AN INVESTIGATION INTO THE SYNTHESIS AND STRUCTURE OF CYCLIC BUTYLIDENE ACETALS

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Doctor of Philosophy

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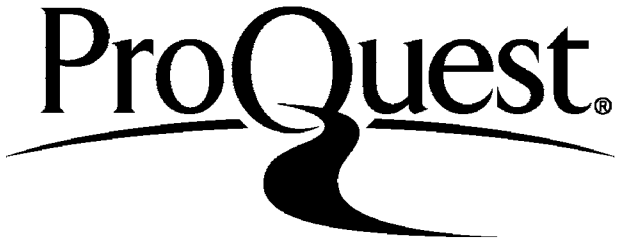

Acknowledgement

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SECTION D - EXPERIMENTAL

GENERAL METHODS IN STRUCTURAL ANALYSIS

Abstract

The acid catalysed condensation reactions of various polyhydroxyl compounds and n-butyraldehyde have been investigated.

Initially these reactions have been examined to determine whether kinetic control was exhibited during the mono acetalisation stages. The products of these polyols, including diacetals, have been isolated and characterised.

For the polyols examined L-threitol, D-arabinitol and 6-deoxy-D-glucitol gave kinetic control (all of these polyols contained an αT configuration of hydroxyl groups which had previously been confirmed to facilitate kinetic control). The kinetic acetals isolated contained the 2,3 structure.

Erythritol, ribitol, xylitol and 1-deoxy-D-xylitol did not give kinetic control (n.b. xylitol and 1-deoxy-D-xylitol contained an αT hydroxyl group configuration).

The thermodynamic acetals isolated contained the 2,4 (βC) ring or alternatively the 1,3 (β) ring in accord with the rules of Barker and Bourne.

Diacetals were isolated for erythritol, L-threitol, ribitol, xylitol, 1-deoxy-D-xylitol and 6-deoxy-D-glucitol. A mixture of diacetals was produced by D-arabinitol, which could not be separated.

Acetalisation of methyl α-D-glucoside was considered in non-aqueous solution: kinetic control was not exhibited. The 4,6 acetal was isolated as the thermodynamic mono acetal, and methyl 2,3 oxido

di-n-butylidene 4,6-O-butylidene α-D-glucoside from the reaction with excess n-butyraldehyde.

Ultimately pentaerythritol and dipentaerythritol were examined: a mono acetal was isolated for penta erythritol whereas both formed diacetals.

The structures of the previously mentioned acetals were confirmed by chemical techniques, where possible.

All of the acetals have been subjected to a spectroscopic examination. This has aided the structural assignments of fully substituted polyol acetals.

Mass spectrometry of the diacetals has shown the 'h-rupture' fragmentation mechanism.

Two nuclei have been considered for nuclear magnetic resonance spectroscopy: ^{1}H and ^{13}C.

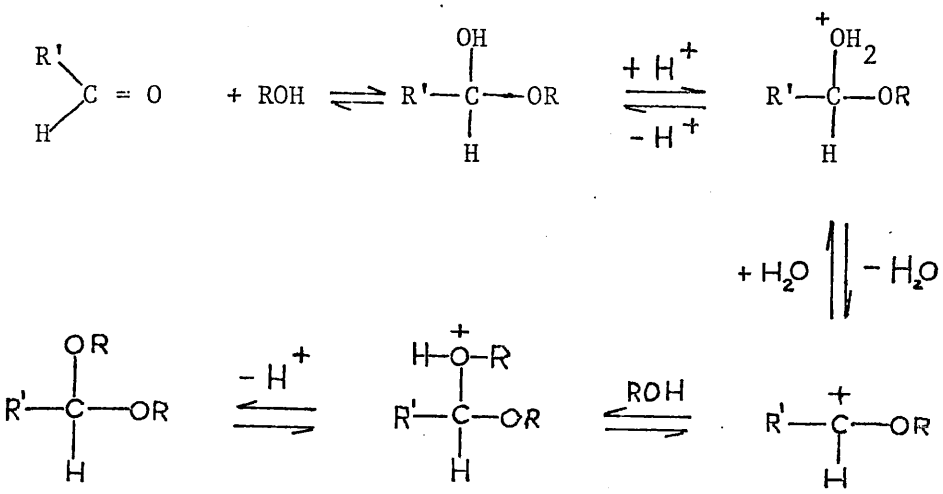
For proton magnetic resonance spectroscopy the correlation between the resonance of the acetal proton and ring size has been confirmed. Similar inferences have been concluded for the resonance of the acetal carbon atom and the acetal ring size for carbon magnetic resonance spectroscopy.

