so the α-chloroether is given more readily than in the five and six membered rings. A similar situation exists in the 2-n-propyl-1, 3-dioxocane.

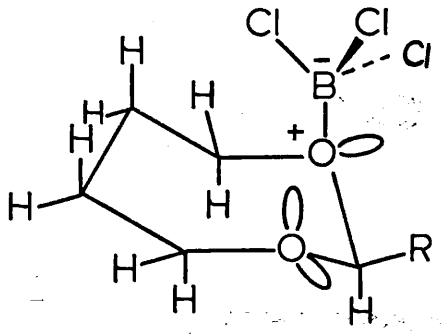


Fig. IID - 14.

IIE. Conclusion.

In conclusion then one of the original aims of this chapter was to investigate the possibility of using boron trichloride plus lithium aluminium hydride as a cleavage reagent for cyclic acetals, in particular those which proved resistant to the aluminium chlorohydrides and borane. This has been largely achieved in that the unsubstituted and 2-chloromethyl derivatives of a number of acetals of different ring sizes and C_4 substituents have been cleaved in good yield and under fairly mild conditions.

Also under consideration was the reaction pathway, especially that prior to addition of the lithium aluminium hydride. The weight of experimental evidence presented above favours a mechanism (fig. IIE - 1) in which rapid formation of the Lewis complex is followed by the acetal ring cleaving via an oxocarbonium ion dominated process. Intramolecular chloride ion transfer then occurs to give an α-chloro-ether and this whole process is repeated twice more until all of the chlorine on the boron has been replaced by cleaved acetal molecules.

The formation of the oxocarbonium ion dominates the reaction to the extent that substituents which electronically stabilize or de-stabilize its formation can effect both the relative ease and direction of cleavage although as the substituents become more bulky or the size of the ring changes steric factors begin to be superimposed upon the electronic picture, with a consequent loss in resolution. This is a necessary drawback in models of this type in that the rationalization shown in figure IIE - 1 can only really be applied to the tailored substrates used above. In more complex molecules one can only extrapolate so far, as seen in the 2, 2, 4-trimethyl-1, 3-dioxolane reaction in which an internal chloride-ion-initiated cleavage alone would have accounted for the observed products. Nevertheless this work does provide a reference point to which more complex molecules can be compared and so it is hoped that the original aims mentioned

in section IIA have been largely achieved.

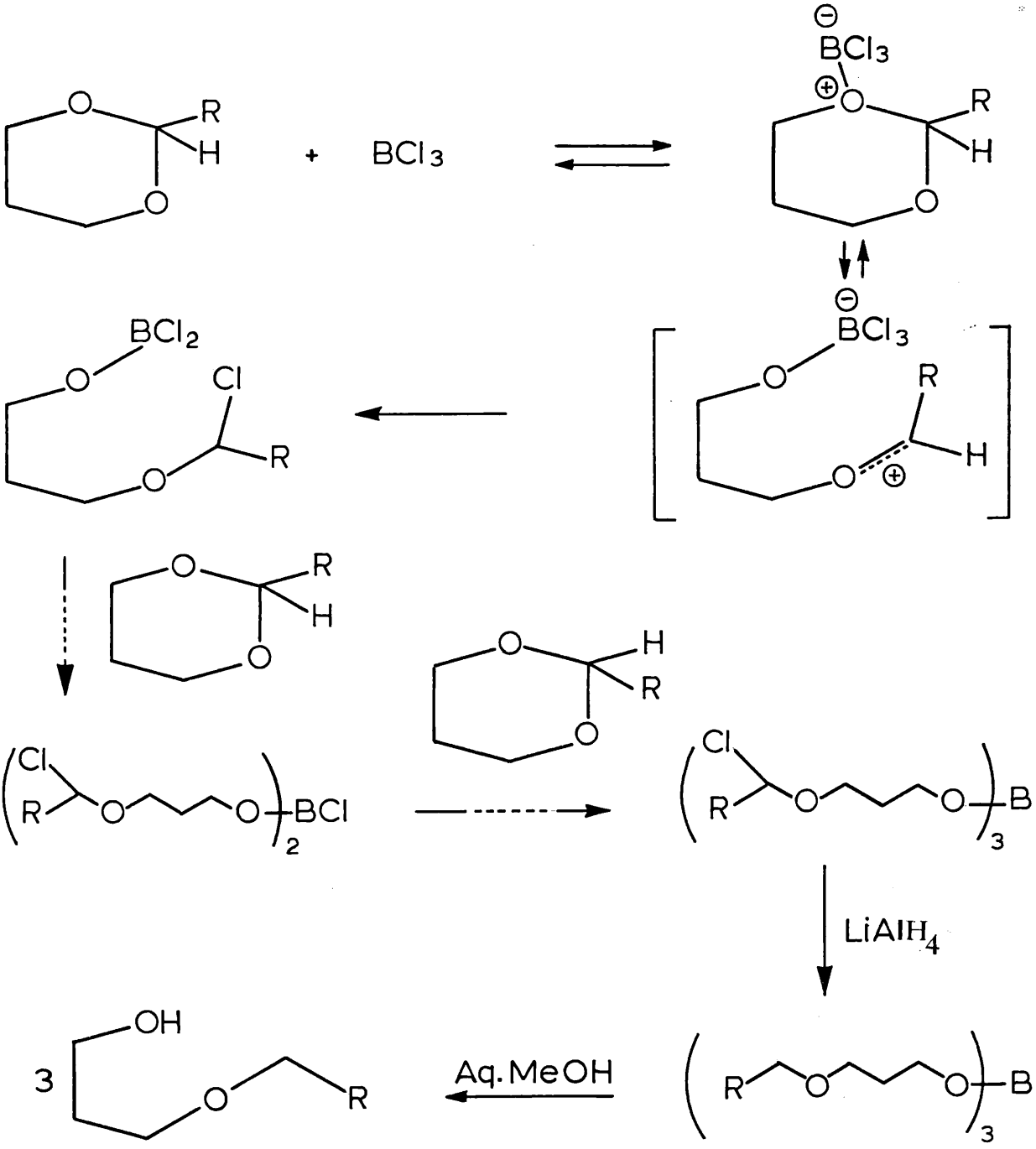


Fig. IIE - 1.

IIF. Experimental.

The details of every experiment mentioned in Chapter II will be given in this section. The experiments are listed largely in the order in which they appear in the text, apart from those dealing with the preparations of the substrate acetals and the preparations of the hydroxy ether reference materials, which are all grouped together at the end of the section.

Experiment 1. General procedure used in all acetal plus boron trichloride/lithium aluminium hydride reactions.

(a) Addition of boron trichloride.

The apparatus shown in figure IIF - 1 was dried at 150° for 2 - 5 h. and then after assembly, allowed to cool with a stream of dry nitrogen passing through it.

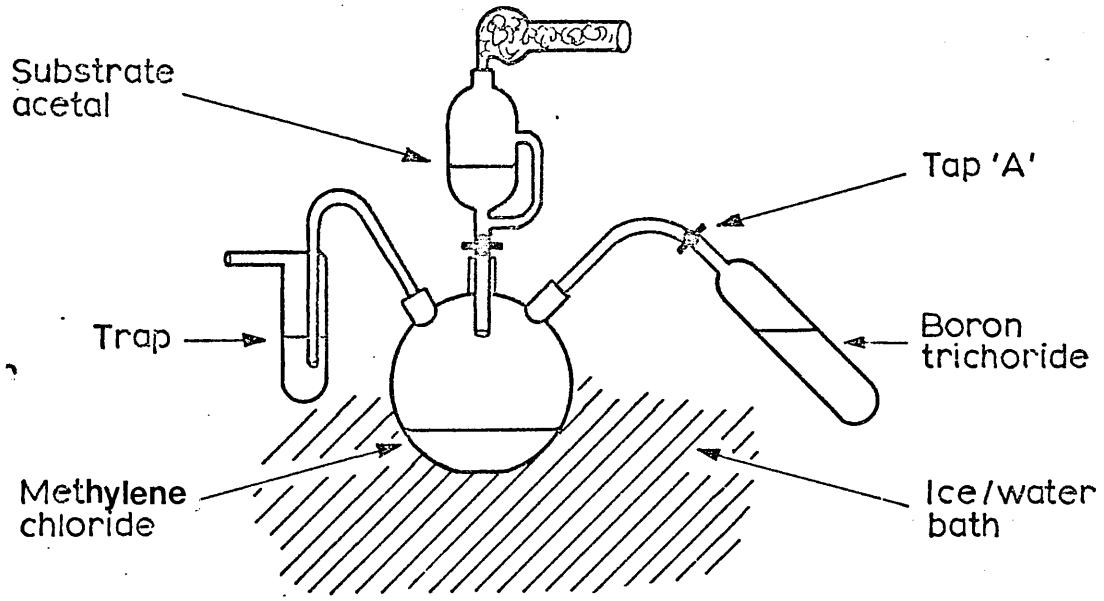


Fig. IIF - 1.

When the apparatus had cooled to room temperature dry methylene chloride was placed in the 3-necked flask. The flask and contents were then weighed.

The flask was then placed into an ice/water bath and the methylene chloride cooled to 0^{o}. Tap "A" was then opened and the boron trichloride allowed to condense over into the stirred methylene chloride: the amount of trichloride present could then be found by reweighing the flask and contents.

(b) Addition of acetal.

The particular acetal under study, dissolved in methylene chloride, was then slowly added via the self-equilibrating funnel to the stirred solution of boron trichloride.

When the required reaction time had elapsed the ice/water bath was removed and a suspension of lithium aluminium hydride in diethyl ether was slowly added to the stirred reaction mixture. The hydrogen evolved due to the addition of the hydride was allowed to escape through the shown trap.

When effervescence had stopped (generally after about 30 minutes), the reaction was worked-up using the procedure outlined on page 38.

The ratio of acetal to boron trichloride used in each case along with the contact time of the two reactants, depended upon the nature of the acetal and the aim of the individual experiment: the values of these parameters will therefore be quoted as the relevant experiments are discussed.

Experiment 2. The reaction of 2-n-propyl-1, 3-dioxane with boron trichloride/lithium aluminium hydride.

(a) Using the above procedure 2-n-propyl-1, 3-dioxane (1.3 g., 0.01 mol.) was reacted with boron trichloride (1.2 g., 0.01 mol.) and lithium aluminium hydride (0.4 g., 0.01 mol.). The product given on work-up was a pale green oil (1.1 g., 83%) which was shown

to consist of two components A (91%) and B(9%) by g.l.c. analysis.

The g.l.c. retention time of the major component (A) was then compared with that of an authentic sample of 3-n-butoxy propan-1-ol; they were identical. Meanwhile B was shown to have the same retention time as propan-1,3-diol.

Distillation of the crude product gave a colourless oil the b.p. and p.m.r. spectrum of which were comparable to those given by 3-n-butoxy propan-1-ol.

Yield 0.9 g. (68%). B.p. 78-80°/ 10 mm. (B.p. of 3-n-butoxy propan-1-ol[18] 81-5°/13 mm).

(b) The experiment was then repeated using different ratios of acetal to boron trichloride/lithium aluminium hydride. The ratios in question along with the yields of 3-n-butoxy propan-1-ol given in each case are shown below in Table IIF - 1.

Ratio of acetal to $BCl_3/LiAlH_4$	Total crude yield (%)	Proportion of hydroxy ether in crude yield (%)	Proportion of acetal in crude yield (%)
1:1	83	91	0
2:1	82	~90	0
3:1	85	>95	0
4:1	90	71	23
5:1	87	57	37

Table IIF - 1.

Note : Approximately 5% diol was present in every reaction.

Experiment 3. The reaction of 2-n-propyl-1, 3-dioxane with boron trichloride/lithium aluminium hydride in the presence of propan-2-ol and ethan-1, 2-diol.

(a) Propan-2-ol (0.51 g., 0.0085 mol.) was slowly added to a stirred solution of boron trichloride (1 g., 0.0085 mol.) in methylene chloride at 0°. The hydrogen chloride evolved was allowed to escape

during a 20 minute period while the reaction mixture was vigorously stirred.

After this time a solution of 2-n-propyl-1, 3-dioxane (2.21 g., 0.017 mol.) in dry methylene chloride (15 ml.) was added and the resulting solution stirred for 5 minutes.

A suspension of lithium aluminium hydride (0.4 g., 0.01 mol.) in dry diethyl ether (5 ml.) was slowly dropped into the reaction mixture which was then stirred until effervescence had stopped.

The reaction was then worked-up in the normal way using cooled aqueous methanol giving a pale-green oil as the product, (2.3 g., 84.5%).

G.l.c. analysis of this product showed that it contained two components which were shown to be propan-2-ol (24%) and 3-n-butoxy propan-1-ol (76%) by comparison of retention times with authentic samples of these two compounds.

(b) Essentially the same procedure was then repeated using ethan-1, 2-diol (0.53 g., 0.0085 mol.), 2-n-propyl-1, 3-dioxane (2.21 g., 0.017 mol.), boron trichloride (1 g., 0.0085 mol.) and lithium aluminium hydride (0.4 g., 0.01 mol.).

G.l.c. analysis of the product mixture given showed that it contained two components. These were shown to be ethan-1, 2-diol (21%) and 3-n-butoxy propan-1-ol (73.3%) by the usual method of retention time comparison with reference compounds.

Experiment 4. An attempted reaction between 2-n-propyl-1, 3-dioxane and hydrogen chloride/lithium aluminium hydride.

Hydrogen chloride (made by dropping concentrated sulphuric acid on to concentrated hydrochloric acid) was bubbled into dry, ice-cooled methylene chloride (25 ml.). The flask and contents had previously been weighed so that the weight of hydrogen chloride added (0.73 g., 0.02 mol.) was given by simple substraction. 2-n-Propyl-1, 3-dioxane (1.7 g., 0.013 mol.) in methylene chloride (10 ml.) was

then also added and the resulting solution stirred for 10 minutes.

An ethereal suspension of lithium aluminium hydride (0.49 g., 0.013 mol. in 10 ml.) was slowly dripped on to the reaction mixture which was then stirred for a further 30 minutes at room temperature.

Work-up in the usual way gave an oil (1.56 g., 92%) which was shown to be a single component by g.l.c. analysis. The retention time and p.m.r. spectrum of this component were identical to those given by 2-n-propyl-1,3-dioxane.

Experiment 5. Experiments to show the participation of an α-chloroether in the acetal-boron trichloride reaction.

(a) 2-n-Propyl-1,3-dioxane (2 g., 0.015 mol.) in dry carbon tetrachloride (10 ml.) was slowly added to a stirred ice-cooled solution of boron trichloride (0.6 g., 0.005 mol.) also dissolved in carbon tetrachloride (25 ml.).

After 2 minutes a sample (2 ml.) of the reaction mixture was removed and its 60 MHz p.m.r. spectrum was taken. This procedure was then repeated at intervals of 30 minutes, 1 h., 5 h., and 24 h.,

The p.m.r. spectra given over this period were essentially the same. They did not contain any signals at the normal acetal proton shift (4.5 δ^{8}) but did contain a triplet at 5.75 δ^{8} integrating to one proton.

(b) The above procedure was then repeated with a 6:1 ratio of acetal (4 g., 0.03 mol.) and boron trichloride (0.6 g., 0.005 mol.).

The 60 MHz p.m.r. spectrum of the mixture (after 2 minutes) showed the presence of both an acetal proton triplet (4.5 δ) and the so-called α-chloroether triplet (5.75 δ).

(c) The reaction mixture used in (a) was then treated with an ethereal suspension of lithium aluminium hydride (0.2 g., 0.005 mol.).

The 60 MHz p.m.r. spectrum of the resulting mixture after 30 minutes contained neither the acetal proton triplet nor the so-called α-chloroether triplet.

Work-up of this mixture in the normal way gave 3-n-butoxy-propan-1-ol as the major product.

(d) 2-n-Propyl-1,3-dioxane (2.34 g., 0.018 mol.) was treated with boron trichloride (0.72 g., 0.006 mol.) at 0° in methylene chloride in the usual way.

The reaction mixture was then allowed to rise to room temperature and the methylene chloride was removed over a 1 h. period under reduced pressure (10 mm.). As the methylene chloride distilled over it was collected in two cold traps immersed in liquid air along with any boron trichloride that may have distilled over.

When all of the methylene chloride had been removed the p.m.r. spectrum of the resulting syrup (3.0 g.) was found to be identical to that taken in (a). The I.R. spectrum of the syrup showed the presence of a large B-O stretch (1340 $cm.^{-1}$), a C-Cl stretch (670 $cm.^{-1}$ and 750 $cm.^{-1}$) while B-Cl stretch (900 $cm.^{-1}$) and OH-stretch (ca. 3500 $cm.^{-1}$) were absent.[9]

Meanwhile the condensed methylene chloride was warmed to room temperature and washed with distilled water (10 ml.) to hydrolyse any boron trichloride present. Titration of these washings with 0.1N sodium hydroxide solution (using phenolphthalein as indicator) showed that 1.5 ml. of alkali was needed to effect neutralization. Thus 0.006 g. of boron trichloride had been collected in the traps.

Experiment 6. The reactions of other cyclic acetals with boron trichloride/lithium aluminium hydride.

The experimental procedure outlined in Experiment 1 was then repeated for the cyclic acetals shown in Table IIC - 1 (p. 51) The yields of the hydroxyethers given in each case are also displayed.

The ratio of acetal to boron trichloride/lithium aluminium hydride was 3:1 in each case, although the 2-chloromethyl-1,3-dioxolane and 2-chloromethyl-1,3-dioxane reactions were repeated using a 1:1 ratio in order to increase the yields of the respective products [2-(2-chloroethoxy)-ethan-1-ol and 3-(2-chloroethoxy)-propan-1-ol].

Experiment 7. The cleavage products given by the 2-chloromethyl substituted acetals (using the procedure described in Experiment 1).

(a) 2-(2-Chloroethoxy)-ethan-1-ol was given by 2-chloromethyl-1,3-dioxolane.

B.p. 174-8° (Lit. b.p. 70°/3 mm.)[1]

(b) 3-(2-Chloroethoxy)-propan-1-ol was given by 2-chloromethyl-1,3-dioxane.

B.p. 68-70°/2 mm.

Analysis: $C_5H_{11}ClO_2$ requires 43.32(C), 7.94(H) %,
found 43.55(C), 8.2(H) %.

Mass spectrum: (of neat compound),
C.I. gives $(M + 1)^+$ at m/e 139, 141.

P.m.r. spectrum: (60 MHz),
3.3 - 3.8δ (m., 8 protons), 2.9δ (s., 1 proton)
1.9δ (q., 2 protons).

G.l.c. retention time:
neat compound = 745 s. (118°, 3% OV-225).

(c) 4-(2-Chloroethoxy)-butan-1-ol was given by 2-chloromethyl-1,3-dioxepane.

B.p. 88 - 90°/ 0.15 mm.

Analysis: $C_6H_{13}ClO_2$ requires 47.2(C), 8.52(H), 23.28(Cl)%,
found 47.42(C), 8.78(H), 23.68(Cl)%.

Mass spectrum: (of neat compound),
C.I. gives $(M + 1)^+$ at m/e 153, 155.

P.m.r. spectrum: (60 MHz),

4.25δ (s., 1 proton), 3.3 - 3.8δ (m., 8 protons)

1.4 - 1.7δ (m., 4 protons).

G.l.c. retention time:

neat compound = 144 s. (174°, 3% OV - 225).

(d) 5-(2-Chloroethoxy)-pentan-1-ol was given by 2-chloromethyl-1,3-dioxocane.

B.p. 100-4°/0.5 mm.

Analysis: $C_7H_{15}ClO_2$ requires 50.45(C), 9.00(H), 21.32(Cl)%,

found 50.78(C), 9.25(H), 21.71(Cl)%.

Mass spectrum: (of neat compound),

C.I. gives $(M+1)^+$ at m/e 167, 169.

P.m.r. spectrum: (60 MHz),

3.3 - 3.8δ (m., 8 protons), 2.9δ (s., 1 proton),

1.3 - 1.7δ (m., 6 protons).

G.l.c. retention time:

neat compound = 235 s. (150°, 3% OV - 225).

Experiment 8. The competitive reactions between two dioxolanes with boron trichloride/lithium aluminium hydride.

(a) 2-n-Propyl-1,3-dioxolane (1.12 g., 0.0097 mol.) and 1,3-dioxolane (0.72 g., 0.0097 mol.) were dissolved in methylene chloride (15 ml.) and treated for 10 minutes with an ice-cooled solution of boron trichloride (0.23 g., 0.002 mol.) in methylene chloride (25 ml.) and then with an ethereal suspension of lithium aluminium hydride (0.11 g., 0.003 mol.) for a further 30 minutes.

Work-up in the usual manner gave a pale-green oil (.87 %). G.l.c. analysis of the product mixture showed that three main components were present. Two of these had the same retention times as the substrate acetals and so were assumed to be the substrates. The third peak was shown to be 2-n-butoxy ethan-1-ol by a similar comparison with an authentic sample of the latter. The only other peak present was due to ethan-1,2-diol: 2-methoxy ethan-

1-ol was not seen.

(b) The experiment was then repeated using 2-chloromethyl-1, 3-dioxolane and 1, 3-dioxolane when the ratio of 2-(2 chloroethoxy)-ethan-1-ol to 2-methoxy ethan-1-ol was found to be approximately 1 to 20.

Experiment 9. Studies into the effects of a C_4 - substituent upon the direction of cleavage of the acetal.

(a) 4-Methyl-1, 3-dioxolane (0.72 g., 0.008 mol.) in methylene chloride (5 ml.) was treated with boron trichloride (0.32 g., 0.0027 mol.) for 10 minutes and lithium aluminium hydride (0.13 g., 0.0034 mol.) for a further 30 minutes.

The product mixture (0.68 g., 94%) was then analysed by g.l.c. which showed the presence of two product peaks, the larger of the two comprising 95% of the product mixture. Comparison of the retention times of these products with the retention times of a known mixture of 2-methoxy propan-1-ol and 1-methoxy propan-2-ol showed that the unknown compounds were the same two compounds: 2-methoxy propan-1-ol was the major component with 1-methoxy propan-2-ol the minor.

The above assumption was further confirmed when the retention time of an authentic sample of 1-methoxy propan-2-ol was compared with that of the minor component.

The reference mixture of 2-methoxy propan-1-ol and 1-methoxy propan-2-ol was prepared from 4-methyl-1, 3-dioxolane after reaction with aluminium dihydrochloride, using the procedure outlined by Leggetter and Brown.[1]

(b) The experiment above was then repeated using the following substrates: 4-chloromethyl-1, 3-dioxolane, 2, 2, 4-trimethyl-1, 3-dioxolane and 4-chloromethyl-2, 2-dimethyl-1, 3-dioxolane. The yields and reaction times for each of these compounds are shown in Table IID - 2 (p.61).

In each case the identities of the cleavage products were determined by comparison with the documented products given by

the same substrates with aluminium dihydrochloride. Also one of each pair of the products was synthesized by an independent route and its retention time was compared with the unknown product mixture.

The compounds that were synthesized and their respective substrates are shown in Table IIF - 2. The practical details of these syntheses are discussed in Experiment 12.

Substrate	Reference product
4-Methyl-1, 3-dioxolane	1-methoxy propan-2-ol.
4-Chloromethyl-1, 3-dioxolane	1-chloro-3-methoxy propan-2-ol.
2, 2, 4-Trimethyl-1, 3-dioxolane	1-isopropoxy propan-2-ol.
4-Chloromethyl-2, 2-dimethyl-1, 3-dioxolane	1-chloro-3-isopropoxy propan-2-ol.

Table IIF - 2.

Experiment 10. The reactions of 2-alkene-1, 3- dioxolanes with boron trichloride/lithium aluminium hydride.

(a) 2-Vinyl-1, 3-dioxolane (2.35 g., 0.024 mol.) was treated with boron trichloride (0.92 g., 0.0078 mol.) and lithium aluminium hydride (0.3 g., 0.0079 mol.) using the procedure outlined in experiment 1. The acetal was left in contact with the boron trichloride for 10 minutes before addition of the hydride.

Work-up in the usual manner (p.38) gave a pale-green oil (2.26 g., 96%) which was shown to contain one main component by g.l.c. analysis. The retention time of the main product (92%) was identical to that of an authentic sample of 2-allyloxy ethan-1-ol, while the retention time of the minor component (8%) was found to be identical to that of ethan-1, 2-diol.

Distillation of the product mixture gave a pure sample of the main product. The I.R. and p.m.r. spectra of the purified

product were identical to those of 2-allyloxy ethan-1-ol.

Yield 1.9 g. (81%). B.p. 58 - 60°/14 mm.

(B.p. of 2-allyoxy ethan-1-ol 46°/ 5 mm.)[2]

(b) The above experiment was then repeated using trans-2-(prop-1-enyl)-1, 3-dioxolane as the acetal substrate.

The main product from the reaction was shown to be trans-2-(but-2-enyloxy)-ethan-1-ol by a similar procedure to that described above, i.e. by use of an authentic sample of trans-2-(but-2-enyloxy)-ethan-1-ol as a reference.

Yield 77%. B.p. 73-5°/12 mm.

(B.p. trans-2-(but-2-enyloxy)-ethan-1-ol 81°/18 mm.)[2]

Experiment 11. Studies into the effects of ring size in the reaction of cyclic acetals with boron trichloride/lithium aluminium hydride.

(a) A mixture of 2-propyl-1, 3-dioxolane (4.64 g., 0.04 mol.) and 2-propyl-1, 3-dioxane (5.2 g., 0.04 mol.) in methylene chloride (25 ml.) was treated with boron trichloride (1.18 g., 0.01 mol.) and lithium aluminium hydride (0.4 g., 0.01 mol.) in the usual manner. The acetals were left in contact with the boron trichloride for 10 minutes.

Work-up gave a pale-green oil (90%) which was shown to contain four main components. By comparison of retention times with reference samples it was shown that these components were the two substrate acetals plus 2-butoxy ethan-1-ol and 3-butoxy propan-1-ol along with small amounts of ethan-1, 2-diol and propan-1, 3-diol.

Integration of the peak areas of the two hydroxyethers showed that they were present in a 1:1.2 ratio, with 3-n-butoxy propan-1-ol as the major component.

(b) The above experiment was then repeated using the following pairs of acetals: 2-propyl-1, 3-dioxane with 2-propyl-1, 3-dioxepane and 2-propyl-1, 3-dioxepane with 2-propyl-1, 3-dioxocane. The relative proportions of the respective hydroxyether products are shown

in Table IID -4 , (p.72).

Experiment 12. Preparation of substrate acetals.

(a) 1, 3-Dioxolane was prepared by the method of Leggetter and Brown.[1]

Yield 64%. B.p. 72-4° (Lit.b.p. 71-3°/700 mm.)

(b) 1, 3-Dioxane was prepared by the same method starting with propan-1, 3-diol.

Yield 72%. B.p. 102-3°. (Lit.b.p. 105°/755 mm.)[19]

(c) 1, 3-Dioxepane was prepared by a slight variation of the above method. Butan-1, 4-diol (22.5 g., 0.25 mol.), paraformaldehyde (9.9 g., 0.33 mol.) and anhydrous magnesium sulphate (25 g.) were refluxed together in the presence of concentrated hydrochloric acid (1 ml.) for 3 h.

The reaction mixture was allowed to cool and then the crude 1, 3-dioxepane was distilled through a 4" Vigreux column on to anhydrous sodium carbonate. Redistillation gave the pure product.

Yield 14.3 g., 57%. B.p. 117-8° (Lit.b.p. 112-7°)[20]

(d) 1, 3-Dioxocane was prepared by the method of Anteunis and Beau.[10]

Yield 75%. B.p. 40-2°/10 mm.

(Lit.b.p. 43°/12 mm.)

(e) 2-Propyl acetals were all prepared by the same general procedure. The relevant diol (0.2 mol.) and butyraldehyde (0.25 mol.) were refluxed together using toluene (250 ml.) as the solvent and p-toluenesulphonic acid (0.2 g.) as the catalyst. The water produced during the reaction was removed as its toluene azeotrope via a modified Dean and Stark apparatus.

When the calculated amount of water (3.6 ml.) had been removed the reaction mixture was cooled and neutralized by stirring with anhydrous sodium carbonate for 30 minutes. After filtering, most of the toluene was then removed using a rotary evaporator.

The crude dark brown residue was then fractionally distilled. Redistillation gave the pure products. The yields and b.p. of the acetals produced by this method are shown in Table IIF - 3, along with their respective diols.

Acetal	Yield(%)	B.p. (°) Found	B.p. (°) Literature	Analysis (%) Expected	Analysis (%) Found
2-Propyl-1,3-dioxolane	85	136-8	136-8[21]		
2-Propyl-1,3-dioxane	60	153-5	154-7[22]		
2-Propyl-1,3-dioxepane	35	167-9	169-71[23]		
2-Propyl-1,3-dioxocane	28	42/2 mm	-	68.35(C), 11.35(H),	68.19(C), 11.60(H).

Table IIF - 3.

(f) 2-Chloromethyl acetals were prepared from the respective diols, 1-chloro-2,2-diethoxyethane and p-toluenesulphonic acid using the procedure outlined by Leggetter and Brown[1] in their preparation of 2-chloromethyl-1,3-dioxolane.

The yields, b.p. and analysis results are shown in Table IIF - 4.

Acetal	Yield %	B.p. (°/mm.) Found	Literature	Analysis (%) Expected	Found
2-Chloromethyl -1, 3-dioxolane	74	158-9	154-5/700[1]	39.18(C), 5.76(H), 28.84(Cl),	39.41(C), 5.83(H), -
2-Chloromethyl -1, 3-dioxane	77	67-9/10	67-9/12[32]	43.95(C), 6.64(H), 25.97(Cl),	43.40(C), 6.90 (H),
2-Chloromethyl -1, 3-dioxepane	76	98-102/14	-	47.83(C), 7.36(H), 23.55(Cl),	48.04(C), 7.58(H), -
2-Chloromethyl -1, 3-dioxocane	62	40-5/0.5	-	51.05(C), 7.96(H), 21.55(Cl),	50.92(C), 8.55(H), 21.71(Cl).

Table IIF - 4.

(g) 4-Methyl-1, 3-dioxolane was prepared using the method of Leggetter and Brown[1] starting from propan-1, 2-diol and paraformaldehyde.

Yield 64%. B.p. 90-1°/752 mm.

(Lit. b.p. 82-3°/700 mm.)

(h) 2, 2, 4-Trimethyl-1, 3-dioxolane was prepared by the method of Fischer and Pfahler[24] starting from propan-1, 2-diol and acetone.

Yield 25%. B.p. 97-9°/752 mm.

(Lit. b.p. 98-9°/760 mm.)

(i) 4-Chloromethyl-1, 3-dioxolane was prepared from 3-chloro propan-1, 2-diol and paraformaldehyde using the procedure outlined by Leggetter and Brown.[1]

Yield 74%. B.p. 153-4°.

(Lit. b.p. 76°/54 mm.)

(j) 4-Chloromethyl-2,2-dimethyl-1,3-dioxolane was prepared from 3-chloro propan-1,2-diol and acetone using the method of Fischer and Pfahler.[24]

Yield 70%. B.p. 47-51°/11 mm.

(Lit. b.p. 157°/767 mm.)

(k) 2-Vinyl-1,3-dioxolane was prepared by the method of Davis and Brown[33] starting from ethan-1,2-diol and acrylaldehyde

Yield 19%. B.p. 114-6°.

(Lit. b.p. 62°/110 mm.)

(l) Trans-2-(prop-1-enyl)-1,3-dioxolane was prepared by the method of Heywood and Phillips[25] starting from ethan-1,2-diol and 3-methylacrylaldehyde.

Yield 11%. B.p. 149-51°/757 mm.

(Lit. b. p. 71°/50 mm.)

Experiment 13. Preparation of hydroxyether reference compounds.

(a) The methoxy and n-butoxy derivatives of ethan-1,2-diol, butan-1,4-diol and pentan-1,5-diol.

These were all prepared by the same general procedure. The relevant diol (0.2 mol.) and alkyl halide (0.2 mol.) were dissolved in dimethyl formamide (300 ml.). Sodium hydride (0.2 mol.) was then added in small quantities over a 15 minute period. The reactants were then stirred at room temperature for 3 h.

More alkyl halide (0.01 mol.) and sodium hydride (0.01 mol) were then added and after stirring for a further 6 h. the bulk of the solvent was removed on a rotary evaporator. The precipitated solids were filtered off and the filtrate was fractionally distilled.

The yields and b.p. of the hydroxyethers prepared by this method are shown in Table IIF - 5. Methyl iodide was the alkyl halide used to prepare the methoxy compounds while n-butyl bromide

was used to prepare the n-butoxy derivatives.

Diol	Hydroxyether	Yield(%)	B.p. (°/mm.) Found	Literature
Ethan-1,2-diol	2-methoxy ethan-1-ol	71	122-4	124.9/767.[26]
Butan-1,4-diol	4-methoxy butan-1-ol	57	63-5/10	63-4/7.[27]
Pentan-1,5-diol	5-methoxy pentan-1-ol	55	102-4/12	60/1.5.[28]
Ethan-1,2-diol	2-n-butoxy ethan-1-ol	64	164-70	170.6/743.[29]
Butan-1,4-diol	4-n-butoxy butan-1-ol	58	208-12	212-4/760.[30]
Pentan-1,5-diol	5-n-butoxy pentan-1-ol	47	118-20/10	118/11.[28]

Table IIF - 5.

(b) 3-Methoxy propan-1-ol was prepared from sodium methoxide and 3-chloro propan-1-ol using the procedure outlined by Leggetter, Diner and Brown.

Yield 18%. B.p. 150-2°.

(Lit. b.p. 144-6°/700 mm.)[31]

(c) 3-n-Butoxy propan-1-ol was prepared by an adaption of the procedure in (b). A mixture of sodium (5g. 0.22 mol.) and n-butanol (200 ml.) was heated to reflux while the sodium dissolved. 3-Chloro propan-ol (19 g., 0.2 mol.) was then added and the procedure given in (b) was followed.

Yield 11.2 g. (42%). B.p. 43.5-45°/0.1 mm.

(Lit. B.p. 81-5°/13 mm.)[18]

(d) 1-Methoxy propan-2-ol was prepared from 1,2-epoxy-propane and sodium methoxide using the procedure outlined by Reeve and Sadle[14].

Yield 56%. B.p. 117-8°/752 mm.

(Lit.b.p. 118.5-9°.)

(e) 1-Isopropoxy propan-2-ol was prepared from 1,2-epoxy-propane and sodium isopropoxide using the procedure outlined by Chitwood and Freure.[15]

Yield 50%. B.p. 137-40°.

(Lit.b.p. 143-4°.)

(f) 1-Chloro-3-methoxy propan-2-ol and 1-chloro-3-iso-propoxy propan-2-ol were both prepared using the method of Flores-Gallardo and Pollard.[13] The yields and b.p. of the two compounds are shown in Table IIF - 6.

		B.p. (°/mm.)	
Hydroxyether	Yield(%)	Found	Literature
1-Chloro-3-methoxy propan-2-ol	65	80-1/11	76.5/20.
1-Chloro-3-isopropoxy propan-2-ol	21	83-5/10	87-7.5/20.

Table IIF - 6.

(g) 2-Allyloxy ethan-1-ol and trans-2-(but-2-enyloxy)-ethan-1-ol were prepared using the procedure of Davis and Brown.[2] The yields and the b.p. of the two compounds are shown in Table IIF - 7.

Hydroxyether	Yield (%)	B.p. (°/mm.) Found	Literature
2-Allyloxy ethan-1-ol	64	44-5/5	46/5.
Trans-2-(but-2-enyloxy) -ethan-1-ol	57	72-5/10	81/18.

Table IIF - 7.

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III. THE REACTIONS OF BORON TRICHLORIDE/LITHIUM ALUMINIUM HYDRIDE WITH SIMPLE DIOXANES CONTAINING OTHER BASIC CENTRES IN THE MOLECULE.

IIIA. Introduction.

In Chapter II the reactions of boron trichloride/lithium aluminium hydride with various model acetal substrates were described and as a result of these a possible mechanism for the reaction was proposed. The intrinsic shortcomings of such an idealized rationale were also pointed out.

It seemed logical then that a series of experiments should be carried out to test the above rationale in situations that had not been completely covered in Chapter II; the particular situation chosen was that in which other basic centres and therefore potential bonding sites for the Lewis acid were present upon the acetal molecule. Hence the products given by the following compounds were investigated: (±)-cis-4-hydroxymethyl-2-propyl-1,3-dioxane (I), (±)-cis-4-n-butoxymethyl-2-propyl-1,3-dioxane(II), 1,3-O-butylidene-DL-erythritol(III), 2,4-di-O-butyl-1,3-O-butylidene-DL-erythritol(IV), 1,3:2,4-di-O-butylidene erythritol (V) and 1,3:4,6-di-O-butylidene galactitol(VI) (fig. IIIA-1).

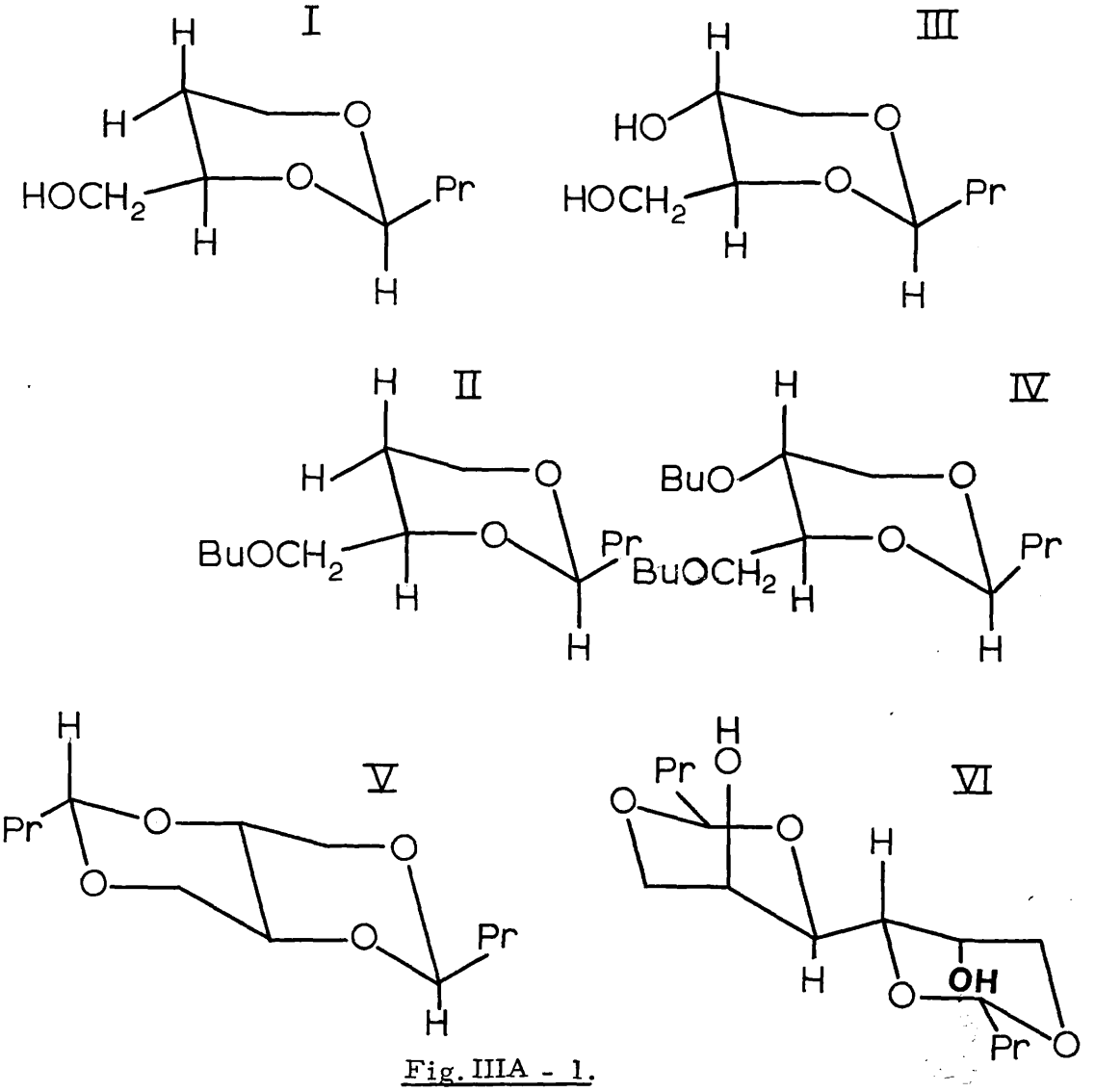


Fig. IIIA - 1.

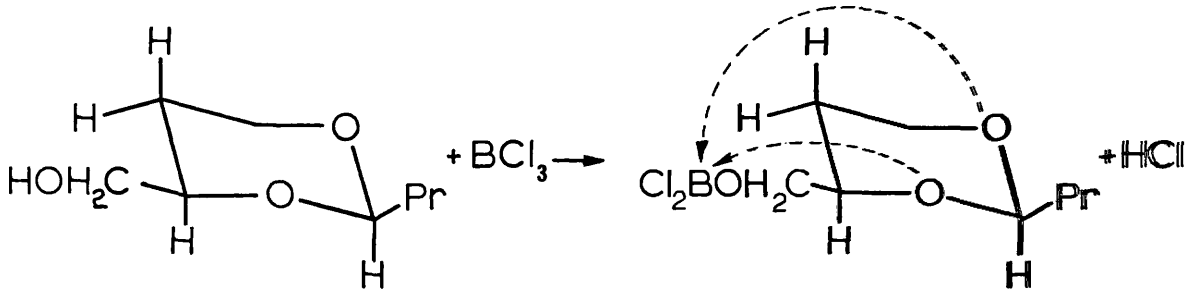
The alternative basic centres in question are the hydroxyl groups in I, III and VI, the n-butoxy groups in II and IV while a second acetal function is present in both V and VI.

The general aim then of this chapter was to slightly increase the complexity of the substrates under attack, in order to investigate the possible use of the boron trichloride/lithium aluminium hydride combination as a synthetic tool.

IIIB. Reaction with (±) - cis-4-hydroxymethyl-2-propyl-1, 3-dioxane (I) and (±) - cis-4-n-butoxymethyl-2-propyl-1, 3-dioxane (II).

i) Introduction.

The idea behind using a 4-hydroxymethyl substituent as an alternative basic site for the boron trichloride, was that the dichloroboronite[1] formed initially (fig. IIIB-1) may give rise to intramolecular α-chloroether formation by attacking either of the oxygens in its own acetal system. Thus as one often has free hydroxyl groups near protecting acetal functions in many syntheses it was hoped to get an insight into their effects upon the acetal cleavage reaction.



4-(methyldichloroboronite)-2-n-propyl-1, 3-dioxane.

Fig. IIIB - 1.

The reasons for using the 4-n-butoxymethyl substituent were two-fold: firstly one wished to examine the effects, either electronic or more likely steric, that the ether function had upon the cleavage and secondly one wished to examine the effects that the cleavage reaction had upon the ether function i. e. to see whether the butoxy function would be cleaved by the boron trichloride[2] (Chapter Ia, page 12).

ii) Results and discussion.

(a) Reaction details and preliminary analysis.

Essentially the same reaction and work-up procedure discussed in section IIB-iia were used in both cases. Hence on

treatment of I (0.017 mol.) with boron trichloride (0.017 mol.) and lithium aluminium hydride (0.017 mol.) a clear syrup (ca. 80%) was obtained after work-up.

Preliminary analysis of the product by 60 MHz p.m.r. spectroscopy showed that the acetal proton had been completely removed while one butoxy function and two hydroxyl groups were probably present.

G.l.c. analysis showed that the crude product consisted of two main components A and B with very similar retention times, plus a third minor component (ca. 3%) shown to be the parent triol (butan-1, 2, 4-triol).

The triol was removed by passing the reaction mixture down a silica gel column and concentrating the appropriate fractions under vacuum.

A similar procedure was repeated for substrate II using a 3:1:1 acetal to boron trichloride to hydride ratio which also gave two main products (C 75.4%, D 24.6%) with very similar retention times. A 60 MHz p.m.r. spectrum of the mixture indicated the presence of two butoxy functions and one hydroxyl group, whilst the acetal proton triplet (ca. 4.5 δ) was absent. The total recovered yield was 91%.

(b) Structural analysis of products.

The evidence obtained from the above preliminary analysis of the product mixture given by I, indicated that two isomeric monobutoxy ethers of butan-1, 2, 4-triol were present. Now, the products one would expect from this reaction based upon the work done in chapter II(IID-iib) are as shown in figure IIIB-2.

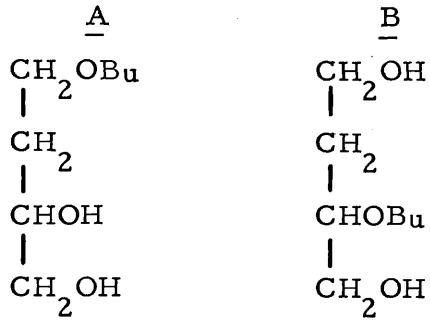


Fig. IIIB - 2.

This assumption was verified when a sample of the acetylated product mixture was analysed using g.l.c./m.s. Analysis of the above mass spectra also showed that compound B was the major component of the mixture (fig. IIIB - 3).

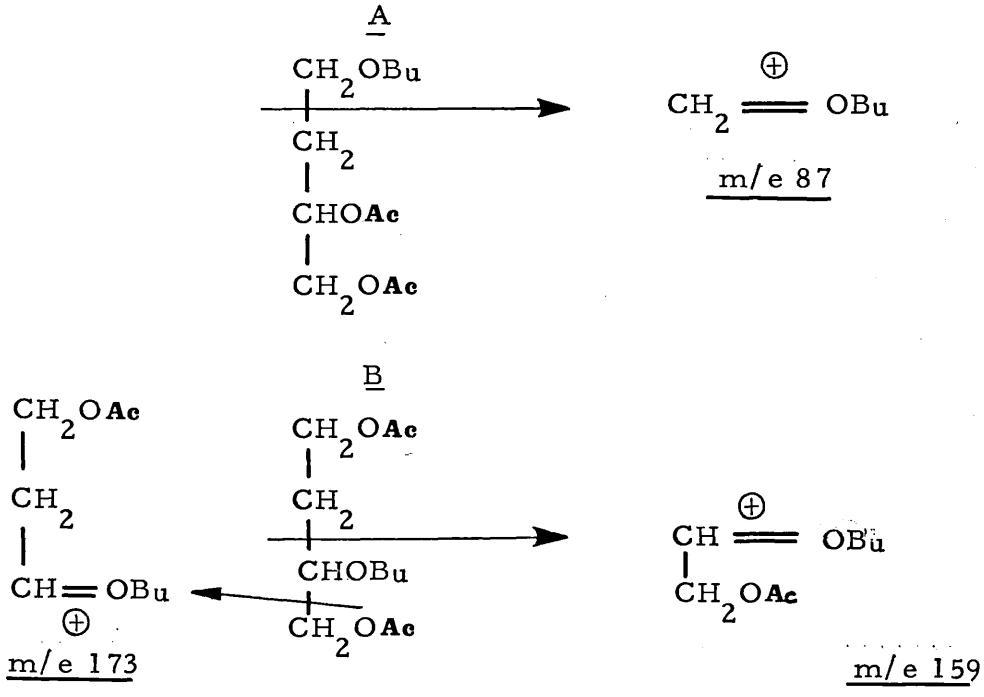


Fig. IIIB - 3.

Meanwhile, periodate oxidation of the mixture suggested that the relative proportions of A and B present were 38% and 62% respectively, which agrees well with the integrated areas of the peaks from the g.l.c. trace of the reaction (34.2%A, 65.8%B).

A similar analysis of the mass spectrum given by the neat product mixture from II's reaction indicates that the major constituent was DL-3, 4-di-O-butyl butan-1, 3, 4-triol(C), with DL-1, 4-di-O-butyl butan-1, 3, 4-triol(D) as the minor constituent (fig. IIIB - 4).

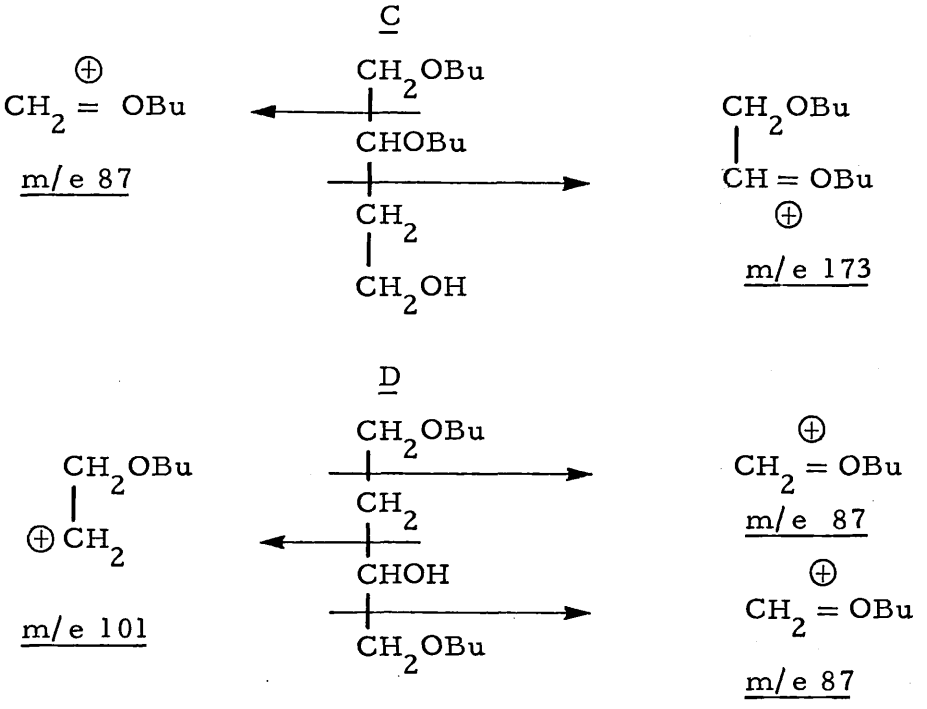


Fig. IIIB - 4.