SECTION A

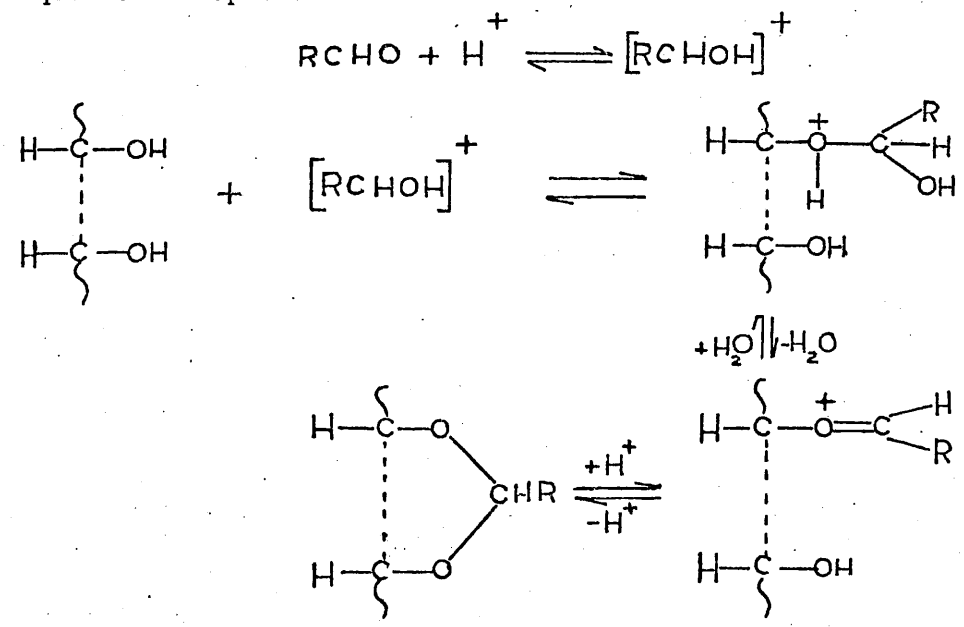
INTRODUCTION

A. INTRODUCTION

The product of the condensation reaction between an alcohol and an aldehyde, in acid media, is an acetal. This reaction may be depicted mechanistically,[1] viz:

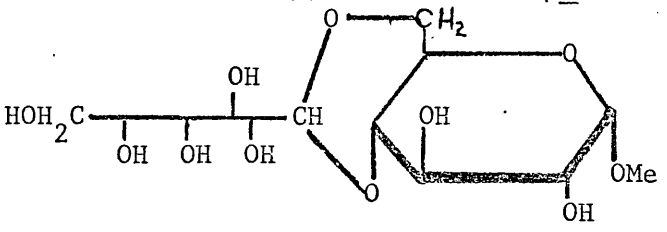


However, if the alcohol used in this reaction is polyhydric, i.e. a polyol, then a cyclic product is obtained. The mechanistic sequence is represented:[2]



In aqueous solution, much of the aldehyde is hydrated: about 40% in the case of n - butyraldehyde. Either the hydrated form or the free aldehyde could give the conjugate acid $[RCHOH]^+$.

These cyclic compounds may be obtained from many other classes of polyhydroxy compounds, as well as polyols. Monosaccharides,[3] glycosides[3] and α-hydroxy carboxylic acids[4] are often encountered examples. The aldehyde in this reaction may be aromatic or aliphatic. Micheel et al[5] have prepared an acetal of methyl α-D-glucoside and the aldehydo form of D-glucose.



A widely differing range of acid catalysts may be employed. Mineral acids, e.g. conc. sulphuric acid, dil. hydrochloric acid, organic acids, e.g. toluene-4-sulphonic acid, Lewis acids, e.g. zinc chloride, anhydrous copper II sulphate or even acid ion-exchange resins may be employed. A recent publication[6] reports the use of pyridine chloride as an acid catalyst for these reactions.