(c) Rationalization of results.

In the introduction to this section (page 99) it was stated that the idea behind using I as a substrate for the boron trichloride/lithium aluminium hydride combination, was that after the initial formation of the Lewis acidic alkyl dichloroborinate (fig. IIIB-1), intramolecular attack by the boron may then occur upon one of the dioxane's oxygens, giving α-chloroether formation and thence upon reduction (with the lithium aluminium hydride) a hydroxyether function.

Ignoring the intermolecular reaction for the moment, the interesting question in the intramolecular reaction is in deciding which oxygen would be attacked; for instance in order to reach O_1 and still maintain the necessary geometry for α-chloroether formation[3], the dioxane system has to "flip" into the boat form (fig. IIIB - 5a), in which the $-CH_2OBCl_2$ group occupies an unfavourable axial position. Meanwhile, fruitful attack at O_3 does not involve any such conformational changes in the dioxane (fig. IIIB - 5b). It does however involve the formation of the shown (cis-fused) five membered ring which - at least when monocyclic - have been shown to be less stable than the corresponding seven membered species on grounds of ring strain,[4] although the necessarily sp^3 geometry of the boron and O_3 would tend to alleviate this[5]. A second destabilising factor to five membered cyclic complex formation is the likely presence of unfavourable steric interaction between the acetal C_2-O_3 bond and the 2-n-propyl group with one of the chlorine atoms attached to the boron (fig. IIIB - 5b).

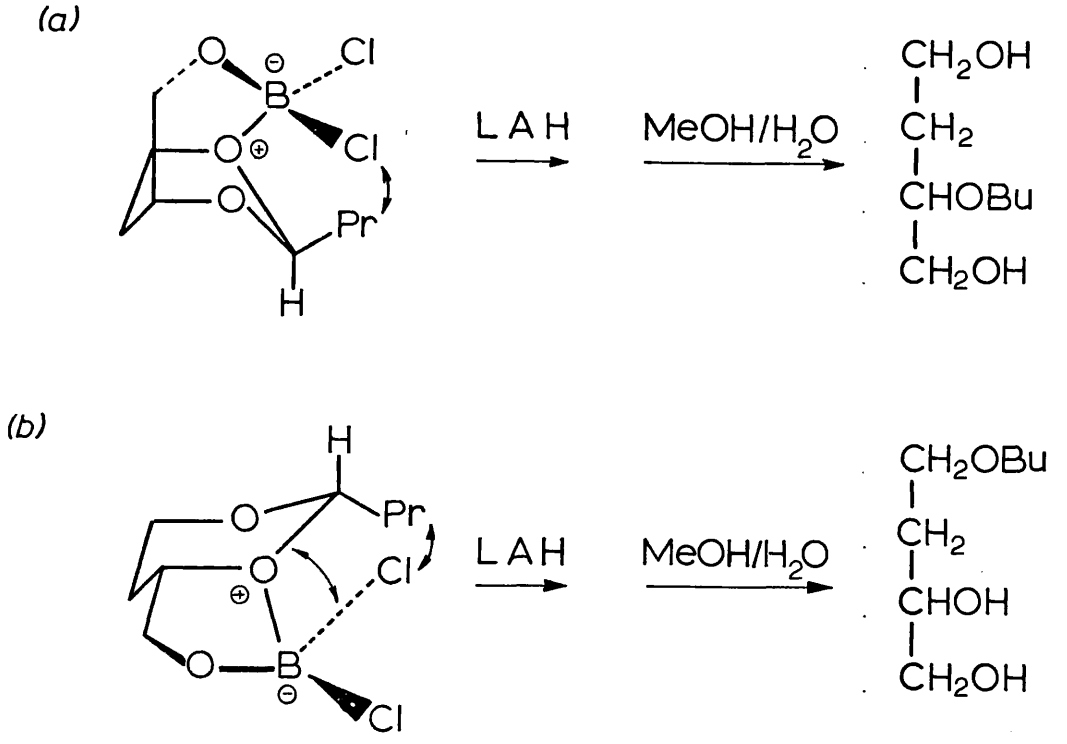


Fig IIIB - 5.

Structural analysis of the products from the reaction has shown that the preferred preliminary to ring cleavage is attack at O_3, which in keeping with the above reasoning suggests that if intramolecular Lewis complex formation does occur, then it occurs mainly via the seven membered cyclic **complex** (fig. IIIB - 5a).

Of course in the intermolecular reaction the -I effect of the $-OBCl_2$ function would favour a product ratio similar to that observed above, in which case both of the intramolecular reactions could be ignored: unfortunately evidence presented later on in this chapter strongly suggests that the intramolecular attack of the boron does occur, rendering the admittedly attractive assumption that it does not occur in the 4-hydroxymethyl-2-propyl-1,3-dioxane's reaction a little unrealistic.

In truth, the isolated product ratio is probably the net result of an interplay between the two intramolecular pathways and the intermolecular pathway, the exact proportions of which cannot really be determined. Again however, evidence presented later on in this chapter, in which the reaction of 1, 3:2, 4-di-O-butylidene erythritol is considered, does imply that seven membered cyclic complex formation occurs to a greater extent than the five membered complex in the reaction of 4-hydroxymethyl-2-propyl-1, 3-dioxane.

Meanwhile in the 4-n-butoxymethyl-2-propyl-1, 3-dioxane's reaction, intramolecular cleavage is not possible without removal of the n-butoxy function. Structural analysis of the products has shown that this does not occur to any appreciable extent, whilst the product ratio indicates that fission of C_2-O_1 occurs to a greater extent than that of C_2-O_3.

The most probable reason for this ratio is that the bulk of the n-butoxy function hinders Lewis complex formation at O_3 especially when the boron becomes substituted with cleaved acetal molecules (fig. IIIB - 6). Also by virtue of its basicity (albeit lower than that of the acetal's oxygens) the n-butoxy function's oxygen may compete for the Lewis acid thereby reducing its ability to cleave the dioxane, as well as increasing the steric hindrance around O_3. The main point however is that the net effect of the n-butoxy function is to direct cleavage in direct opposition to that which would have been expected from a purely electronic standpoint, taking into consideration the electron withdrawing nature of the n-butoxy group.

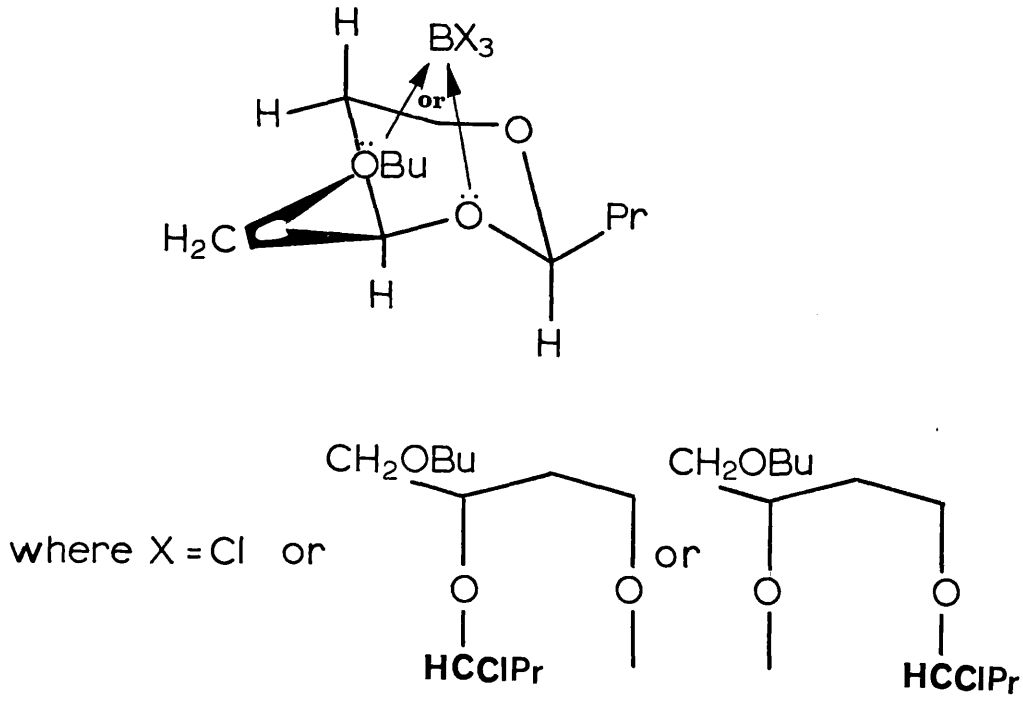


Fig. IIIB - 6.

In summary then, what was considered to be the primary aim of this section has been demonstrated in that the presence of other basic centres upon the dioxane molecule does augment the simple, electronically dominated, view of the directive effects upon cleavage discussed in chapter II. A summary of the results is given in Table IIIB - 1.

Substrate	Products	Relative proportions (%)	Isolated yield (%)
I	A + B	34 + 66	ca. 80
II	C + D	75.4 + 24.6	91

Table IIIB - 1.

(d) Preparation of substrates.

The (±)-cis-4-hydroxymethyl-2-propyl-1, 3-dioxane (I) was prepared from an equimolar mixture of butyraldehyde and butan-1, 2, 4-triol suspended in toluene using p-toluenesulphonic acid as

the catalyst (fig. IIIB - 7): the water produced in the reaction was removed azeotropically with toluene using a modified Dean and Stark apparatus.

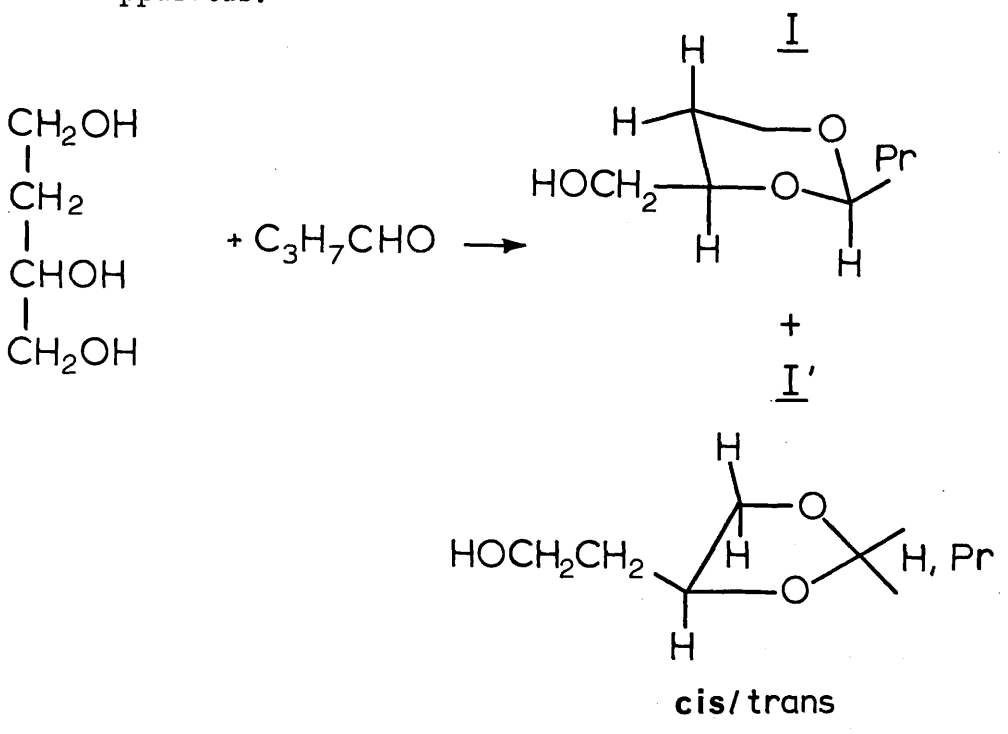


Fig. IIIB - 7.

Fractional distillation of the resulting mixture (63.6% I plus 36.4% I') gave a pure sample of I, although the lower boiling 4-(2-hydroxymethyl)-2-propyl-1,3-dioxolane could not be separated from its six membered isomer by use of this method.

The difference in shift of the acetal protons belonging to the respective isomers was the parameter used to distinguish them, (4.5δ for the dioxane and 4.9δ for the dioxolane[6]). Meanwhile g.l.c. enabled their relative proportions to be established.

Treatment of I with n-butyl bromide and sodium hydride in D.M.F.[7] was the method used to prepare (±)-cis-4-n-butoxymethyl-2-propyl-1,3-dioxane (II) (fig. IIIB - 8).

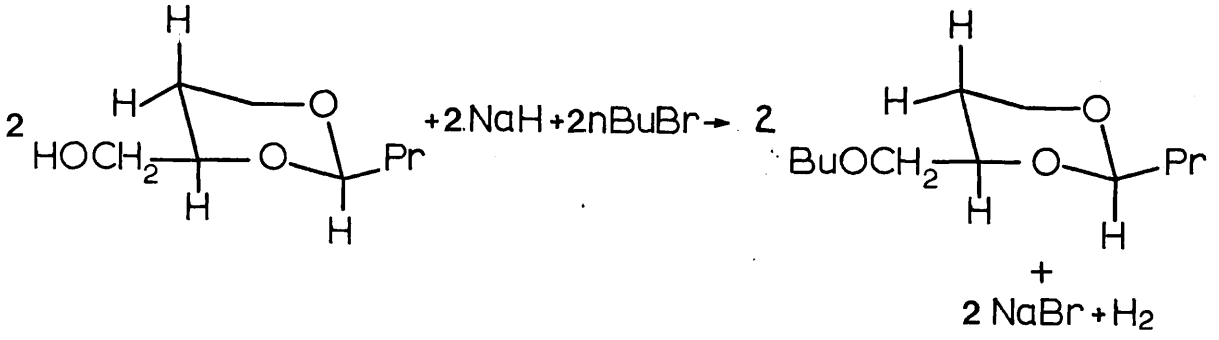


Fig. IIIB - 8.

The product, an oil, was purified by passing down a silica gel column eluting with toluene/methanol (9:1). Its infra-red spectrum showed the absence of a hydroxyl group (OH stretch at ca. 3500 $cm.^{-1}$) while a 60 MHz p.m.r. spectrum of II showed the presence of one dioxane acetal proton and one butoxy function. The mass spectrum of II also agreed with the shown structure (p.169).

IIIC. Reaction of 1,3-0-butylidene-DL-erythritol (III) and 2,4-di-0-butyl-1,3-0-butylidene-DL-erythritol(IV). (Preparation of 1,2,3-tri-0-butyl-DL-erythritol.)

i) Introduction.

In the previous section the electrochemical and stereochemical effects that a single hydroxyl group and a single n-butoxy function had upon the ring cleavage of a dioxane were discussed.

The next section will consider the effects that two hydroxyl groups and two n-butoxy functions have upon the same reaction. The particular substrates used were 1,3-0-butylidene-DL-erythritol(III) and 2,4-di-0-butyl-1,3-0-butylidene-DL-erythritol(IV) respectively (fig. IIIA - 1, page 98).

ii) Results and discussion.

(a) Reactions and preliminary analysis.

1,3-O-Butylidene-DL-erythritol(III) (0.0092 mol.) was treated with boron trichloride (0.0092 mol.) and then lithium aluminium hydride (0.01 mol.). Work-up in the usual manner gave a clear syrupy product (86%).

A 60 MHz p.m.r. spectrum of the crude material showed the absence of the acetal proton triplet but the presence of one butoxy function and three hydroxyl groups.

G.l.c. analysis of the acetylated product mixture confirmed the absence of the substrate and showed that the two main products were present in a 19.3 : 1 ratio.

The tentative conclusion drawn from these observations was that the substrate acetal had been cleaved to yield a mixture of two monobutoxy derivatives of erythritol.

A similar reaction between IV (0.012 mol.) and the boron trichloride/lithium aluminium hydride (0.004 mol./0.004mol.) combination also gave a clear syrupy product (82%) which was shown to contain mainly one component (97%) by g.l.c. analysis of the acetylated mixture.

A 60 MHz p.m.r. spectrum of the product suggested the presence of three butoxy functions and one hydroxyl group while the acetal proton triplet of IV was not present. Thus as with III the butylidene ring had opened to give a butoxy function.

(b) Structural analysis of products.

The two products one would expect from ring cleavage of III are shown in figure IIIC - 1.

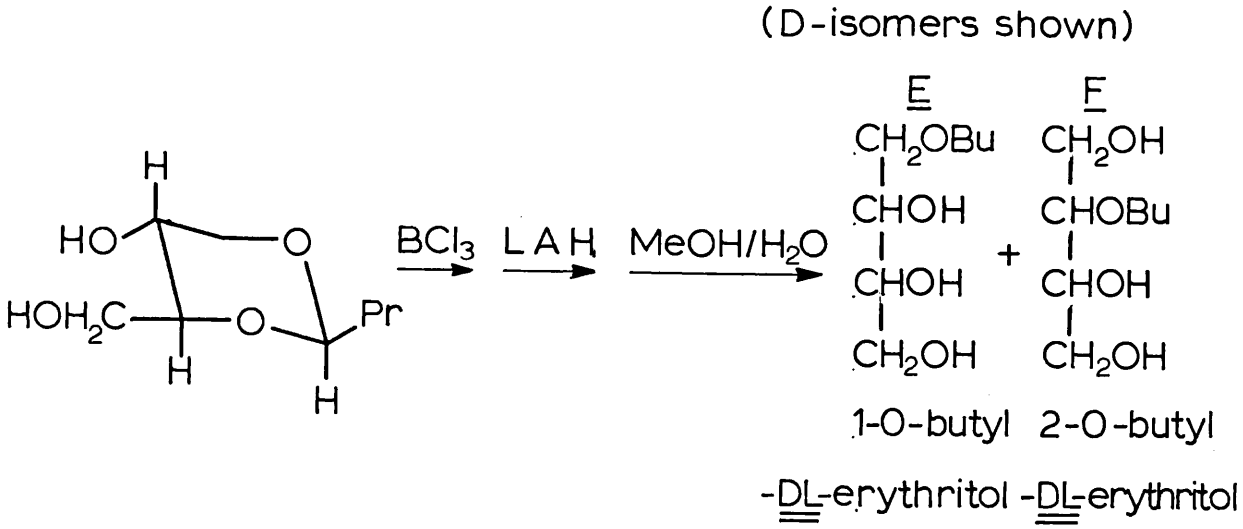


Fig. IIIC - 1.

G.l.c. /m.s. analysis of the acetylated product mixture showed that the major component is in fact the 2-O-butyl-DL-erythritol while the minor component is 1-O-butyl-DL-erythritol.

Meanwhile periodate oxidation data suggested that the product mixture was made up of 95.9% F and 4.1% E.

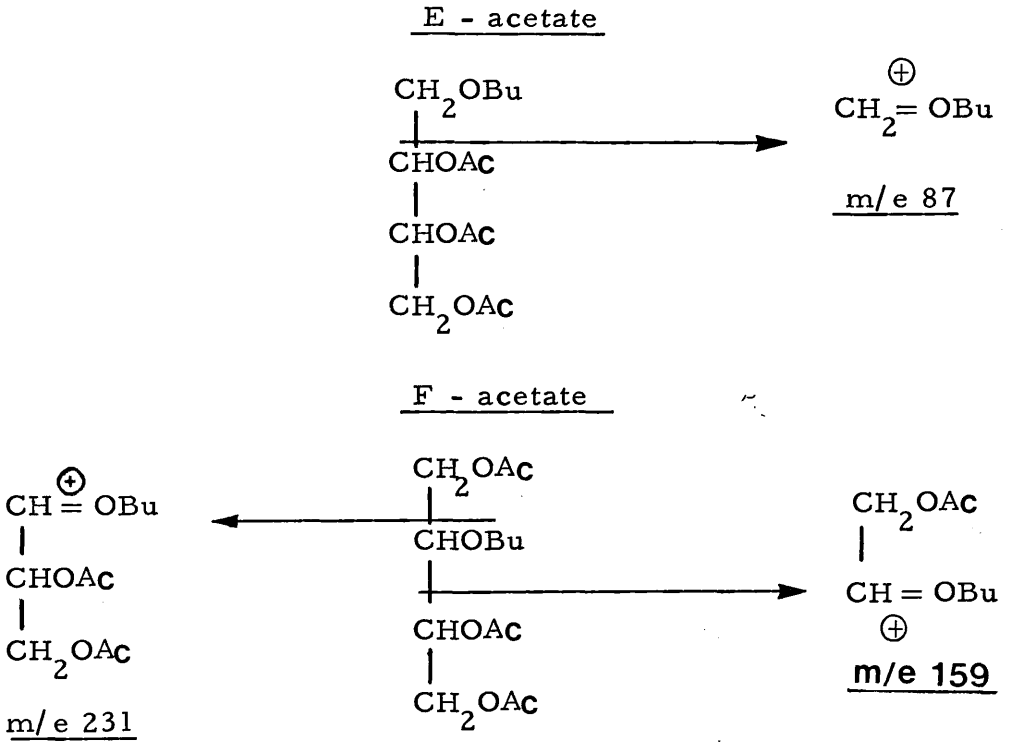


Fig. IIIC - 2.

The two isomers that could result from reductive fission of the acetal ring in IV are 1,2,4-tri-0-butyl-DL-erythritol(H) and 1,2,3-tri-0-butyl-DL-erythritol(G) (fig. IIIC - 3).

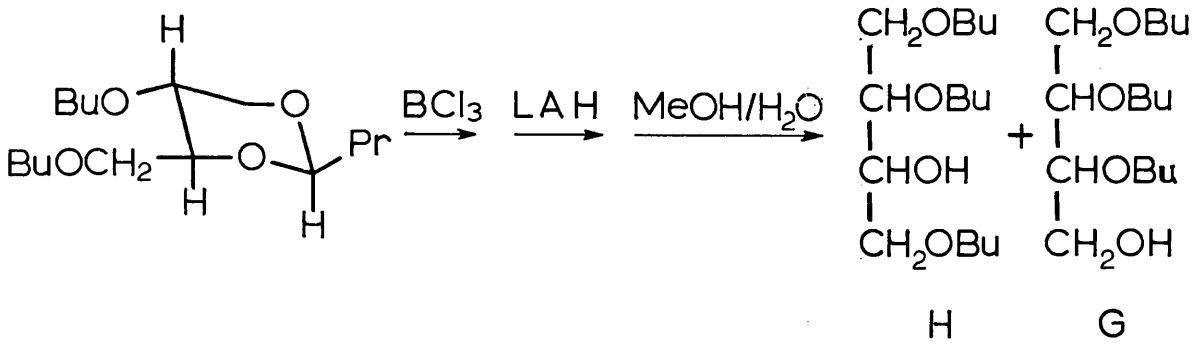


Fig. IIIC - 3.

The mass spectrum given by the acetate of the main product in question suggested that the three butoxy functions are all arranged in a contiguous manner (i.e. G) and not in the 1, 2, 4 array of H (fig. IIIC - 4).

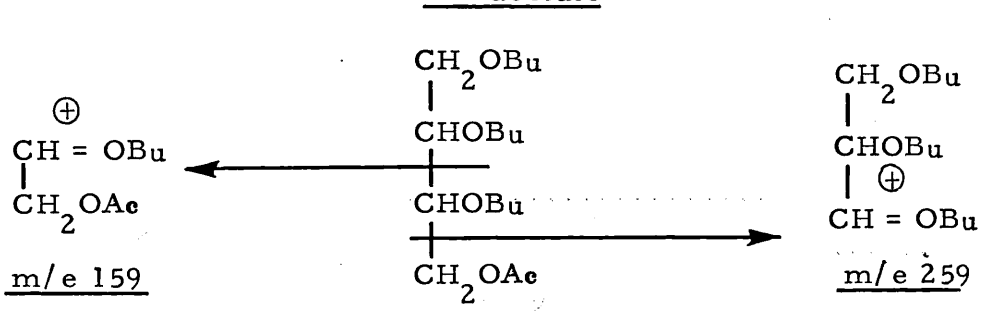


Fig. IIIC - 4.

Meanwhile the mass spectrum of the minor product's acetate did suggest the 1, 2, 4 array of butoxy functions (fig. IIIC - 5).

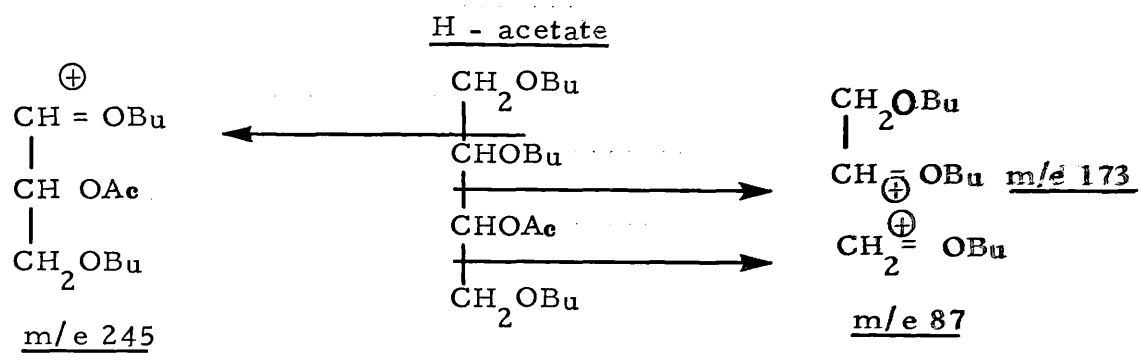


Fig. IIIC - 5.

Elemental analysis of a purified sample of G confirmed its empirical formula as $C_{16}H_{34}O_4$.

When the reaction between boron trichloride/lithium aluminium hydride and III was repeated using a 3:1 ratio of "reagent" to acetal, keeping the reaction time and temperature constant, g.l.c./m.s. analysis of an acetylated sample of the product mixture showed that the proportion of E in the reaction mixture had risen to 27.6%.

Similarly, when the ratio of boron trichloride/lithium aluminium hydride to IV was increased to 1:1, the proportion of H was shown to have increased to 16.3%.

A summary of the results obtained in this section is shown in Table IIIC - 1.

Substrate	Reaction* time (min.)	Substrate/ reagent ratio	Products	Product ratio (%)
III	10	1:1	E + F	5 + 95
III	10	1:3	E + F	27.6 + 72.4
IV	10	3:1	G + H	97 + 3
IV	10	1:1	G + H	83.7 + 16.3

Table IIIC - 1.

* Reaction time refers to time in contact with BCl_3, both are then stirred with L A H for 20 minutes.

(c) Rationalization of results.

In the 1, 3-0-butylidene-DL-erythritol(III) reaction cleavage has occurred mainly by attack at O_1 and subsequent cleavage of the C_2-O_1 bond, as in fact happened with the 4-hydroxymethyl-2-propyl-1, 3-dioxane(I), although the proportion of the primary ether given in the latter reaction was much higher than that in the former (34% and 5% respectively).

It was suggested in section IIIB-iic that in an equimolar reaction the hydroxyl group essentially fixes the position of the boron, thereby facilitating intramolecular α-chloroether formation. However, the two hydroxyl groups in III mean that in a similar equimolar reaction with boron trichloride, the initial product is probably a cyclic chloroboronate[9] (fig. IIIC - 6). Thus the boron is even more rigidly fixed than in I in that it is contained within a six membered ring.

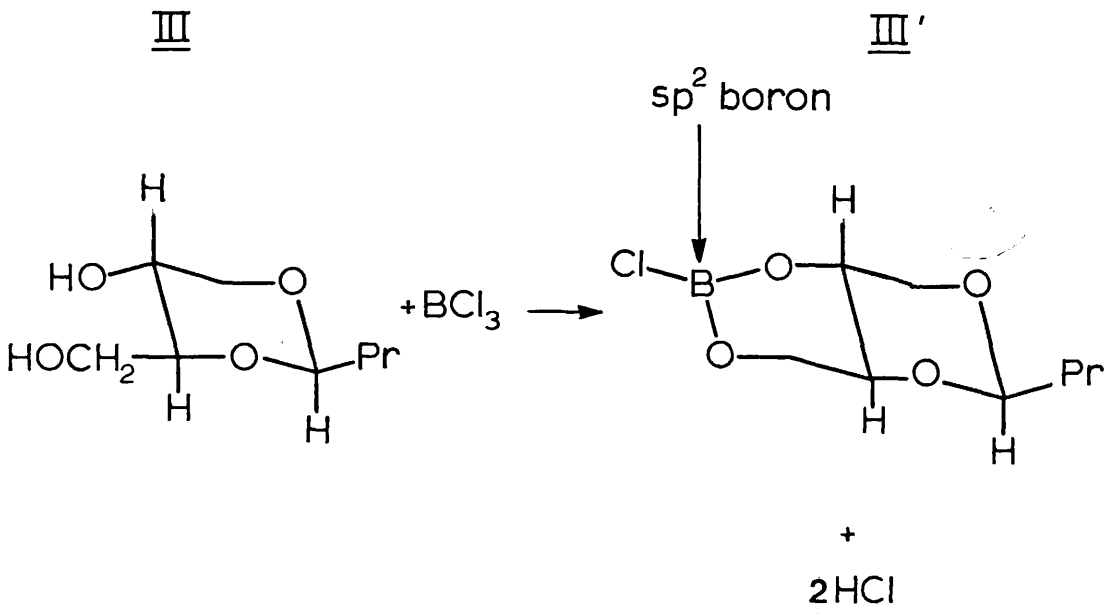


Fig. IIIC - 6.

This ring, containing the sp^2 hybridized boron is trans-fused to the 1, 3-dioxane ring and hence one can appreciate immediately the major difference between this and the acyclic dichloroborinate formed from I, in that intramolecular Lewis complex formation is impossible in the former case.

Consider then the alternative intermolecular reaction when the reasons for the observed preference for cleavage of the C_2-O_1 bond become apparent.

1) The attacking Lewis acid is probably a second molecule of III' in the 1:1 reaction.

2) For effective α-chloroether formation the attacking species must bond with the axially disposed lone pair of electrons upon either O_1 or O_3 of the acetal ring (see IID - iic, p.68).

3) Also, for efficient 4-centre chloride ion transfer the B-Cl bond of the "Lewis acid" prefers to be in the same plane as the O-C_2 bond about to be cleaved (see IID - iic).

4) The boron in the cyclic chloroboronate species is in the sp^2 state, which means that the two molecules must approach each other in essentially parallel planes. Hence when the Lewis bond is formed the relative dispositions of the two molecules will be approximately as shown in figure IIIC- 7.

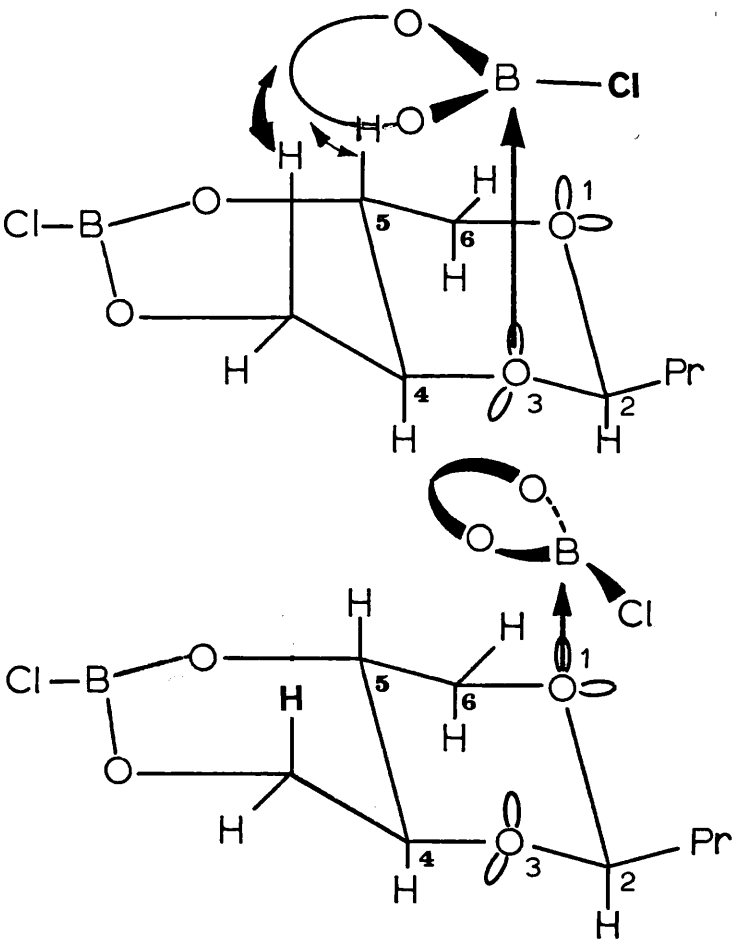


Fig. IIIC- 7.

It can be seen then that attack at O_3 causes considerably more steric hindrance than the corresponding attack at O_1. The main interaction occurs between the axially disposed protons upon the 'Lewis acid" and the C_5 axial proton upon the 'Lewis base", an interaction which is completely absent when attack occurs at O_1.

In summary then, the selectivity shown in the reaction between 1,3 -0-butylidene-DL-erythritol and boron trichloride/ lithium aluminium hydride combination is essentially steric in nature, brought about by the added conformational limitations imposed upon the acetal by the cyclic chloroboronate initially formed from the two hydroxyl groups and the boron trichloride.

This assumption is supported by the fact that when the boron trichloride to acetal ratio was increased to 3:1 the proportion of E in the reaction mixture was increased. The reason for this is presumably because with a higher boron trichloride ratio the proportion of the cyclic chloroboronate and its inherent directive effects is reduced. Also of relevance is the fact that the probable formation of the methyldichloroborinate function upon C_4 of the 1,3-dioxane system (fig. IIIC-8, III") brings in the possibility of the intramolecular α-chloroether formation mentioned earlier with regard to 4-hydroxymethyl-2-propyl-1,3-dioxane. The average size of the Lewis acid will also have been reduced from the cyclic chloroboronate to monosubstituted boron trichloride and boron trichloride itself.

The main point here is that the direction of cleavage is no longer dominated by the stereochemistry of the cyclic chloroboronate due to the alternative reaction pathways opening up, such as the intramolecular cleavage, resulting in a much more complex situation.

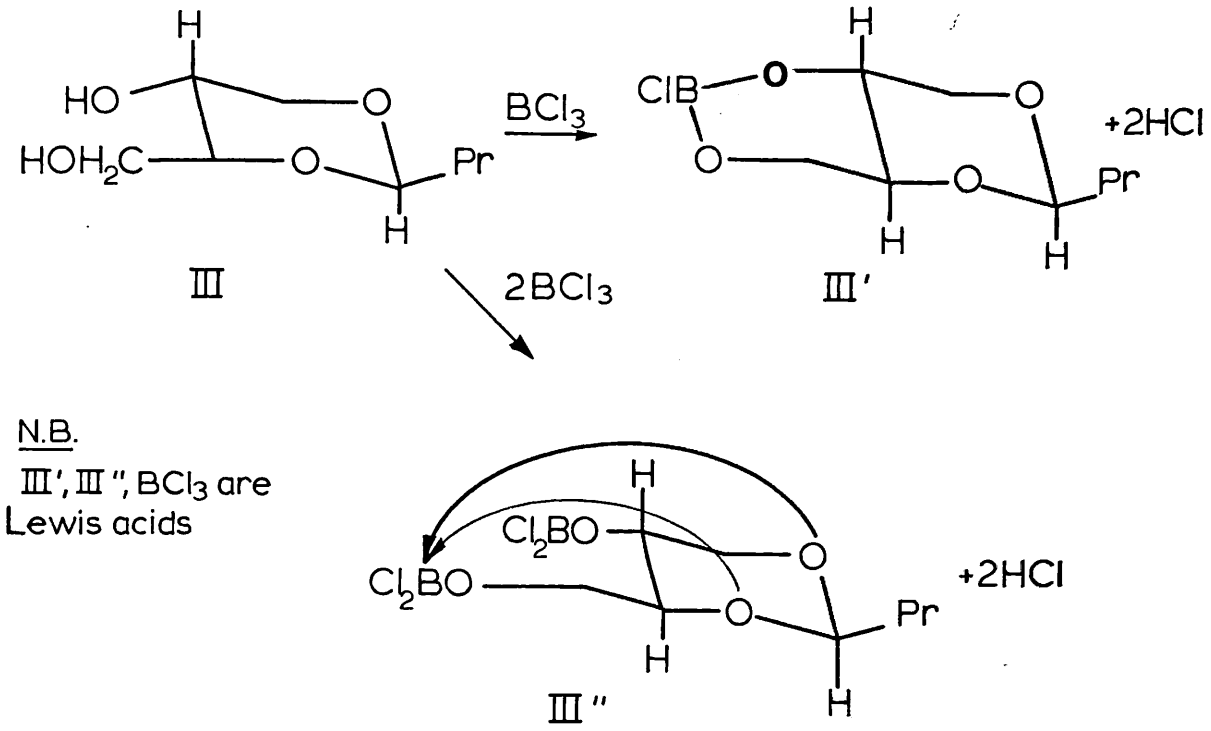


Fig. IIIC - 8.

Meanwhile in the 2, 4-di-O-butyl-1, 3-O-butylidene-DL-erythritol reaction the main product given with a 3:1 acetal to "reagent" ratio is that resulting from cleavage of the C_2-O_1 bond (fig. IIIC - 9).

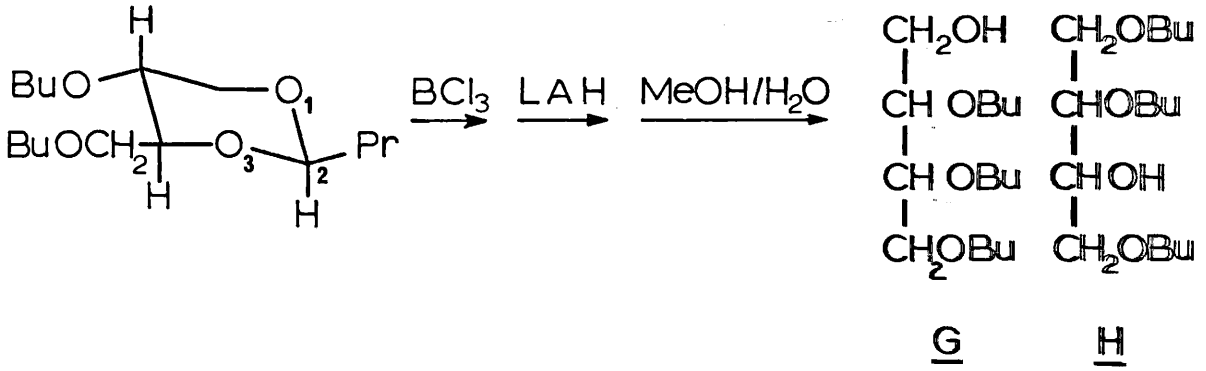


Fig. IIIC - 9.

The most probable reasons for the specificity of this reaction are as follows.

1) The steric congestion around O_3 is much greater than that around O_1, mainly due to the presence of the 4-n-butoxymethyl function. Hence the Lewis complex formed at O_3 will be more congested and less favourably given than that at O_1, especially when the boron becomes substituted with cleaved acetal molecules.

2) The Lewis basicity of the butoxy functions means that they can compete for association with the Lewis acid. This competition easily occurs at O_3 where the 4-n-butoxymethyl group's oxygen is readily situated. An added consequence of this inhibition to cleavage - if it does occur - is that the steric congestion around O_3 will be increased even more.

Meanwhile similar competition at O_1 cannot be given by the 4-n-butoxy group because of its equatorial disposition and it will only be given by the 4-n-butoxy group if the acetal ring "flips" into the unfavourable boat conformation, shown in figure IIIC - 10.

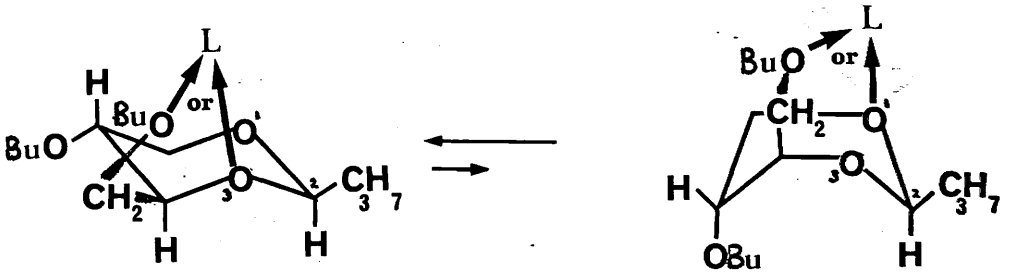


Fig. IIIC - 10.

Thus as in the reaction of III steric factors seem to control the direction of cleavage for IV and as was also seen in III's reaction increasing the proportion of boron trichloride brings about an increase in the proportion of H in the product mixture. Keeping in line with the above discussion then the observed product ratio (1:1) fromIV must be due to the decreased size of the Lewis acid, although intramolecular cleavage is obviously not possible here.

(d) Preparation of substrates.

1, 3-0-Butylidene-DL-erythritol was prepared by the method of T. J. Julnes[10] from meso erythritol and n-butyraldehyde, using concentrated hydrochloric acid as the catalyst (fig. IIIC - 11).

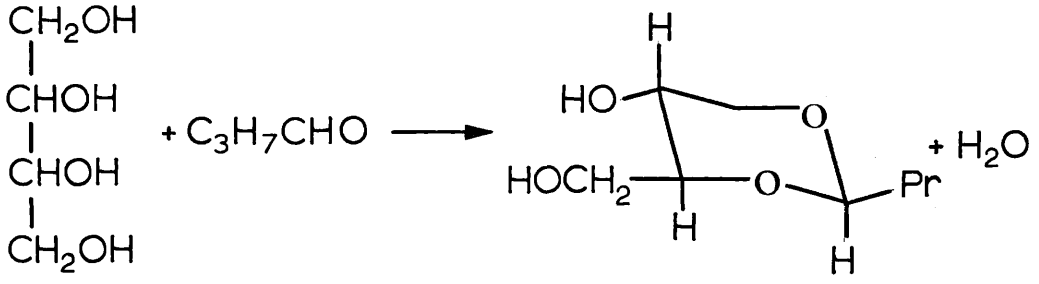


Fig. IIIC- 11.

The monoacetal was then butylated using sodium hydride and n-butyl bromide in D. M. F.,[7] when 2, 4-di-0-butyl-1, 3-0-butylidene-DL-erythritol was given (fig. IIIC - 12).

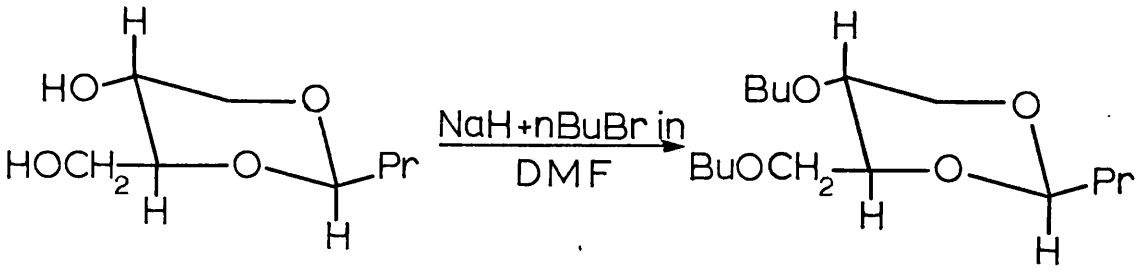


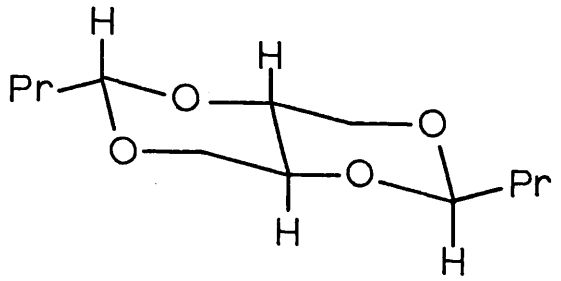
Fig. IIIC - 12.

IIID. Reaction with 1, 3:2, 4-di-0-butylidene erythritol. (Preparation of 1, 2-di-0-butyl-DL-erythritol.)

i) Introduction.

In the previous sections of this chapter the reactions of boron trichloride/lithium aluminium hydride with 1, 3-dioxane systems in the presence of one then two hydroxyl and n-butoxy systems have been considered. It was then decided to look at the behaviour of a diacetal of erythritol in which the hydroxyl groups relative to those in 1, 3-0-butylidene-DL-erythritol, are not only substituted but are also part of another dioxane system.

The particular acetal chosen was 1, 3:2, 4-di-0-butylidene erythritol (V) which contains a trans-fused ring (fig. IIID-1).



1,3: 2,4 - di-O-butylidene erythritol (V)

Fig. IIID - 1.

ii) Results and discussion.

(a) The reaction and preliminary analysis.

When 1, 3:2, 4-di-O-butylidene erythritol (0.008 mol.) was allowed to react with boron trichloride/lithium aluminium hydride (0.008 mol./0.008 mol.) in the usual way, a clear syrupy product mixture was obtained on work-up (92%).

A 60 MHz p.m.r. spectrum of the mixture suggested that the product contained two butoxy functions and two hydroxyl functions while both acetal proton triplets (ca. 4.5δ) had been removed: the presence of the hydroxyl groups was confirmed by an I.R. spectrum of the neat syrup.

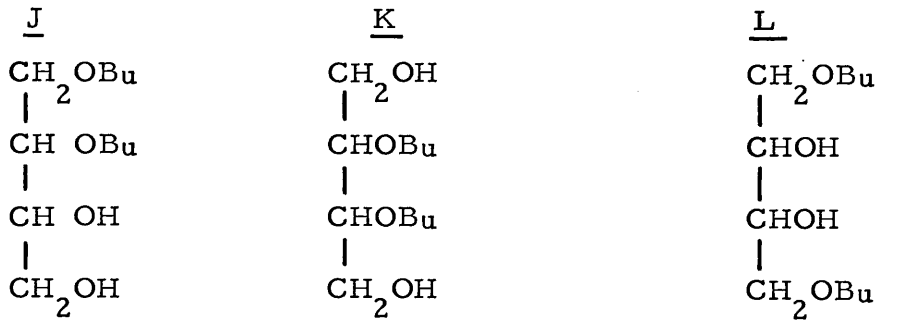
G.l.c. analysis of an acetylated sample of the isolated syrup confirmed that one main compound (J) was present (88.2%) along with two smaller components (7.18% and 4.61%) at a similar retention time.

The preliminary evidence then, suggested that the main product from the reaction was a dibutyl ether of erythritol with perhaps smaller amounts of two other isomers.

(b) Structural analysis of the products.

The three possible dibutyl ethers that can be produced in the above reaction are the 1, 2(3, 4), 2, 3 and 1, 4 isomers

(fig. IIID - 2).



1, 2-di-0-butyl-DL-erythritol

2, 3-di-0-butyl erythritol

1, 4-di-0-butyl erythritol

Fig. IIID - 2.

G.l.c./m.s. analysis of the acetylated product mixture showed that the main component (J) is the 1, 2-di-0-butyl-DL-erythritol (fig. IIID - 3).

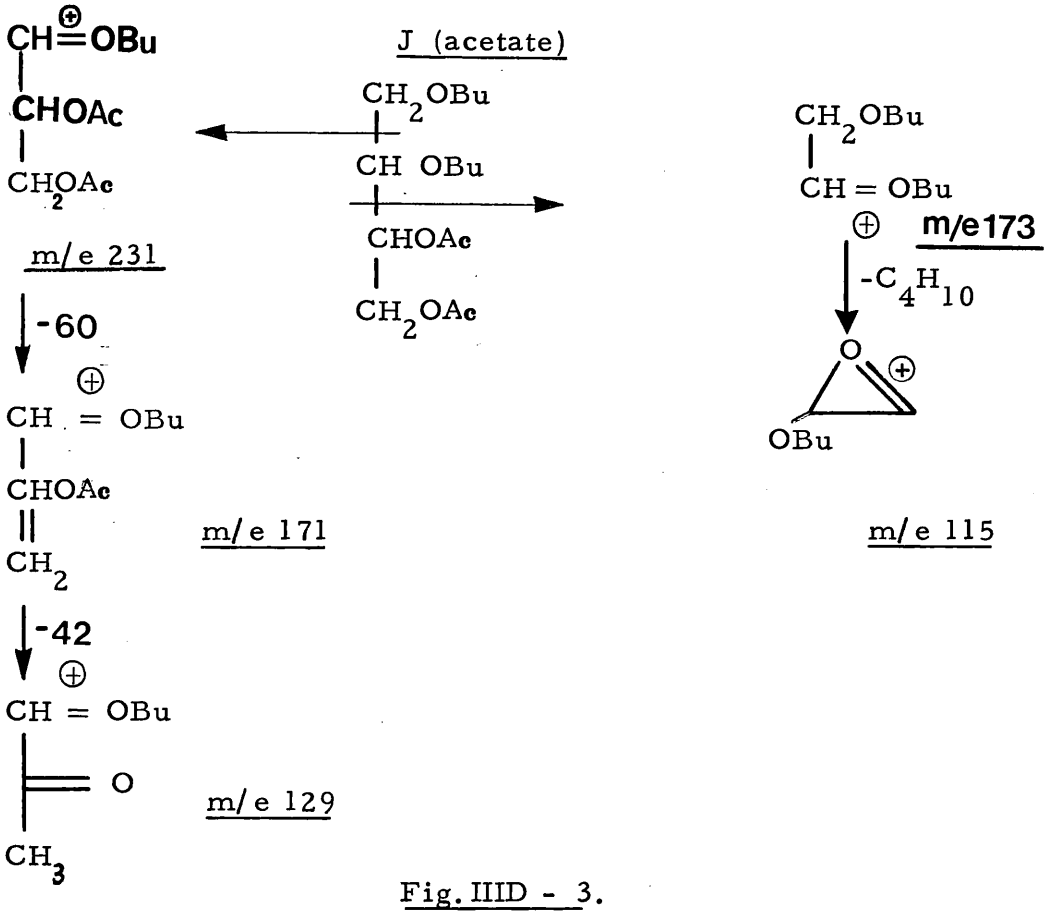


Fig. IIID - 3.

While the larger of the two minor components was shown to be the 2, 3-0-dibutyl ether (fig. IIID - 4).

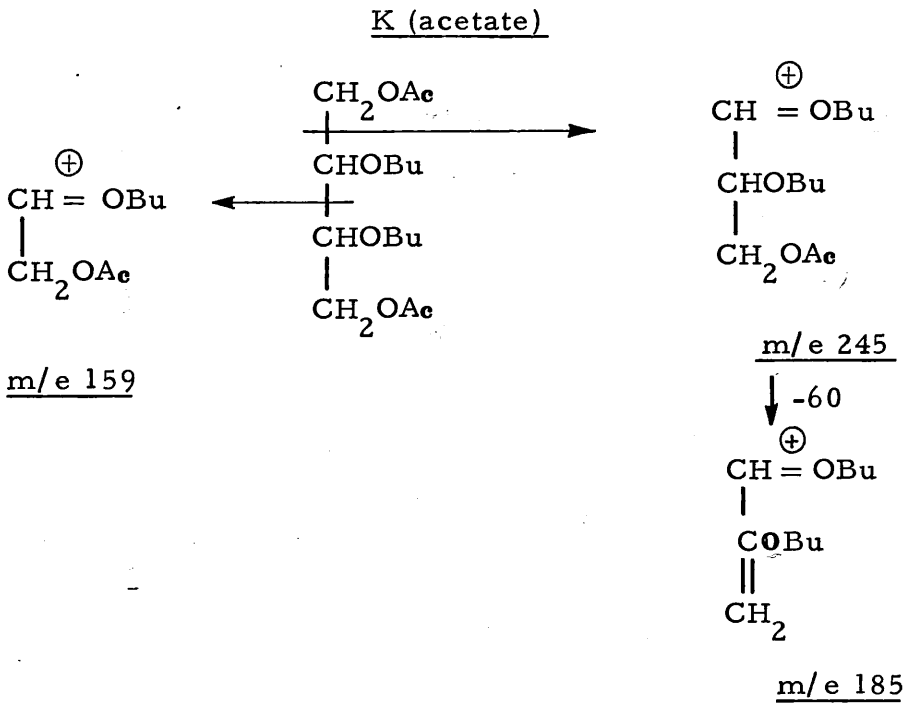


Fig. IIID - 4.

The structure of the smallest component of the reaction mixture was not absolutely clear from the g.l.c./m.s. data: this is because it was not possible to completely separate the smallest peak from that of the main product.

However the base peak of the spectrum was a fragment at m/e 87 and a smaller fragment was present at m/e 159. The fragment at m/e 87 could have been given by the 1,2-di butoxy isomer, but the fact that this fragment so dominated the spectrum strongly suggested that it was from 1,4-di-O-butyl erythritol (fig. IIID - 5) in which it would be expected to be intense.

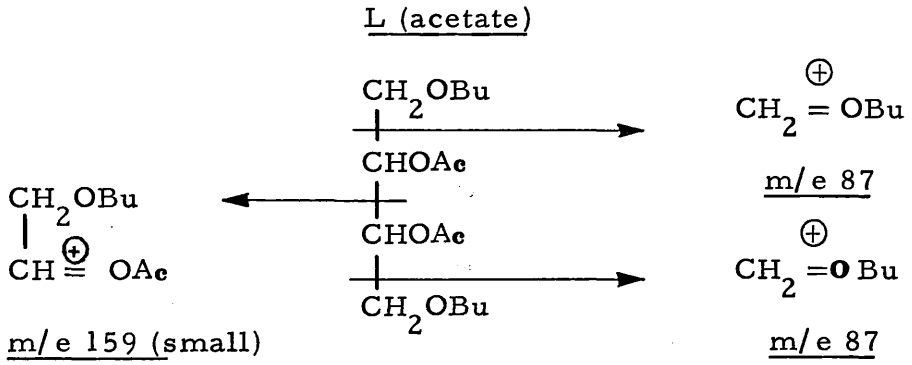


Fig. IIID - 5.

A pure sample of the main product was given when the reaction mixture was repeatedly passed down a silica gel column eluting with toluene/methanol (9:1) although isolation of the smaller components was not possible.

Periodate oxidation of this pure sample confirmed the contiguous nature of the hydroxyl groups (fig. IIID - 6).

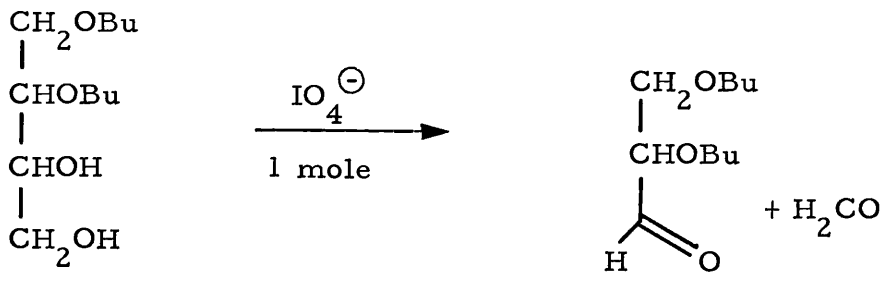


Fig. IIID - 6.

Meanwhile elemental analysis(C, H) confirmed the empirical formula ($C_{12}H_{26}O_4$) of the dibutyl ether.

(c) Rationalization of results.

It has been demonstrated in the previous section that the main product from the reaction of 1, 3:2, 4-di-0-butylidene erythritol is 1, 2-di-0-butyl-DL-erythritol along with smaller amounts of the 1, 4 and 2, 3 di-0-butyl isomers. The most interesting feature of these results is the specificity of the reaction, so that any rationalization of the mode of cleavage must try and take this into account.

Consider then the attack of a molecule of boron trichloride upon a molecule of the trans- fused diacetal. The substrate presents essentially two types of reaction site in which O_1 and O_3 possess equivalent geometries, as do O_2 and O_4: thus if, say, the 1, 3 ring is considered then the following discussion would apply equally to the 2, 4 ring.

The results discussed in section IIIC - iic, in which the reaction of 1, 3-0-butylidene-DL-erythritol was described showed that for an analogous choice of reaction sites, attack occurs mainly at O_1 with subsequent cleavage of the C_2-O_1 bond: the size of the attacking Lewis acid in the 1, 3-0-butylidene-DL-erythritol reaction was much more bulky than the unsubstituted

boron trichloride considered here however, so that one might expect a similar qualitative relationship towards attack at O_1 of the above 1, 3 ring in the diacetal. The reason for this is the unfavourable steric interaction between the insipiently bonded boron trichloride and the two axially disposed protons upon C_2 and C_4, that would be present in the O_3-BCl_3 complex (fig. IIID - 7b). Hence one would expect isomer *α* to be the major component after cleavage of the 1, 3 ring (fig. IIID - 7a).

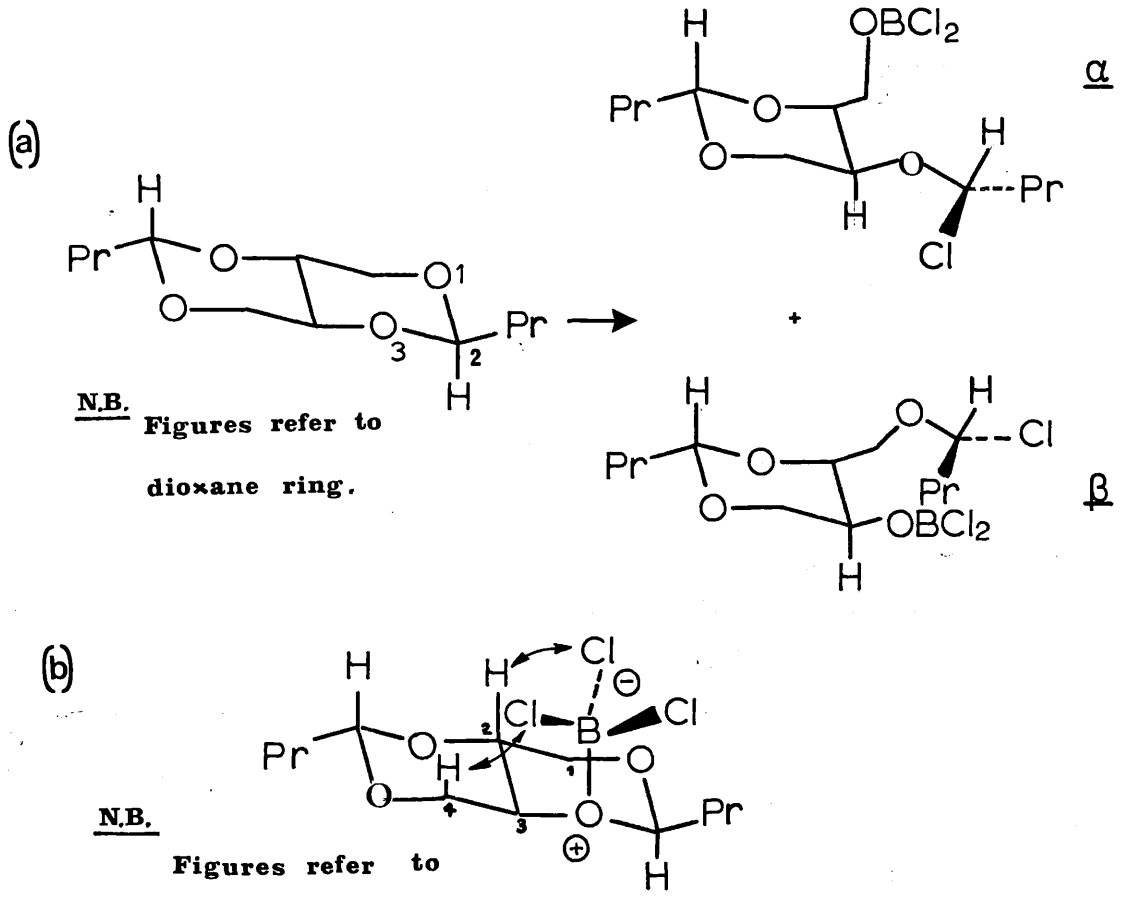


Fig. IIID - 7.

It can be appreciated that as far as product β is concerned, further intramolecular attack of the C_3 dichloroboronite's boron upon either O_2 or O_4 is not possible without the 2,4 ring "flipping" into a conformation in which the n-propyl, the dichloroboronite and the α-chloroether functions become axially disposed (fig. IIID - 8); an untenable situation which will not be considered further.

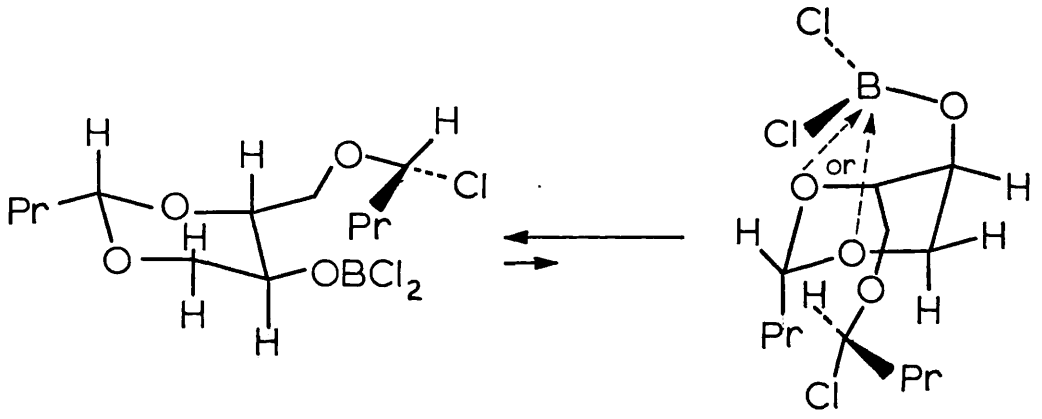


Fig. IIID - 8.

Hence, in the event of the alternative intermolecular Lewis-complex formation the Lewis acid (either boron trichloride or another molecule of α or β) is faced with a choice of reaction sites analogous to those present in the 2,4-di-O-butyl-1,3-O-butylidene-DL-erythritol reaction (section IIIC - ii, page 109), in which almost total formation of the secondary α-chloroether was observed. Evidently in β's case the steric hindrance afforded by the α-chloroether function to Lewis complex

formation is also sufficient to reduce attack at O_2 to such a level that the 1,4-di-O-butyl erythritol - given after reduction and work-up - is relegated to the role of a minor component, while the cleavage of the C_2-O_4 bond by attack at O_4 occurs to a much greater degree, giving 1,2-di-O-butyl-DL-erythritol as the major product (fig. IIID - 9).

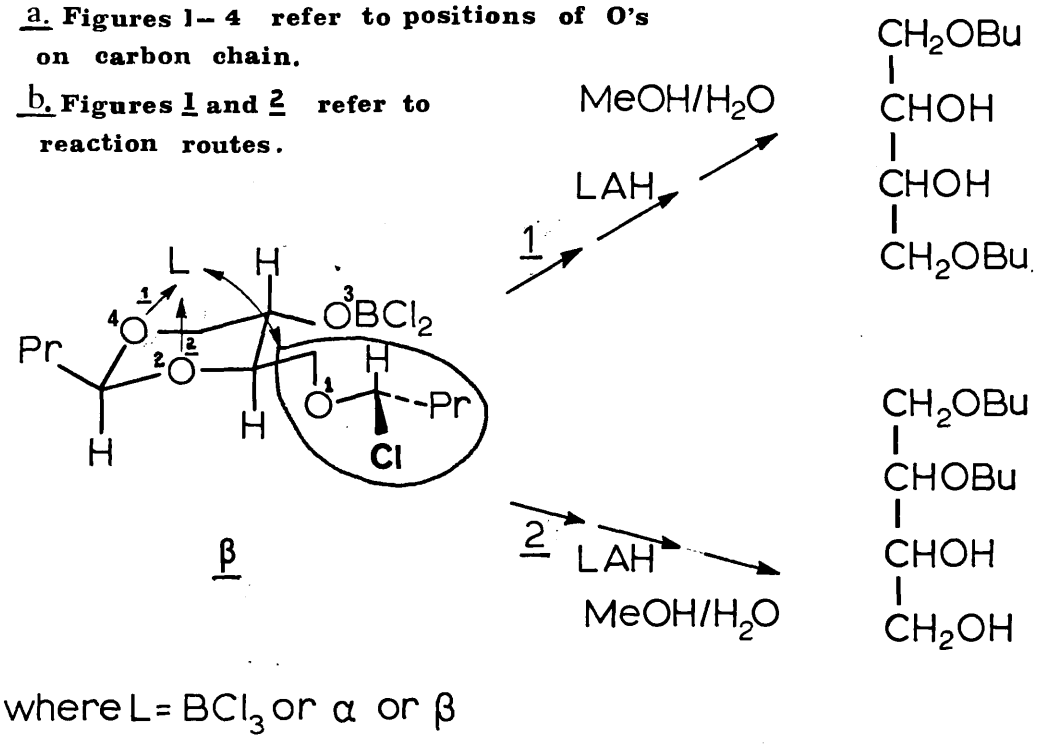
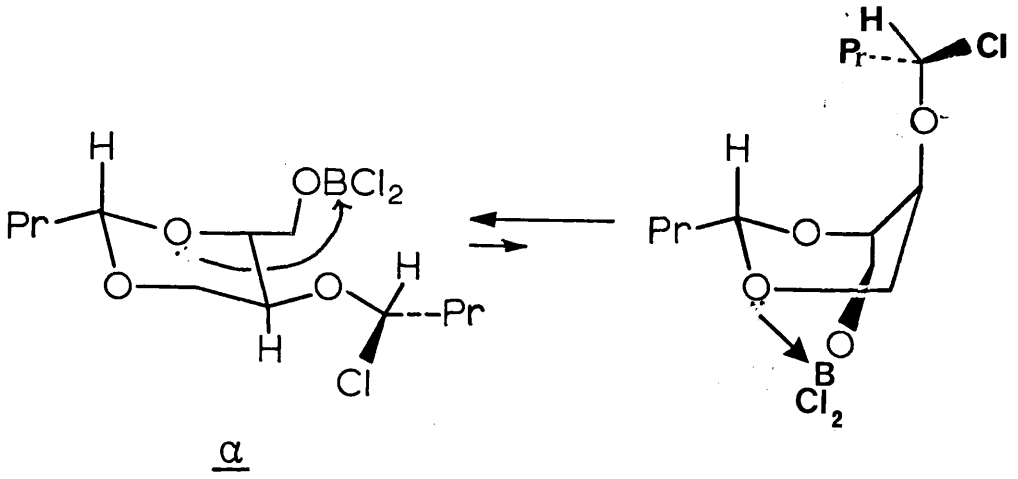


Fig. IIID - 9.

Meanwhile for product α both intermolecular and intramolecular Lewis-complex formation are possible and hence the situation is more complex than for product β, being similar in fact to the situation that existed in the 4-hydroxymethyl-2-propyl-1,3-dioxane reaction. Direct extrapolation from this analogy results in the prediction that the 2,3-di-O-butyl erythritol would be the major component of the reaction mixture, with the 3,4 isomer as the minor.

As this is not the case one either has to make the assumption that β is by far the major product after initial attack upon the diacetal system or that some factor (or factors) are present in α that significantly modify its reaction with the boron trichloride/lithium aluminium hydride with respect to that of the 4-hydroxymethyl-2-propyl-1,3-dioxane.

Discounting the former option, one possible modifying factor in α's reaction is the presence of the large equatorially disposed α-chloroether function upon C_3: this would tend to restrict the formation of the intramolecular seven membered cyclic **complex** because the ring flip inherent in the latter's generation would place the α-chloroether function in a highly unfavourable axial position (fig. IIID - 10). Hence the intramolecular ring opening would be expected to go via the five membered cyclic **complex** to give the 3,4-di-O-butyl ether as the main product. The inevitable conclusion of the above discussion with the experimental result in mind is that the intramolecular α-chloroether formation must outweigh the intermolecular reaction as far as α is concerned. Hence it is possible to give an explanation for the specificity of the 1,3:2,4-di-O-butylidene erythritol reaction in which intramolecular α-chloroether formation plays a large part although a totally a priori rationalization was not possible: a further example of the importance of intramolecular ring cleavage will be discussed in the following section.



α

Fig. IIID - 10.

(d) Preparation of substrate.

The 1, 3:2, 4-di-0-butylidene erythritol was prepared from erythritol and butyraldehyde using the procedure outlined by T. J. Julnes[10] (fig. IIID - 11).

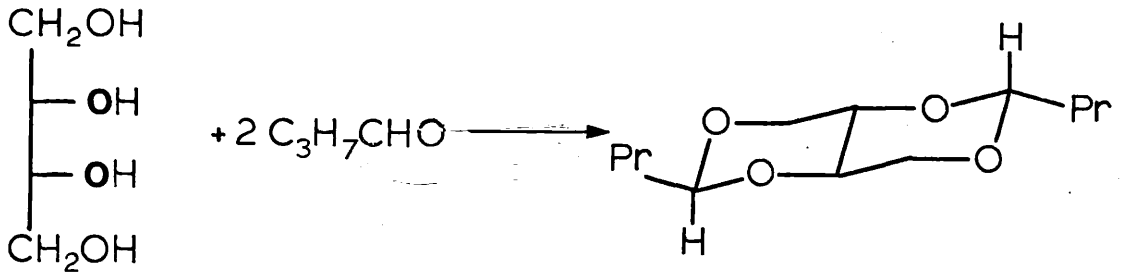


Fig. IIID - 11.

IIIE. Reaction with 1, 3:4, 6-di-0-butylidene galactitol (VI).

i) Introduction.

The conformation of 1, 3:4, 6-di-0-butylidene galactitol (VI) has been shown by various chemical and physical techniques to be as shown in figure IIIE - 1[6]. Thus keeping in mind the work done herein upon (±)-cis-4-hydroxymethyl and 1, 3-di-0-butylidene-DL-erythritol, one would expect the 2 and 5 hydroxyl groups upon the diacetal to react with the boron trichloride to give either a di-dichloroborinate derivative or a cyclic chloroboronate (fig. IIIE - 1) depending upon the relative ratios of the diacetal and Lewis acid.

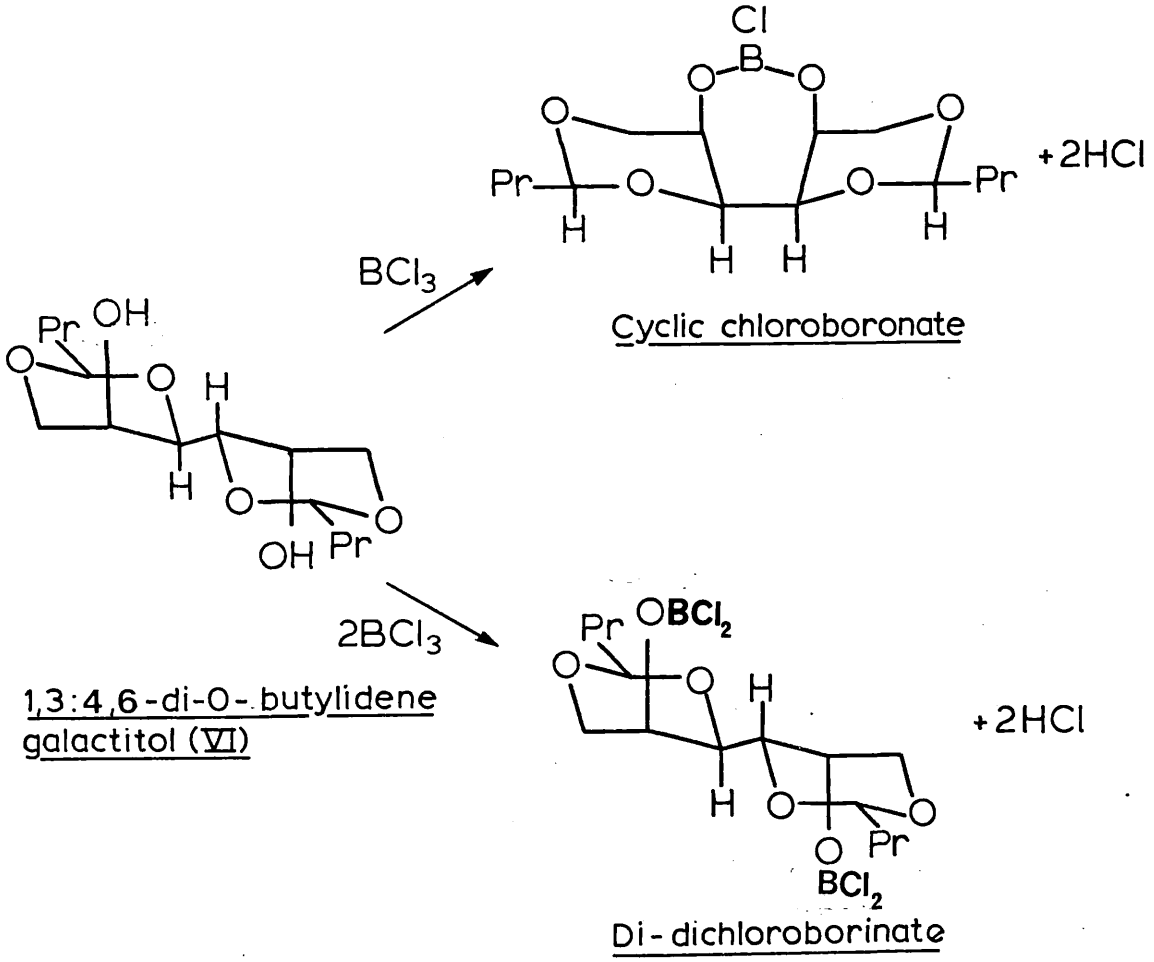


Fig. IIIE - 1.

It can be appreciated that both intermolecular and intramolecular α-chloroether formations are then possible with both.

The aim of this section then, is to examine the reactions of the diacetal with various amounts of boron trichloride/lithium aluminium hydride to see if indeed the reaction can be interpreted via the above model.

ii) Results and discussion.

(a) Reaction and preliminary analysis.

1,3:4,6-Di-O-butylidene galactitol(VI), (0.0076 mol.) was allowed to react with boron trichloride (0.023 mol.) for 15 minutes in dry methylene chloride at 0^{o}. After this time an ethereal suspension of lithium aluminium hydride (0.023 mol.) was added and the reaction mixture was stirred until effervescence had ceased.

After work-up in the usual manner a slightly cloudy syrup (82%) was obtained, the 60 MHz p.m.r. spectrum of which showed an absence of both acetal proton triplets.

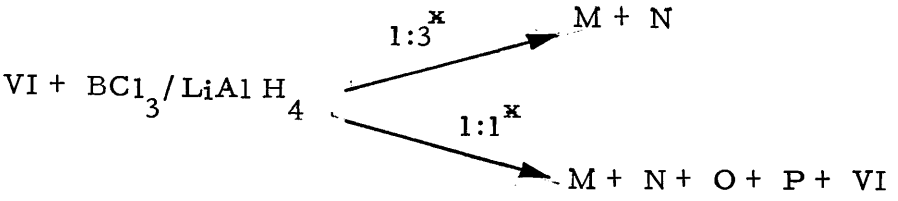
G.l.c. analysis of an acetylated sample of the syrup showed that it contained two components, M (72.3%) and N (27.7%). These two compounds were separated by fractional crystallization from chloroform/carbon tetrachloride.

The 60 MHz p.m.r. spectra of M and N suggested that they were both dibutyl ethers of galactitol.

The above reaction was then repeated using a 1:1 ratio of VI to boron trichloride/lithium aluminium hydride, leaving the acetal in contact with the Lewis acid for only 30 seconds.

A t.l.c. of the worked-up material indicated the presence of a more complex mixture than was given in the first reaction: a g.l.c. of an acetylated sample of the former showed that fourmain products were present along with unreacted substrate (fig. IIIE - 2). Two of the components were shown to be M and N

by comparison of their retention times with acetylated reference samples of the two dibutyl ethers. The remaining two components (O and P) possessed similar retention times which were both greater than that of the substrate, their relative proportions were 21.9% O and 3.2% P. Thus taking the reactions of 1, 3:4, 6-di-O-butylidene galactitol as a whole the respective product mixtures are as shown in figure IIIE - 2.



ˣ = VI to ($BCl_3/LiAlH_4$) ratio

Fig. IIIE - 2.

O and P were separated from M and N by passing the reaction mixture down a silica gel column eluting with toluene/methanol (9:1), when on evaporation of the appropriate fractions a white crystalline mixture of O and P was given. Repeated recrystallization of this mixture from methanol enabled a pure sample of O to be obtained, although it was not possible to get a pure sample of P.

The 60 MHz p.m.r. spectrum of O suggested that only one of the acetal rings of VI had been cleaved by the boron/trichloride/lithium aluminium hydride. Thus the acetal proton triplet was present (ca. 4.5δ) along with three hydroxyl groups and a butoxy function.

Further analysis into the structures of M, N, O and P will be given in the next section.

(b) Structural analysis.

The tentative conclusion reached after a preliminary analysis of compounds M and N was that they are both di-O-butyl ethers of galactitol. The possible ethers that could arise from VI are shown in figure IIIE - 3.

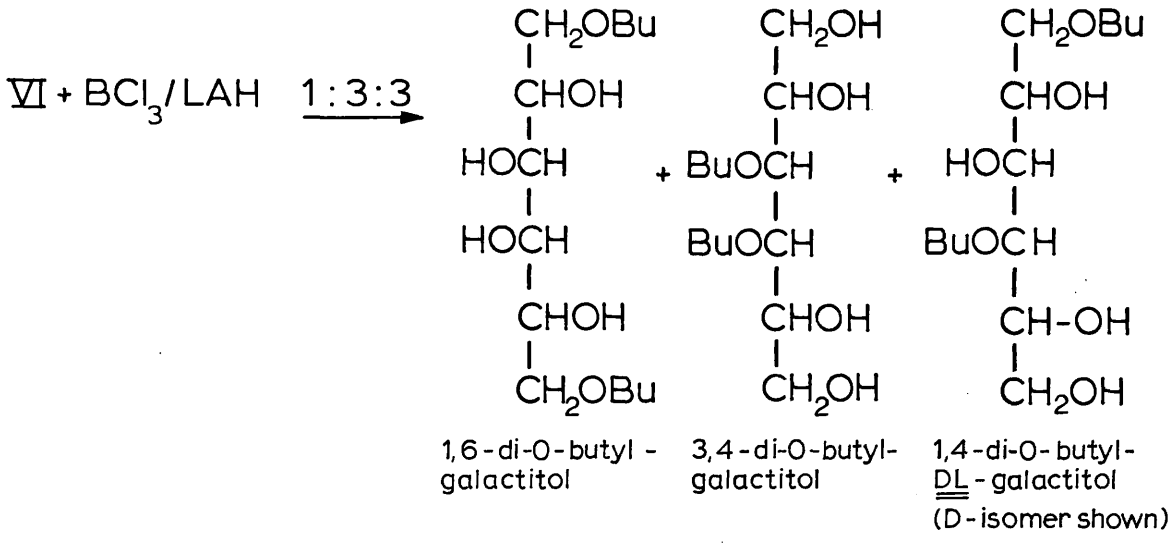


Fig. IIIE - 3.

Periodate oxidation of a small sample of M showed that one mole of the latter consumed three moles of periodate and liberated two moles of formic acid, which means that of the indicated structures M must be the 1,6-dibutyl ether. This assumption was further corroborated when M was shown to migrate under molybdate ionophoresis ($\frac{M}{\text{galactitol}}$ 0.75), therefore suggesting the presence of four contiguous hydroxyl groups[12] which can form a complex of the shown structure with dimolybdate ion (fig. IIIE - 4).

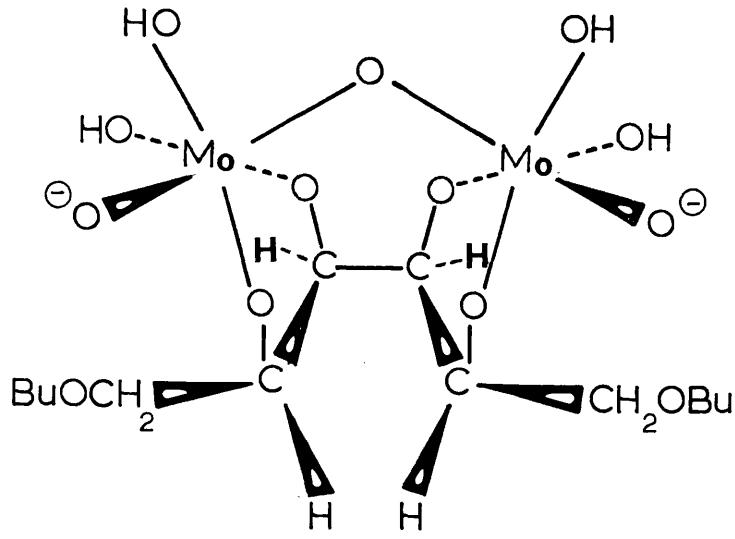


Fig. IIIE - 4.

Mass spectral analysis of an acetylated sample of M also confirmed the 1,6 array of its butyl groups (fig. IIIE - 5).

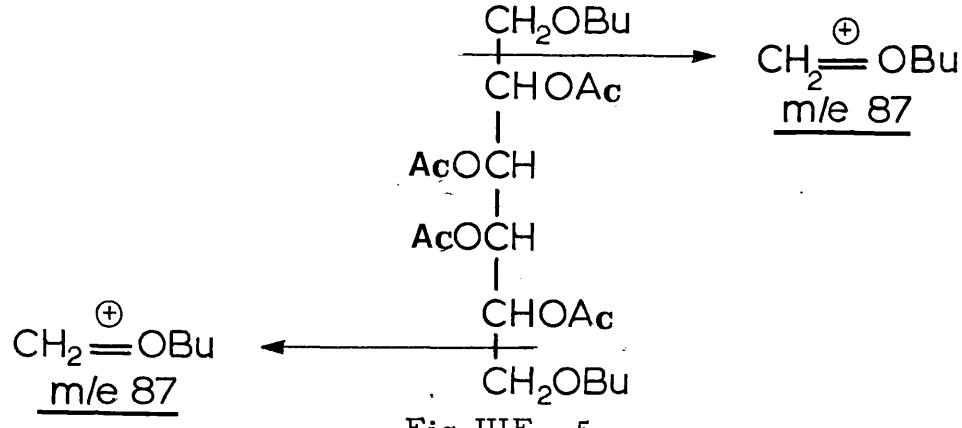


Fig. IIIE - 5.

Meanwhile the empirical formula ($C_{14}H_{30}O_6$) of M was confirmed by elemental analysis (C, H).

One mole of N was then shown to consume two moles of periodate ion and to liberate one mole of formaldehyde which strongly suggested that it was the 1, 4-dibutyl ether of galactitol. This was confirmed on analysis of the mass spectrum of an acetylated sample of N (fig. IIIE - 6) and by the fact that N did not

migrate at all under molybdate ionophoresis conditions.

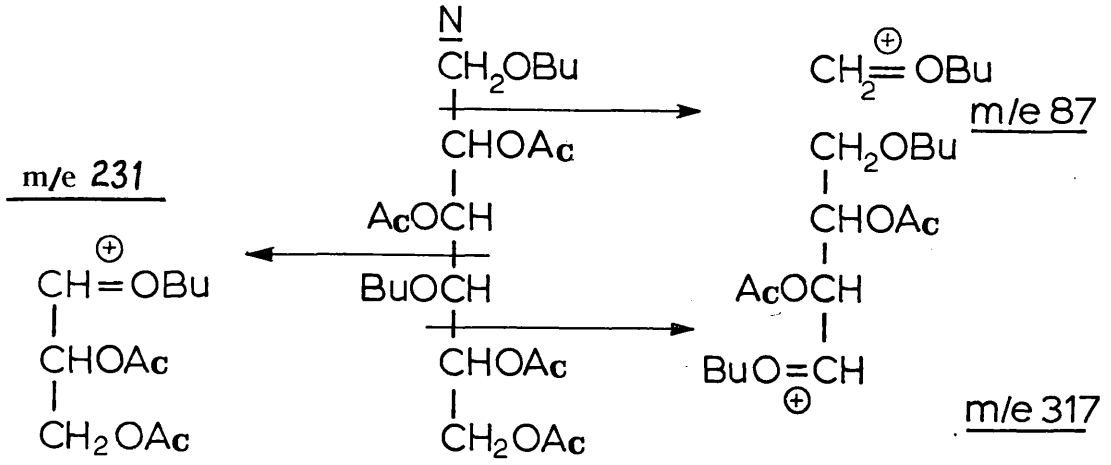


Fig. IIIE - 6.

Elemental analysis (C,H) showed that N's empirical formula ($C_{14}H_{30}O_6$) was that of a dibutyl derivative of galactitol.

Turning now to the structure of O, preliminary analysis suggested that it was the product given when one of the acetal rings upon 1, 3:4, 6-di-O-butylidene galactitol underwent cleavage, which means that one of the two structures shown in figure IIIE - 7 is probably the correct one.

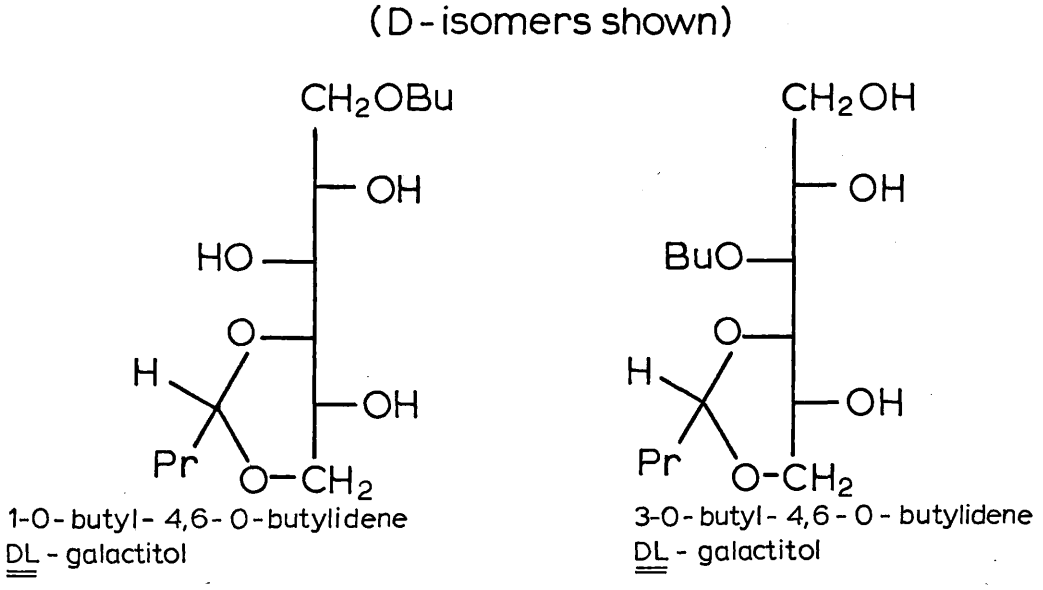


Fig. IIIE - 7.

The lack of liberated formaldehyde in a periodate oxidation experiment along with the consumption of one mole of periodate ion per mole of O, strongly suggested that O was the 1-O-butyl isomer while the 3-O-butyl isomer was definitely ruled out.

Mass spectral analysis of an acetylated sample of O supported the presence of both a primary butoxy group and a terminal acetal function, as can be seen in the shown breakdown pattern (fig. IIIE - 8).

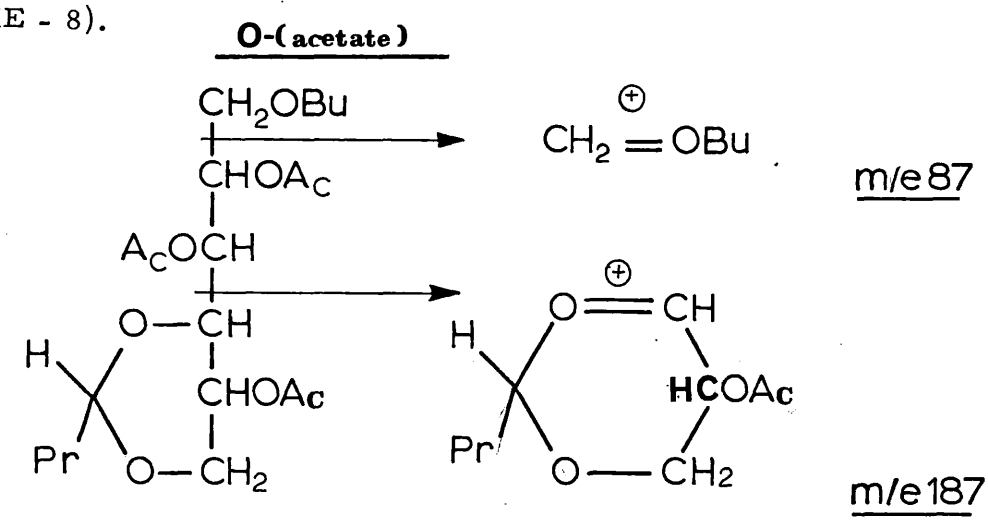


Fig. IIIE - 8.

Also when the acetal function upon O was removed by acid hydrolysis and the single hydrolysis product acetylated, a mass spectrum of the latter contained a large fragment at m/e 87 which further corroborated the presence of a 1-O-butyl group in O (fig. IIIE - 9).

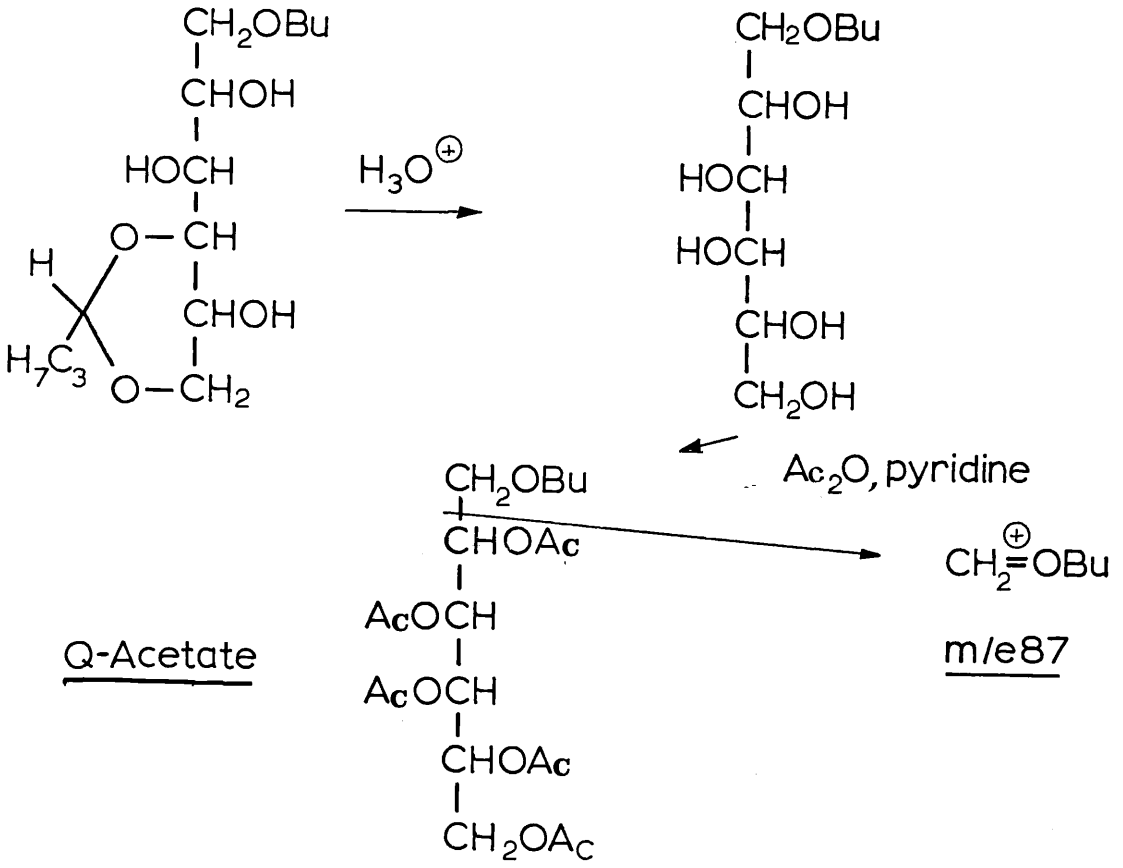


Fig. IIIE - 9.

Elemental analysis (C, H) of the unacetylated hydrolysis product (Q) confirmed that it was a monobutyl ether of a hexitol, while periodate oxidation demonstrated that it contained a primary ether function (fig. IIIE - 10).

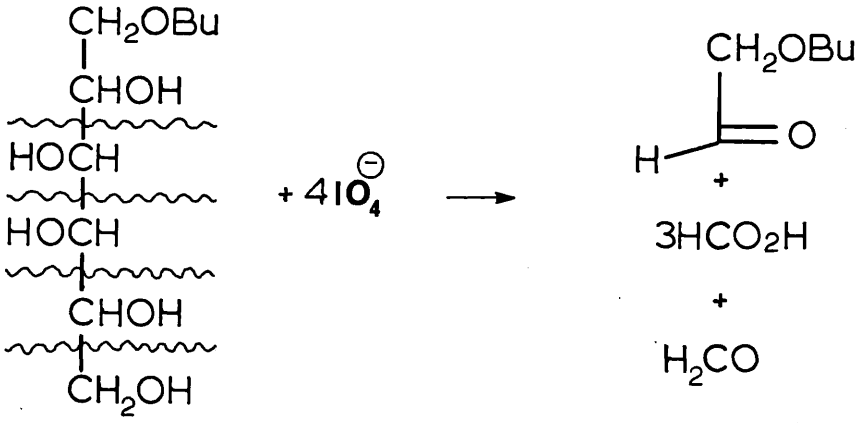


Fig. IIIE - 10.

Thus as the structure of O has been shown to be 1-O-butyl-4, 6-O-butylidene-DL-galactitol, then by the process of elimination - admittedly ignoring possible side reactions - the structure of P was thought to be that of 3-O-butyl-4, 6-O-butylidene-DL-galactitol. The only experimental evidence available to support this assumption is mass spectral, as it was not possible to separate P from O: hence g.l.c. / m.s. analysis gave the displayed fragmentation pattern (fig. IIIE - 11). Future reference to P within this thesis will take the above assumption as being correct.

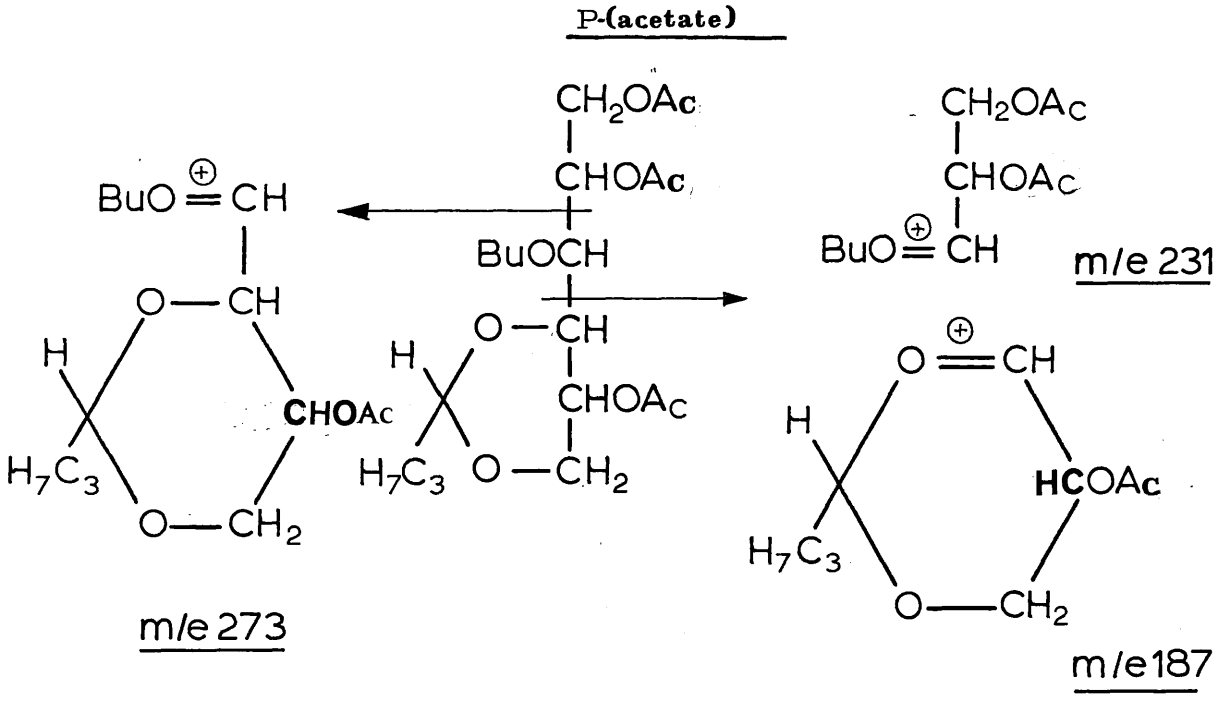


Fig. IIIE - 11.

In summary then the products given from the reaction of 1, 3:4, 6-di-0-butylidene galactitol and the boron trichloride/lithium aluminium hydride combination are as shown in Table IIIE - 1.

Substrate	Substrate/BCl_3 $LiAlH_4$ ratio	Main products	Relative amounts (%)
VI	1:3:3	M + N^x	72.3, 27.7
VI	1:1:1	M + N + O + P^{xx}	41.3, 14.8, 21.9, 3.2
VI	2:1:1	M + O + P^{xx}	11.5, 29.4, 5.9
O	xxx	M + N	41.6, 58.4

Table IIIE - 1.

x Small amounts of O and P also present.

xx Residual substrate also present.

xxx 1:1 mixture of O + BCl_3 treated with further BCl_3 and $LiAlH_4$ i.e. (1:1):1:2.

(c) Rationalization of results.

Earlier in this chapter the idea of intramolecular Lewis complex formation was introduced: it was suggested that the presence of hydroxyl groups adjacent to an acetal function provided an "anchor-point" for the boron, by formation of di-dichloroborinates or cyclic chloroboronates with boron trichloride thereby allowing the subsequent intramolecular reaction to occur (fig. IIIE - 1).

With a 1:1:1 ratio of 1, 3:4, 6-di-0-butylidene galactitol to boron trichloride to lithium aluminium hydride, it has been shown in the previous section that one of the major products was 1-0-butyl-4, 6-0-butylidene-DL-galactitol (O) while 3-0-butyl-4, 6-0-butylidene-DL-galactitol (P) was the minor monoacetal component.

One can rationalize the above observation by considering the structure of the 1:1 diacetal/boron trichloride complex that is

likely to exist prior to the cleavage reaction (fig. IIIE - 12a). If the reasonable assumption is then made that this species comprises the bulk of the complexed acetal, then the reason for the observed specificity becomes clear.

In intramolecular α-chloroether formation, it can be seen in figure IIIE - 12b that attack by the boron upon either O_3 or O_4 to give O' is a much more facile process than attack upon O_1 or O_6 in which P' is given, due to the greater steric distortion required for the latter process. Thus one would expect O to be the dominant product from the intramolecular process.