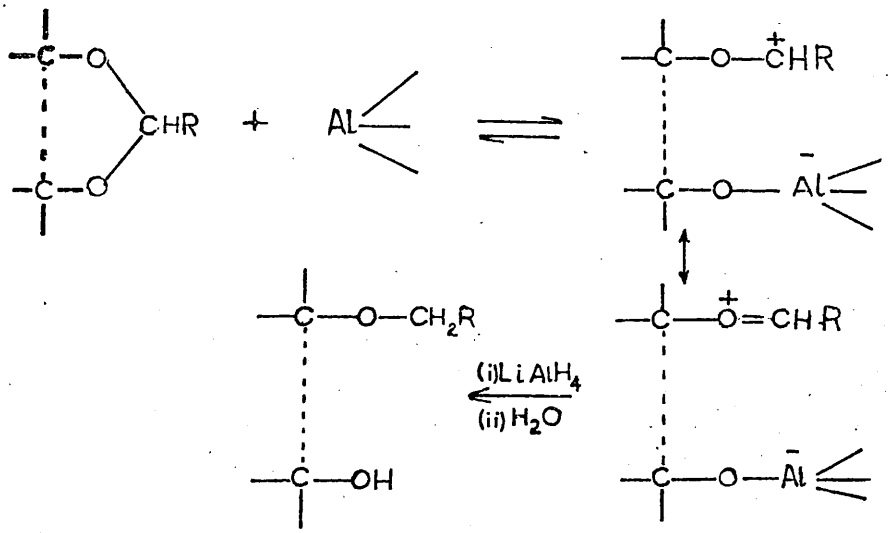
These acetalisations can occur in aqueous or non-aqueous media, e.g. anhydrous dimethyl formamide.

The formation of di and poly acetals is aided by an increase in acid strength or an increase in the molar amount of aldehyde present in the reaction mixture.

It is these cyclic acetals which form the context of this thesis.

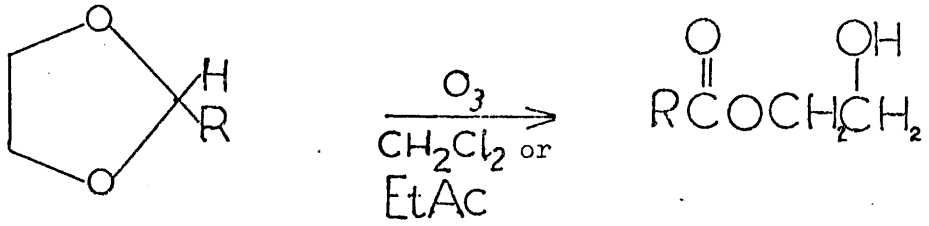
The importance of cyclic acetals as acid labile blocking groups, and as derivatives like esters (e.g. acetates and tosylates) or ethers (e.g. benzyl or triphenyl methyl) in carbohydrate chemistry and other natural product chemistry has been well documented[3,49]. The ring opening of acetals has become a widely used technique for the synthesis of ethers[7].

$$LiAlH_4 + Al\,Cl_3 \rightleftharpoons 2AlH_2Cl + LiCl$$



Lithium aluminium hydride-aluminium trichloride was a reagent which could be used for this specific process, e.g. cyclic benzylidene acetals were opened to give the corresponding benzyl ethers.

Ozone has been employed to convert cyclic acetals to their corresponding esters[8], viz:-



Barton et al[9] have oxidised ketals with trityl tetra fluoroborate to keto compounds.

For a polyol, the large number and differing stereochemistry of the hydroxy groups on the carbon chain would be expected to give rise to a large array of cyclic acetal derivatives. In practice, however, it has been observed that certain products would be obtained preferentially to others, for a specific polyol, but some acetals would not be formed in the reaction.

An initial attempt to account for these results, and to relate the structures of the cyclic acetals to their parent polyol was made by Hann and Hudson[10,11]. An examination of the known cyclic methylene acetals of D-glucitol, D-mannitol and galactitol enabled a set of empirical rules to be formulated. These rules were extended to ribitol, xylitol and 6-deoxy-D-glucitol and found to be justified.

These rules were later amended and extended by Barker and Bourne[12] to cover the reactions of most polyols with acetaldehyde and benzaldehyde. These authors introduced a system of nomenclature which defined the product with respect to the polyol precursor. The Greek letters α, β and δ were used to indicate the number of carbon atoms separating the reacting hydroxyl groups, and the symbols

C (cis) and T (trans) used to denote the geometry of the reacting hydroxyl groups with respect to the Fischer projection formula for the polyol. The latter symbol need only be envoked when both reacting hydroxyl groups were secondary [Hough and Richardson[13] have advocated replacing the C and T terms with erythro and threo, i.e. the optical configurations, according to the I.U.P.A.C. Convention, since the Fischer projection formula failed to represent the molecular conformation].