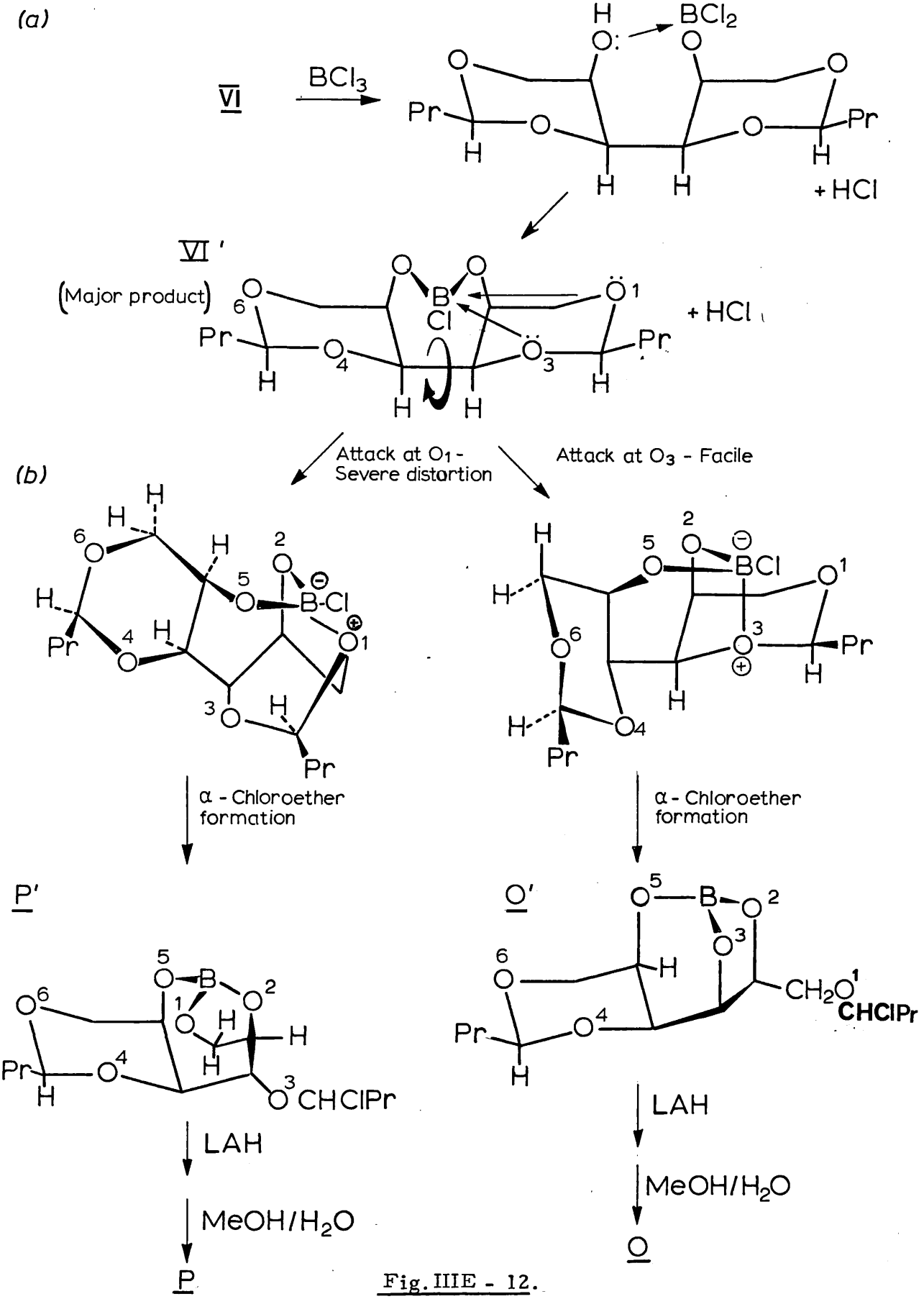

(a)
VI
BCl3
+HCl
VI'
(Major product)
+HCl
Attack at O1 - Severe distortion
Attack at O3 - Facile
(b)
α - Chloroether formation
α - Chloroether formation
P'
O'
LAH
MeOH/H2O
LAH
MeOH/H2O
P
O

Fig. IIIE - 12.

The ease with which the stereochemistry for complex formation between O_3 (or O_4) and the cyclic chloroboronate's boron is given tends to suggest that intermolecular attack of a second molecule of Lewis acid - either unbonded BCl_3 or more likely a second molecule of VI' - at O_3 (or O_4) would be most unlikely.

For instance consider intermolecular attack upon the species shown in figure IIIE - 13, where the cyclic chloroboronate's boron has bonded to O_3. Thus intermolecular attack at O_4 is greatly hindered by the presence of the borate complex involving O_2, O_3 and O_5. Attack at O_1 is possible but subsequent cleavage of the O_1-CHPr bond is made highly unlikely by the positive charge present upon O_3 which would destabilize the oxocarbonium transition state involved in the cleavage of O_1-CHPr. It can be seen that only attack at O_6 would be relatively unhindered and would also afford a viable oxocarbonium ion transition state during the cleavage of the O_6-CHPr bond: the product from this reaction is compound P'' which then upon reduction and work-up yields compound P.

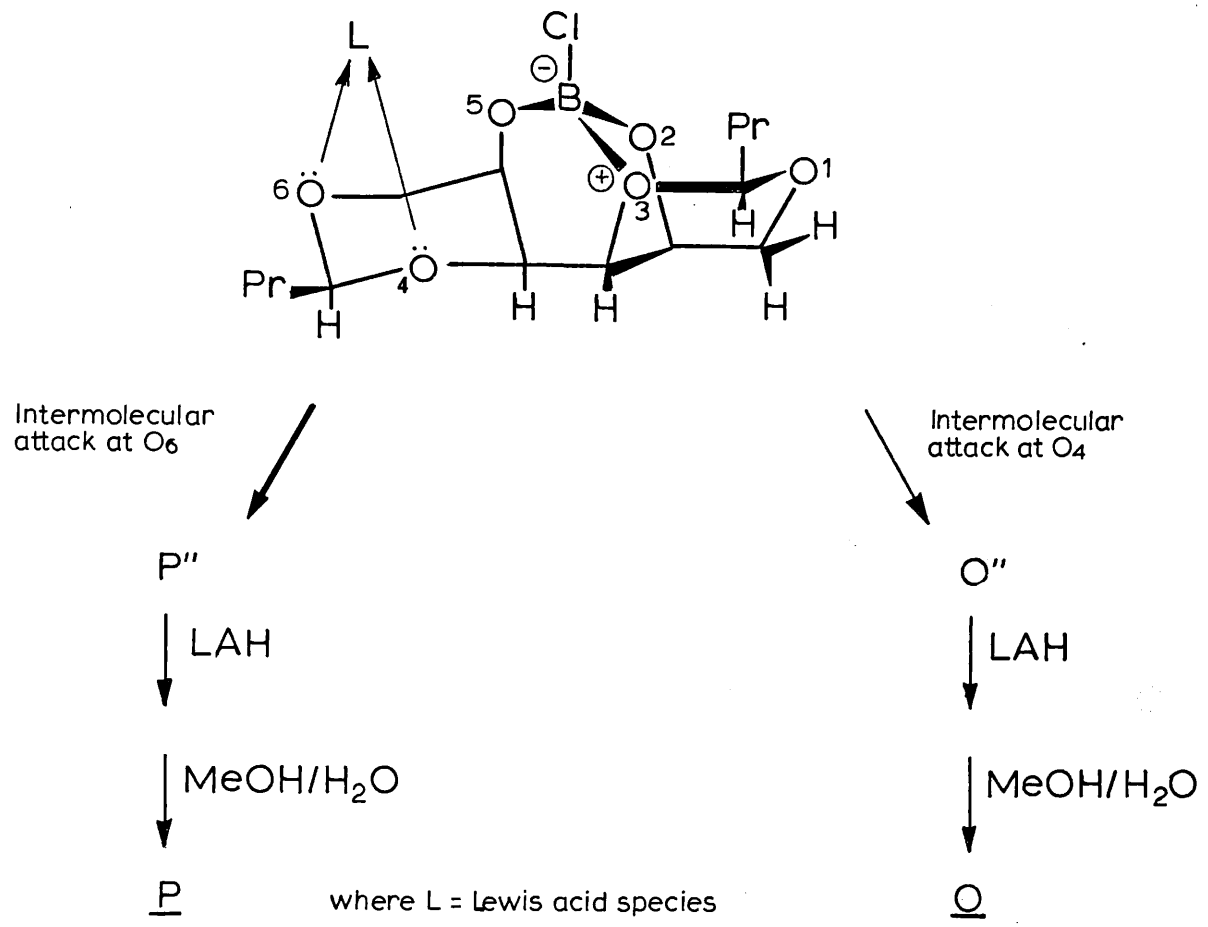


Fig. IIIE - 13.

To summarize what has been considered so far then, in the 1:1:1 reaction the main pathway by which cleavage of the first acetal-ring in 1, 3:4, 6-di-O-butylidene galactitol(VI) would be expected to occur is via the intramolecular pathway yielding compound O, while the minor intermolecular pathway (via complex P'') would give compound P. These reactions are schematically represented in figure IIIE - 14.

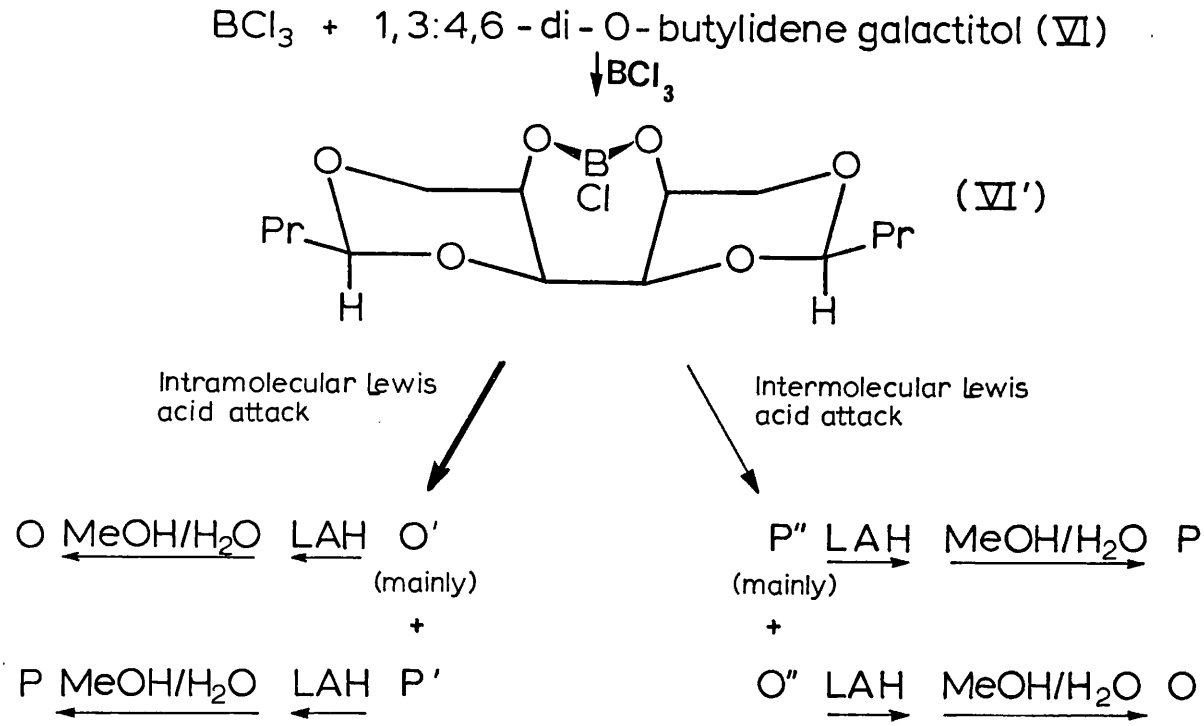


Fig. IIIE - 14.

Now the other two products in the 1:1:1 reaction were 1, 6-di-O-butyl galactitol (M) and 1, 4-di-O-butyl-DL-galactitol (N). Both of these compounds would be given by the cleavage of both of the acetal rings in compound VI, so it would seem logical to look at the cleavage products of compound O' (fig. IIIE -12). when considering the formation of M and N. Figure IIIE - 15 shows that M and N are given during the intermolecular cleavage of compound O' although models suggest that the presence of the borate complex would tend to hinder formation of a Lewis bond at O_4 more than at O_6. Hence on these grounds one would expect compound N' (and thence on reduction and work-up compound N) to be the major product given by O' with M', and thence M, the minor product.

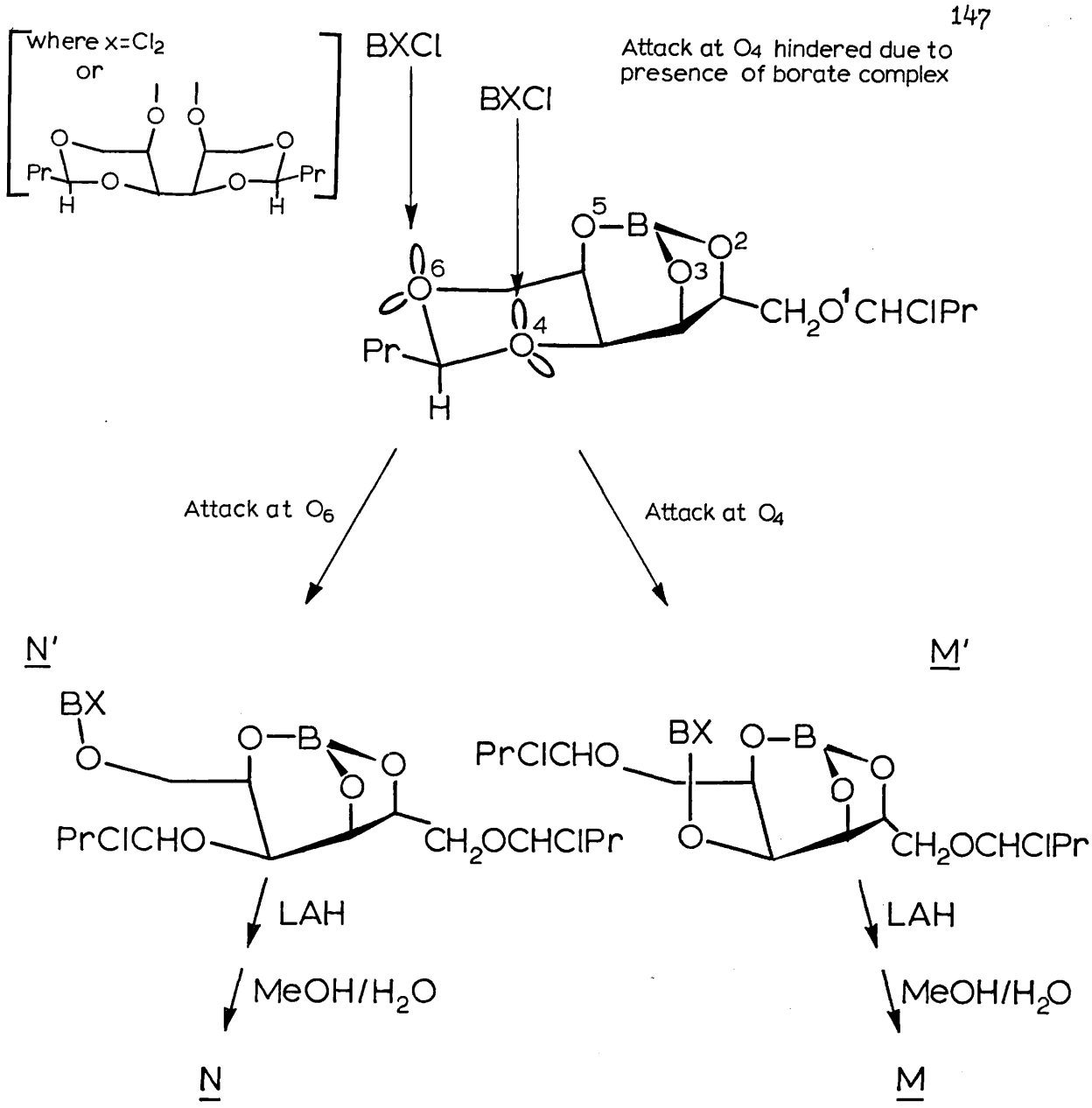


Fig. IIIE - 15.

Table IIIE - 1 however shows that although compound N was present in the final product mixture from the 1:1:1 reaction, it was compound M which was the main dibutyl ether product present.

Thus either the assumption that the attack of the Lewis acid at O_6 occurring in preference to O_4 is incorrect or "some other process" is operating.

An experiment was then carried out in which O (0.003 mol.) was treated with boron trichloride (0.003 mol.) and then with boron trichloride/lithium aluminium hydride (0.003 mol./0.006 mol.) in the usual fashion. The reason for doing this was that it was hoped that the three hydroxyl groups would react with the

first mole equivalent of boron trichloride to yield the complex shown in figure IIIE - 16 which is similar to the situation that exists in O': thus subsequent treatment of this 1:1 mixture with boron trichloride/ lithium aluminium hydride and analysis of the products given would hopefully give some insight into the mode of cleavage operating in O'.

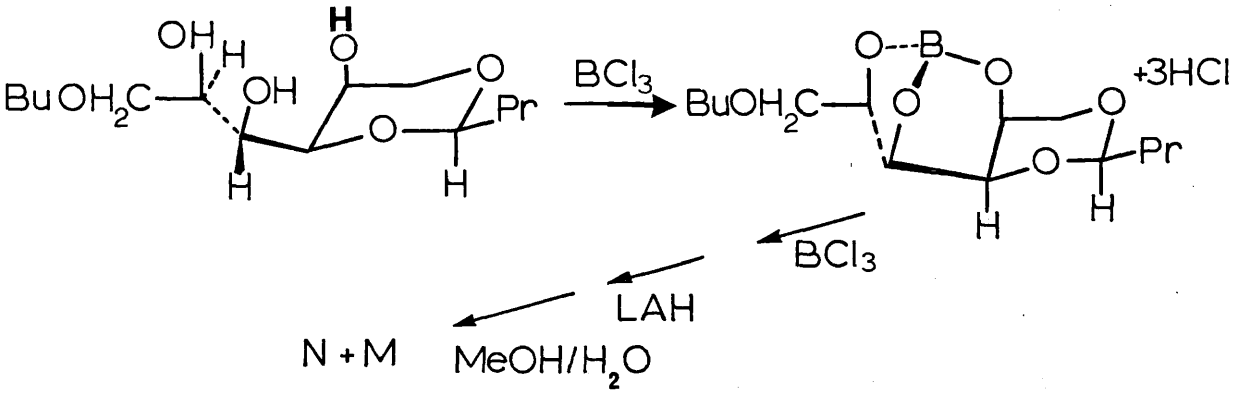


Fig. IIIE - 16.

G.l.c. /m.s. analysis of the product mixture given in the above reaction showed that M and N were both present, but that this time N was the major component (Table IIIE - 1). This seems to suggest that the rationale shown in figure IIIE - 14 is correct in its analysis of the cleavage of O' and more importantly that the observed predominance of M over N in the 1:1 reaction is in fact the result of some other process not considered above.

Further experimental proof that the latter assumption was the case was given when the ratio of acetal to boron trichloride/ lithium aluminium hydride was raised to 2:1:1. The idea behind using this ratio was that it was hoped it would reduce the likelihood

of both acetal rings undergoing cleavage to a very small degree, while at the same time permitting one ring to be cleaved. It can be seen in Table IIIE - 1 that the resulting product mixture contained both O and P (29.4% and 5.9% respectively). The most interesting feature of the reaction however was the presence of a substantial amount of M whilst N was not given at all.

The conclusion drawn from these experiments was that the "alternative process" discussed above must run concurrently with the pathways which produce O' and P''. Also the fact that it appears to give M' as its main product leads one to suggest that what is occurring is the cleavage of both rings by one molecule of boron trichloride.

Hence one can consider a process in which the boron trichloride bonds to say O_3 (yielding O' upon cleavage of the 1, 3 acetal ring) and subsequently to O_4 giving M'' (upon cleavage of the 4, 6 ring), which is then reduced to M by the lithium aluminium hydride (fig. IIIE - 17). So M is not only produced as the minor component during the intermolecular cleavage of O' shown in figure IIIB - 14, it is also given by the alternative intramolecular route discussed above.

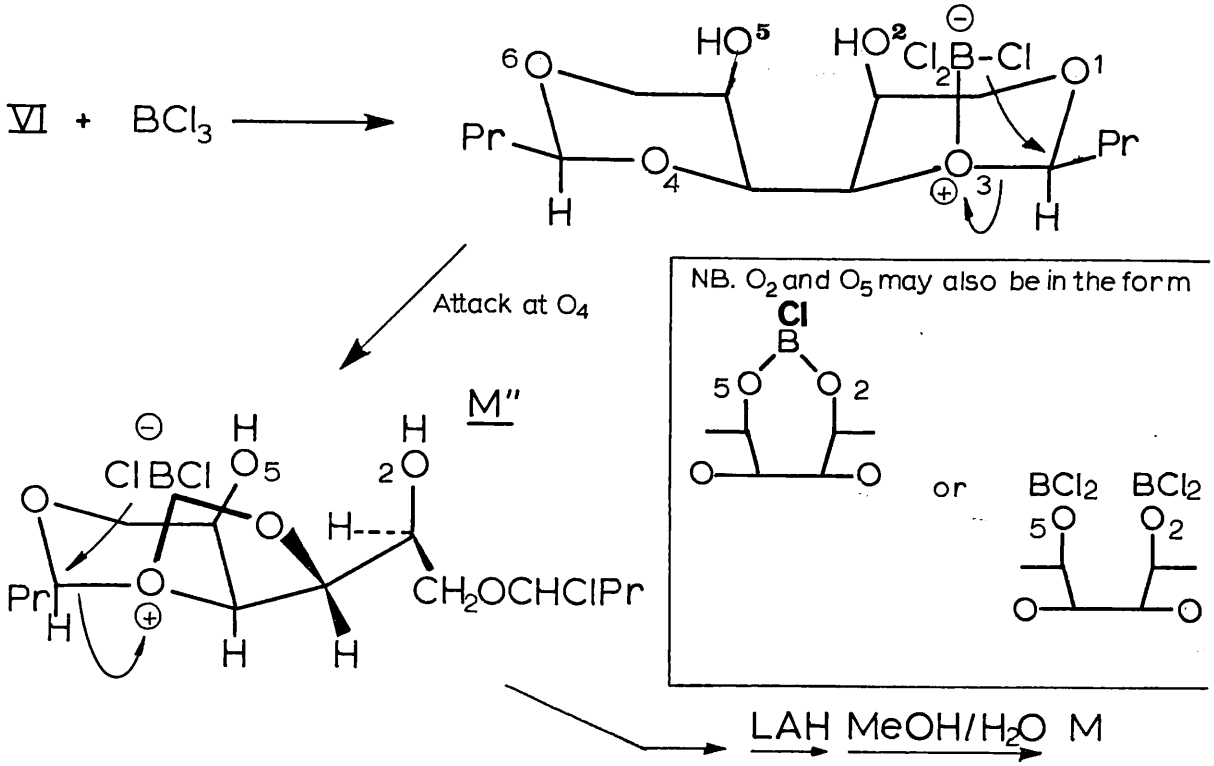


Fig. IIIE - 17.

The modified scheme then for the 1:1:1 reaction may be represented as shown in figure IIIE - 18.

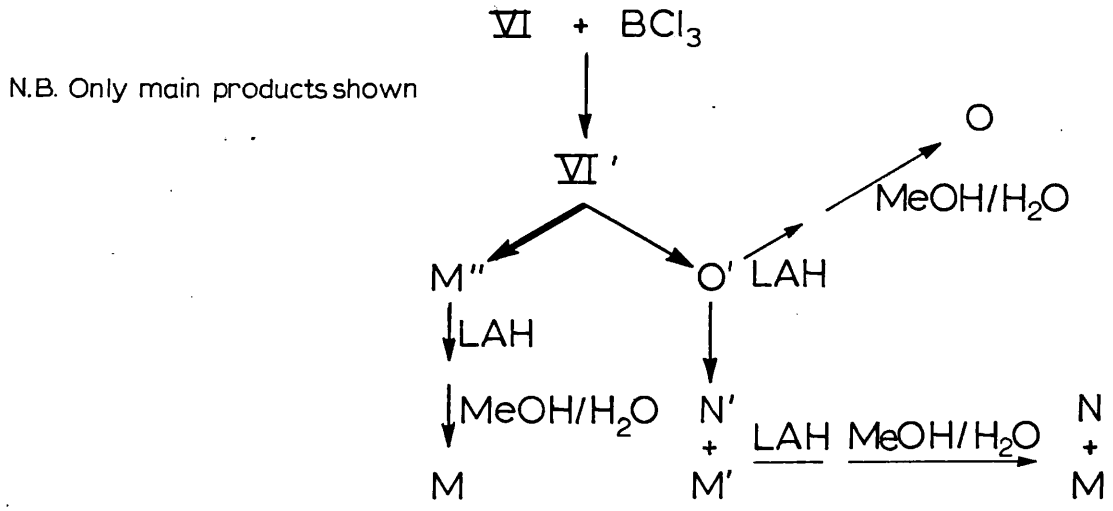
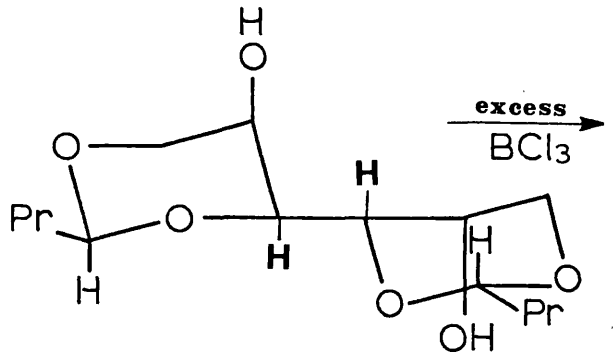
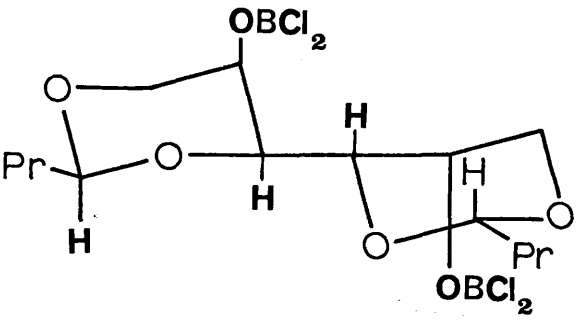


Fig. IIIE - 18.

Meanwhile in the 1:3:3 reaction the acetal is now in the presence of excess Lewis acid and so a di-dichloroborinate type complex would be expected to be the initial product from the reaction of the diacetal's hydroxyl groups and the boron trichloride (fig. IIIE - 19).

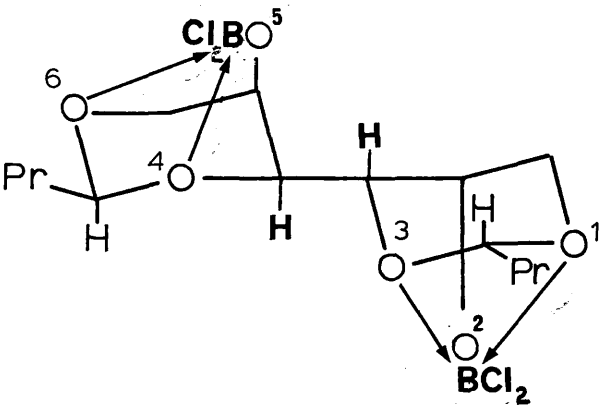


1,3:4,6 - di - O - butylidene galactitol (VI)



2,5 - di - O - dichloroborinate - 1, 3:4,6, - di - O - butylidene galactitol (VI")

(VI")



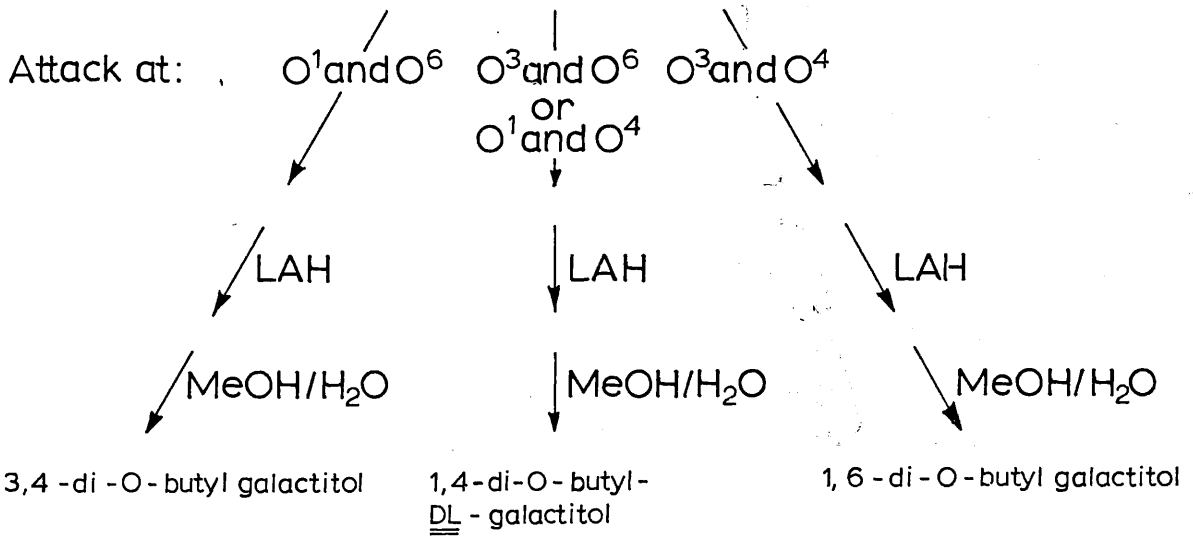


Fig. IIIE - 19.

Now the presence of the dichloroborinate species would tend to prevent intermolecular attack by the excess boron trichloride upon the acetal rings of VI'' in much the same way that intermolecular attack upon VI' was hindered by the presence of the 2, 5-cyclic chloroboronate species (fig. IIIE - 13). Hence only the intramolecular attack of the boron atoms - belonging to the two dichloroborinate species - upon their respective acetal rings will be considered.

The three possible products that could result from the attack (after reduction of the respective α-chloroethers and work-up) are 1, 6-di-O-butyl galactitol(M), 1, 4-di-O-butyl-DL-galactitol(N) and 3, 4-di-O-butyl galactitol (fig. IIIE - 19). Analysis of the product mixture given in the 1:3:3 reaction however showed that although the 1, 6 and 1, 4-dibutyl ethers were seen the 3, 4-dibutyl ether was not present to any significant degree.

The reason for the absence of the 3, 4 isomer is not really clear and may be due to a number of factors that have not been considered by the model used herein to describe the cyclic acetal/boron trichloride reaction, such as the effect of the released hydrogen chloride upon the system or the possible effects that the formation of the dichloroborinate functions have upon the conformation of the substrates.

Of no insignificance to the absence of the 3, 4 isomer is the fact that it was also absent in the 1:1:1 reaction, although here its absence was not surprising due to the presence of the cyclic chloroboronate species (p. 132). It would be tempting to suggest then that the cyclic chloroboronate function is also present even when compound VI is in the presence of excess boron trichloride, due perhaps to a mutual rearrangement reaction between the two dichloroborinate species as seen for instance in ethylene bis-dichloroborinate[14] (fig. IIIE - 20). The result of such a rearrangement would be that one would expect to see the same dibutyl ether products as one saw in the 1:1:1 reaction which is in fact the case. Unfortunately the

only evidence available for suggesting the rearrangement is this very state of affairs.

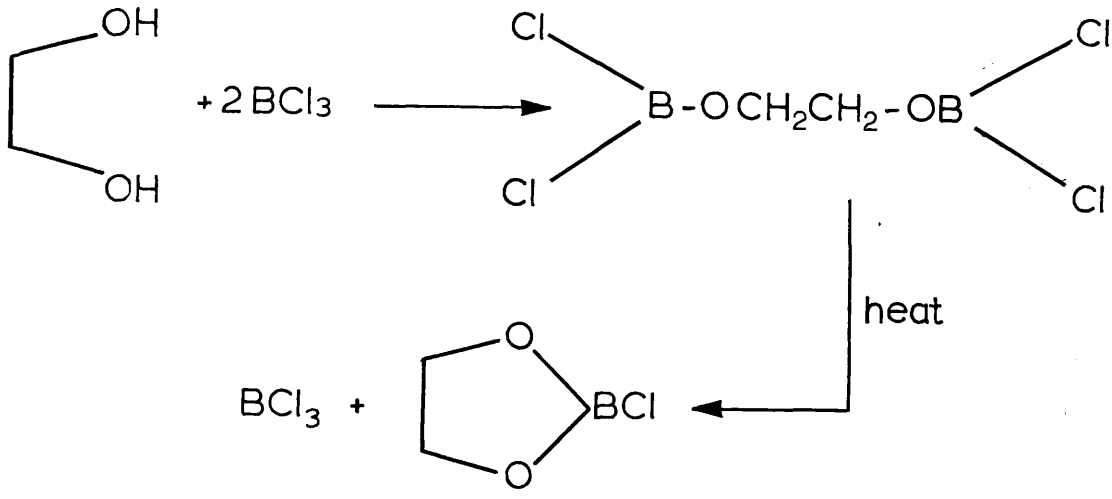
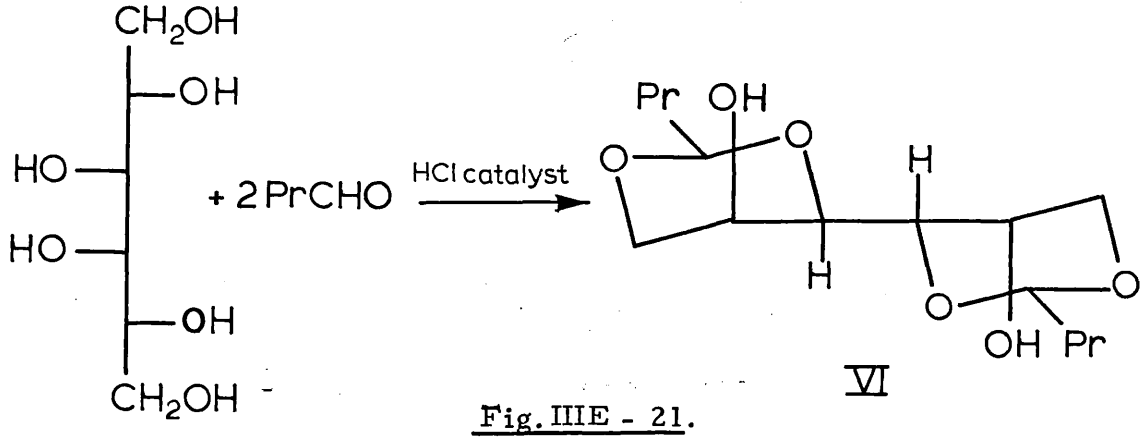


Fig. IIIE - 20.

(d) Preparation of substrate.

The 1, 3:4, 6-di-O-butylidene galactitol was prepared directly from galactitol and butyraldehyde using the method of L. Yüceer[13] (fig. IIIE - 21).



VI

Fig. IIIE - 21.

IIIF. Conclusion.

It was stated in the introduction that the general aim behind the work contained in this chapter was that of slightly increasing the complexity of the substrate acetals, in order to test the rationale put forward in chapter II to describe the cyclic acetal/boron trichloride plus lithium aluminium hydride reaction.

The particular facet of the above rationale that seemed most in need of extrapolation was the simple electronically based view of the direction of cleavage. This in fact had already been shown to be inadequate in the case of 2, 2, 4--tri-0-methyl-1, 3-O-dioxolane, where the direction of cleavage was thought to be governed by a complex interplay of electronic and steric factors: a situation that would not be uncommon in molecules in which an acetal function is used as, say, a protecting group.

It has been shown that the presence of a large equatorially disposed basic group adjacent to the 1, 3-dioxane system favours cleavage of the C_2-O bond further from it: thus the n-butoxymethyl function at C_4 in compound II favours cleavage of the C_2-O_1 bond. This is in direct opposition to the n-butoxymethyl group's electron withdrawing nature. The above effect is magnified by the presence of a second n-butoxy function at C_5 (as seen in compound IV) when cleavage occurs almost exclusively at the C_2-O_1 bond.

The statement that the above directing ability of the butoxy group is due solely to the steric hindrance it affords to the formation of the Lewis complex is an obvious over-simplification, as the basicity of the ether's oxygen will enable it to compete for the Lewis acid against the acetal's oxygens thereby creating an electronically based steric factor relevant to the ensuing cleavage reaction.

This concept becomes more important when hydroxyl groups are present in the acetal molecule as for instance has been demonstrated in the reaction of 1, 3-0-butylidene-DL-erythritol, when the cyclic borate produced drastically altered the indigenous stereochemistry of the acetal: the fact that boron trichloride possesses three replaceable chlorine atoms makes the above effect possible.

Meanwhile for the same reason, the question of intermolecular versus intramolecular cleavage becomes important when less than three hydroxyl groups or acetal groups are present in the same molecule. It has been suggested in the light of the results from the 4-hydroxymethyl-2-propyl-1, 3-dioxane and 1, 3:2, 4-di-0-butylidene erythritol reactions that where possible the intramolecular reaction may be dominant and also that when the choice exists between the formation of a seven membered or a five membered cyclic boronate type complex that the former is preferred: this is not contradicted by other workers.[4] Finally the work with 1, 3:4, 6-di-0-butylidene galactitol emphasised the complexity of the boron trichloride/cyclic acetal reaction when more than one bonding site is present and also consolidated the view expressed above that the intramolecular α-chloroether formation is a major factor to be considered in this reaction.

The synthesis in quite good yields of the 1, 2-di-0-butyl and 1, 2, 3-tri-0-butyl ethers of erythritol along with 1-0-butyl-4, 6-0-butylidene-DL-galactitol, 1-0-butyl-DL-galactitol, 1, 4-di-0-butyl-DL-galactitol and 1, 6-di-0-butyl galactitol are considered to be examples of the synthetic application of the boron trichloride/lithium aluminium hydride combination.

Perhaps the most interesting feature of the work in this chapter from the synthetic point of view has been the potential directing influence that unmasked hydroxyl groups have upon the cleavage reaction. Closely related to this however lies perhaps

the greatest disadvantage in the use of the boron trichloride/lithium aluminium hydride combination: thus because of the high reactivity of the boron trichloride (relative to, say, the aluminium chlorohydrides) and also because of its three replaceable chlorine atoms a complex series of reactions is possible especially when more than one bonding site is present within the same molecule. This can of course be useful as has been demonstrated but in the main one would have to conclude that the best results are given with simple acetals where no more than one other bonding site for the boron trichloride is available.

IIIG. Experimental.

Experiment 1. General experimental procedure used in acetal plus boron trichloride/lithium aluminium hydride reactions.

The basic reaction procedure used throughout this section was essentially the same as that described in chapter II, experiment 1. Meanwhile the work-up procedure was the same as that discussed on p. 38 (Ch. II).

Experiment 2. The reaction of (±)-cis-4-hydromethyl-2-propyl-1,3-dioxane(I) with boron trichloride/lithium aluminium hydride.

(a) Isolation of the main products.

Compound I (2.72 g., 0.017 mol.) in methylene chloride (15 ml.) was treated with boron trichloride (1.99 g., 0.017 mol.) in methylene chloride (30 ml.) for 10 minutes at 0^{o} and then with ethereal lithium aluminium hydride (0.65 g., 0.017 mol.) for 30 minutes.

After work-up in the usual manner (Ch. II, p. 38) a clear syrupy product (2.2 g., 80%) was isolated. The 60 MHz p.m.r. spectrum of this syrup showed that the acetal proton triplet (4.5δ) was not present.

G.l.c. analysis of the crude product showed the presence of two main components A and B which comprised

approximately 97% of the isolated material. A third minor component C was also present which accounted for about 3% of the isolated material. Comparison of the retention time of C with that of butan-1, 2, 4-triol showed them to be identical.

The mixture of A plus B was separated from the triol by passing the crude worked-up material down a silica gel column (110 g.) eluting with toluene/methanol (9:1) when A and B passed through together while C remained immobile.

The fractions containing the mixture of A plus B were combined and the solvent removed under vacuum leaving a clear syrup (ca. 2 g.).

(b) Structural determination of A and B.

A sample (ca. 10 mg.) of the mixture was acetylated using acetic anhydride (1 ml.) in pyridine (1 ml.) via the procedure described in the General Methods Section (p.259).

The g.l.c. of the acetylated sample showed that the mixture was composed of 34.2% A and 65.8% of B.

The acetylated sample was then analysed by g.l.c./m.s. The spectra given indicated that A was DL- 1-O-butyl butan-1, 3, 4-triol and that B was DL-3-O-butyl butan-1, 3, 4-triol.

Periodate oxidation of the mixture of A plus B (10 mg.) using the procedure discussed in General Methods (p.264), showed that 38% of the mixture was "active" to the periodate ion. This confirmed that the mixture was composed of A and B in an approximated 1:2 ratio.

G.l.c. retention times:

A = 2229 s., B = 2427 s., (130^{o}, OV - 225).

Experiment 3. The reaction of (±)-cis-4-n-butoxymethyl-2-propyl-1,3-dioxane(II) with boron trichloride/lithium aluminium hydride.

Compound II (2.6 g., 0.012 mol.) in methylene chloride (15 ml.) was treated with boron trichloride (0.47 g., 0.004 mol.) for 10 minutes at 0° and then with ethereal lithium aluminium hydride (0.2 g., 0.0052 mol.) for a further 30 minutes.

Work-up in the usual manner gave a clear syrupy product (2.36 g., 91%). G.l.c. analysis of this syrup showed that it contained two components C (75.4%) and D 24.6% neither of which had the same retention time as the substrate.

The 60 MHz p.m.r. spectrum of the mixture showed that neither C nor D contained an acetal proton (4.5δ triplet).

The syrup was then subjected to g.l.c./m.s. analysis. This showed that C was DL-3,4-di-O-butyl butan-1,3,4-triol and that D was DL-1,4-di-O-butyl butan-1,3,4-triol.

G.l.c. retention times:

C = 812 s., D = 599 s., (129°, 3% OV-225).

Experiment 4. The reaction of 1,3-O-butylidene-DL-erythritol(III) with boron trichloride/lithium aluminium hydride.

(a) Isolation of products.

Compound III (1.62 g., 0.0092 mol.) in methylene chloride (25 ml.) was treated with boron trichloride (1.08 g., 0.0092 mol.) for 10 minutes at 0° and then with ethereal lithium aluminium hydride (0.38 g., 0.01 mol.) for 30 minutes. Work-up in the usual manner gave a clear syrupy product (1.41 g., 86%).

Acetylation of a small sample (ca. 10 mg.) of this material (General Methods p. 259) followed by g.l.c. analysis showed that two components E (4.9%) and F (95.1%) were present, neither of which had the same retention times as an acetylated sample of the substrate.

Periodate oxidation of the mixture (General Methods p.264) showed that 1 mole of the mixture consumed 1.05 moles of periodate ion and liberated 1.01 moles of formaldehyde and 0.041 moles of formic acid.

(b) Structural determination of E and F.

G.l.c./m.s. analysis of a small acetylated sample (ca. 10 mg.) of the product mixture showed that compound E was 1-O-butyl-DL-erythritol.

G.l.c. retention time:

acetate derivative = 1156 s., (180°, 3% OV-225).

R_F = 0.14, (solvent A).

Mass spectrum: (acetate derivative),

m/e 73 (38%), 86 (33.5%), 87 (91.3%), 103 (43.5%),

m/e 115(100%), 129 (98.5%), 142(72.6%), 159 (3.7%),

m/e 171(4.0%), 184(11.4%), 231(2.3%).

Meanwhile compound F was shown to be 2-O-butyl-DL-erythritol.

G.l.c. retention time:

acetate derivative = 1275 s., (180°, 3% OV-225).

R_F = 0.14 (solvent A).

Mass spectrum: (acetate derivative),

See Ch. V. p.220.

(c) Reaction using 1:3 ratio of III to boron trichloride/lithium aluminium hydride.

Compound III (0.88 g., 0.005 mol.) was treated with boron trichloride (1.76 g., 0.015 mol.) and lithium aluminium hydride (0.57 g., 0.015 mol.) using the procedure outlined in (a).

The syrupy product (0.69 g., 78%) was found to be composed of 27.6% E and 72.4% F by g.l.c. analysis of the acetylated mixture.

Experiment 5. The reaction of 2,4-di-O-butyl-1,3-O-butylidene-DL-erythritol (IV) with boron trichloride/lithium aluminium hydride.

(a) Isolation of the main product.

Compound IV(3.45 g., 0.012 mol.) in methylene chloride (35 ml.) was treated with boron trichloride (0.47 g., 0.004 mol.) in methylene chloride (25 ml.) for 10 minutes at 0° and then with ethereal lithium aluminium hydride (0.15 g., 0.004 mol.) for 30 minutes. Work-up in the usual manner gave a clear syrupy product (2.83 g., 82%).

G.l.c. analysis of an acetylated sample (10 mg.) of this syrup showed that it contained two main components G (97%) and H (3%).

A pure sample of G (1.16 g.) was obtained by passing the crude syrup (1.5 g.) down a silica gel column (75 g.) eluting with toluene/methanol (9:1).

(b) Structural determination of G and H.

Compound G did not react with sodium periodate (General Methods p.264) which showed that it does not contain two adjacent hydroxyl groups: a similar result was given with compound H.

The mass spectrum of an acetylated sample of G (Ch. V, p. 225) showed that it was 1,2,3-tri-O-butyl-DL-erythritol.

Analysis: $C_{16}H_{34}O_4$ requires 66.15(C), 11.8(H)%,
found 65.99(C), 11.71(H)%.

G.l.c. retention time:
acetate derivative = 400 s. (190°, 3% OV-225).

R_F = 0.5 (solvent A).

Meanwhile the mass spectrum of an acetylated sample of H (via g.l.c./m.s.) showed that it was 1,2,4-tri-O-butyl-DL-erythritol.

Mass spectrum: (of acetate derivative),
m/e 87 (22.8%), 117(53.2%), 129(56.6%), 171(100%),
m/e 173 (28.8%), 185(82.8%), 245 (18.2%).

G.l.c. retention time:
acetate derivative = 502 s.(190°, 3% OV-225).

(c) Reaction using a 1:1 ratio of acetal to boron trichloride/lithium aluminium hydride.

Compound IV (2.13 g., 0.0074 mol.) was treated with boron trichloride (0.87 g., 0.0074 mol.) and lithium aluminium hydride (0.29 g., 0.0075 mol.) using the procedure outlined in (a).

G.l.c. analysis of an acetylated sample of the syrup showed that it was composed of 83.7% G and 16.3% H.

Experiment 6. The reaction of 1,3:2,4-di-O-butylidene erythritol(V) with boron trichloride/lithium aluminium hydride.

(a) Isolation of the main product.

Compound V (1.84 g., 0.008 mol.) in methylene chloride (25 ml.) was treated with boron trichloride (0.94 g., 0.008 mol.) in methylene chloride (30 ml.) for 10 minutes at 0^{o} and then with ethereal lithium aluminium hydride (0.3 g., 0.008 mol.) for 30 minutes. Work-up in the usual way gave 1.69 g. (92%) of a clear syrupy product.

G.l.c. analysis of an acetylated sample of this product showed that there were three products present: J (88.2%), K (7.2%) and L (4.6%).

The syrup (1.5 g.) was then dissolved in toluene/methanol (9:1, 5 ml.) and passed down a silica gel column (75 g.) eluting with the same solvent. The separation procedure outlined in experiment 4 gave a pure sample (0.65 g.) of J, although the procedure had to be repeated three times. It was not possible to obtain pure samples of K or L by this procedure.

(b) Structure determination of compounds J, K and L.

One mole of compound J was found to consume one mole of periodate ion and to liberate one mole of formaldehyde.

The mass spectrum of a small acetylated sample of J (ca. 10 mg.) showed that J was 1,2-di-O-butyl-DL-erythritol (Ch. V, p. 222).

Analysis: $C_{12}H_{26}O_4$ requires 61.49(C), 11.19(H)%,
found 61.02(C), 10.94(H) %.

G.l.c. retention time:

acetate derivative = 1126 s. (160°, 3% OV - 225).

$\underline{R}_F$ = 0.27 (solvent A).

Meanwhile analysis of the mass spectra given by the acetylated derivatives of K and L (via g.l.c./m.s.) showed that they were 2,3-di-O-butyl erythritol and 1,4-di-O-butyl erythritol respectively.

Mass spectra: for the acetate derivative of K,

m/e 73 (42.4%), 103 (100%), 115 (71.1%), 129 (36%),

m/e 159 (81.9%), 171 (33.7%), 185 (21.6%), 245 (36%).

G.l.c. retention time:

acetate derivative = 1245 s. (160°, 3% OV -225).

Mass spectra: for the acetate derivative of L,

m/e 45 (59.3%), 57 (70%), 87 (100%), 103 (18.3%),

m/e 115 (22.4%), 129 (36.6%), 159 (15.5%), 203 (18.2%),

m/e 259 (22%).

G.l.c. retention time:

acetate derivative = 994 s.(160°, 3% OV - 225).

Experiment 7. The reaction of 1,3:4,6-di-O-butylidene galactitol (VI) with boron trichloride/lithium aluminium hydride.

i) 1:3 Ratio of acetal to $BCl_3/LiAlH_4$.

(a) Isolation of products.

Compound VI (2.2 g., 0.0076 mol.) was treated with boron trichloride (2.7 g., 0.023 mol.) for 15 minutes at 0° and then with ethereal lithium aluminium hydride (0.87 g., 0.023 mol.) for 30 minutes. After work-up in the usual manner a slightly cloudy syrup was obtained (1.82 g., 82%).

G.l.c. analysis of an acetylated sample of the syrup (10 mg.) showed that two main products were present, M (72.3%) and N (27.7%).

The bulk of the syrup (1.75 g.) was dissolved in hot chloroform and then carbon tetrachloride was slowly added until the solution went turbid. The solution was then reheated to dissolve this precipitated material and then stored at 5°, when after two days a small amount of a crystalline compound was precipitated.

This was filtered off, acetylated (General Methods, p.259) and subjected to g.l.c. analysis which showed that it was a pure sample of compound M (m.p.135 - 6°).

The above procedure was then repeated 5 times until the bulk of M had been separated from the mixture. Compound N was then obtained by evaporating the mother liquors from the final filtration until precipitation had just begun to occur, the solution was then reheated to dissolve the precipitate and then stored at 5°. Compound N crystallized after several days (m.p. 100-1°).

(b) Structure determination of compounds M and N.

Periodate oxidation (see General Methods p.264) of a small sample of M (ca. 10 mg.) along with mass spectral analysis of an acetylated sample of M (ca. 10 mg.) showed that it was 1,6-di-O-butyl-galactitol (Ch. V , p.229).

Molybdate ionophoresis (see General Methods, p.263) showed that the mobility of M was $\underline{M}_{\text{galactitol}}$ 0.75.

Analysis: $C_{14}H_{30}O_6$ requires 57.12(C), 10.27(H) %,
found 56.69(C), 10.13(H)%.

G.l.c. retention times:

acetate derivative = 2517 s.(179°, 7.5% A.P.K.),

trimethylsilyl derivative = 779 s. (170°, 3% OV - 225).

$\underline{R}_F$ = 0.23 (solvent A), 0.5 (solvent B).

Meanwhile periodate oxidation of a small sample of N (ca. 10 mg.) along with mass spectral analysis of an acetylated sample of N (ca. 10 mg.) showed that it was 1,4-di-O-butyl galactitol (see Ch. V ,p.231).

Analysis: $C_{14}H_{30}O_6$ requires 57.12(C), 10.27(H) %,
found 57.38(C), 10.41(H) %.

G.l.c. retention times:

acetate derivative = 2068 s. (179°, 7.5% A.P.K.),

trimethylsilyl derivative = 668. s.(170° 3% OV - 225).

$\underline{R}_F$ = 0.23 (solvent A), 0.46 (solvent B).

ii) 1:1 Ratio of acetal to $BCl_3/LiAlH_4$.

(a) Isolation of compound O.

1, 3:4, 6-Di-O-butylidene galactitol (2.75 g., 0.0095 mol.) was then treated with boron trichloride (1.1 g., 0.0094 mol.) for 30 seconds at 0° and then lithium aluminium hydride (0.36 g., 0.0095 mol.) for 30 minutes. Work-up of the reaction in the usual way gave a white crystalline product (2.4 g., 87%).

G.l.c. analysis of a small acetylated sample of this material (ca. 10 mg.) showed that it was composed of four components:
M (41.3%), N (14.8%), O (21.9%) and P (3.2%) along with unreacted substrate.

The crude product mixture was then passed down a silica gel column (120 g.) eluting with toluene/methanol (9:1), this enabled the mixture of O and P to be separated from the other components of the mixture.

A pure sample of O (0.41 g.) was then obtained by fractional crystallization of the mixture of O plus P from methanol, m.p. 80 - 2°.

(b) Structure determination of compounds O and P.

Periodate oxidation (General Methods, p.264) of a small sample of O (ca. 10 mg.) showed that one mole of O consumed 1.01 moles of periodate ion after 20 h.

The mass spectrum of an acetylated sample of O (ca. 10 mg.) showed that O was 1-O-butyl-4, 6-O-butylidene-DL-

galactitol (Ch. V , p.233).

Analysis: $C_{14}H_{28}O_6$ requires 57.49(C), 9.65(H)%
found 57.51(C), 9.58(H)%.

G.l.c. retention times:

acetate derivative = 2070 s.(186°, 7.5% A.P.K.),

trimethylsilyl derivative = 1755 s.(156°, 3% OV - 225).

R_F = 0.72 (solvent A).

Meanwhile acetylation and g.l.c./m.s. analysis of a small sample (ca. 10 mg.) of the mixture of O and P enabled a mass spectrum of P to be taken: this showed that P was 3-O-butyl-4,6-O-butylidene-DL-galactitol.

Mass spectrum: (acetate derivative),
m/e 115 (100%), 129 (39%), 171 (20.1%), 187 (13.7%),
m/e 231 (11.6%), 273 (26.6%).

G.l.c. retention time:

acetate derivative = 1860 s. (186°, 7.5% A.P.K.).

iii) 2:1 Ratio of acetal to $BCl_3/LiAlH_4$.

1,3:4,6-Di-O-butylidene-galactitol (4.76 g., 0.0164 mol.) was treated with boron trichloride (0.96 g., 0.0082 mol.) for 5 minutes at 0° and then with lithium aluminium hydride (0.31 g., 0.0082 mol.) for 30 minutes at room temperature.

After work-up in the usual manner a white crystalline solid (4.2 g., 88%) was isolated. A small sample of this solid (ca. 10 mg.) was then acetylated and subjected to g.l.c. analysis. This showed that it was composed of three main product components M (11.5%), O (29.4%) and P (5.9%) along with unreacted substrate (51.2%).

Experiment 8. The acid hydrolysis of 1-O-butyl-4,6-O-butylidene DL-galactitol.

Compound O (0.2 g., 0.0007 mol.) in ethanol/water (7:3, 20 ml.) was refluxed and stirred with Amberlite IR-120 (H^+) resin (7 ml.) for 2 h. After this time the resin was filtered off and the filtrate concentrated on a rotary evaporator until all of the solvent had been removed: a white solid (0.13 g., 80%) was deposited, 1-O-butyl-DL-galactitol.

This material was twice recrystallized from ethyl acetate, m.p. 134-5°.

Analysis: $C_{10}H_{22}O_6$ requires 50.39(C), 9.31(H)%,
50.66(C), 9.27(H)%.

G.l.c. retention time:

acetate derivative = 3585 s. (198°, 3% OV - 225),

trimethylsilyl derivative = 333 s (180°, 3% OV - 225).

R_F = 0.22 (solvent B).

Mass spectrum: (E.I. of acetylated sample).

m/e 57 (100%), 87 (25.5%), 115(35.84%),

m/e 129 (45.7%), 157 (21.7%), 171 (24.1%).

(C.I. of pure compound):

m/e 239.

Experiment 9. The reaction of 1-O-butyl-4,6-O-butylidene-DL-galactitol (O) with boron trichloride/lithium aluminium hydride.

Compound O (0.88g., 0.003 mol.) was treated with boron trichloride (0.35 g., 0.003 mol.) for 10 minutes at 0° in methylene chloride and then with more boron trichloride (0.37 g., 0.003 mol.) for a further 10 minutes. Ethereal lithium aluminium hydride (0.23 g., 0.006 mol.) was then added.

After stirring at room temperature for 30 minutes and the usual work-up procedure a clear syrupy product was isolated,

(0.74 g., 84%). A small sample of this syrup (ca. 10 mg.) was acetylated and then subjected to g.l.c. analysis: this showed that the syrup was composed of 1,6-di-O-butyl galactitol (41.6%) and 1,4-di-O-butyl-DL-galactitol (58.4%) (see experiment 8).

Experiment 10. Preparation of the acetal substrates.

(a) 4-Hydroxymethyl-2-propyl-1,3-dioxane(I).

n-Butyraldehyde (7.2 g., 0.1 mol.) and p-toluene-sulphonic acid (0.15 g., $8 \cdot 10^{-4}$ mol.) were added to a suspension of DL- butan-1,2,4-triol (10.7 g., 0.1 mol.) in toluene (100 ml.). The reactants were then refluxed together until the theoretical amount of water (1.8 ml.) distilled over as its toluene azeotrope. A modified Dean and Stark apparatus was used to collect the water.

The apparatus and contents were then allowed to cool to room temperature after which anhydrous sodium carbonate (5 g.) was added to the reaction mixture. After stirring for 10 minutes, filtering and further drying (anhydrous Na_2SO_4) the dark-brown filtrate was transferred to a rotary evaporator where the toluene was removed.

Fractional distillation of the syrupy residue gave a fraction (12 g., 75%, b.p. 186°) which was shown by g.l.c. to be composed of two compounds I (63.6%) and I' (36.4%). These were 4-hydroxymethyl-2-propyl-1,3-dioxane and its isomer 4-(2-hydroxymethyl)-2-propyl-1,3-dioxolane. The difference in shift of the acetal protons belonging to the respective isomers was the parameter used to distinguish them, (4.5δ for the dioxane and 4.9δ for the dioxolane[6]).

Further fractional distillation enabled a pure sample of I to be isolated although I' could not be separated from contaminating I.

Yield of I = 6 g. (37.5%) B.p. 210-2°.

Analysis: $C_8H_{16}O_3$ requires 59.96 (C), 10.06(H)%,

found 59.95 (C), 10.12 (H)%.

G.l.c. retention time:

neat compound = 720 s. (75^{o}, 7.5% A.P.K.).

(b) 4-n-Butoxymethyl-2-propyl-1,3-dioxane (II).

4-Hydroxymethyl-2-propyl-1,3-dioxane (4.5 g., 0.028 mol.) and sodium hydride (1.35 g., 0.056 mol.) were added to dry D.M.F. (50 ml.) and stirred together at 0^{o} for 20 minutes. n-Butyl bromide (7.7 g., 0.056 mol.) was then added in small amounts over a 10 minute period. The reactants were then allowed to warm to room temperature and were stirred together for 24 h.

After this time methanol (7 ml.) was cautiously added to the rapidly stirred mixture to remove any excess sodium hydride. The slightly yellow solution was then filtered free of precipitated halide and the solvent was removed upon a rotary evaporator: a yellow oily residue remained (3.5 g., 57.4%). A t.l.c. of this material showed that one product was present ($\underline{\underline{R}}_F$ = 0.65) along with unreacted substrate $\underline{\underline{R}}_F$ = 0.5 (solvent A).

The product was isolated by passing the crude material down a silica gel column (175 g.), eluting with toluene/methanol (9:1).

Yield 3.1 g., (51%). $\underline{\underline{R}}_F$ = 0.65 (solvent A).

Analysis: $C_{12}H_{24}O_3$ requires 66.61(C), 11.19(H)%,
found 66.27(C), 10.86(H)%.

Mass spectrum: (of neat compound),
m/e 57 (74.8%), 85 (20.9%), 86 (13.8%), 87 (27%),
m/e 117 (6.6%), 129 (100%), 145 (6.4%), 173(23.2%)
m/e 215 (3.5%).

G.l.c. retention time:

neat compound = 332 s. (140^{o}, 3% OV - 225).

(c) 1, 3-0-Butylidene-DL- erythritol(III) and 1, 3:2, 4-di-0-butylidene erythritol(V).

These compounds were prepared by the method of T. J. Julnes[10] starting from erythritol and n-butyraldehyde.

A solution of erythritol (7.5 g., 0.061 mol.) in N HCl (250 ml.) was mixed with n-butyraldehyde (4.5 g., 0.062 mol.). The reactants were then thoroughly mixed by shaking and then left for 20 h. at room temperature.

After this time the crystals of 1, 3:2, 4-di-0-butylidene erythritol that had separated were filtered off, washed with water and recrystallized from ethanol.

Yield 1.2 g., m.p. 76-7°

(Lit. yield 1.5 g., m.p. 76-7°).

The filtrate was then neutralized with sodium hydrogen carbonate, evaporated to dryness and the residue extracted with hot ethanol (3 x 30 ml.). The ethanolic extracts were evaporated to dryness to yield a syrup , which was then exhaustively extracted with hot benzene to give plate-like crystals of 1, 3-0-butylidene-DL-erythritol on cooling.

Yield 5 g., m.p. 99 - 101°.

(Lit. yield 6.6 g., m.p. 99 - 101°).

(d) 2, 4-Di-0-butyl-1, 3-0-butylidene-DL-erythritol(IV).

1, 3-0-Butylidene-DL- erythritol (3 g., 0.017 mol.) was treated with n-butyl bromide (11.7 g., 0.085 mol.) and sodium hydride (2.1 g., 0.087 mol.) using the procedure outlined in (b).

The syrup given after removal of the solvent was dispersed between a mixture of water (30 ml.) and chloroform (70 ml.)

The organic layer was then separated, dried (anhydrous Na_2SO_4) and the chloroform removed via a rotary evaporator, leaving a clear syrupy product (4.2 g., 86%).

T.l.c. analysis (in solvent A) showed that a small amount of substrate was still present in the syrup. The substrate was removed by passing the crude product down a silica gel column (210 g.) eluting with toluene/methanol (9:1).

Yield 3.9 g. (79.6%).

$\underline{\underline{R_F}}$ = 0.77 (solvent A).

Analysis: $C_{16}H_{32}O_4$ requires 66.62(C), 11.18(H)%,

found 66.50(C), 10.98(H)%.

Mass spectrum: (of neat compound),

m/e 83 (87.9%), 85 (100%), 87 (25%),

m/e 127 (12.6%), 129 (12.2%), 145 (18.1%),

m/e 201 (14%), 215 (13.8%), 217 (29.7%),

m/e 245 (28.9%), 287 (11.3%), 289 (9.3%).

G.l.c. retention time:

neat compound = 165 s. (200°, OV - 17).

(e) 1,3:4,6-Di-O-butylidene galactitol(VI).

This was prepared by the method described by L. Yuceer[13] in which galactitol (7.5 g., 0.041 mol.) and n-butyraldehyde (12 ml., 0.14 mol.) were shaken with hydrochloric acid (5 N, 20 ml.) for 5 days.

After this time the reaction mixture was extracted with chloroform (3 x 50 ml.), the organic layers combined and washed with sodium bicarbonate solution and water. The chloroformic solution was then dried (anhydrous Na_2SO_4), the chloroform removed on a rotary evaporator and to the syrupy product obtained was added petroleum ether (b.p. 40-60°, 30 ml.):

crystals of 1, 3:4, 6-di-O-butylidene galactitol were rapidly deposited from this mixture. They were recrystallized from petroleum ether (b.p. 40 - 60°).

Yield 4 g., (34%). M.p. 133-5°.

(Lit. m.p. 133-5°)

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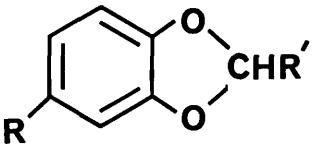
IV. THE REACTIONS OF BORON TRIBROMIDE/LITHIUM ALUMINIUM HYDRIDE AND BORON HYDROCHLORIDES WITH CYCLIC ACETALS.

PART ONE.

IV(1)A. Introduction.

The previous two chapters have been concerned with the reactions given by boron trichloride/lithium aluminium hydride with various cyclic acetals under a number of different electrochemical and stereochemical environments. It was then decided to look at the closely associated boron tribromide/lithium aluminium hydride combination and to use the results obtained with the trichloride system as a guide-line.

Boron tribromide is a more powerful Lewis acid than boron trichloride[1] and so one would expect it to be the more powerful cleavage reagent of the two (p. 36): a factor which prompted investigation into the possible use of the boron tribromide/lithium aluminium hydride combination with substrate acetals of lower basicity than the heterocyclic systems considered above. In particular the reactions of 1,3-benzodioxole(VII) and 2-phenyl-1,3-benzodioxole(VIII) will be considered (fig.IV(1)A) along with the heterocyclic systems.



where in:

VII R = R′ = H

VIII R = H, R′ = C_6H_5

Fig. IV(1)A - 1.

IV(1) B. Reaction of boron tribromide/lithium aluminium hydride with simple cyclic acetals.

i) Introduction.

In this section the reactions of boron tribromide/lithium aluminium hydride with 2-propyl-1, 3-dioxane, 1, 3-dioxane and 2-chloromethyl-1, 3-dioxane will be considered. The products given in the reactions and the operating stoichiometry therein are looked into, along with evidence for the participation of an α-bromo-ether in the mechanism of the reactions.

ii) Results and discussion.

(a) Reaction details and analysis of products.

The experimental procedure used was essentially the same as that used with the boron trichloride/lithium aluminium hydride combination. Thus 2-n-propyl-1, 3-dioxane (0.01 mol.) was treated with boron tribromide (0.01 mol.) for 2 minutes at 0° and then with lithium aluminium hydride (0.01 mol.).

Work-up in the usual manner (p. 38) gave a light brown oily product (84 %) which on g.l.c. analysis proved to be mainly one component: the retention time of the main component was identical to that of a reference sample of 3-n-butoxy-propan-1-ol, while the minor component (8%) had the same retention time as propan-1, 3-diol.

The preceding reaction was then repeated with a 3:1 and 5:1 acetal to boron tribromide/lithium aluminium hydride ratio.

The main product in both reactions was 3-n-butoxy propan-1-ol, although there was a large proportion of unchanged substrate (38%) in the product mixture isolated from the 5:1 reaction. Meanwhile the 3:1 reaction gave a 95% yield of the hydroxyether with 5% of the diol: there was no observable substrate remaining. The total material recovered in each case was between 85 - 90%.

The 3:1 ratio was then used with confidence upon the acetals shown below in Table IV(1)B - 1.

Substrate	Product	% Yield	Reaction time (min.)
2-Propyl-1,3-dioxane	3-n-butoxy propan-1-ol	95	2.
1,3-Dioxane	3-methoxy propan-1-ol	87	2.
2-Chloromethyl-1,3-dioxane	3-(2-chloroethoxy) -propan-1-ol	82	15.

Table IV(1)B - 1.

(b) Preparation of substrates and reference materials.

The dioxanes used above were prepared using methods already described within this thesis (Chapter II, p. 53), as were the hydroxyether reference compounds (Chapter II, p. 55).

(c) Evidence for the α-bromoether.

In Chapter II section IIB - iic, the question under consideration was the participation of an α-chloroether in the acetal cleavage reaction when using boron trichloride/lithium aluminium hydride as the cleavage reagents. The main experimental evidence in favour of the α-chloroether was the p.m.r. spectrum of the 3:1 acetal/boron trichloride mixture in carbon tetrachloride.

When this experiment was repeated using boron tribromide as the Lewis acid, the p.m.r. spectrum of the mixture again showed the disappearance of the acetal proton's triplet (4.5δ) and the presence of a triplet at 5.6δ. Meanwhile, addition of lithium aluminium hydride to the above system gave the 3-n-butoxy-propan-1-ol as the sole product after work-up.

Thus keeping in mind the observed 3:1 stoichiometry of the dioxane/boron tribromide-lithium aluminium hydride reaction

it was concluded that an α-bromoether was participating in the cleavage of the acetal as shown in figure IV(1)B - 1.

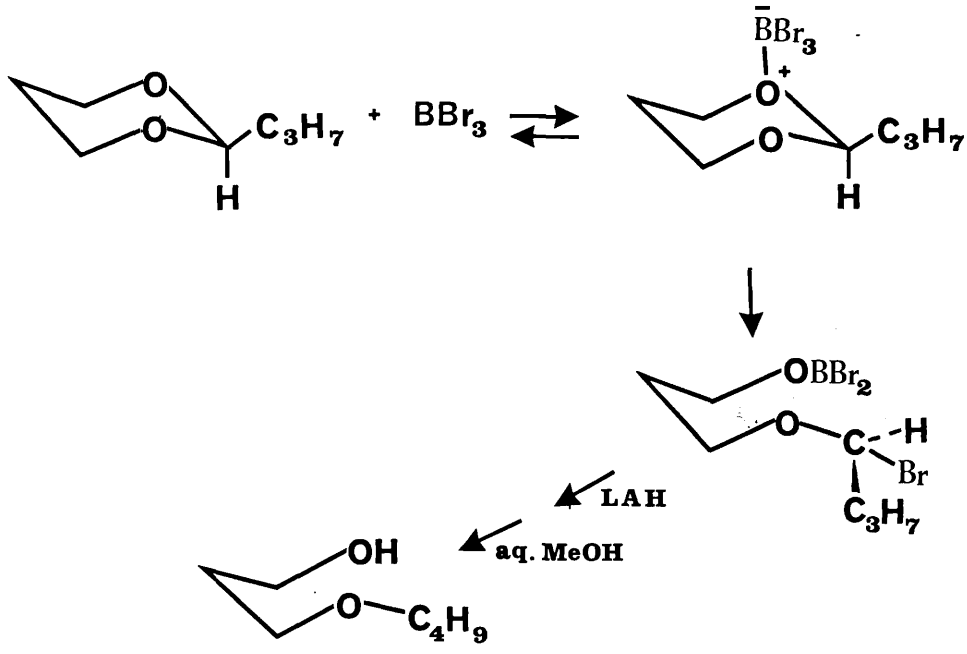


Fig. IV(1) B - 1.

(d) Rationalization of results.

As expected then the boron tribromide/lithium aluminium hydride reaction appears to be homologous with the boron trichloride/lithium aluminium hydride process and so probably proceeds via an oxocarbonium transition state to the α-bromoether intermediate, which is then reduced by the lithium aluminium hydride (fig. IV(1) B - 2).

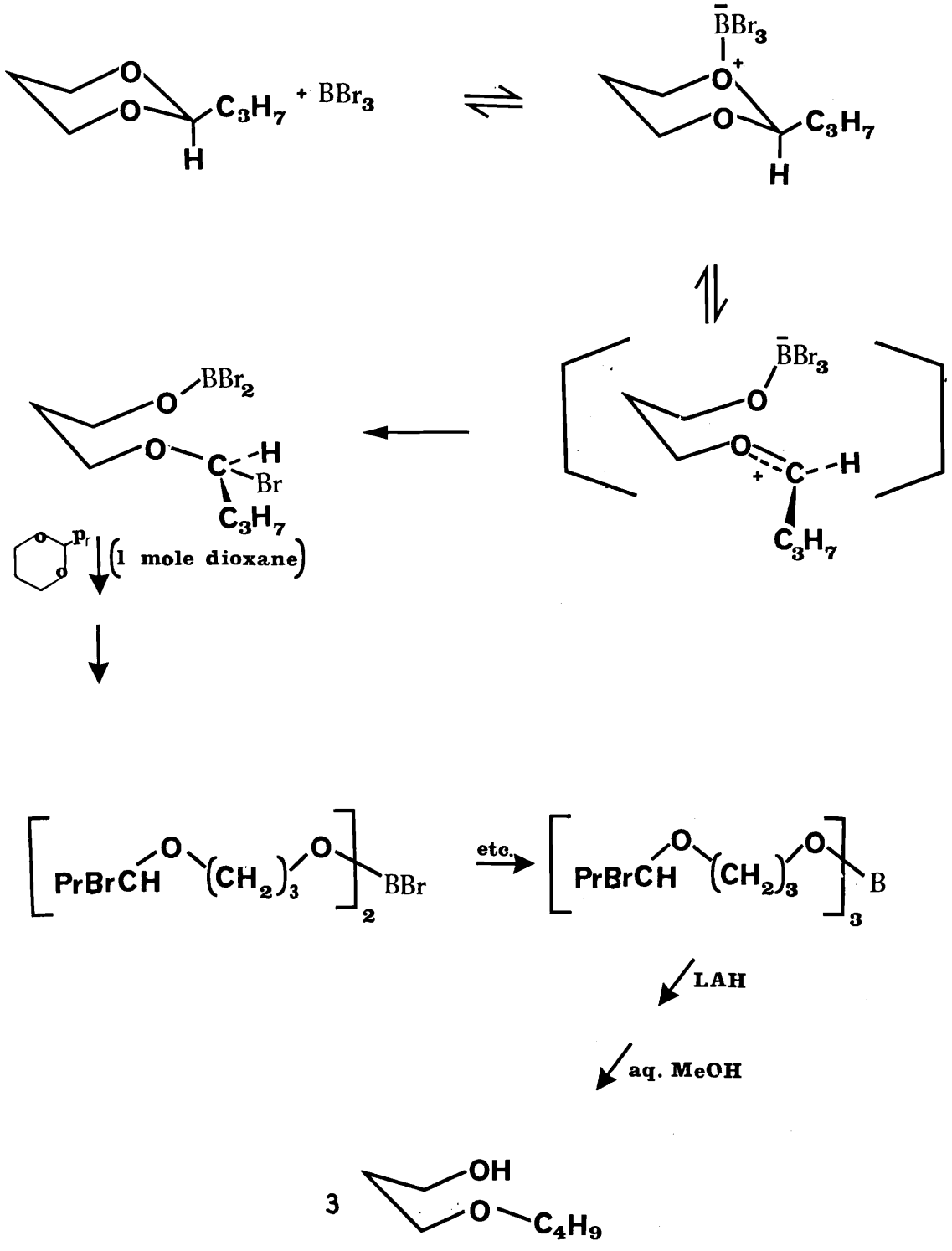

+ BBr3
C3H7
H
O
BBr3
BBr2
Br
(1 mole dioxane)
PrBrCH
(CH2)3
BBr
etc.
B
LAH
aq. MeOH
OH
C4H9
3

Fig. IV (1) B - 2.

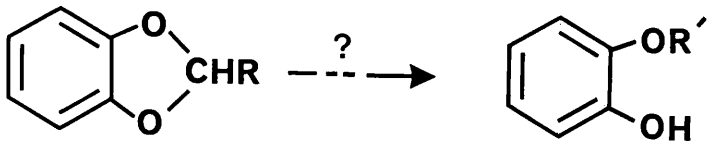
The facility with which the 2-chloromethyl-1, 3-dioxane was cleaved relative to the boron trichloride reaction suggests that the tribromide is the more powerful cleavage reagent of the two, a factor which will be considered in the next section of this thesis.

IV(1) C. Reaction of boron tribromide/lithium aluminium hydride with 1, 3-benzodioxoles.

i) Introduction.

It is known that the oxygens in the 1, 3-benzodioxole system[2] are less basic than those in the corresponding heterocyclic acetals. This lower basicity is probably due to the coordination of the lone-pair upon the 1, 3-benzodioxole's oxygens into the aromatic nucleus and is the main reason for the much greater stability shown by the 1, 3-benzodioxoles to both protonic and Lewis acids: an example of the former is seen in the nitration of 1, 2-methylenedioxybenzen-4-al with concentrated nitric acid.[3] Generally the order of stability of the 1, 3-benzodioxoles towards acid hydrolysis is the same as that which is predicted for the heterocyclic acetals i.e. for C_2 substituents $CH_2 > CHR > CHPh > C\,Ph_2$.

Thus although there are a number of reagents that will completely remove say the methylene function,[4] no report in the literature has been found which refers to a hydrogenolysis reaction that has been successfully carried out upon a 1, 3-benzodioxole to yield the respective alkoxy phenol function (fig. IV(1)C - 1).



where $R' = CH_2R$

Fig.IV(1)C - 1.

The aim of this next section then, was to examine the possibility of using the boron tribromide/lithium aluminium hydride combination to effect such a cleavage.

ii) Results and discussion.

(a) Reaction details and analysis of products.

1,3-Benzodioxole (0.0092 mol.) was added to a methylene chloride solution of boron tribromide (0.0092 mol.) and the resulting mixture was stirred at 0^{o} for 5 hours, after which

time an ethereal suspension of lithium aluminium hydride (0.01 mol.) was added and when the resulting effervescence had ceased the reaction was worked-up in the usual manner.

The crude product was a dark crystalline solid which was shown to contain two major components by t.l.c. analysis, the less polar of which had the same $\underline{R}_F$ as the substrate.

Extraction of a chloroformic solution of the reaction mixture with dilute sodium hydroxide enabled the more polar products to be largely separated from the substrate. Acidification of this aqueous phase and extraction with chloroform gave on evaporation of the organic solvent a solid product which was shown to be mainly one component by t.l.c. analysis (yield 68%).

The 60 MHz spectrum of this compound suggested that it was the monomethoxy ether of 1, 2-dihydroxybenzene: a suggestion which was corroborated when the p.m.r. and the I.R. spectra of a reference sample of 2-methoxy phenol were compared with those of the isolated product. Meanwhile the organic layer from the first extraction was shown to contain the starting material.

Further experiments using different ratios of acetal to boron tribromide/lithium aluminium hydride ranging from 3:1 to 1:3 showed that the best yields of the 2-methoxy phenol (ca. 68%) were given with the 1:2 and 1:3 systems: a more pertinent fact however was the poor yields given when a 2:1 ratio was used and similarly for the 3:1 system. This suggests that the stoichiometry of the 1, 3-benzodioxole / boron tribromide reaction is perhaps not the same as in the corresponding heterocyclic acetal's reaction (p. 40).

Similar experiments were then repeated using 2-phenyl-1, 3-benzodioxole as the substrate, when a good yield (ca.80%) of 2-benzyloxy phenol was given after 15 minutes contact time with the boron tribromide at 0^{o}..

The above results are summarized in table IV(1)C-1.

Substrate	Reaction time (h.)[x]	Yield of substrate(%)	Yield of product(%)
1, 3-Benzodioxole	5	30-40	60-70.
2-Phenyl-1, 3-benzodioxole	0.25	0	83.[xx]

x This denotes the time the substrate was in contact with the boron tribromide.

xx 17% 1, 2-dihydroxybenzene also isolated.

Table IV(1) C - 1.

(b) Rationalization of results.

It has been shown then that the 1, 3-benzodioxoles can be cleaved using the boron tribromide/lithium aluminium hydride combination. The next step was to look at the mechanism operating during the reaction, especially that between the boron tribromide and the 1, 3-benzodioxoles. Taking into consideration the structure of the substrates it has been assumed that the main principles pertaining to the heterocyclic acetal/boron tribromide rationale are also relevant to the 1, 3-benzodioxole system.

Thus one would expect to see a greater facility in the cleavage of 2-phenyl-1, 3-benzodioxole than in that of the unsubstituted 1, 3-benzodioxole due to the greater stabilization of the former's oxocarbonium transition state by the 2-phenyl function (fig. IV(1) C - 2), a prediction that has been qualitatively verified by the above experiments.

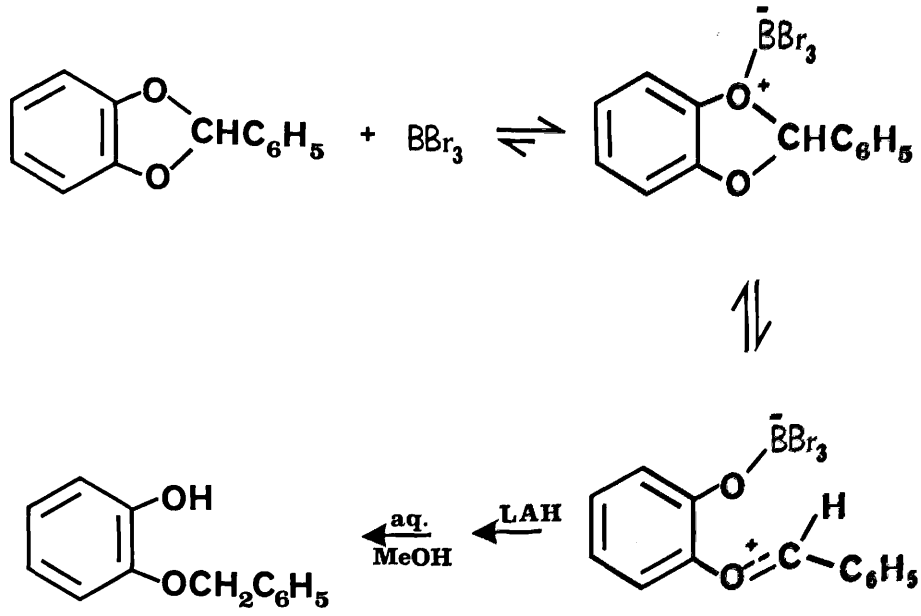


Fig. IV(1) C - 2.

An area in which the 1, 3-benzodioxoles' reaction does seem to differ from that of the heterocyclic acetals is in its stoichiometry; it has been shown that it was not possible to cleave three moles of VIII with one mole of boron tribromide (p. 181).

Whether this implies that the operating mechanism is different to that in the heterocyclic acetals' reaction or that it is merely a result of a difference in facility of the same mechanism, is not absolutely clear but one would tend to hold to the latter: thus it is thought that the Lewis acidity of the substituted boron tribromide is not sufficiently powerful to form a Lewis-bond capable of polarizing the second or third molecule of 1, 3-benzodioxole to the extent that cleavage can occur (fig. IV (1) C - 3). In the 1:1 complex however this polarization must be sufficient to give cleavage (fig IV (1) C - 2).

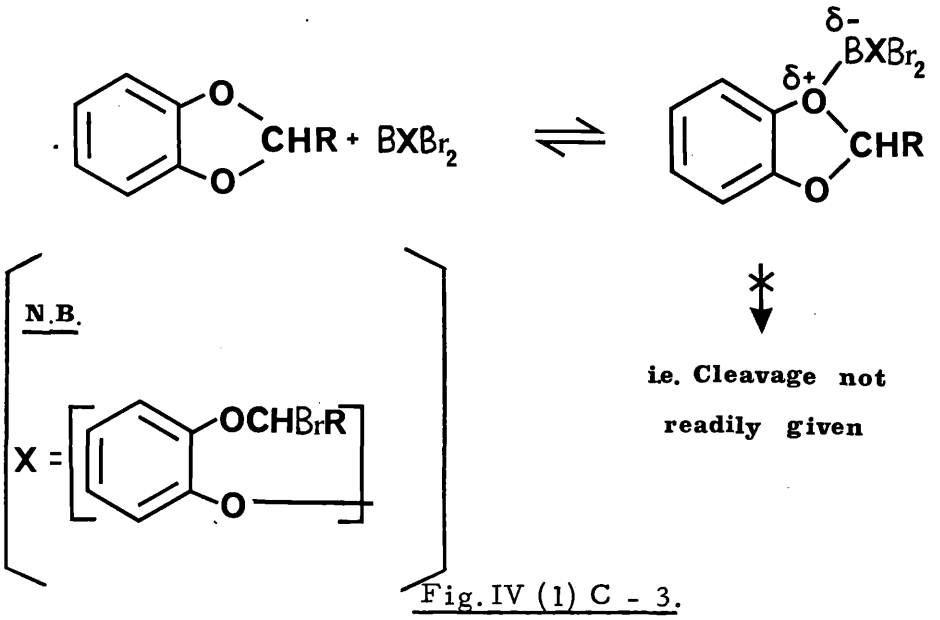


Fig. IV (1) C - 3.

The question as to whether an α-bromoether is formed from the 1:1 complex is again mainly supported by analogy to the heterocyclic acetals reaction. The main experimental evidence available is the appearance of a singlet (6.7δ) integrating to one proton in the 60 MHz p.m.r. spectrum of VIII in the presence of excess boron tribromide (fig.IV (1) C - 4a).

On work-up of this mixture after treatment with lithium aluminium hydride, the only product given was 2-benzyloxy phenol and so one might tentatively assume that the observed singlet is analogous to the triplet seen in the spectrum of the 2-propyl-1, 3-dioxane/boron tribromide reaction and belongs to the α-bromoether proton (fig.IV (1) C - 4b).

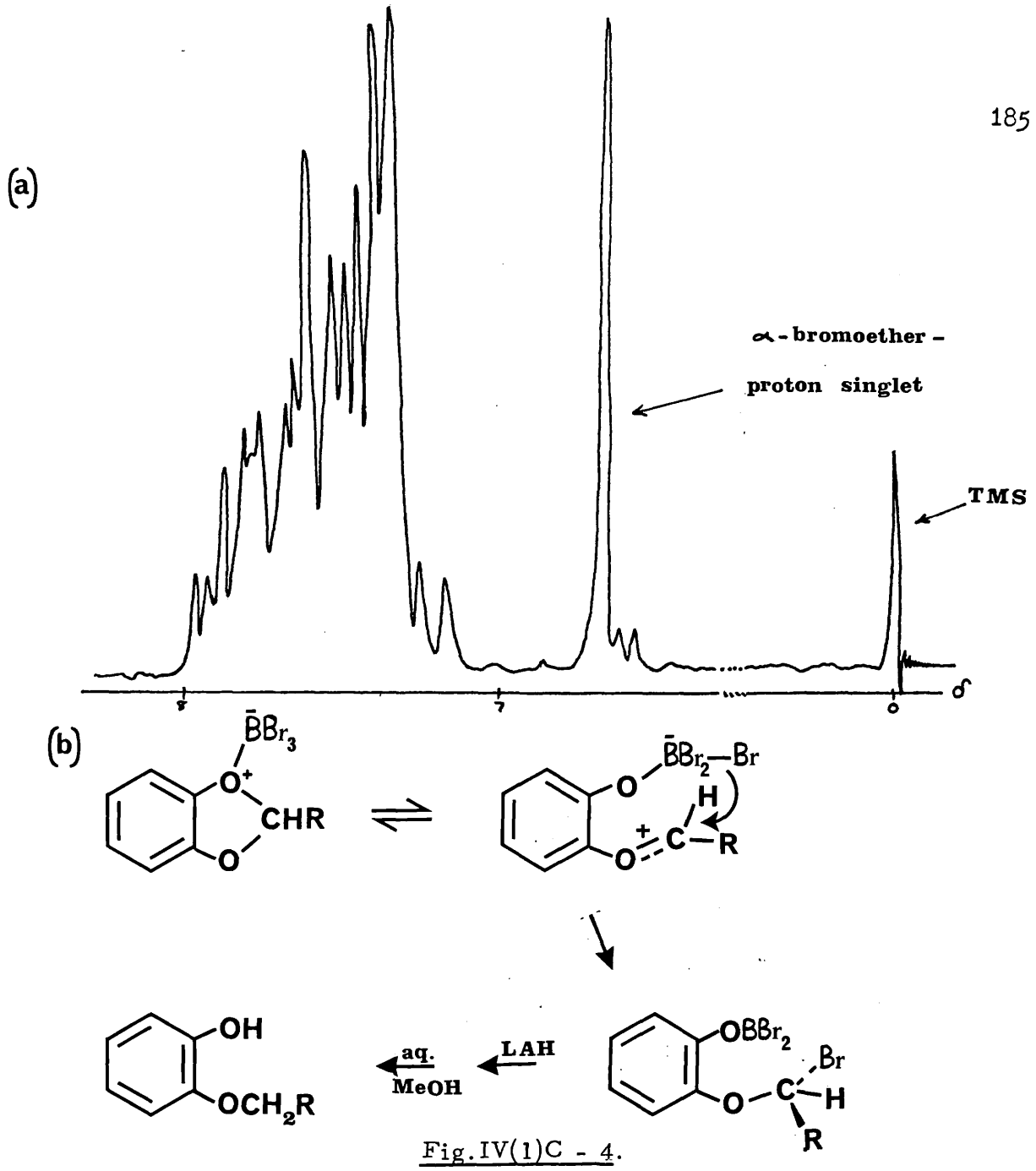


Fig.IV(1)C - 4.

(c) Preparation of substrates and reference materials.

1, 3-Benzodioxole was prepared by the method of Bonthrone and Cornforth[5] from 1, 2-dihydroxybenzene and methylene chloride in dimethylsulphoxide using sodium hydroxide as the base (fig.IV(1) C - 5).

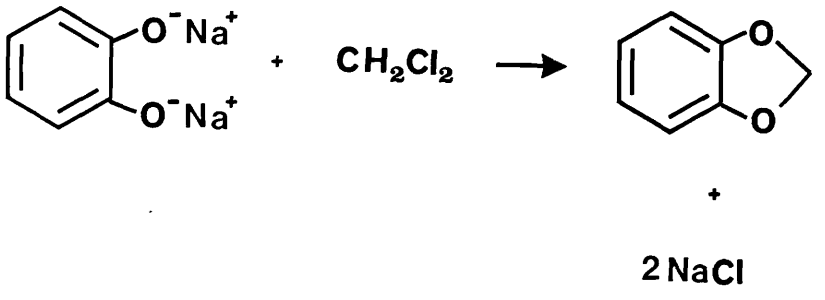


Fig. IV (1) C - 5.

Meanwhile 2-phenyl-1, 3-benzodioxole was given in the reaction between equimolar amounts of 1, 2-dihydroxybenzene and benzylidene chloride[6] using pyridine as the solvent and the base (fig. IV(1) C - 6).

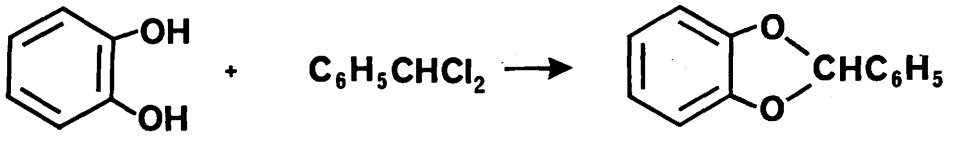


Fig. IV (1) - 6.

The 2-benzyloxyphenol used as a reference compound in VIII's reaction was prepared from 1, 2-dihydroxybenzene and benzyl chloride using sodium ethoxide as the base[7] (fig. IV(1) C-7).

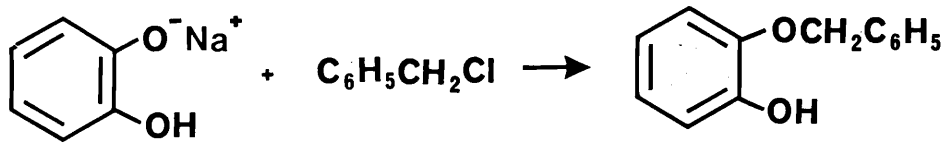


Fig. IV (1) C - 7.

The 2-methoxyphenol used as the reference compound in VII's reaction was a commercial sample (Aldrich Ltd.).

PART TWO.

IV(2)A. Introduction.

It was seen in chapter II how the boron trichloride/lithium aluminium hydride combination could successfully be used to cleave a number of heterocyclic acetals. It was shown that the facility of the cleavage varied depending upon the ring size and (for a given ring size) the C_2 substituent. Thus the 2,2-dimethyl-1,3-dioxolanes were only in contact with the boron trichloride for 2 minutes before the addition of the hydride. Now the limiting case for this type of "external hydride donor" reaction would be when the hydride and boron trichloride were both present as the substrate acetal was added.

An alternative way of doing this would be to have an "internal hydride donor" in the sense that the Lewis acid and insipient hydride ion were part of the same molecule, as has been the case in the work of Fleming, Bolker[8] and Brown et al[9].

This was the reasoning, then, behind the investigations into the possible use of the boron hydrochlorides as hydrogenolysis reagents for the heterocyclic acetals.

There are a number of well documented syntheses for the boron hydrochlorides (see chapter Ib, p.28). The method which was adopted herein was that devised by Brown and Tierney[10] in which boron trichloride is treated with either sodium or lithium borohydride[11] (fig. IV(2) A - 1).

$$BCl_3 + LiBH_4 \longrightarrow LiCl + 2H_2BCl$$

$$3BCl_3 + NaBH_4 \longrightarrow NaCl + 4BHCl_2$$

Fig. IV (2) A - 1.

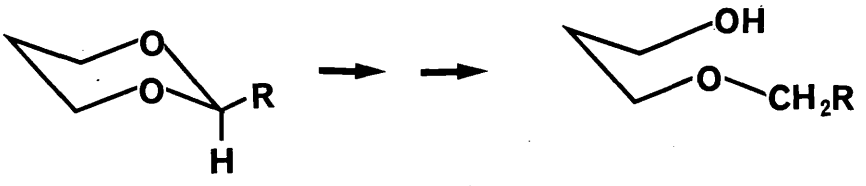
The work that follows then is an introduction to the use of these reagents (mainly boron monohydrochloride) and only really covers the limitations of the reaction along with, and closely associated to, the effects of acetal's C_2 substituents. Thus other interesting features of the reaction such as the stoichiometry and substituent directive effects have not been covered and may perhaps be an area for further research.

IV(2) B. Reaction of boron monohydrochloride ($BHCl_2$) with simple cyclic acetals.

i) Introduction.

The substrates used in this next section were the simple 1, 3-dioxanes shown below in figure IV(2) B - 1.

The principal method of structure proof used was the same as that in chapters II and IV(1) in that the products obtained in the hydrogenolysis reactions were compared with independently synthesized samples of the expected hydroxyethers.



where R = H, Pr, Ph and CH_2Cl

Fig. IV(2) B - 1.

(ii) Results and discussion.

(a) Preparation of reagent and reaction details.

The boron monohydrochloride was prepared by the addition of the calculated amount (fig.IV(2)A - 1) of sodium or lithium borohydride to a stirred solution of boron trichloride in diethyl ether at 0^{o} [10]. The reactants were then stirred together for about 20 minutes during which time the solution went turbid due to the precipitation of the sodium or lithium halide.

An ethereal solution of 2-n-propyl-1, 3-dioxane was added and the reaction mixture was allowed to reach room temperature. The molar proportions of hydrohalide to acetal was either 2:1 or 3:1.

Aliquots of the reaction mixture were then taken at regular intervals. The reaction was then worked-up when g.l.c. analysis showed that either the acetal had been completely used up or when an approximately constant ratio of substrate to product was given over two aliquots. Both the preparation of the aliquots for analysis and the final work-up for the reaction were carried out using the procedure described in chapter II (p.38).

The above procedure was then repeated using 2-phenyl-1, 3-dioxane, 1, 3-dioxane and 2-chloromethyl-1, 3-dioxane as substrates.

(b) Analysis of products.

The oily product isolated from the 2-n-propyl-1, 3-dioxane reaction was shown by g.l.c. analysis to consist of mainly one component, the retention time of which was identical to that of a reference sample of 3-n-butoxy propan-1-ol. Comparison of the p.m.r. spectra and I.R. spectra of the two compounds also proved positive.

A similar analysis of the products given with the other substrates gave the data shown in Table IV(2) B - 1.

Substrate	Reaction time (h.)	Yield of subtrate(%)	Yield of product (%)
2-Phenyl-1, 3-dioxane	0.05-0.08	~1	~99
2-Propyl-1, 3-dioxane	1	~1	~99
1, 3-Dioxane	12	30	70
2-Chloromethyl-1, 3-dioxane	48	ca. 100%	very little

Table IV(2) B - 1.

The recovery yield in each case was high (85-90%) and unlike the boron trichloride/lithium aluminium hydride reaction very little diol was present in the product mixture.

(c) Rationalization of results.

It can be seen then that boron monohydrochloride is capable of hydrogenolysing certain 1, 3-dioxanes to their respective hydroxyethers in quite high yields under the discussed conditions.

The best yields were obtained with the 2-n-propyl and 2-phenyl substituents while the 2-chloromethyl derivative did not appear to undergo any appreciable reaction at all.

These observations are consistent with a mechanism in which the formation of an oxocarbonium ion is the rate controlling step (fig. IV (2) B - 2), similar to that which has been shown to operate with the aluminium chlorohydrides.

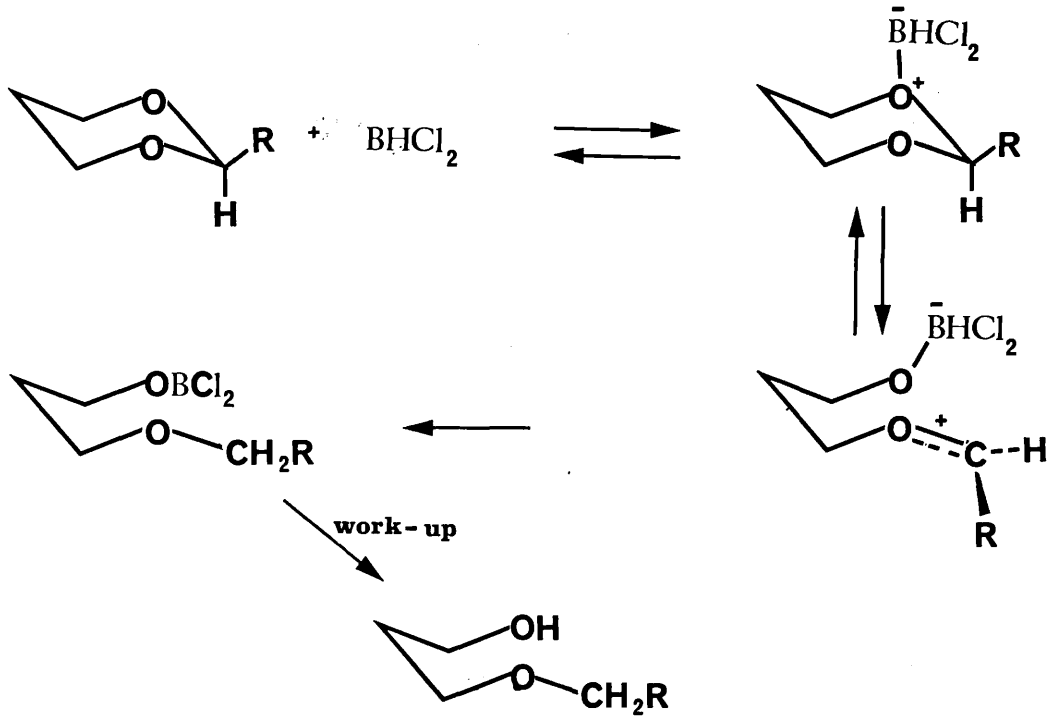


Fig. IV (2) B - 2).

It is true that the data presented above is far from complete in its support for the shown rationale, however taking into account the analogous aluminium hydrochloride and borane systems the likelihood of a grossly different process operating in the boron hydrochlorides' reaction seems remote.

Conclusion (to Parts One and Two).

The work in this chapter has been little more than an introduction into the use of boron tribromide/lithium aluminium hydride and boron monohydrochloride as cleavage reagents for various types of cyclic acetal.

In part one it was demonstrated how the use of the boron tribromide/lithium aluminium hydride enabled the relatively inert 1, 3-benzodioxole system to undergo cleavage to the respective alkoxy or aryloxy phenol. It was also suggested that the mechanism of the cleavage reaction is similar to that operating in the 1, 3-dioxanes' reaction in which an α-haloether intermediate is reduced by the lithium aluminium hydride.

Future work with this system would have to include a more complete study into the mechanism of the reaction especially into the relevant substituent directive effects, for instance into the products given by the systems shown in fig. IV(2) C - 1.