The Barker-Bourne rules may be stated as:-

(i) the thermodynamically most stable acetal contains the βC; i.e. this is the first preference

(ii) the next most favoured ring is the β form

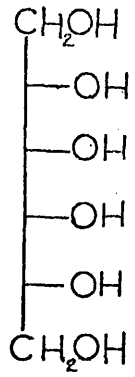
(iii) the third preference is the α, αT, βT or γT rings

(iv) in conditions of methylenation or benzylidenation rule (iii) may be modified.

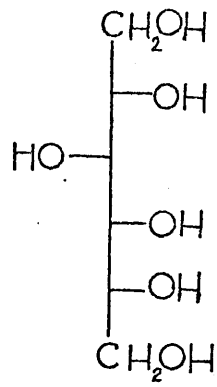
i.e. βC > β > α, αT, βT or γT.

Rules (i), (ii) and (iii) were essentially as derived by Hann and Hudson, but rule (iv) incorporated new parameters.

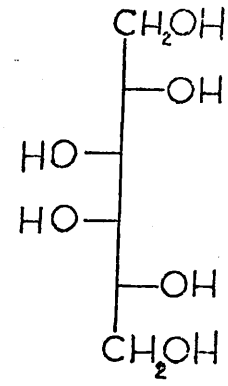
Consider the application of these rules to allitol, D-glucitol and galactitol,



Allitol

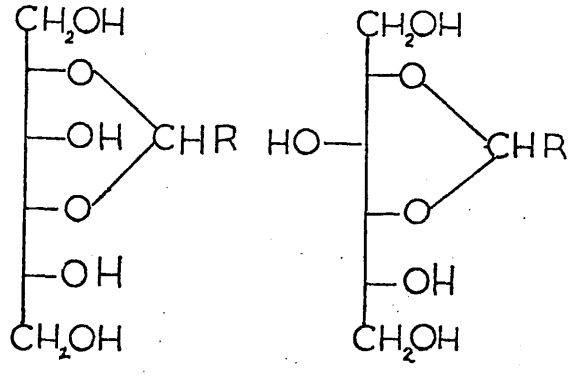


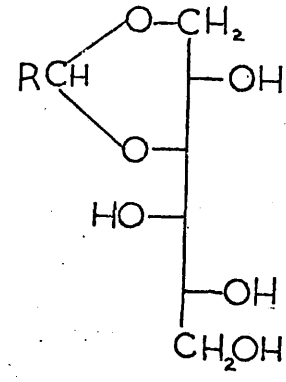
D-Glucitol



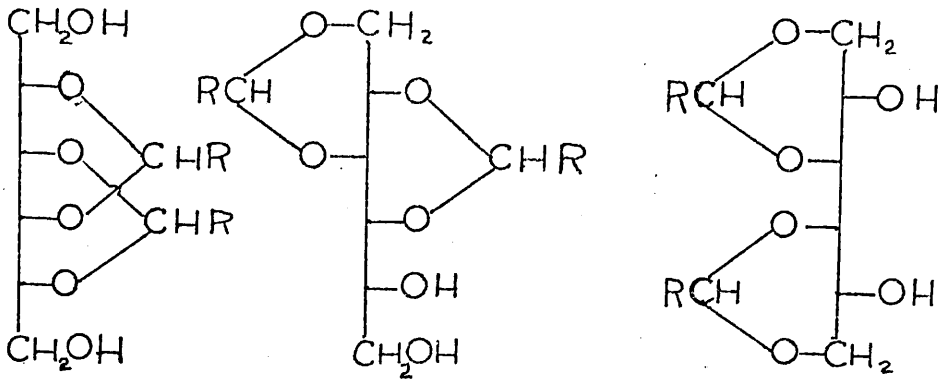
Galactitol

For allitol and D-glucitol the 2,4 (βC) mono acetal would be formed, but galactitol would form the 1,3 (β) compound.