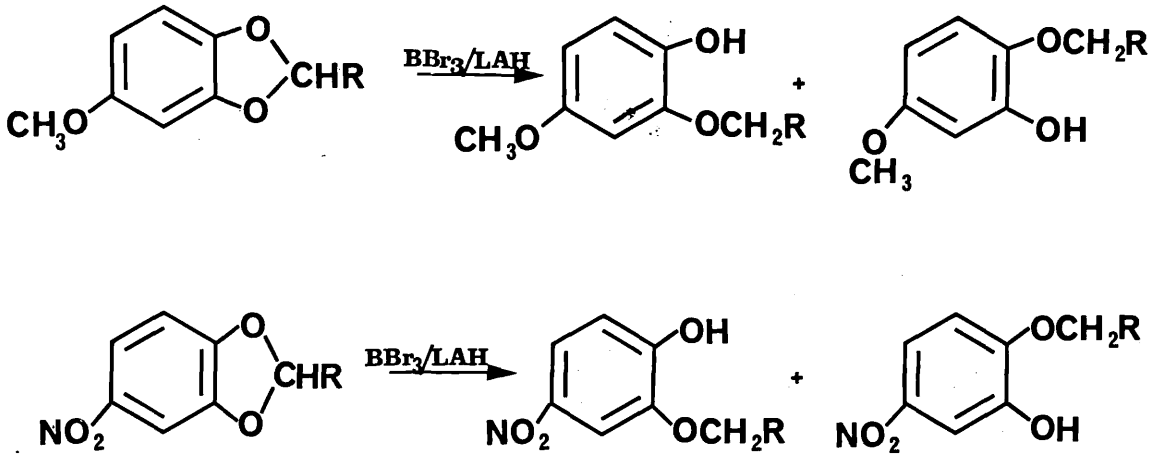


Fig. IV (2) C - 1.

Also of interest would be the possible use of oxothiolanes and dithiolanes as cleavage substrates, as the C - S bond has up to now proved inert to such as the aluminium chlorohydrides.[12]

Meanwhile, boron monohydrochloride proved to be a much milder hydrogenolytic reagent than either boron trichloride/lithium aluminium hydride or the homologous boron tribromide combination and would appear to be of use with the more activated acetals such as the 2-phenyl or 2, 2-dimethyl species.

The "reactivity" of boron monohydrochloride appears to be approximately equal to that of the aluminium hydrochlorides, although it does have the advantage that the boric acid produced on work-up is more easily removed (as its volatile trimethyl ester) than the corresponding "aluminium hydroxide".

The presence of the latter compound also tends to occlude the more polar hydrogenolysis products which reduces yields and makes extrac tion difficult.

The obvious disadvantages of the boron compounds are all associated with the handling difficulties arising from the use of boron trichloride.

When compared with the "borane" reagent, which again covers approximately the same substrate range, the reaction times of the boron monohydrochloride are much shorter. For instance with 2-phenyl-1, 3-dioxane the respective cleavage times are 15 minutes and 40 hours[8] although the yield in the latter (borane) reaction is slightly higher.

Taking an overall view then of the Lewis acid/ hydride donor class of cleavage reagents one may make the generalization shown in Table IV(2)C - 1, in which a number of acetal substrate types varying in their degree of activation (i. e. C_2-substituent) are correlated with the appropriate cleavage system.

	Substrate with C_2 substituent	Reagents
Heterocyclic acetals	Highly activated e. g. phenyl or dimethyl	BH_3, $BHCl_2$, $AlHCl_2$.
	Activated e. g. alkyl	$BCl_3/LiAlH_4$, $BHCl_2$, $AlHCl_2$.
	Non-activated e. g. hydrogen	$BCl_3/LiAlH_4$ $BBr_3/LiAlH_4$.
	Deactivated e. g. chloromethyl	$BBr_3/LiAlH_4$.
	1, 3-Benzodioxole	$BBr_3/LiAlH_4$.

Table IV (2) C - 1.

IV Experimental.

Experiment 1. Reaction of 2-n-propyl-1, 3-dioxane with boron tribromide/lithium aluminium hydride.

(a) Boron tribromide (2.51 g., 0.01 mol.) was pipetted into dry, ice-cooled methylene chloride (25 ml.). 2-n-Propyl-1, 3-dioxane (1.3 g., 0.01 mol.) in methylene chloride (10 ml.) was then slowly added and the reactants were stirred together for 2 minutes at 0^{o}.

After this time an ethereal suspension of lithium aluminium hydride (0.4 g., 0.01 mol.) was dripped into the reaction mixture and the reactants were stirred until effervescence had ceased (ca. 30 minutes).

After work-up (Ch. II, p.38) the product a light brown oil, (1.09 g.,84%), was shown to consist of two components: A (92%) and B (8%).

The retention time of A the major product was the same as that of a reference sample of 3-n-butoxy propan-1-ol, while B had the same retention time as propan-1, 3-diol.

(b) The above procedure was then repeated using different ratios of acetal to boron tribromide/lithium aluminium hydride. The yields of 3-n-butoxy propan-1-ol given in each of these reactions are shown in Table IV - 1 below.

Ratio of acetal to $BBr_3/LiAlH_4$	Yield of 3-n-butoxy propan-1-ol (%)
1:1	91-3
3:1	95
5:1	54 [x]

Table IV - 1

[x] 38% = unreacted substrate.

Experiment 2. Reactions of other acetals with boron tribromide/lithium aluminium hydride.

The procedure outlined in experiment I (a) was then repeated using 1, 3-dioxane and 2-chloromethyl-1, 3-dioxane as substrates. The yields and products for these reactions are shown in Table IV (1) B - 1 (p.176).

The acetal substrates and hydroxyether reference compounds used in this experiment were prepared using the procedures outlined in chapter II (experiments 11 and 12).

Experiment 3. Studies to demonstrate the involvement of an α-bromoether in the acetal-boron tribromide reaction.

2-n-Propyl-1, 3-dioxane (2.73 g., 0.021 mol.) was treated with boron tribromide (1.75 g., 0.007 mol.) in carbon tetrachloride (25 ml.).

The p.m.r. spectrum of the mixture taken approximately 5 minutes after the reagents were mixed, showed the absence of the acetal proton triplet (4.5δ) but the presence of a triplet at 5.6δ integrating to one proton: this was assumed to be due to the α-bromoether proton.

Addition of an ethereal suspension of lithium aluminium hydride (0.4 g., 0.01 mol.) to the above 3:1 mixture and work-up in the usual manner gave 3-n-butoxy propan-1-ol.

Experiment 4. The reaction of 1, 3-benzodioxoles with boron tribromide/lithium aluminium hydride.

(a) 1, 3-Benzodioxole (1.12 g., 0.0092 mol.) in methylene chloride (15 ml.) was slowly added to an ice-cooled solution of boron tribromide (2.3 g., 0.0092 mol.) in methylene chloride (25 ml.). After stirring the reactants for 5 hours an ethereal suspension of lithium aluminium hydride (0.4 g., 0.01 mol.) was added to the mixture which was then stirred for a further 30 minutes until no more hydrogen was evolved.

Work-up using the procedure outlined in chapter II (p.38) gave a dark brown solid mass (0.94 g., 84%). T.l.c. analysis of this solid showed that two main components were present at the R_F values of 0.26 and 0.53. The less polar of these compounds had the same R_F as 1, 3-benzodioxole (0.5).

The crude product was dissolved in chloroform (25 ml.) and then extracted with N sodium hydroxide solution (3 x 10 ml.). The aqueous alkaline fractions were combined and treated with hydrochloric acid (5 N) until the pH of the solution reached 6.5. The slightly acidic solution was then extracted with chloroform.

A t.l.c. of the chloroformic extract showed the presence of one component and after drying (anhydrous Na_2SO_4) and evaporation of the chloroform under reduced pressure an off-white crystalline mass was given (0.76 g., 68%).

Recrystallization from water gave white crystals m.p. 29-30°. The m.p. of 2-methoxyphenol is 32°.[13] The p.m.r. and I.R. spectra of the isolated product and 2-methoxyphenol were also comparable.

Meanwhile the organic layer from the first extraction was dried (anhydrous Na_2SO_4) and the chloroform removed on the rotary evaporator: this left 0.15 g. of a clear

liquid. The p.m.r. of this liquid showed that it was 1, 3-benzodioxole.

(b) The previous experiment was then repeated using different ratios of acetal to boron tribromide/lithium aluminium hydride. The different ratios used and the associated yields of 2-methoxyphenol are shown in Table IV - 2.

Ratio of acetal to $BBr_3/LiAlH_4$	Yield of 2-methoxyphenol (%)
3:1	27
2:1	36
1:1	68
1:2	69
1:3	74

Table IV - 2.

(c) The procedure outlined in (a) was then repeated when 2-phenyl-1, 3-benzodioxole was treated with boron tribromide for 15 minutes at 0^{o} and then with lithium aluminium hydride for a further 30 minutes.

Work-up in the usual manner gave a dark-brown oily mass (85%) which was shown to be comprised of two main components A ($\underline{R}_F$ 0.54) and B ($\underline{R}_F$ 0.18) by t.l.c. analysis using toluene/methanol (9:1) as the developing solvent.

The two products were isolated and separated by passing the crude product mixture down a silica gel column eluting with toluene/methanol (9:1).

Compound A an oil (83%) was shown to be 2-benzyloxy phenol by a comparison of the p.m.r. and I.R. spectra of the product with an authentic sample of this compound.

Meanwhile compound B (17%) was shown to be

1, 2-dihydroxybenzene by a similar comparison with a reference sample of the latter.

Experiment 5. Evidence for the participation of an α-bromoether in the reaction between 2-phenyl-1, 3-benzodioxole and boron tribromide.

2-Phenyl-1, 3-benzodioxole (2.3 g., 0.012 mol.) was treated with boron tribromide (0.97 g., 0.0039 mol.) in carbon tetrachloride (25 ml.) at 0°.

After 5 minutes the p.m.r. spectrum of the mixture was taken and is shown in figure IV(1) C - 4a.

The most significant feature of the spectrum is the singlet at 6.7δ integrating to one proton which is thought to be due to the α-bromoether proton.

After treatment of the 3:1 mixture with an ethereal suspension of lithium aluminium hydride (0.2 g., 0.0053 mol.) and work-up in the usual manner, 2-benzyloxyphenol was isolated in 83% yield.

Experiment 6. Preparation of substrate 1, 3-benzodioxoles.

(a) 1, 3-Benzodioxole was prepared by the method of Bonthrone and Cornforth[5] starting from 1, 2-dihydroxybenzene and methylene chloride.

Yield 85%. B.p. 172-3°/754 mm.
(Lit. b.p. 60°/9 mm., 173-5°/760 mm.)

(b) 2-Phenyl-1, 3-benzodioxole was prepared by the procedure outlined by Capon and Page[6] starting from 1, 2-dihydroxy-benzene and benzylidene chloride.

Yield 54%. M.p. 50-1°.
(Lit. m.p. 49 - 50°)

Experiment 7. Preparation of reference compounds.

(a) 2-Methoxyphenol was obtained commercially from Aldrich Ltd.

(b) 2-Benzyloxyphenol was prepared from 1, 2-dihydroxybenzene and benzyl chloride, according to the procedure given by Jones and Young.[7]

Yield 37%. B.p. 110-2°/0.05 mm.
(Lit.b.p. 133-5°/0.1 mm.)

Experiment 8. The preparation of boron monohydrochloride.[10]

Boron trichloride (3.4 g., 0.029 mol.) was condensed into dry, ice-cooled diethyl ether (30 ml.). A solution of lithium borohydride (0.21 g., 0.0097 mol.) in dry diethyl ether (7 ml.) was then slowly added. The reactants were stirred together for a further 20 minutes by which time the solution had turned milky due to the precipitation of lithium chloride.

Experiment 9. The reaction of boron monohydrochloride with 1, 3-dioxanes.

The dioxane (0.01 mol.) in dry diethyl ether (10 ml.) was slowly added to the stirred ethereal solution of boron monohydrochloride (0.03 mol.) at room temperature.

Aliquots were taken from the reaction mixture through a rubber septum using a 2 ml. syringe, at the following intervals: every 15 minutes for the first hour, every 30 minutes for the next 3 hours and then once every two hours.

The aliquots were worked-up by quenching in aqueous methanol (Ch.II, p.38) and then analysed using g.l.c. The whole of the reaction mixture was then worked-up when either the substrate had been consumed or when the ratio of the substrate and product peaks became approximately constant.

The products given in these reactions were characterised in the usual way, by comparing the retention times of

the product peaks with those of authentic samples of the expected hydrogenolysis materials.

The substrates and products dealt with in this experiment are shown in figure IV(2) B - 1, (p.189).

Experiment 10. The preparation of the 1, 3-dioxane substrates.

(a) 1, 3-Dioxane, 2-propyl-1, 3-dioxane and 2-chloromethyl-1, 3-dioxane were prepared by the procedures outlined in chapter II, experiment 10.

(b) 2-Phenyl-1, 3-dioxane was prepared using the method given by Leggetter, Diner and Brown[14] starting from propan-1, 3-diol and benzaldehyde.

Yield 62%. B.p. 50°/1 mm.,
m.p. 47-9°.
(Lit. b.p. 95-6°/12 mm.; m.p. 45-6°.)

Experiment 11. The preparation of the hydroxyether reference compounds.

(a) 3-Methoxy propan-1-ol and 3-n-butoxy propan 1-ol were prepared as previously described in chapter II, experiment 11.

(b) 3-Benzyloxy propan-1-ol was prepared by the procedure outlined by Leggetter, Diner and Brown.[14]

Yield 32%. B.p. 92-6°/0.2 mm.
(Lit. b.p. 107°/1.5 mm.)

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V.

PART ONE

SOME ASPECTS OF THE E.I. MASS SPECTRA GIVEN BY THE CLEAVAGE PRODUCTS OF CYCLIC ACETALS.

V(1)A. Introduction.

In concert with periodate oxidation experiments the mass spectral technique has been used extensively throughout this thesis to determine the structures of the various ether products, given upon cleavage of their respective acetal substrates. Both electron impact ionization (E.I.) and chemical ionization (C.I.) modes were employed and so the first part of this chapter will deal with the former whilst the latter will be considered in part two.

The basic principles of the electron impact ionization mode have been comprehensively covered in many texts[1] and so will not be dealt with in any great detail.

Briefly then the sample molecules in the vapour phase are bombarded with electrons of sufficient energy to remove one of their electrons, which results in the formation of positively charged "molecular ions" (fig. V(1) A - 1).

$$M + e \longrightarrow M^{+\bullet} + 2\,e$$

Fig. V (1)A - 1.

The molecular ions are then accelerated out of the ionization chamber and subsequently pass through an homogenous magnetic field wherein they are forced to describe a circular flight-path, the radius of which is a function of their mass to charge (m/e) ratios. The relative abundance of the thus separated ion species are then electronically recorded.

The ions spend approximately 10^{-6} seconds in the ionization chamber and take approximately 10^{-5} seconds to be accelerated and deflected. Hence the molecular ions will be

collected and recorded if their decomposition rate constants $k < 10^5$ sec^{-1} whereas those which have rate constants $k > 10^6$ sec^{-1} will fragment and so their "daughter ions" will be recorded.

The latter fact as far as this thesis is concerned is the most important aspect of the electron impact mass spectral technique, in that structure determination essentially involves the reassembly of these "daughter ions" to give a number of possible arrangements for the parent ion. Then on consideration of other sources of experimental data (mainly periodate oxidation data) the non-consistent structures were eliminated and generally a single accordant structure was obtained.

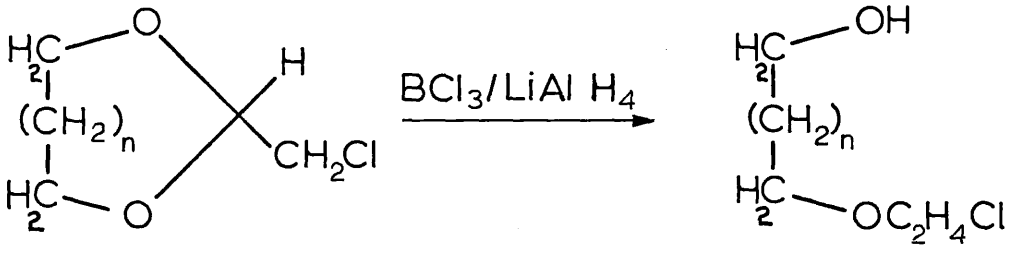
A third class of parent ions is those whose rate constants be between 10^5 sec^{-1} and 10^6 sec^{-1} which consequently decompose en route to the analyser. These are the meta-stable ions: thus for the decomposition of m_1 to m_2 neither m_1 nor m_2 are recorded upon the analyser but rather a small diffuse "meta stable peak" is seen at m^* where $m^* = m_2^2/m_1$. It can be appreciated then that the analysis of such peaks provides direct evidence of specific fragmentation processes.

V (1)B. Mass spectra of the cleavage products given by the 2-chloromethyl substituted cyclic acetals.

i) Introduction.

In chapter II (p.50) the reaction of the boron trichloride/lithium aluminium hydride combination with a number of 2-chloromethyl substituted cyclic acetals was considered. In each case a single main product was given which was then subjected to I.R., 60 MHz p.m.r., and elemental analysis.

After this the structures of the products were fairly confidently taken to be the mono 2-chloroethyl ether derivatives of the relevant parent diol (fig. V(1) B - 1): the E.I. mass spectra given by these products were then used to confirm these structures.



when n = 0, 1, 2, 3

Fig. V (1) B - 1.

This section then will consider the main aspects of the spectra given by the products while the relative intensities of all the ions present (relative to the respective base peaks) are displayed in Appendix I.

ii) Results and discussion.

The spectra, as one would expect from an homologous series, were all very similar and so they will be considered as a group rather than individually.

(a) Molecular ions.

The molecular ion was not present in any of the spectra looked at although the $(M+1)^+$ and $(M+3)^+$ ions were both present in low abundance.

The $(M+3)^+$ ion is of course due to the natural abundance of ^{37}Cl in some of the 2-chloroethyl ether derivatives.

This pairing of ions differing by two mass units persists throughout all of the spectra.

(b) Ions due to the 2-chloroethoxy function.

The presence of the chloroethoxy function is well demonstrated in all of the spectra by the appearance of abundant ions at m/e 63 and 65: in fact the m/e 63 species is the base peak in the spectrum of 4-(2-chloroethoxy)-butan-1-ol (fig. V (1) B - 2).

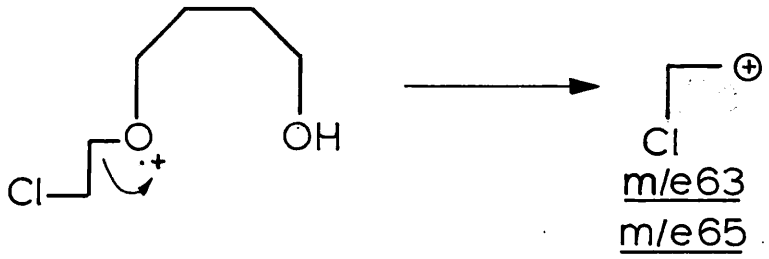


Fig. V (1) B - 2.

The ions at m/e 49 and 51 were also present in each of the spectra looked at. They are due to the $CH_2{=}\overset{+}{\underset{}{}}{=}{}^{35}Cl$ and $CH_2{=}\overset{+}{\underset{}{}}{=}{}^{37}Cl$ ions[9].

(c) Ions due to β-fission of the hydrocarbon chain (with respect to the oxygens).

Charge retention upon the molecular ion is the most likely triggering process for the decomposition of the 2-chloroethyl ether derivatives during mass spectral analysis. Bearing this in mind it is not surprising to find that primary fragments and their

progeny resulting from β-cleavage of the hydrocarbon chain (with respect to the oxygens) accounts for a large proportion of the most abundant ions in the 2-chloroethyl ether derivatives' spectra.

The ions given via β-fission in the spectrum of 4-(2-chloroethoxy)-butan-1-ol are shown in figure V (1) B - 3.

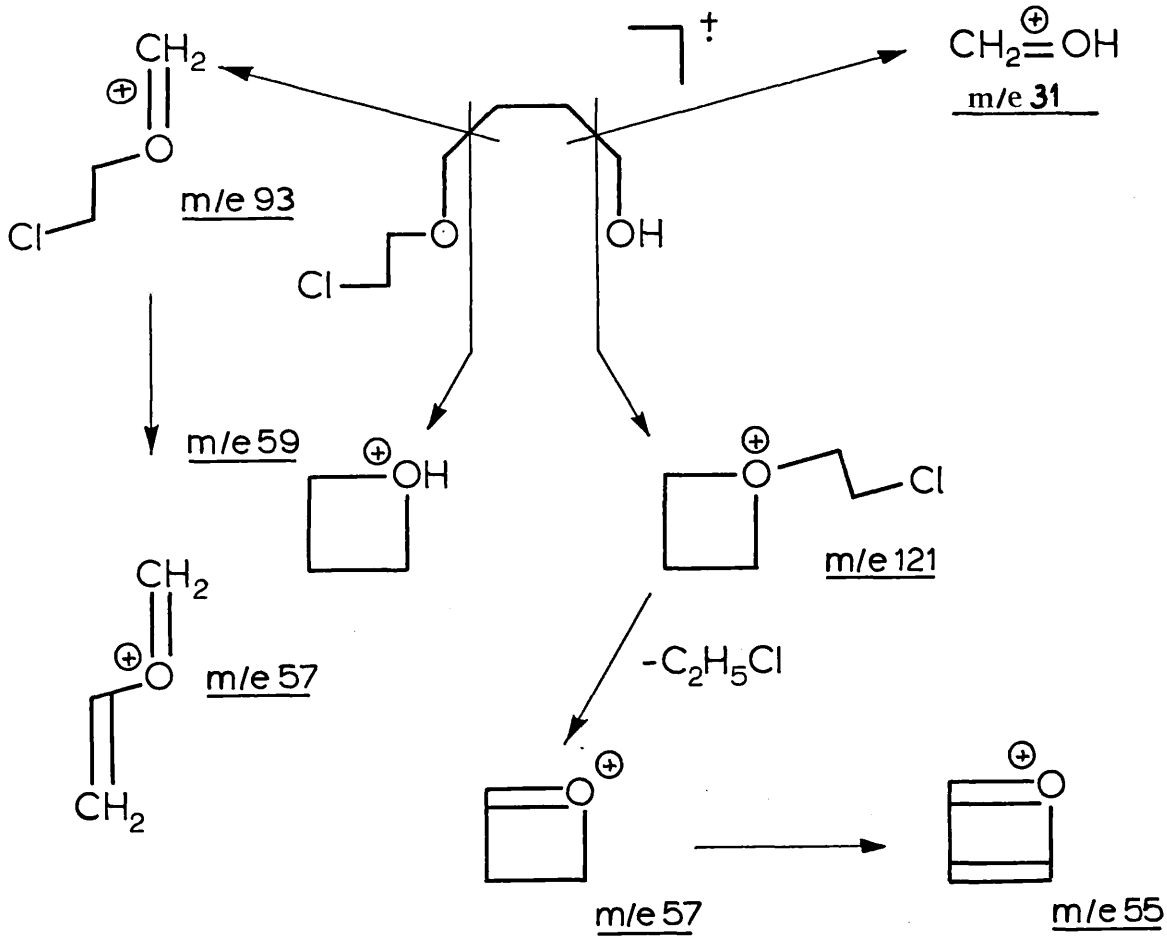


Fig. V (1) B - 3.

γ-Fission of the hydrocarbon chain was also evident in the fragmentation pattern of 4-(2-chloroethoxy)-butan-1-ol and 5-(2-chloroethoxy)-pentan-1-ol, although not to the same degree as the β-fission.

Thus fragments of small abundance at **m/e 107, and at** m/e 44 are seen in the spectrum of the former compound (fig. V (1) B - 4).

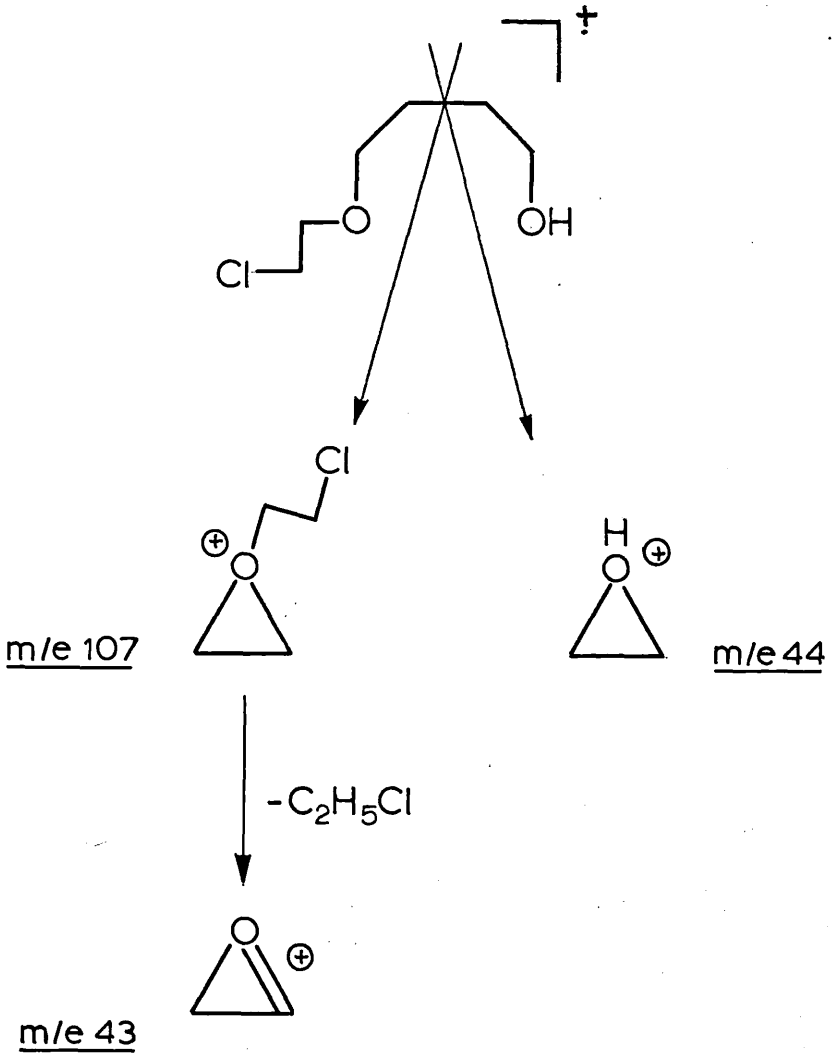


Fig. V (1) B - 4.

(d) Other ions.

All of the spectra looked at apart from that of 2-(2-chloroethoxy)-ethan-1-ol, contain abundant ions at the m/e values of 83 and 85. It is thought that they are produced during fragmentation of the m/e 121 species shown below in figure V(1)B-5.

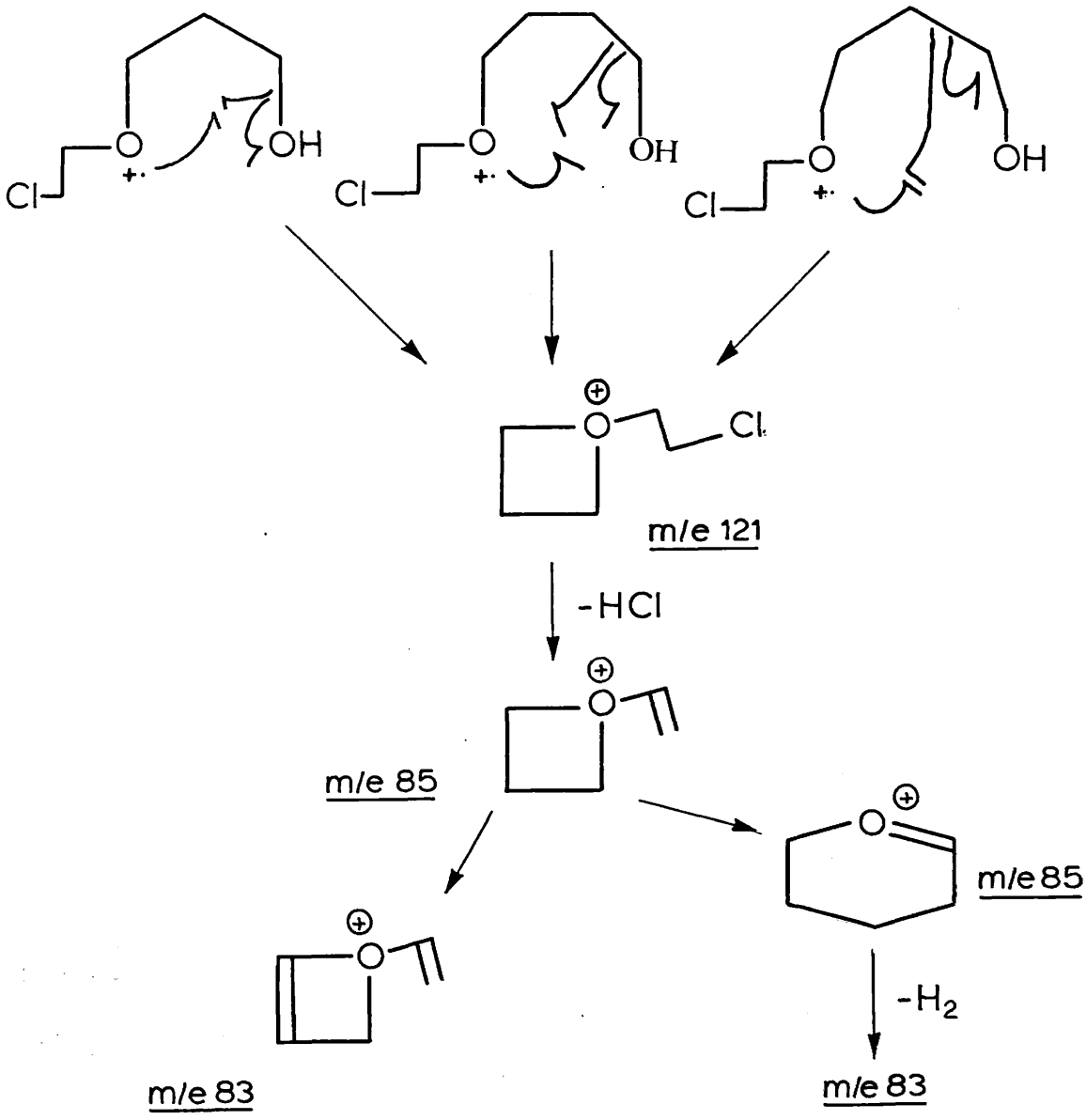


Fig. V (1) B - 5.

The loss of HCl from the m/e 121 ion - via 1,2 elimination - is quite a viable process especially when the more favourable 1,3-elimination cannot occur.[10]

iii) Conclusion.

The E.I. mass spectral data given by the cleavage products of the 2-chloromethyl acetals confirms that they are the mono 2-chloroethyl ether derivatives of the respective parent diols.

The fragmentation processes operating for these compounds appear to be a mixture of those given by simple aliphatic alcohols, ethers and chlorides. Thus for example the $CH_2{=}\overset{+}{=}OH$ ion (m/e 31) typical of aliphatic alcohols[11] was present in high abundance in all of the spectra considered[12], as was the R^+ ion ($Cl\,C_2H_4^+$, m/e 63, 65) typical of simple ethers. Finally the presence of the $CH_2{=}\overset{+}{=}Cl$ ions (m/e 49, 51) and the two $(M+1)^+$ ions are both common features of the spectra given by aliphatic alkyl chlorides.[13]

V (1) C. Mass spectra of some partially butylated alditol acetates.

i) Introduction.

The utilization of the mass spectral technique in the structural analysis of partially methylated alditol acetates is well established in carbohydrate chemistry, especially in the polysaccharide field where it is often used in conjunction with gas-liquid chromatography[2] (g.l.c. - m.s.).

The value of the technique rests upon the occurrence of fragmentation patterns which are characteristic of certain mutual arrangements of the methoxy and acetate groups upon the alditol's carbon backbone (although the molecular ion is rarely seen). For instance there are three main types of cleavage given by the carbon chains themselves, the relative facilities of these cleavage processes have been found to be in the order shown in figure V(1) C - 1.

Fragmentations such as those in which the C-C bonds of the alditol are broken are called "primary fragmentations".

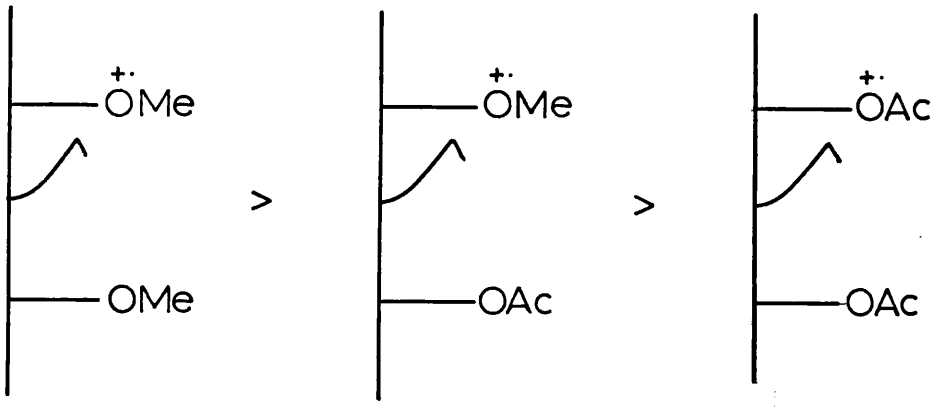


Fig. V (1) C - 1.

An oft occurring exception to the above hierarchy however is found when a primary methoxy function is attached "γ" to a second methoxy function and "δ" to an acetoxy group (fig. V (1) C - 2): here the primary fragment at m/e 89 is always more abundant than at the m/e 45.

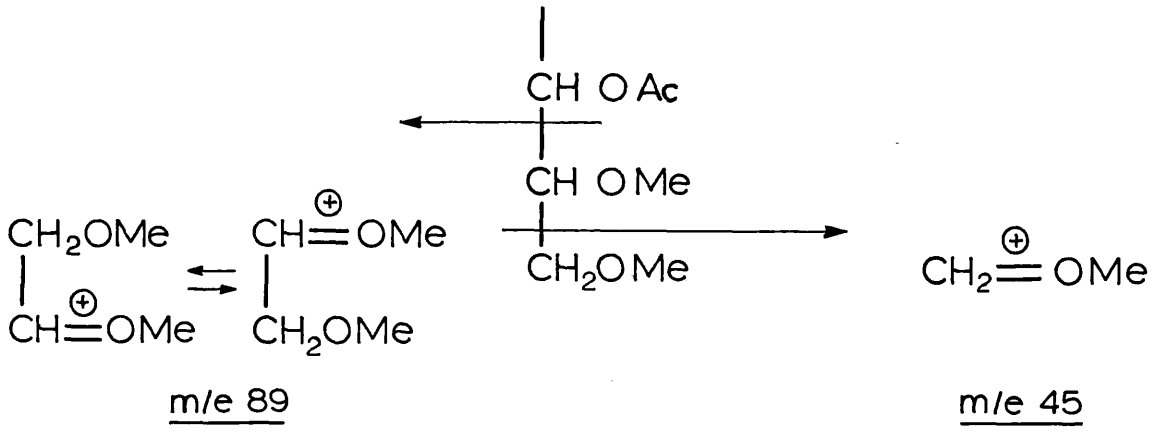


Fig. V (1) C - 2.

The most probable reasons for the above anomaly are to be found in the inherent stability of the m/e 89 fragment (due to a mutual sharing of the positive charge by the methoxy groups) and also in the fact that the m/e 45 fragment is a primary carbonium ion.

Meanwhile the primary fragments of the partially methylated alditol acetates will often lose simple molecules such as formaldehyde (30), methanol (32), ketene (42), acetic acid (60) and methyl acetate: the products from these generally sequential processes are called "secondary fragments".

The main aim of the work considered in this section was to help in the elucidation of the structures of the various n-butoxy derivatives given after cleavage of their respective acetals. Thus the mass spectra of the major cleavage products given by the following substrate acetals will be considered:

(a) cis-4-Hydroxymethyl-2-propyl-1, 3-dioxane(I).

(b) 1, 3-0-Butylidene-DL-erythritol(III) and 2, 4-di-0-butyl-1, 3-0-butylidene-DL-erythritol(IV).

(c) 1, 3: 2, 4-Di-0-butylidene erythritol(V) and 1, 3:4, 6-di-0-butylidene galactitol(VI).

The second aim of this section will be to compare any general trends detected in the fragmentation patterns of the partially butylated alditol acetates with those given by the partially methylated analogues.

General notes.

1) All of the spectra discussed herein contained both the acetylium ion ($CH_3C\equiv\overset{+}{O}$, m/e 43)[2] and the n-butyl ion ($C_4H_9^+$, m/e 57)[3] in higher abundance than any of the other ions. It was therefore found useful to consider the third most abundant species as the "base peak" (or most abundant ion) as a means of amplifying the differences in the fragmentation patterns of the various ethers.

2) The most abundant ions found in the spectra of every compound mentioned in the text are displayed in Appendix II.

ii) Results and discussion.

(a) Partially butylated acetates of butan-1, 3, 4-triol.

G.l.c. analysis of the product mixture from the reaction of (±)-cis-4-hydroxymethyl-2-propyl-1, 3-dioxane with boron trichloride/lithium aluminium hydride had shown the presence of two main products. Periodate oxidation of the purified mixture of products showed that the major component was the -3-0-butyl ether of DL-butan-1, 3, 4-triol(B) which left DL-1-0-butyl butan-1, 3, 4-triol(A) as the minor product; fig. V(1) C - 3 shows the acetate derivatives of A and B .

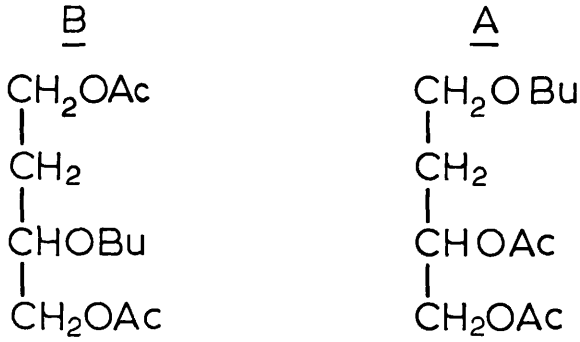


Fig. V (1) C - 3.

The base peak of B's spectrum is due to an ion of m/e 70, while other important ions present are those at the following m/e values: 99, 117, 126, 159 and 173.

The species at m/e 70 is thought to have arisen after the molecular ion had lost two molecules of acetic acid, followed by one molecule of butene (probably but-1-ene). The sequential loss of acetic acid in this manner is a well documented fragmentation reaction of compounds bearing acetoxyl functions while the loss of an alkene is a typical fragmentation reaction of butyl ethers [4] (fig. V (1) C - 4).

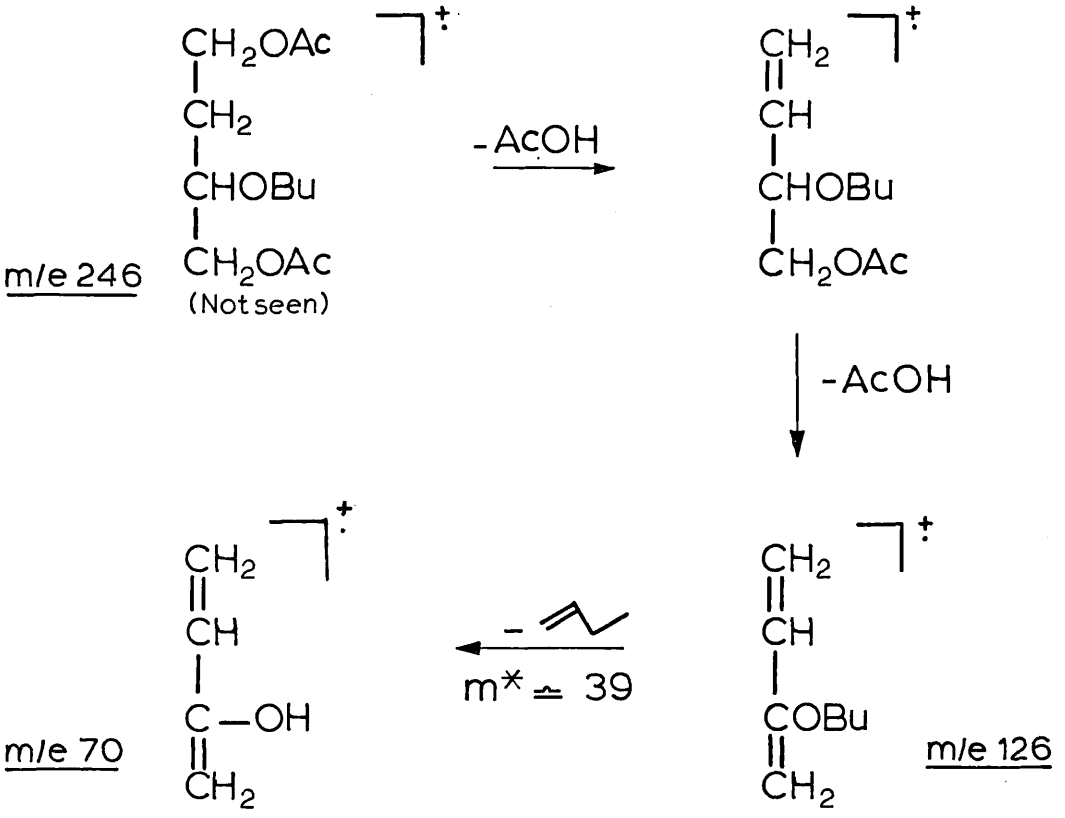


Fig. V(1) C - 4.

The remainder of the spectrum is a result of primary fragmentation of the C_2 - C_3 and C_3 - C_4 bonds (yielding m/e 159 and m/e 173 respectively) and the associated secondary fragmentation reactions (fig. V (1) C - 5).

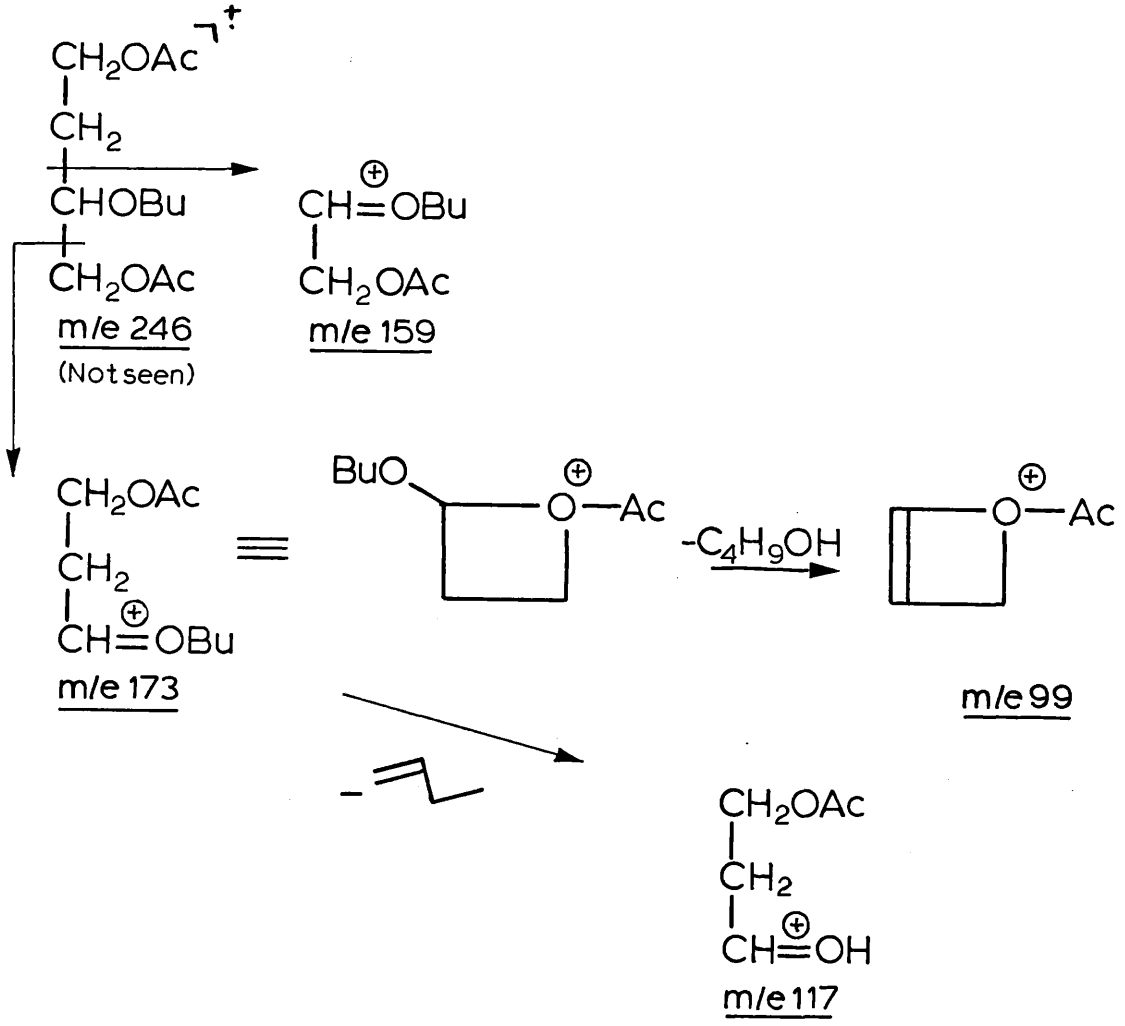


Fig. V (1) C - 5.

The presence of a methylene function in an alditol is known to suppress the primary cleavage reactions of the bonds immediately connected to it[1] (due to the instability of the resulting methylene radical). Thus the C_2 methylene function in B is the most probable reason for the low intensity of the m/e 159 ion and also the fact that the fragmentation pattern of B is dominated by the products given on cleavage of C_3 - C_4 and those resulting directly from the molecular ion.

In the light of the above discussion on the effects of the methylene group upon primary fragmentation, the spectrum of the 1-O-butyl butan-1, 3, 4-triol is rather misleading. This is because the most abundant ion present is at m/e 87 which suggests that fission of the C_1 - C_2 bond is quite a facile process in spite of the fact that C_2 is a methylene function.

An alternative route to an m/e 87 ion is shown in figure V(1) C - 6 : the main evidence in favour of this rationale is first of all that most of the abundant ions of A's spectrum are given in this pathway and secondly the stability of the CH_2 - C bond is well documented in the literature.

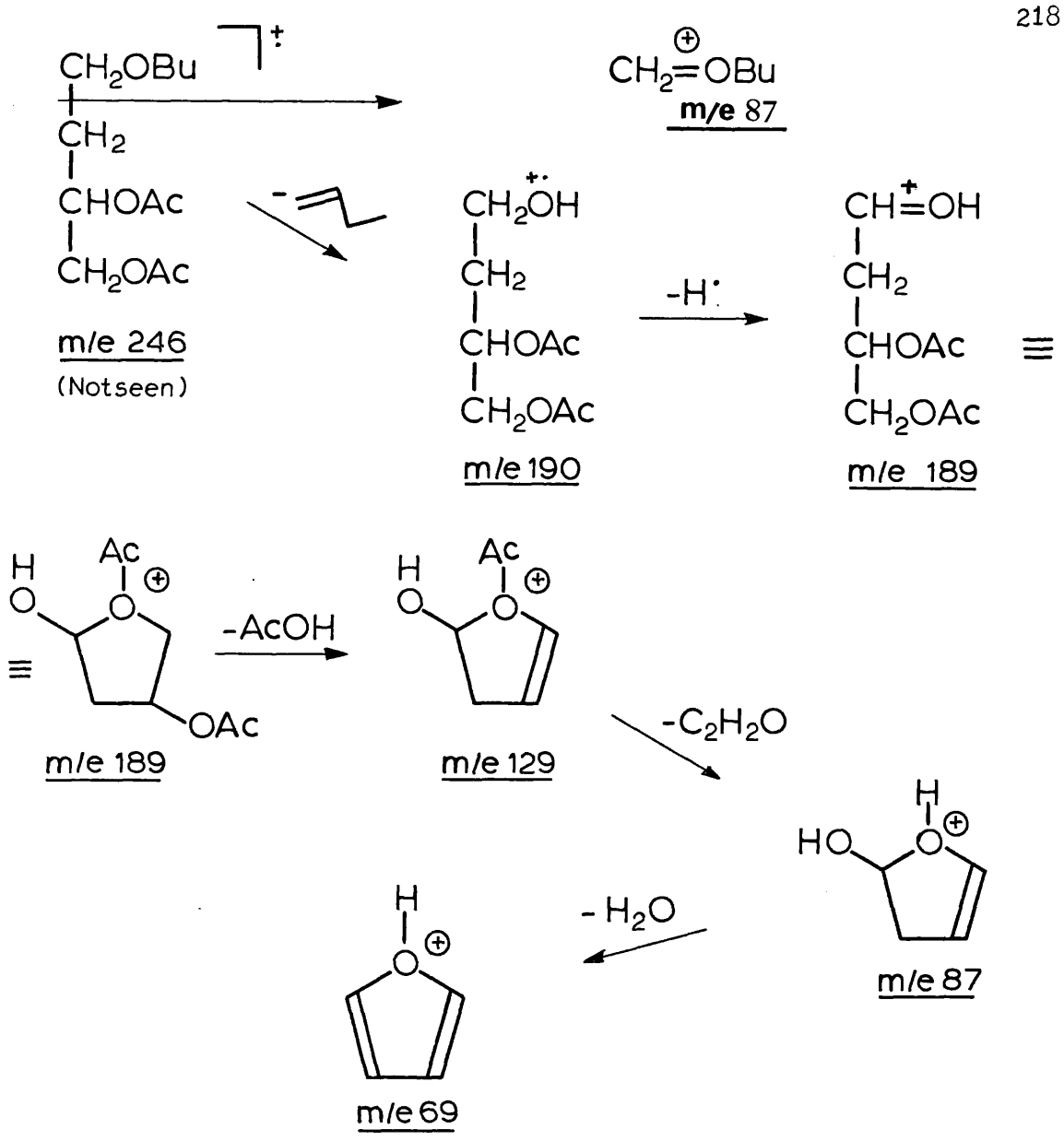

CH2OBu
CH2
CHOAc
CH2OAc
m/e 246
(Notseen)
CH2=OBu
m/e 87
CH2OH
CH2
CHOAc
CH2OAc
m/e 190
-H·
CH=OH
CH2
CHOAc
CH2OAc
m/e 189
≡
-AcOH
m/e 189
m/e 129
-C2H2O
HO
m/e 87
-H2O
m/e 69

Fig. V (I) C - 6.

Cleavage of C_3 - C_4 does occur to some extent, so that the m/e 173 ion is seen (fig. V(1) C - 7) although this species does not play the dominant role that is played by its analogue in the spectrum of compound B. The most probable reason for this is that, as has been seen in the partially methylated alditol acetates, cleavage of the C - C bond connecting two acetoxyl functions is not as favourable a process as the cleavage of the C - C bond connecting an acetoxy group and an ether function.

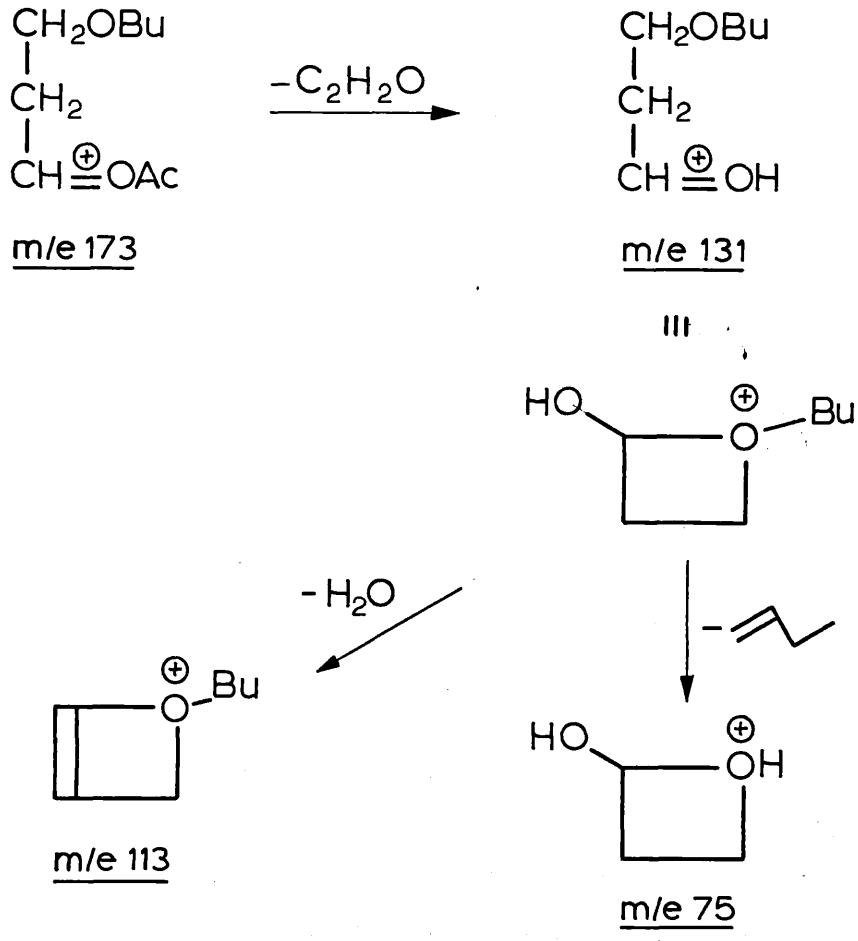


Fig. V (1) C - 7.

(b) Partially butylated erythritol acetates.

The three acetalated erythritol derivatives that were reacted with boron trichloride/lithium aluminium hydride were 1, 3-0-butylidene-DL-erythritol(III), 2, 4-di-0-butyl-1, 3-0-butylidene-DL-erythritol(IV) and 1, 3:2, 4-di-0-butylidene erythritol(V).

Periodate oxidation experiments upon the product mixture given from the reaction of III suggested that the main product was 2-0-butyl-DL-erythritol(F) the acetate of which is shown in figure V(1) C - 8.

F(acetate)

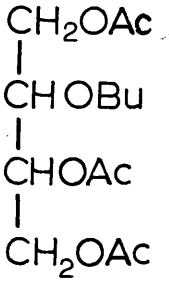


Fig. V(1) C - 8.

The most abundant ions in the spectrum of F are at the following m/e values: 57, 73, 103, 115, 129, 159, 171 and 231. Now if the periodate data is taken to be correct one would expect peaks at m/e 159 and m/e 231, as these would result from the primary fragmentation of the $C_2 - C_3$ and $C_1 - C_2$ bonds respectively.

It can then be shown that the secondary fragmentation of these two ions accounts very well for the spectrum given by F (fig. V(1)C - 9).

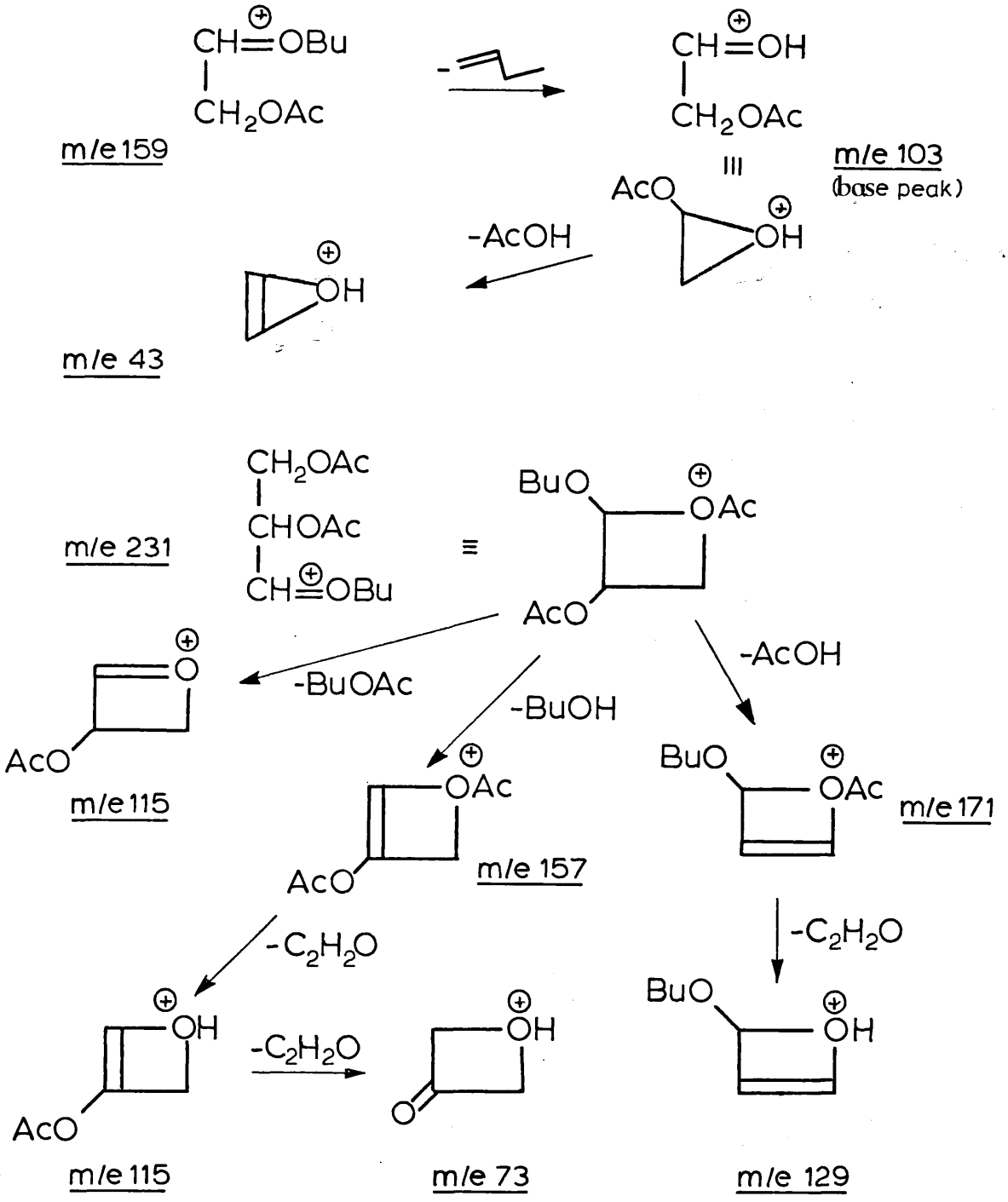


Fig. V (1) C - 9.

Apart from the fragments at m/e 43 (due to the $CH_3 - C \equiv {}^{+}O$ ion) and m/e 57 (due to the $C_4H_9{}^{+}$ ion), the base peak of F's spectrum is at m/e 103 and is probably given by the expulsion of but-1-ene from the m/e 159 fragment. The facility with which the butylated alditol functions undergo this process is one of the main features of this section.

Apart from this one particular instance, the other secondary fragmentation processes appear to be analogous to those operating in the methylated alditol acetates: thus the loss of butanol (74) and butyl acetate (116) by F is equivalent to the loss of methanol and methyl acetate in the methylated compounds.

Turning now to the main product given with 1,3:2,4-di-O-butylidene erythritol, periodate oxidation suggested a contiguous array of the two hydroxyl groups as is present in 1,2-di-O-butyl-DL-erythritol (J). The base peak of J's spectrum is at m/e 115 while other large peaks are also found at the m/e values 117, 129, 171, 173 and 231, all of which can be accounted for on consideration of the secondary fragmentation itineraries of the primary ions m/e 173 and m/e 231 fig. V (1) C - 10.

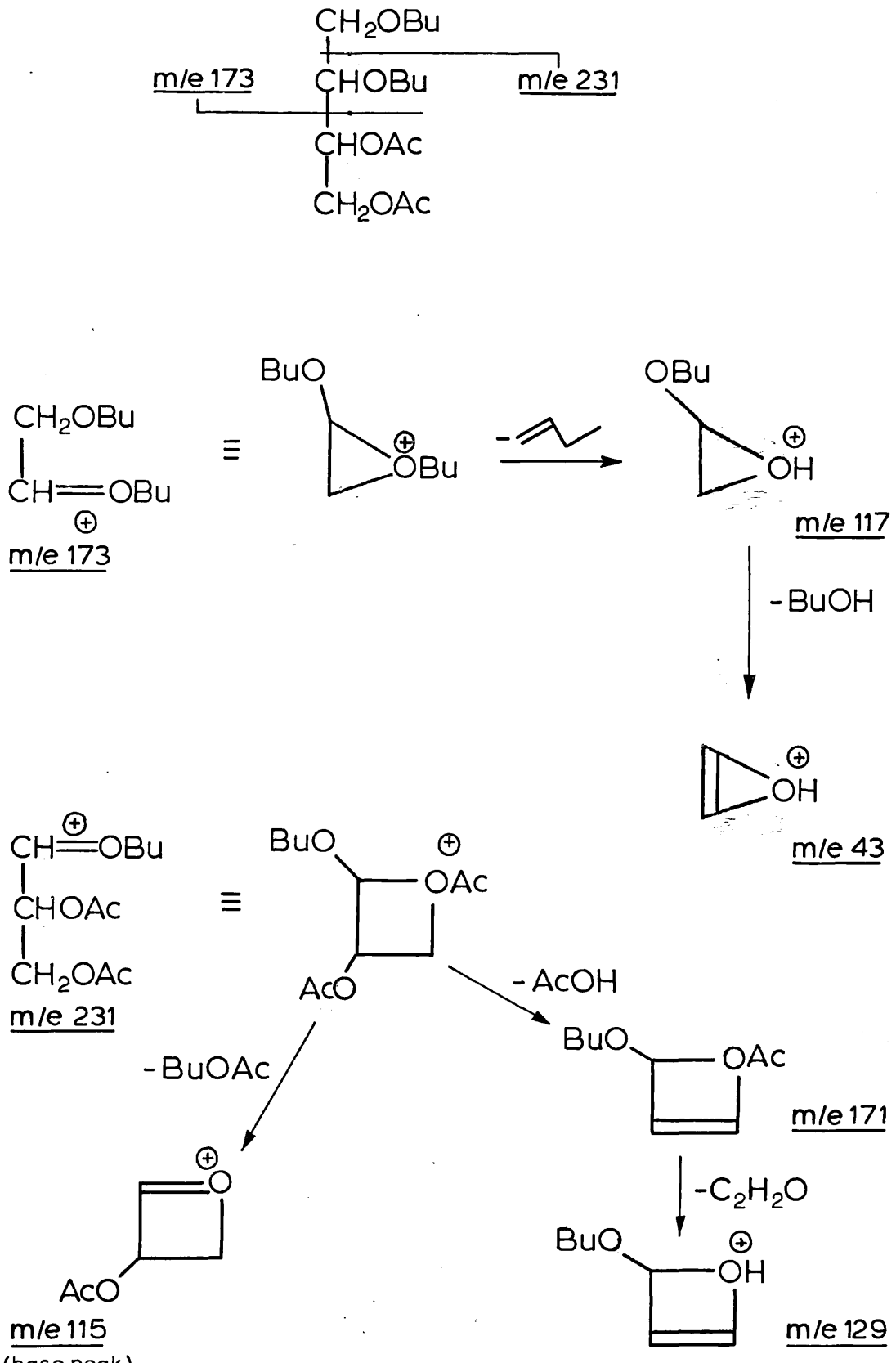

CH2OBu
CHOBu
CHOAc
CH2OAc
m/e 173
m/e 231
BuO
OBu
OH
m/e 117
-BuOH
m/e 43
m/e 173
m/e 231
AcO
-AcOH
-BuOAc
m/e 171
-C2H2O
m/e 129
m/e 115
(base peak)

Fig. V (1) C - 10.

An interesting feature of J's spectrum is the small abundance of the $CH_2 = {}^{+}OBu$ ion (m/e 87), especially when compared to the abundance of the ion at m/e 173 and its secondary fragments. This difference in the abundance of these two ions is analogous to the situation that exists in the methoxylated alditols where the $CH_2 = {}^{+}OMe$ ion (m/e 45) is not seen when the possibility exists for formation of the $CH(CH_2OMe) = {}^{+}OMe$ species (m/e 89).

Also the fact that the base peak (at m/e 115) of the spectrum is derived from the primary ion at m/e 231 suggests that primary fission between two butoxylated carbons can occur more readily than that between a butoxylated and an acetoxylated carbon (apart from the case cited above), presumably due to the greater stability of the butyloxylated radical relative to the acetoxylated radical (fig. V (1) C - 11).

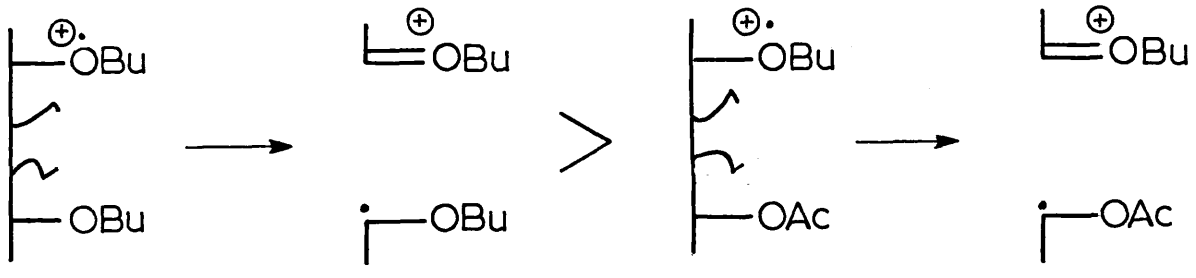


Fig. V (1) C - 11.

The two possible cleavage products that could result from the reaction of 2,4- di -0-butyl-1,3-0-butylidene-DL-erythritol are 1,2,3-tri-0-butyl-DL-erythritol(G) and 1,2,4-tri-0-butyl-DL-erythritol(H) (fig. V(1) C - 12 shows their acetate derivatives).

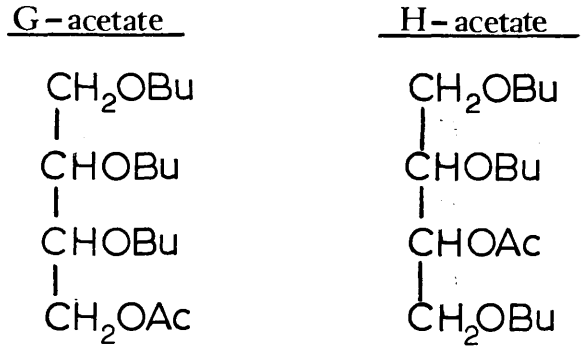


Fig. V (1) C - 12.

Now, the most abundant ions in the spectrum of the main cleavage product are at the following m/e values: 43, 57, 61, 73, 103, 129 and 159 plus smaller peaks at m/e 245 and m/e 259.

One would expect to see fragments at m/e 43, 57 and 245 in the spectra of both the 1,2,3 and 1,2,4-tri-0-butyl derivatives, fig V (1) C - 13a, however the presence of an ion at m/e 259 suggests that the main product contains three contiguous butoxy functions. Also the high abundance of the m/e 159 fragment would tend to point to the 1,2,3 array in that the albeit possible, production of this ion from the 1,2,4 array involves the cleavage of the bond between acetoxy and butoxy bearing carbon atoms, whereas the former arrangement involves the more favourable cleavage of the C_2 - C_3 bond in which

both carbons bear butoxy functions.

The secondary fragmentation pattern shown in figure V(1) C - 13b bears out this supposition and confirms that G is in fact 1, 2, 3-tri-0-butyl-DL-erythritol.

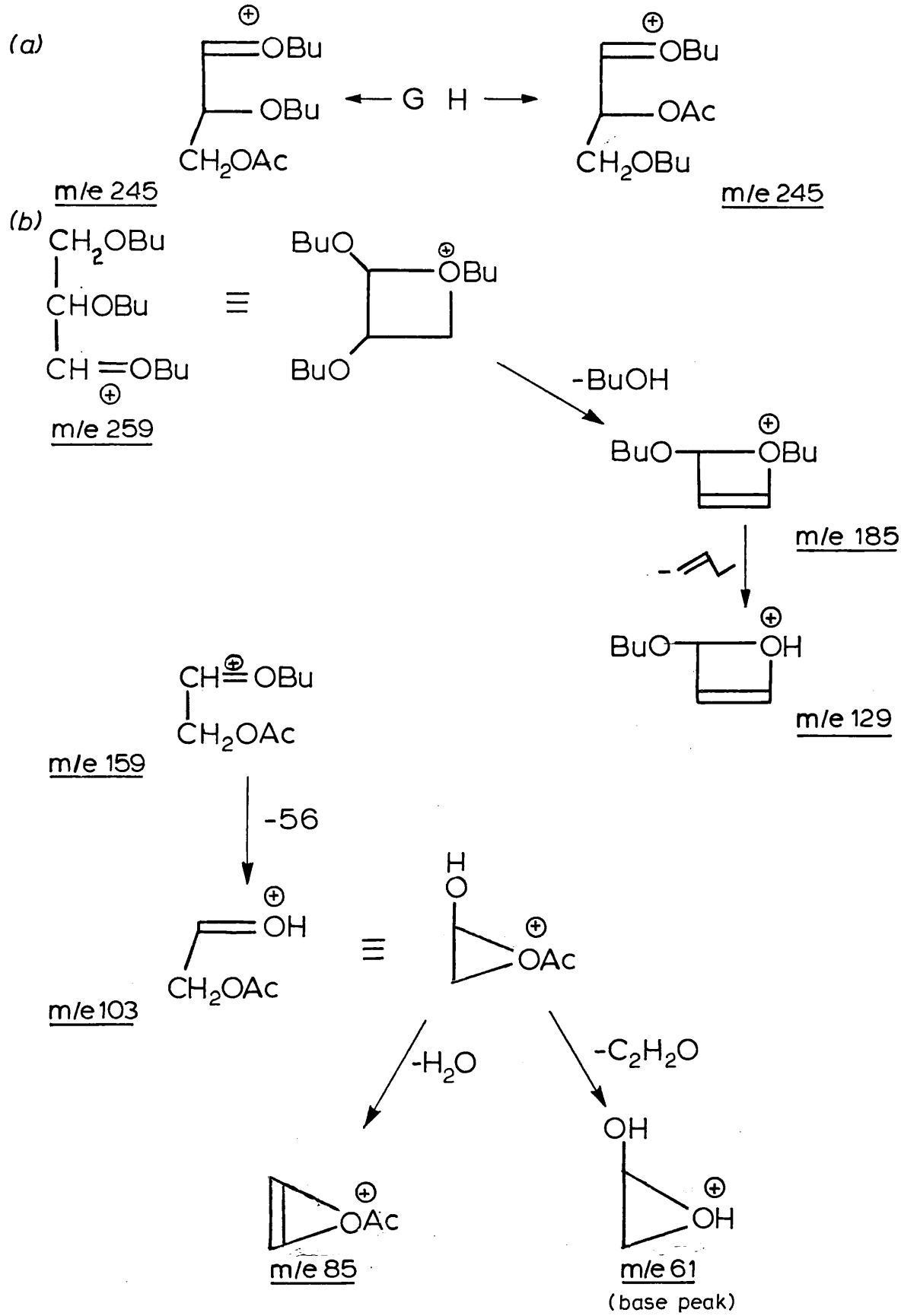

(a)
OBu
OBu
CH2OAc
G H
OBu
OAc
CH2OBu
m/e 245
m/e 245
(b)
CH2OBu
CHOBu
CH OBu
m/e 259
BuO
OBu
BuO
-BuOH
BuO
OBu
m/e 185
BuO
OH
m/e 129
CH OBu
CH2OAc
m/e 159
-56
OH
CH2OAc
m/e 103
H
O
OAc
-H2O
-C2H2O
OAc
m/e 85
OH
OH
m/e 61
(base peak)

Fig. V (1) C - 13.

The base peak of G's spectrum is the ion at m/e 61 (a secondary fragment of m/e 159) although the fragment at m/e 103 (also derived from m/e 159) and m/e 159 itself are of comparable abundance.

(c) Partially butylated galactitol acetates.

The next group of compounds to be considered is the cleavage products given with 1,3:4,6-di-O-butylidene galactitol(VI). Again only the main products will be looked at.

Two main products were isolated from the reaction in which a 1:3 ratio of IX to boron trichloride/lithium aluminium hydride was used. Periodate oxidation and molybdate ionophoresis experiments suggested that the crystalline product M was the 1,6-di-O-butyl derivative of galactitol while periodate oxidation suggested that the crystalline product N was the DL-1,4-di-O-butyl ether, (fig. V (1) C - 14 shows their acetate derivatives).

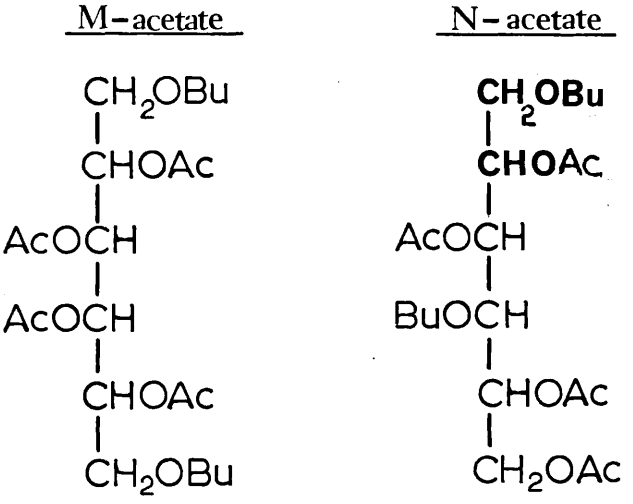


Fig. V (1) C - 14.

The base peak of M's spectrum is at m/e 129 while other major peaks are present at the following m/e values: 43, 57, 87, 115, 129, 157, 171, 213 and 215 with smaller peaks at 231 and 159.

Apart from the m/e 87 ion none of the other primary fragments are present in any great abundance, which is what one would expect from a molecule containing four contiguous acetyloxy carbon atoms.

Figure V(1) C - 15 shows the relevant fragmentation patterns based upon the loss of but-1-ene (56), acetic acid (60), butan-1-ol (74) and butyl acetate (116), all of which have been shown to be relevant in the spectra of the butylated erythritol acetates discussed earlier.

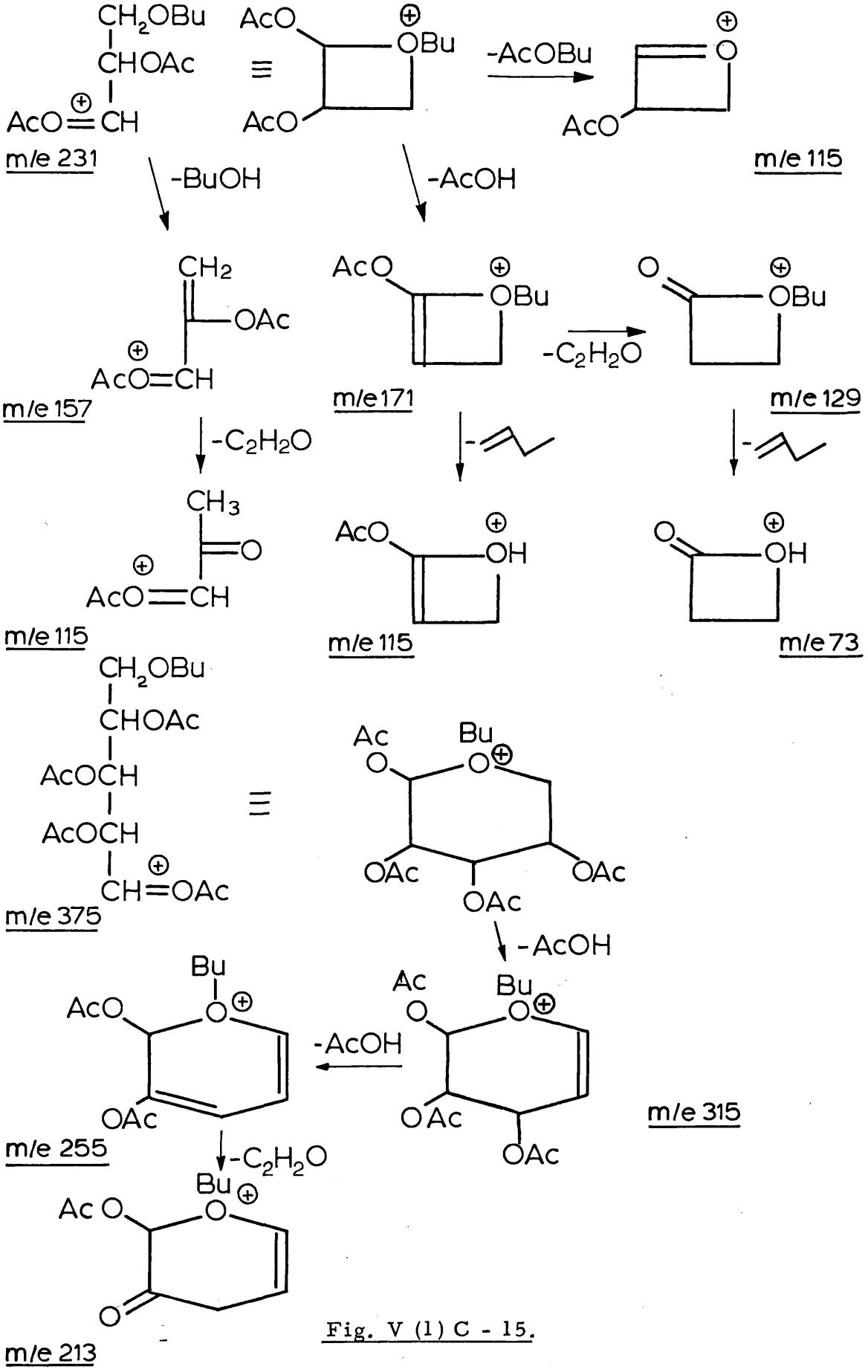

CH2OBu
CHOAc
AcO⊕=CH
m/e 231
AcO
OBu
AcO
≡
-AcOBu
m/e 115
-BuOH
-AcOH
CH2
OAc
AcO⊕=CH
m/e 157
AcO
OBu
m/e 171
-C2H2O
O
OBu
m/e 129
-C2H2O
CH3
O
AcO⊕=CH
m/e 115
AcO
OH
m/e 115
O
OH
m/e 73
CH2OBu
CHOAc
AcOCH
AcOCH
CH⊕=OAc
m/e 375
≡
Ac
Bu
OAc
OAc
OAc
-AcOH
Bu
AcO
OAc
m/e 255
-AcOH
Ac
Bu
OAc
OAc
m/e 315
-C2H2O
Bu⊕
Ac O
O
O
m/e 213

Fig. V (1) C - 15.

Meanwhile compound N as would be expected from a 1, 4 distribution of butoxy functions gives a base peak derived from the primary fragment m/e 231, which on losing acetic acid yields the m/e 171 ion. Also prominent is the primary fragment at m/e 317 given upon cleavage of the C_4 - C_5 bond.

Figure V (1) C - 16 shows the most relevant fragmentation patterns.

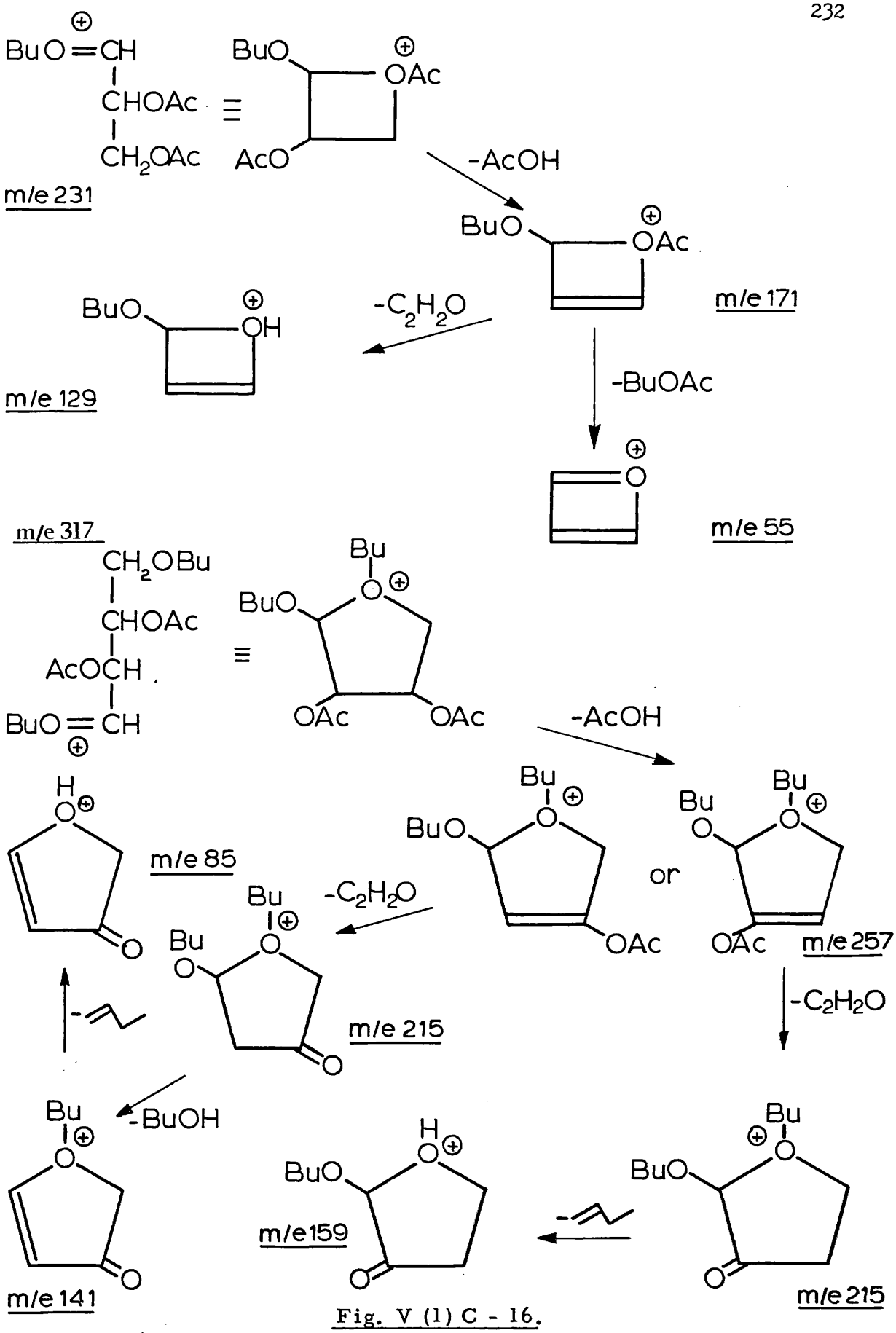

m/e 231
-AcOH
m/e 171
-C2H2O
m/e 129
-BuOAc
m/e 55
m/e 317
-AcOH
m/e 85
-C2H2O
m/e 257
or
m/e 215
-C2H2O
-BuOH
m/e 159
m/e 141
m/e 215

Fig. V (1) C - 16.

Keeping in mind the periodate data then, the structures of M and N were confidently concluded to be 1,6-di-O-butyl galactitol and 1,4-di-O-butyl-DL-galactitol respectively.

(d) Partially butylated mono butylidene acetals of galactitol as their acetate derivatives.

In this section the mass spectra of the main product given by 1,3:4,6-di-O-butylidene galactitol(VI) in the 1:1 acetal to boron trichloride/lithium aluminium hydride reaction will be considered.

Thus VI gave a crystalline compound O as its major product. This was shown to be 1-O-butyl-4,6-O-butylidene-DL-galactitol by periodate oxidation experiments and also in the light of the fact that 1-O-butyl-DL-galactitol was the sole product given by O after acid hydrolysis (Ch. III, p.138).

The acetate derivative of compound O is shown in figure V (1) C - 17.

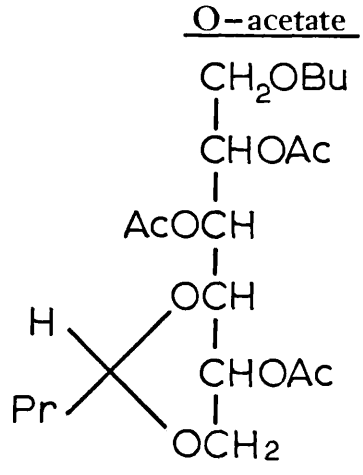


Fig. V (1) C - 17.

The most abundant ion in O's spectrum (apart from m/e 43 and 57) is at m/e 115, while other large peaks are present at the following m/e values: 85, 87, 129, 157, 171 and 375, with smaller peaks at m/e 187 and 303.

As one would expect from a molecule which contains both a partially butylated moiety and a cyclic acetal function, the spectrum shows the characteristic fragmentation reactions of both species.

Thus a well defined $(M - 1)^+$ ion is present along with the $(M - 43)^+$ ion. These two ions correspond to loss of the acetal hydrogen and the acetal n-propyl group respectively. Further fragmentation of these species is also in evidence, as well as the primary fragment given upon cleavage of the $C_3 - C_4$ bond (m/e 187) (fig. V (1) C -18).

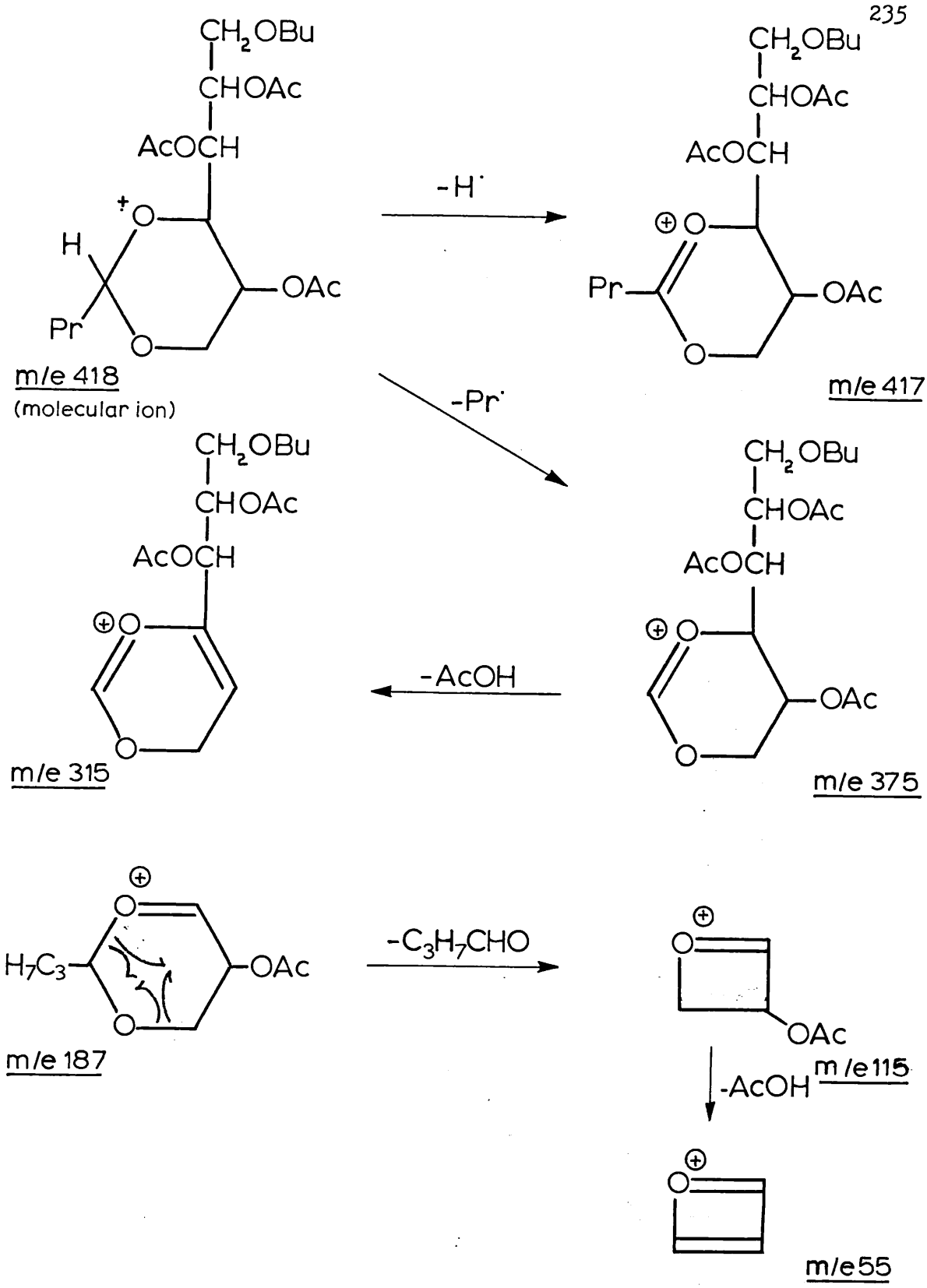

CH2OBu
CHOAc
AcOCH
OAc
H
Pr
m/e 418
(molecular ion)
-H·
m/e 417
-Pr·
-AcOH
m/e 315
m/e 375
H7C3
-C3H7CHO
m/e 187
-AcOH
m/e 115
m/e 55

Fig. V (1) C -18 .

Meanwhile the alternative primary fragment resulting from cleavage of C_3 - C_4 (m/e 231), is the partially butylated alditol acetate half of the molecule and so gives the secondary fragments shown in figure V (1) C - 19 .

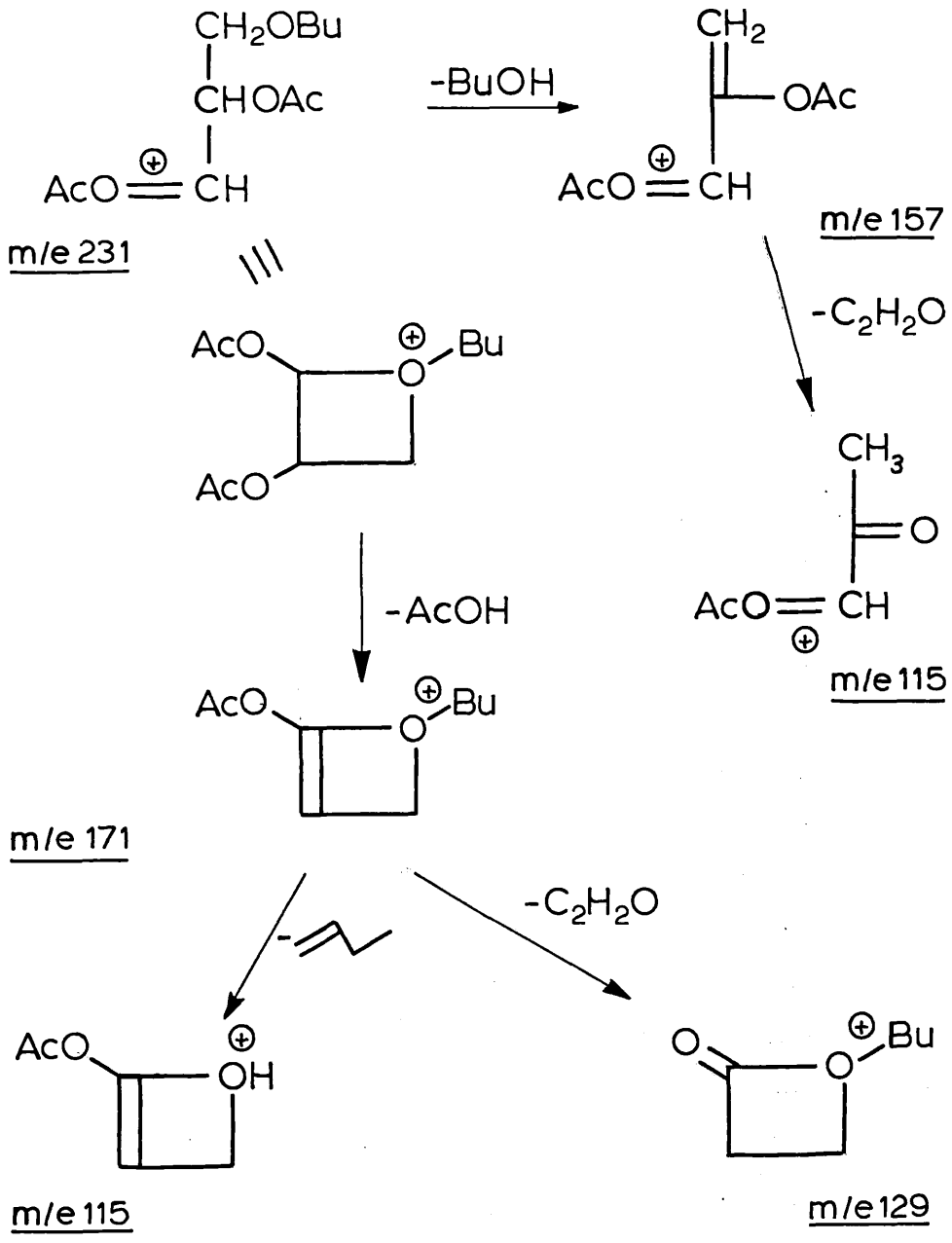


Fig. V (1) C - 19 .

The peak at m/e 87 is of course due to the $CH_2 = \overset{+}{=}OBu$ ion.

In conclusion then the mass spectrum of compound O confirmed that it was 1,-0-butyl-4,6- 0-butylidene-DL-galactitol.

iii) Conclusion.

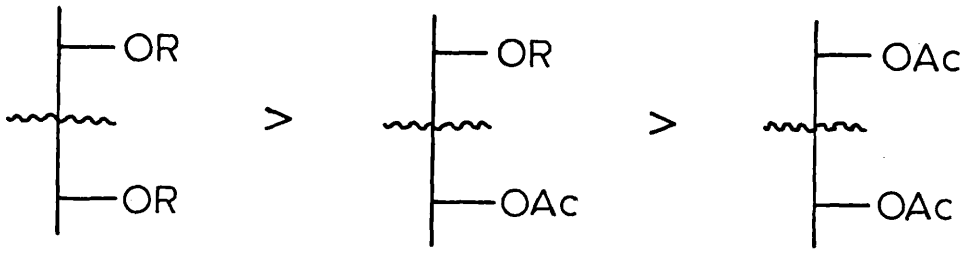
It was stated in the introduction to this section that apart from the structure elucidation of the various compounds under study, it was hoped that enough mass spectral data concerning the partially butylated alditol acetates could be collected to make a comparison between the latter and the mass spectra of the partially methylated alditol acetates feasible. Hopefully this aim has been achieved.

Thus it has been shown that in direct analogy to the propensity of the partially methylated alditol acetates to lose methanol, ketene, acetic acid and methyl acetate, the partially butylated alditol acetates can lose butanol, ketene, acetic acid and butyl acetate during their secondary fragmentation reactions.

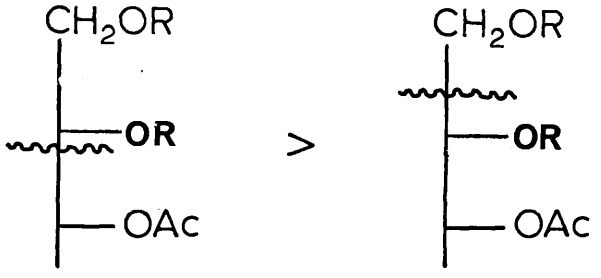
In conjunction with the above however, the partially butylated alditol acetates also undergo two processes characteristic of the mass spectral behaviour of the higher ethers: thus they readily lose an alkene (probably but-1-ene) during secondary fragmentation and also give the R^+ ion ($C_4H_9^+$, m/e 57). The latter ion in fact often competes with the acetylium ion (m/e 43) for the role of base peak in the partially butylated acetate's spectra.

Also the relative facility and direction with which the primary fragmentation processes occur in the partially butylated alditol acetates are analogous to those of the partially methylated alditol acetates (fig. V (1) C -20).

Thus:



where R = Me or n - Bu



where R = Me or n-Bu

Fig. V (1) C -20 .

The spectra of the monobutylated butan-1, 3, 4-triol acetates (especially that of the 3-0-butyl ether) have also demonstrated the effect that a methylene carbon has upon the primary fragmentation processes: thus the low stability of the methylene radical tends to retard cleavage of the CH_2 - COR bonds (where R = Ac or Bu) as shown in figure V (1) C - 21 .

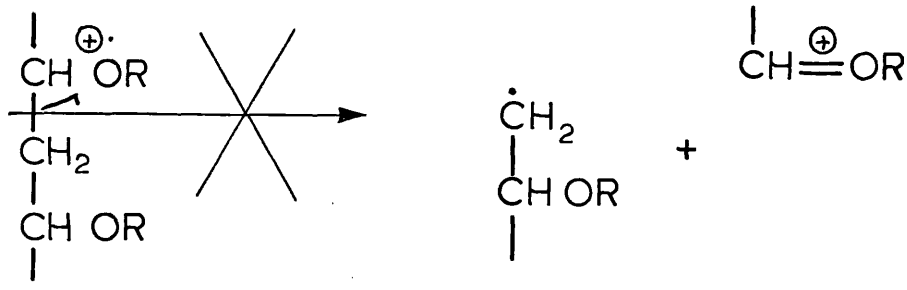


Fig. V (1) C -21 .

Finally, it has been shown that when an acetal function is present in the same molecule as the partially butylated alditol acetate moiety then the spectra produced show the characteristic fragmentation processes of both species. Thus the effect of the butylidene acetal function is seen in the presence of a well defined molecular ion M^+ along with the $(M - 1)^+$ and $(M - 43)^+$ species in the spectrum of compound O.

V.

PART TWO

SOME ASPECTS OF THE C.I. MASS SPECTRA OF SIMPLE CYCLIC ACETALS.

V (2)A. Introduction.

The basic currency of the mass spectrometer is made up of different types of ionic species which can be produced in a variety of different ways, such as electron impact ionization, field ionization or chemical ionization: it is the last technique which will be considered in this section.[5]

In chemical ionization mass spectrometry the sample molecules are introduced as a vapour (at ca. 10^{-6} torr) into the ionization chamber in the presence of a large excess of the "reactant gas" (at ca. 0.1-3 torr depending upon the nature of the gas and the machine used). The most commonly used reactant gases are hydrocarbons (CH_4, i-C_4H_{10}) although water, ammonia and the rare gases have been used by some workers. Now as the degree of excess of the reactant gas is so large, primary ionization due to electron bombardment in the ionization chamber occurs almost exclusively to the reactant gas molecules. The latter then undergo a series of ion-molecular interactions amongst themselves until a steady state plasma is given: it is this plasma which gives rise to the "chemical ionization" spectrum of the particular sample under study via a series of ion-molecular interactions.

The reactant gas used in this work was isobutane. Figure V (2) A - 1 shows the main species present in isobutane "plasma" and also illustrates the reactions given by this plasma with a sample compound[6] "SH".

$$C_4H_{10} + e \longrightarrow C_4H_{10}^{\oplus\cdot} + 2e$$

$$C_4H_{10}^{+\cdot} \longrightarrow C_3H_7^{\oplus} + CH_3^{\cdot}$$

$$C_3H_7^{\oplus} + C_4H_{10} \longrightarrow C_3H_8 + C_4H_9^{\oplus}$$

m/e 57

then $C_4H_9^{\oplus} + SH \longrightarrow SH_2^{\oplus} + C_4H_8$ H^+ addition

$C_4H_9^{\oplus} + SH \longrightarrow S^{\oplus} + C_4H_{10}$ H^- abstraction

then say $SH^{\oplus} \longrightarrow F_1^{\oplus} + N_1$

$F_1^{\oplus} \longrightarrow F_2^{\oplus} + N_2$ etc.

Fig. V (2) A - 1.

The observed net effect of these reactions however is that the $(M + 1)^+$ and/or the $(M - 1)^+$ ion are the most abundant species in the spectrum of SH, rather than the large amount of ion fragmentation that would be expected in the corresponding electron impact spectrum.

A second major difference between the C.I. and E.I. modes is the fact that the C.I. spectrum of a particular sample is significantly dependent upon the nature of the reactant gas. Thus the C.I. spectra discussed herein are the products of what is essentially a series of even electron, gaseous Brønsted acid-base reactions whereas if say, N_2^+ had been used as the reactant ion then the spectra given would be the result of odd electron, oxidation-reduction chemistry.

It also follows that the intensity of a given chemical ionization reaction can be varied by varying the reactant gas. Thus methane yields a plasma which has a much greater proton donating power than isobutane, while Ne^+ is such an effective

odd-electron ionizing agent that it can give a greater degree of fragmentation than the electron impact mode for any given sample.

In summary then the main areas in which the even electron chemical ionization spectra considered herein differ from the electron impact spectra are as follows.

(1) The degree of fragmentation is much smaller in the C.I. spectra.

(2) The $(M+1)^+$ and/or the $(M-1)^+$ ions are generally the most abundant ions in the spectra.

(3) The ions comprising the spectra tend to be located in the higher mass range of the sample used.

V(2)B. Mass spectra of simple dioxolanes, dioxanes, dioxepanes and dioxocanes.

(i) General characteristics.

The C.I. mass spectra of the title compounds substituted at C_2 with H, n-Pr and CH_2Cl will be considered in this section along with 2-vinyl-1,3-dioxolane, 2-vinyl-1,3-dioxane and 2-(prop-1-enyl)-1,3-dioxolane.

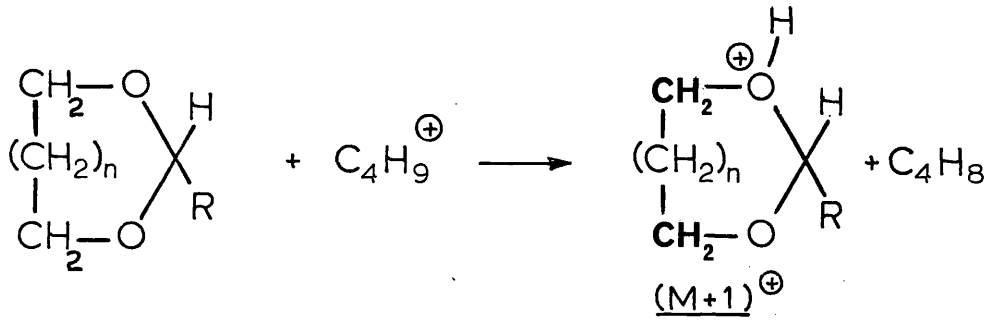
A number of characteristics were present in all of the spectra considered. These are listed below.

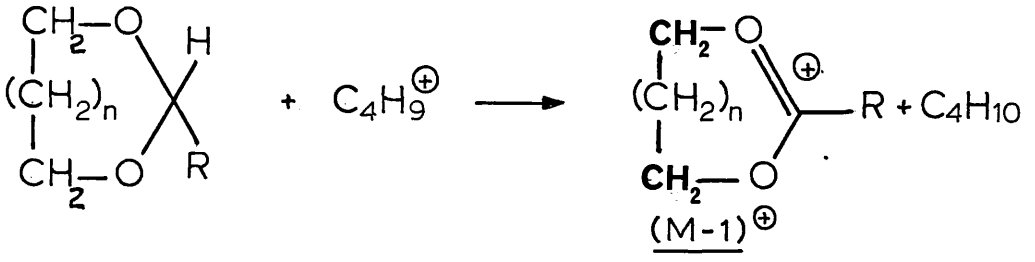
(a) The $C_3H_7^+$ ion (m/e 43) and the $C_4H_9^+$ ion (m/e 57).

These species are the most abundant ions present in the isobutane plasma[6] and consequently are present in every spectra in which the latter is used as the reactant gas. The ion at m/e 57 is generally the most abundant species in all of the spectra considered in this section, while the m/e 43 ion is often the second most abundant ion: thus when the "base peak" is referred to in the following discussion this refers to the most abundant ion given by the particular compound under study and not necessarily to the most abundant ion in its spectrum.

(b) The $(M + 1)^+$ and $(M - 1)^+$ ions.

These are respectively produced by direct proton addition and direct hydride abstraction reactions between the isobutane plasma and the acetal under study [5] (fig. V(2)B - 1).





where n = 0, 1, 2, 3

Fig. V (2) B - 1.

The $(M+1)^+$ ion is generally the most abundant ion given by the simple cyclic acetals with the $(M-1)^+$ species occupying quite a minor role in most cases. It is only in the dioxolanes that the $(M-1)^+$ ion reaches any significance in the spectra of the cyclic acetals.

This is well illustrated in Table V (2) B-1 , where the ratios of the relative intensities of the $(M+1)^+$ and $(M-1)^+$ ions are displayed for a series of cyclic acetals substituted at C_2 with H and n-Pr.

Size of ring	$(M+1)^+/(M-1)^+$ ratios	
	H at C_2	n-Pr at C_2
5	3.6	2.9
6	10.7	11.6
7	21.7	23.8
8	83.3	125.6

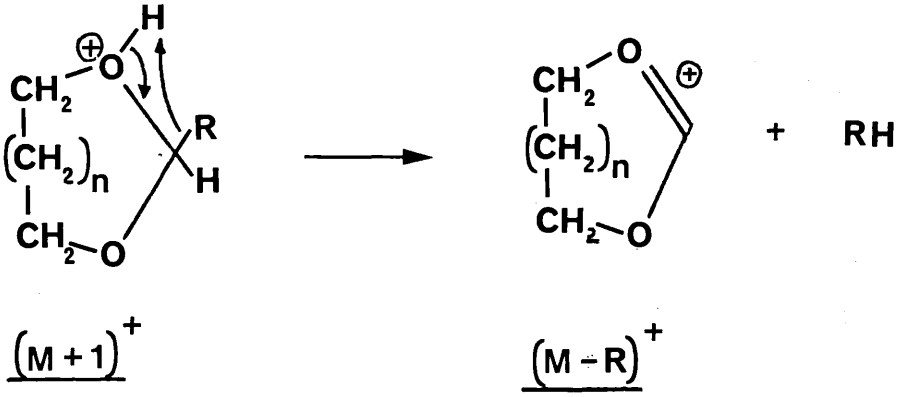
Table V (2) B-1

The main point to note here is that the $(M+1)^+/(M-1)^+$ ratios increase steadily in value as one goes from the 1,3 - dioxolanes to the 1,3 - dioxocanes .

One possible interpretation of the above values is that the relative $(M+1)^+/(M-1)^+$ ratios give an insight into the relative facilities with which the various cyclic acetals undergo protonation by the isobutane plasma in the gaseous phase i.e. an insight into their relative basicities. Thus the data suggests that the basicities of the acetals are in the order $5 < 6 < 7 < 8$ in the gaseous phase.

(c) The $(M-R)^+$ ion.

This species was present in the spectra of every acetal looked at: a possible rationale for its formation is shown in figure V (2) B - 2 which suggests expulsion of RH from the $(M+1)^+$ ion.



where n 0,1,2,3

Fig. (2)B - 2.

ii) Specific characteristics in particular those associated with the different C_2 substituents.

(1) The unsubstituted cyclic acetals i.e. 1,3-dioxolane, 1,3-dioxane, 1,3-dioxepane and 1,3-dioxocane.

(a) The $(M - 29)^+$ and $(M - 31)^+$ ions.

These two species are the only other ions present in the spectra of the unsubstituted acetals apart from the $(M - 1)^+$ and $(M + 1)^+$ ions. They are thought to be formed when one molecule of formaldehyde is lost from the $(M + 1)^+$ and the $(M - 1)^+$ ions respectively (fig. V (2) B - 3).

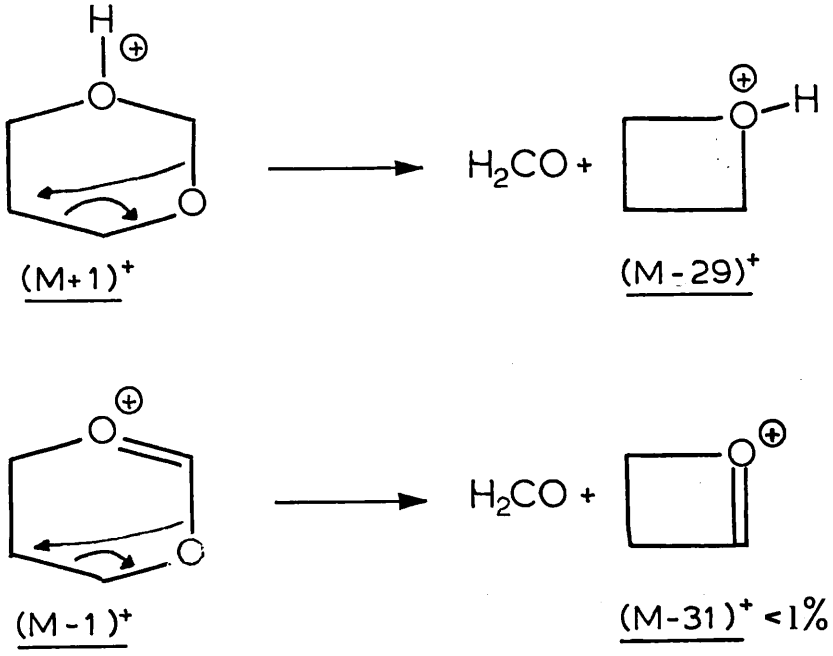


Fig. V (2) B - 3.

(2) The 2- n- propyl derivatives.

(a) The $PrC \equiv O^+$ ion.

All of the n-butylidene acetals' spectra contained an intense peak at m/e 71. It is thought to be given by the mechanism shown in figure V (2) B -4 in which 2-n-propyl-1, 3-dioxane is used as an example.

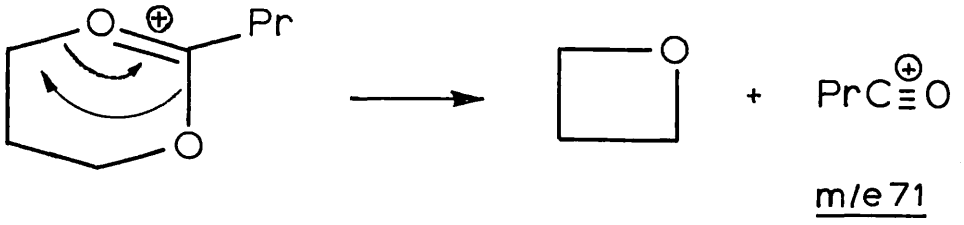


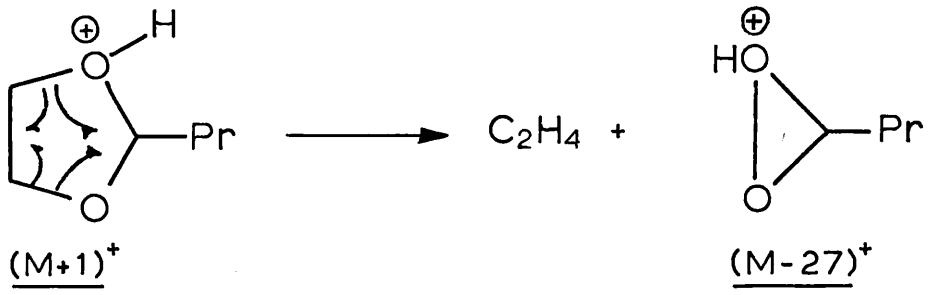
Fig. V (2) B -4 .

(b) The $(M - 29)^+$ and $(M - 31)^+$ ions.

These two ions are both given by the 2-n-propyl homologues and as in the spectra of the unsubstituted acetals are thought to be the result of loss of formaldehyde from the $(M + 1)^+$ and $(M - 1)^+$ ions respectively.

(c) Other ions.

The species at $(M - 27)^+$ is a major feature of 2-propyl-1, 3-dioxolane's spectrum: it is thought to be given when a molecule of ethylene is lost from the $(M + 1)^+$ ion as shown in figure V (2) B - 5.



$(M+1)^+$ $(M-27)^+$

Fig. V (2) B - 5.

(3) The 2-chloromethyl derivatives.

(a) The $(M + 3)^+$ ion.

The $(M + 3)^+$ ion is present in all of the spectra of the 2-chloromethyl derivatives. It is of course due to the "$(M + 1)^+$ ion" of the acetal molecules which contain the ^{37}Cl isotope rather than the more abundant ^{35}Cl isotope.

This pairing of species differing by 2 m.u. persists whenever a chlorine atom is present in a given fragment and will be represented herein by the subscripts 35 and 37 e.g. $(M + 1)^+_{35,37}$.

(b) The $(M - Cl)^+$ ion.

The direct abstraction of a chloride ion by the plasma in C.I. mass spectroscopy is a well documented process.[7] Thus it is not surprising to find this ion in the 2-chloromethyl derivatives' spectra (fig. V (2) B - 6).

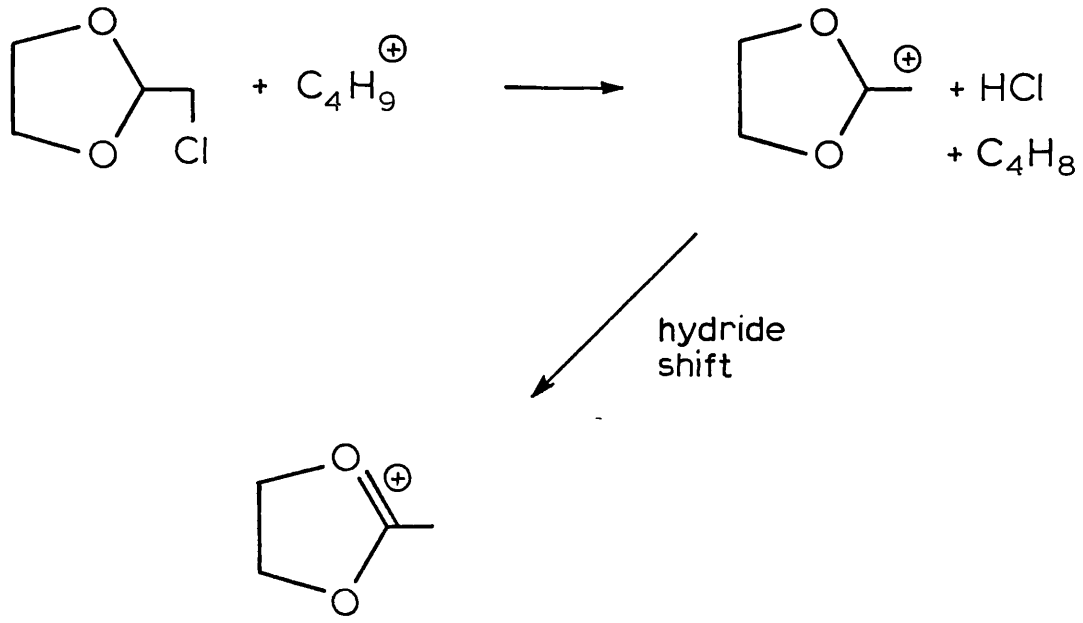


Fig. V (2) B - 6.

(c) The $(M-37)^+$ ion.

This ion is present in all of the 2-chloromethyl derivatives' spectra although a rationalization for its formation is not readily available. It may perhaps be due to loss of hydrogen from the $(M-Cl)^+$ species (fig. V (2) B - 7), although why this should not occur in the $(M-R)^+$ or $(M-1)^+$ ions of the other 2- substituted analogues is not clear.

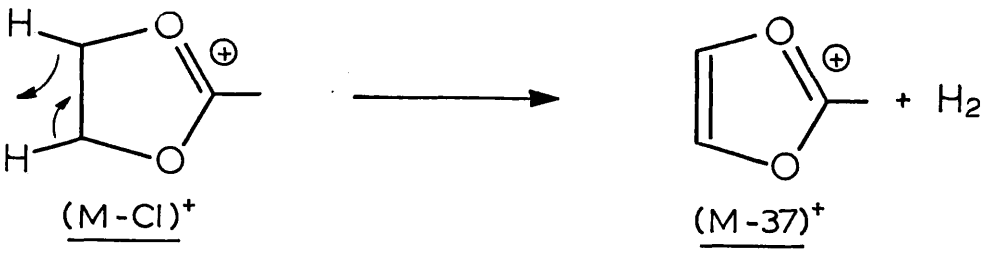


Fig. V (2) B - 7.

(4) The 2- alkene derivatives.

This includes the spectra of 2- vinyl-1, 3-dioxolane, 2-vinyl- 1, 3-dioxane and 2-(prop-1-enyl) -1, 3-dioxolane.

(a) M^+ ion.

This is seen in the spectra of all three compounds. Field[8] et al have demonstrated that the M^+ ion is a general feature of the C.I. spectra of most olefins. They have attributed its formation to charge exchange reactions that occur between the olefin molecule and the ethylene ion ($C_2H_4^+$) which was present in small amounts in the methane plasma used in their experiments.

Presumably then the M^+ ion present in the spectra of the title compounds is due to the C_2 - olefinic moieties undergoing analogous charge exchange reactions with the isobutane plasma (fig. V (2) B -8).

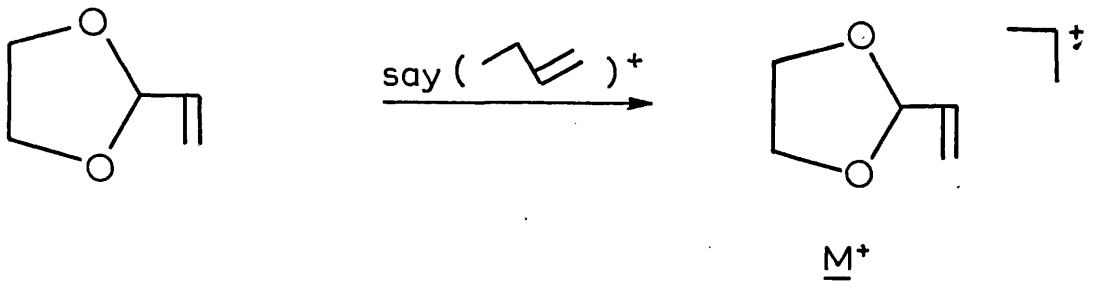


Fig. V (2) B -8 .

(b) (M-29)$^+$ ion.

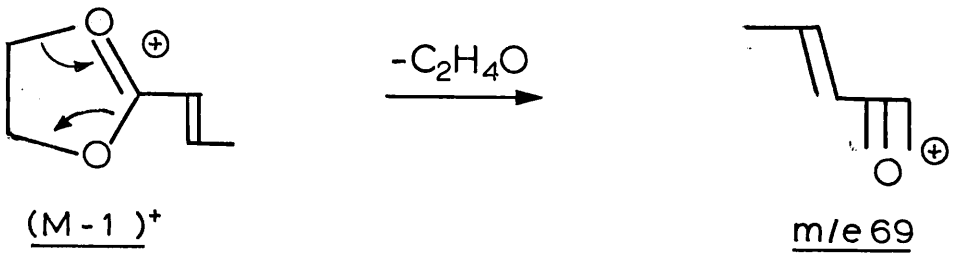
2-Vinyl-1, 3-dioxolane and 2-(prop-1-enyl)-1, 3-dioxolane both have the (M-29)$^+$ ion in their spectra. It is probably due to loss of formaldehyde from the (M + 1)$^+$ ion as has been described earlier (p.246).

(c) Other ions.

The spectrum of 2-(prop-1-enyl)-1, 3-dioxolane contains ions of low intensity at the m/e values 69, 71 and 87.

The ion at m/e 69 is thought to be due to loss of C_2H_4O from the (M - 1)$^+$ ion (fig. V (2) B - 9a), while the m/e 87 species is probably given by loss of ethylene from the (M + 1)$^+$ ion via the mechanism shown in figure V (2) B - 9b. Thus carbons 4 and 5 of the dioxolane ring are thought to be lost as the alkene. This process has also been discussed in the fragmentation of 2-n-propyl-1, 3-dioxolane.

(a)



(b)

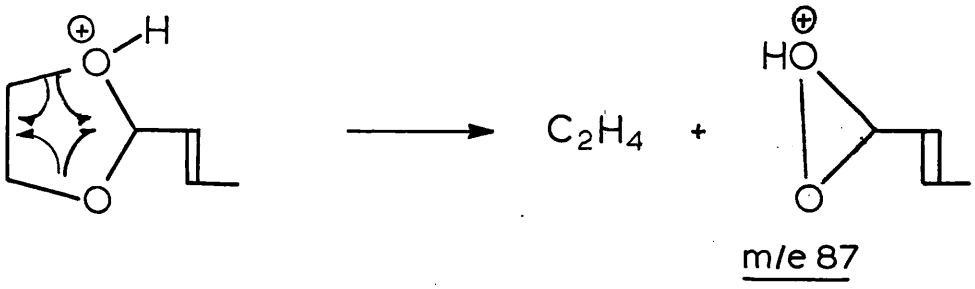


Fig. V (2) B - 9 .

Finally 2-(prop-1-enyl)-1, 3-dioxolane also gives an $(M - 43)^+$ ion which is thought to be the result of the shown rearrangement of the $(M + 1)^+$ species. (fig. V (2) B -10).

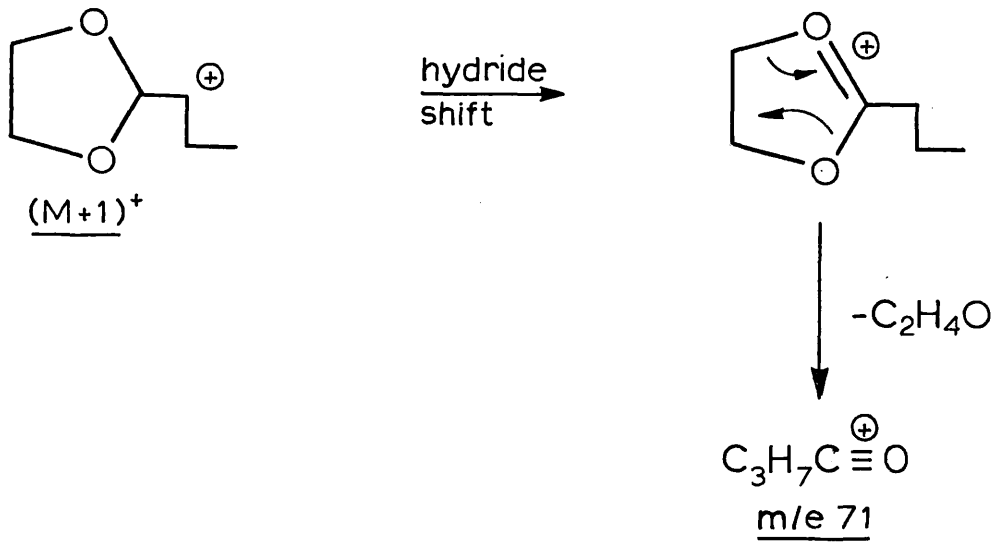
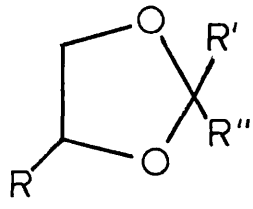


Fig. V (2) B - 10.

V(2)C. The 2,4-disubstituted dioxolanes.

This section will consider the spectra given by the dioxolanes shown in figure V (2) C - 1.



(cis / trans)

(1)	R = CH_3	R' = H	R'' = H
	"	"	R'' = CH_3
	"	"	R'' = Pr
	"	R' = CH_3	R'' = CH_3
(2)	R = CH_2Cl	R' = H	R'' = H
	"	"	R'' = CH_3
	"	"	R'' = Pr
	"	R' = CH_3	R'' = CH_3

Fig. V (2) C - 1.

i) General characteristics.

(a) The $(M + 1)^+$, $(M - 1)^+$ and $(M - R)^+$ ions were present in all of the spectra looked at, the $(M - 1)^+$ ion holding base-peak status in each case.

(b) The $(M - R'R''CO)^+$ ion.

All of the 4-methyl substituted dioxolanes gave an ion at m/e 59: this is thought to be given by the mechanism shown in figure V(2) C - 2a and is one of the most abundant species in the 4-methyl derivatives' spectra.

Meanwhile the 4-chloromethyl compounds all contain abundant ions at m/e 93 and m/e 95. These ions are thought to result when the $(M + 1)^+$ species lose their relevant aldehydes (or ketone) in a similar process to the 4-methyl compounds (fig. V (2) C - 2b).

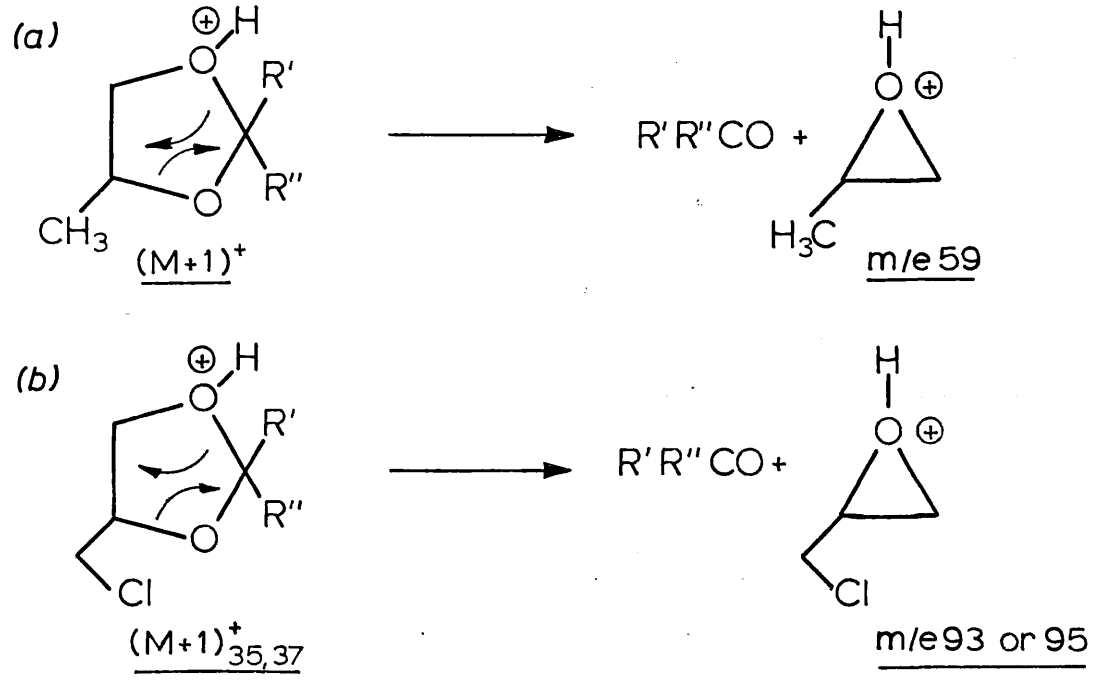


Fig. V (2) C - 2.

ii) Specific characteristics.

1. 4-Methyl derivatives.

(a) The $PrC\equiv^{+}O$ ion.

This species (m/e 71) was present in the spectrum of 4-methyl-2-propyl-1,3-dioxolane: it is a general feature of the butylidene acetals' spectra (p.247).

(b) The $(M-27)^{+}$ ion.

Both the 4-methyl-2-propyl and the 2,2,4-trimethyl compounds gave an $(M - 27)^{+}$ ion, probably via loss of ethylene from their respective $(M + 1)^{+}$ species, (p.247).

2. 2-Alkyl-4-chloromethyl derivatives.

(a) The $(M + 3)^{+}$ ion.

The presence of two naturally occurring isotopes of chlorine means that the spectra of the title compounds all contain the $(M + 1)^{+}_{35}$ and $(M + 1)^{+}_{37}$ ions.

This pairing of ions differing by two mass units is seen throughout the title compounds' spectra whenever chlorine remains in the fragments.

(b) The $(M - Cl)^{+}$ ion.

This is thought to be given by direct abstraction of a chloride ion by the isobutane plasma, (fig. V(2) C - 3), in a similar manner to that which occurred in the 2-chloromethyl-1,3-dioxolanes (p.248).

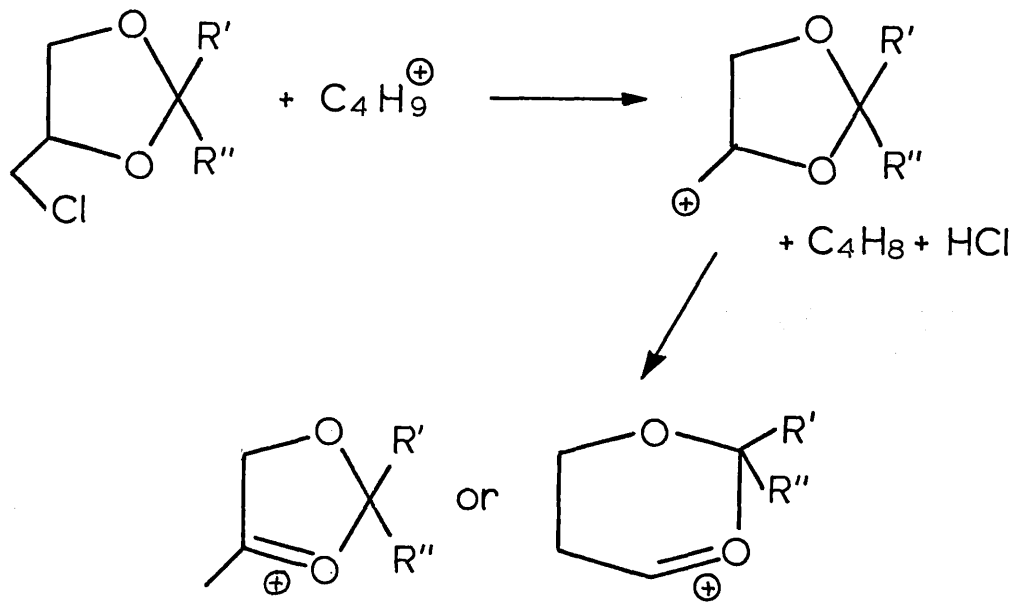


Fig. V (2) C - 3.

(c) Other ions.

The 4-chloromethyl-2-propyl derivative gave the expected PrC $\equiv \overset{+}{O}$ ion (m/e 71) while 4-chloromethyl-1,3-dioxolane gave an ion at m/e 73 which is thought to be due to loss of methyl chloride from the $(M + 1)^+$ ion: a similar fragmentation of the $(M - 1)^+$ species yields the m/e 71 ion (fig. V (2) C - 4).

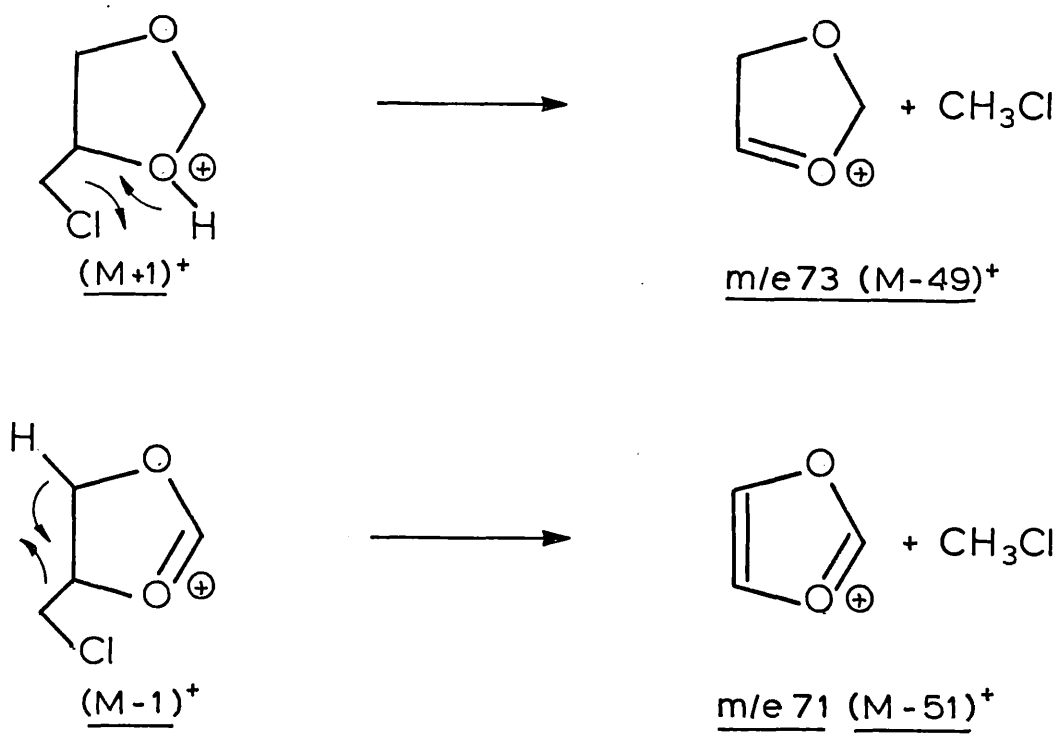


Fig. V (2) C - 4.

The fact that the analogues of these two ions are not present in the spectra of the other 4-chloromethyl derivatives casts doubt over the above rationales, although it is difficult to envisage more suitable alternatives.

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11. Ibid, Ch. 2, p. 94.
12. Ibid, Ch. 6, p. 227.
13. Ibid, Ch. 12, p. 429.

VI. GENERAL METHODS AND TECHNIQUES.

Introduction.

In this chapter the techniques most commonly used in the work presented in this thesis are elaborated upon. This entails naming the specific type of equipment used in the various general experiments and in certain cases (such as periodate oxidation) experimental details are presented.

1. Gas liquid chromatography (G.l.c.).

i) Machinery. In all g.l.c. experiments a Pye 104 chromatograph with flame ionization detector was used.

A Hewlett Packard 3370 B integrator was also used when specific peak areas had to be obtained.

ii) Stationary phases.

a) Apiezon - K (7.5%) on Chromasorb - W.

b) OV-225 (3%) on Chromasorb - W.

iii) Derivatisation.

a) Acetates.

The sample (ca. 10mg.) was dissolved in dry pyridine (1 ml.) and then acetic anhydride (1 ml.) was added. The reaction mixture was then heated upon a boiling water bath for 1h. after which time the solvent was removed using a rotary evaporator.

The resulting generally light yellow syrup was

then dissolved in dry diethyl ether and injected into the g.l.c. or g.l.c./m.s. systems.

b) Trimethylsilyl ethers.[1]

The sample (10-20mg.) was dissolved in dry pyridine (1 ml.) and then treated with hexamethyldisilazane (0.2 ml.) and trimethylsilyl chloride (0.1 ml.) for about 3 minutes at 40°.

After removal of the resulting precipitate via centrifugation the supernatant liquor was ready for analysis.

iv) Gases.

a) The carrier gas used was nitrogen at a flow rate of 40 ml./min.

b) The flame ionization detector burnt a hydrogen and air flame at 25 p.s.i. and 15 p.s.i. respectively.

2. Thin layer chromatography (t.l.c.).

i) Plates.

The commercially available plastic plates (5 x 20 cm.) supplied by Camlab of Cambridge were used for all t.l.c. work: they were precoated with silica gel (0.25 mm of Polygram Sil G).

All quoted R_F values were taken with these plates.

ii) Solvent systems.

a) Solvent A - toluene/methanol (9:1).

b) Solvent B - butanone saturated with water.

iii) Developing the plates.

When the solvent front had reached approximately 20 cm. from the top of the t.l.c. plate it (the solvent front) was marked and then a hot-air blower was used to remove the solvent.

The plate was then sprayed with an ethanol/water/sulphuric acid (40:40:10) mixture and heated at ca. 120° until no more dark coloured spots appeared: this generally took ca. 30 minutes.

3. Column Chromatography.

i) Machinery.

Various column sizes were used depending upon the amount of material that had to be fractioned. A Central fraction collector and fraction cutter were used with every column.

ii) Packing material.

Silica gel (Kieselgel 60, 70-230 mesh ASTM) commercially available from Merck was the packing material used in all column work.

4. Mass spectrometry.

i) Machinery.

a) Electron impact (E.I.) mode - a VG micromass 12F spectrometer was used with a 70 eV ionization potential.

b) Chemical ionization (C.I.) mode -

the same machine was used under the shown operational conditions.

Electron energy	-	50 eV
Emission current	-	100 μA
Repeller voltage	-	2 V
Pressure of isobutane	-	ca. 0.15 torr
Temperature of source	-	190°

c) Gas liquid chromatography/mass spectrometry (g.l.c./m.s.) - here the VG micromass 12F spectrometer was linked (via a jet separator interface) to a Pye 104 chromatograph.

The stationary phase used was generally OV-225 (3%) on Chromasorb - W while helium at 30 ml./min. was the carrier gas. The column was heated to 200°.

5. Nuclear magnetic resonance (N.M.R.) spectroscopy.

i) Machinery.

The 60 MHz proton resonance (p.m.r.) spectra used in the preliminary analysis work were taken on a Varian EM 360 spectrometer.

ii) Solvents.

In most cases deuterochloroform was used.

iii) Other data.

The spectra were all ran at ambient temperature and the signal given by the protons in tetramethylsilane (T.M.S.) was used as the reference signal (internal) in each case.

6. Melting points.

All melting points were taken using a Thomas-Hoover melting point apparatus and are uncorrected.

7. Elemental analysis.

All of the elemental analyses (C, H, Cl) quoted in this thesis were given by Butterworth's Microanalytical Consultancy, Teddington.

8. Molybdate Ionophoresis.

i) Machinery.

A Shandon electrophoresis machine was used.

ii) Procedure.

The procedure used was essentially that described by Foster[2]. Thus the sample plus a galactitol standard were applied to a 100 × 12·5 cm. strip of Whatman No. 2 paper which was then soaked in sodium molybdate (pH 5) solution and placed onto the ionophorimeter. The two ends of the paper strip were left immersed in the sodium molybdate (pH 5) solution and so acted as wicks. A current of 85 milliamps at 9000 volts was then applied for ca. 45 minutes.

After drying, the strip was developed by treatment with solutions of silver nitrate and sodium hydroxide. The developed spots were "fixed" with sodium thiosulphate solution. The distance the sample spot had moved from the base line was then

expressed as a decimal fraction of the distance moved by the galactitol standard: this is the "mobility" of the sample.

9. Periodate oxidation and related reactions[3,4]

i) Determination of periodate ion (IO_4^-) uptake.

Analar solutions (100 ml., 0.15M) of sodium metaperiodate and sodium iodate were prepared. An aliquot from each (1 ml.) was then made up to 250ml. and then the absorbance of the two solutions were measured at 222.5 nm. via a Unicam SP 500 spectrophotometer. Using these two values a calibration plot could then be made relating absorbance to ionic composition for a given solution: this is based upon the quite reasonable assumptions that the periodate solution contains 100% IO_4^- ions and 0% IO_3^- and visa versa.

An accurately weighed sample (ca. 10mg.) of the compound under study was then dissolved in the 0.15M periodate solution (10 ml.).

Aliquots (1 ml.) were then periodically withdrawn, made up to 250 ml. and their absorbances obtained at 222.5 nm. When two consecutively constant readings were obtained the reaction was judged complete.

Using the final absorbance value obtained the molar uptake of periodate ion per mole of sample was then obtained from the calibration plot. The method was checked for accuracy by using the oxidation of 2,5-O-methylene mannitol as a standard and running the two reactions concurrently.

ii) Formaldehyde determination.

This was done spectrophotometrically using the colour reaction given by formaldehyde with chromotropic acid reagent.

The chromotropic acid reagent was prepared by the addition of a sulphuric acid/water mixture (2:1, v/v) to an aqueous solution of chromotropic acid sodium salt (0.5g., in 50 ml.) and making the volume up to 250 ml.

To determine the amount of formaldehyde liberated by the sample after 24h. an aliquot (1 ml.) of the aforementioned sample/periodate solution was diluted to 10 ml. Meanwhile aliquots (1 ml.) of the standard 2,5-O-methylene mannitol/periodate solution were diluted to 10 ml., 25 ml. and 50 ml.

An aliquot (1 ml.) of the above solutions was then mixed with sodium sulphite solution (20%, 0.1 ml.) and the chromotropic acid reagent (8.4 ml.) and heated on a boiling water bath for 1h. A blank of water was similarly treated.

After this period the solutions had developed the characteristic violet colour to various intensities. Thiourea solution (0.4%, 0.5 ml.) was then added to each solution and its absorbance was taken at 570 nm. against the water blank.

Using the absorbance values obtained from the standard 2,5-O-methylene mannitol a calibration graph relating absorbance to formaldehyde concentration was plotted. The number of moles of formaldehyde liberated per mole of sample could then be found.

iii) Formic acid determination.

When periodate oxidation was completed an aliquot (2 ml.) of the sample/periodate solution was treated with several drops of ethylene glycol (to destroy any remaining periodate ion) and then titrated against dilute sodium hydroxide (0.01M) using methyl red as indicator. A sample of the bulk periodate solution was similarly treated: the difference between the two titres was then used to calculate the number of moles of formic acid liberated per mole of sample.

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APPENDIX I

E.I. mass spectra of the 2-chloromethyl acetal products.

1. 2-(2-Chloroethoxy) - ethan-1-ol.

m/e	% of base peak
31	100
41	17.5
45	54.3
57	25.7
63	60.4
65	18.2
71	8.7
93	22
95	6.6

2. 3 - (2 - Chloroethoxy) - propan - 1 - ol.

m/e	% of base peak
31	100
41	21.9
45	32.8
49	9.4
51	2.3
57	23.4
59	25
63	62.5
65	18.8
71	3.9
75	4.7
83	17.2
85	12.5
89	31.3
93	14.8
130	11.7
131	1.5
132	2.3

3. 4 - (2 - Chloroethoxy) - butan - 1 - ol.

m/e	% of base peak
31	87.4
41	4.2
43	71.6
44	58.9
49	9.5
51	2.1
55	89.5
57	12.6
63	100
65	30.5
71	37.9
73	97.9
83	42.1
85	24.2
89	16.8
93	28.4
95	10.5
151	-
153	-
155	-

4. 5 - (2 - Chloroethoxy) - pentan - 1 - ol.

m/e	% of base peak
31	99
41	100
43	31.1
45	17.5
49	15.5
51	3.9
55	29.1
57	36.9
63	82.5
65	27.2
69	16.3
83	58.3
85	43.7
87	14.6
93	27.2
95	9.7
99	7.8
119	23.3
121	7.7
148	3.9
149	9.2
167	7.8
169	1.9

APPENDIX II

E.I. mass spectra of some partially n-butylated polyol acetates.

1. 2,3,4-Tri-O-acetyl-1-O-butyl-DL-erythritol.

m/e	% of base peak
73	38
84	33.5
87	91.3
99	9.4
103	43.5
115	100
129	98.5
142	72.6
159	3.8
171	4.0
184	11.4
231	2.3

2. 1,3,4-Tri-O-acetyl-2-O-butyl-DL-erythritol.

m/e	% of base peak
73	17.4
103	100
115	86.6
129	15.8
145	5.3
159	89.1
171	28.5
231	7.9

3. 2,3-Di-O-acetyl-1,4-di-O-butyl-DL-erythritol .

m/e	% of base peak
45	59.3
87	100
103	18.3
115	22.4
129	36.6
159	15.5
203	18.2
259	22

4. 3,4-Di-O-acetyl-1,2-di-O-butyl-DL-erythritol .

m/e	% of base peak
73	42.4
103	71.1
115	100
129	36
159	81.9
171	33.7
173	16.2
185	21.6
231	11.2
245	36

5. 3-O-Acetyl-1,2,4-tri-O-butyl-DL-erythritol .

m/e	% of base peak
87	23
117	53.2
129	56.6
171	100
173	28.8
185	82.8
245	18.2

6. 4-O-Acetyl-1,2,3-tri-O-butyl-DL-erythritol.

m/e	% of base peak
61	100
85	30.5
87	18.6
103	100
115	18.0
117	23.4
129	45.5
159	89.8
185	27.5
245	8.4
259	9.6

7. 2,3,4,5,6-Penta-O-acetyl-1-O-butyl-DL-galactitol.

m/e	% of base peak
87	55.8
115	78.3
129	100
157	47.5
171	52.7
226	22.7

8. 2,3,4,5-Tetra-O-acetyl-1,6-di-O-butyl-galactitol.

m/e	% of base peak
73	23.9
85	23.2
87	60
103	11.3
115	31.3
129	100
157	19.4
159	7.4
171	40.3
183	29.7

m/e	% of base peak
213	25.8
217	31.6
255	14.5

9. 2,3,5,6-Tetra-O-acetyl-1,4-di-O-butyl-DL-galactitol.

m/e	% of base peak
55	13.8
73	36.5
85	42.8
87	15.1
103	32.9
115	69.7
129	82.9
141	16.4
159	39.5
171	100
185	29.6
215	17.8
231	72.4
257	14.5
317	20.7
388	16.4

10. 1,2,5-Tri-O-acetyl-3-O-butyl-4,6 -O-butylidene-DL-galactitol.

m/e	% of base peak
115	100
129	39
171	20.1
187	13.6
231	11.7
273	26.6

11. 2,3,5-Tri-O-acetyl-1-O-butyl-4,6-O-butylidene-DL-galactitol.

m/e	% of base peak
85	39
87	26.2
115	100
129	85.1
157	39.7
171	57.6
187	26.6
199	12.9
243	11
303	16.2
345	35.4
375	34.2
417	56.7
418	13.2

12. DL-1,4-Di-0-acetyl-3-0-butyl butan-1,3,4-triol.

m/e	% of base peak
70	100
99	26.7
117	41.3
126	42.5
159	7.5
173	13.3

13. DL-3,4-Di-0-acetyl-1-0-butyl butan-1,3,4-triol.

m/e	% of base peak
69	85.9
75	22.7
87	100
101	15.4
129	20.0
131	12.7
189	20.5

14. DL-3,4-Di-0-butyl butan- 1,3,4- triol.

m/e	% of base peak
75	100
87	47.7
113	21.5
115	28.0
117	22.4
131	90.7
173	39.3

15. DL-1,4-Di-O-butyl butan- 1,3,4-triol.

m/e	% of base peak
75	100
87	61.2
100	15.7
101	23.6
115	36.7
131	68.2.

APPENDIX III

C.I. mass spectra of some simple cyclic acetals.

The $(M+1)^+$ and $(M-1)^+$ ions are the dominating features of C.I. spectra in general, consequently the intensities of the relevant fragment ions are relatively small. For this reason ions with intensities below 10% of the respective base peak intensities have been considered.

1. 1,3 - Dioxolane.

m/e	% of base peak
45	5.5
73	27.8
75	100

2. 1,3 - Dioxane.

m/e	% of base peak
59	8.4
87	9.3
89	100

3. 1,3 - Dioxepane.

m/e	% of base peak
73	19.4
101	4.6
103	100

4. 1,3 - Dioxocane.

m/e	% of base peak
85	1.1
87	13.1
115	1.2
117	100

5. 2-n-Propyl-1,3-dioxolane.

m/e	% of base peak
71	26.8
73	22
85	4.9
87	4.6
89	29.3
115	34.1
117	100

6. 2-n-Propyl-1,3-dioxane.

m/e	% of base peak
71	1.7
75	1.5
87	8.2
91	9.1
101	1.3
117	1.7
129	8.6
131	100

7. 2-n-Propyl-1,3-dioxepane.

m/e	% of base peak
71	2.6
101	20.8
111	2.0
113	3.8
115	4.0
131	5.3
143	4.2
145	100

8. 2-n-Propyl-1,3-dioxocane.

m/e	% of base peak
71	18.4
115	44.2
127	6.1
129	3.4
159	100

9. 2-Chloromethyl-1,3-dioxolane.

m/e	% of base peak
73	13.2
85	3.5
87	1.1
121	11.4
123	100
125	31.1

10. 2-Chloromethyl-1,3-dioxane.

m/e	% of base peak
87	9.6
99	3.1
101	1.4
137	100
139	30.9

11. 2-Chloromethyl-1,3-dioxepane.

m/e	% of base peak
101	16.5
113	7.4
115	5.4
151	100
153	31.4

12. 2-Chloromethyl-1,3-dioxocane.

m/e	% of base peak
115	33.6
127	6.8
129	3.5
165	100
167	32.1

13. 2-Vinyl-1,3-dioxolane.

m/e	% of base peak
71	1.6
73	5.1
99	7.6
100	4.8
101	100

14. 2-(Prop-1-enyl)-1,3-dioxolane.

m/e	% of base peak
69	2.5
71	9.6
73	9.9
85	4.8
87	3.9
99	6.4
113	4.6
114	1.9
115	100

15. 4-Methyl-1,3-dioxolane.

m/e	% of base peak
58	26
59	35.8
69	19.3
87	32.7
89	100

16. 2,4-Dimethyl-1,3-dioxolane.

m/e	% of base peak
87	12.7
101	4.9
103	100

17. 2,2,4-Trimethyl-1,3-dioxolane.

m/e	% of base peak
89	13.6
101	12.8
103	100

18. 4-Methyl-2-n-propyl-1,3-dioxolane.

m/e	% of base peak
59	18.5
71	10.4
87	14.9
89	10.1
101	5.2
103	16.0
129	15.6
131	100

19. 4-Chloromethyl-1,3-dioxolane.

m/e	% of base peak
67	2.8
69	5.4
71	6.2
73	10.3
87	5.4
93	15.3
95	4.9
121	21.9
123	100
125	33.6

20. 4-Chloromethyl-2-methyl-1,3-dioxolane.

m/e	% of base peak
93	12.7
95	4.1
101	5.1
119	8.9
121	6.7
123	2.5
135	22.2
137	100
139	31.7

21. 4-Chloromethyl-2,2-dimethyl-dioxolane.

m/e	% of base peak
93	4.5
95	2.1
115	5.1
135	11.1
137	3.6
149	2.1
151	100
153	32.9

22. 4-Chloromethyl-2-n-propyl-1,3-dioxolane.

m/e	% of base peak
71	5.6
93	4.7
95	2.2
121	10.9
123	4.4
129	3.6
163	4.2
165	100
167	31.8