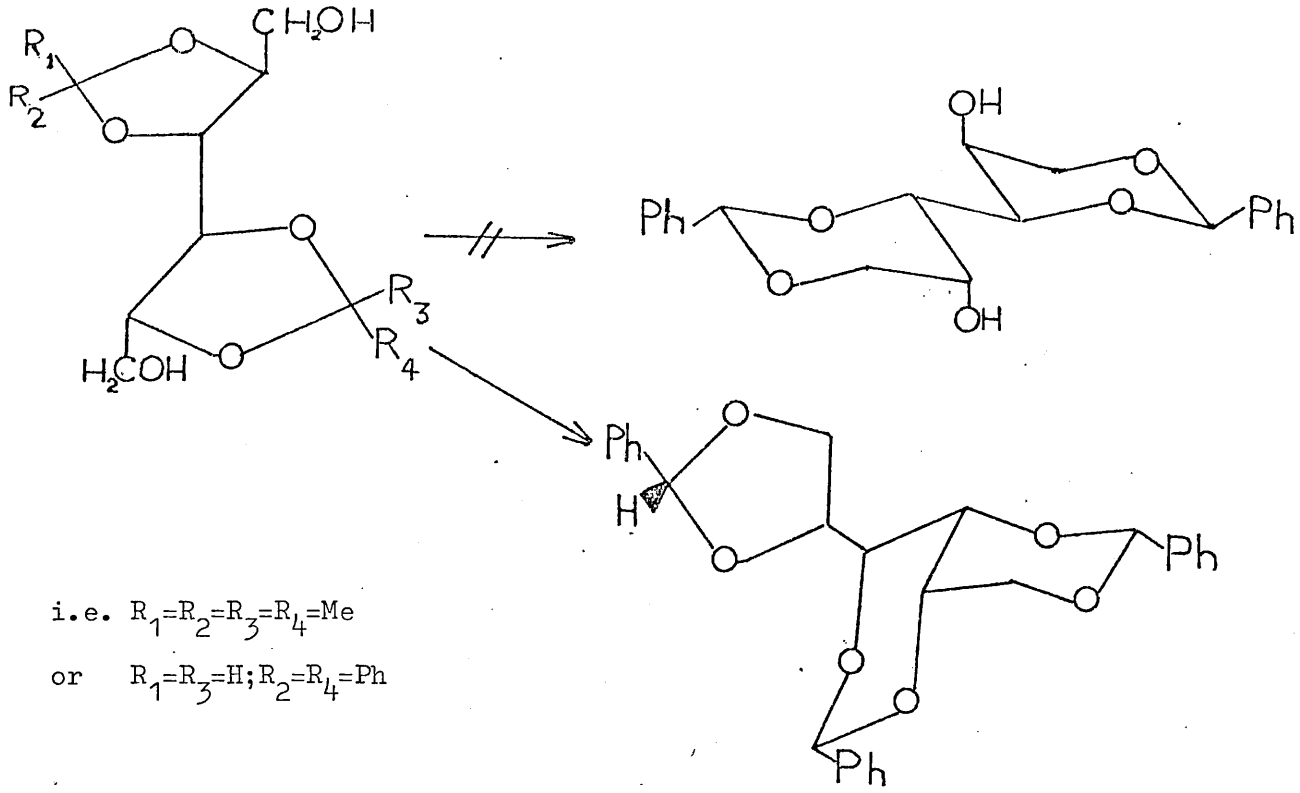
The structure of allitol would enable the diacetal to contain two βC rings, i.e. 2,4:3,5, whereas D-glucitol would form the β:βC, i.e. 1,3:2,4 and galactitol two β rings, i.e. 1,3:4,6.



The triacetal of D-glucitol would be expected to possess the 1,3:2,4:5,6 structure, i.e. β, βC α : controlled acid hydrolysis would result in the 5,6 ring being removed preferentially, with the 2,4 ring being the most stable to acid hydrolysis.

A recent publication by Bonn and Dijong[14] proposed that the foregoing rules were valid only if acetalisation was governed by kinetic control[15] , i.e. the reaction was influenced by the activational energy parameters as opposed to the thermodynamic parameters (essentially free energy factors), which applied when the reaction had attained thermodynamic equilibrium. However, it must be stated that Barker and Bourne's[12] rules applied at thermodynamic not kinetic equilibrium, so were not applicable to the initial kinetically influenced stages of these reactions.

Bonn et al[14] considered the reaction of 2,3:4,5-di-O-benzylidene galactitol and 2,3:4,5-di-O-isopropylidene galactitol with benzaldehyde and zinc chloride, i.e. both compounds contained two αT rings.



i.e. $R_1=R_2=R_3=R_4=Me$

or $R_1=R_3=H; R_2=R_4=Ph$

The product of both of these reactions was 1,3:2,4:5,6 tri-O-benzylidene galactitol, i.e. β, βT, α not 1,3:4,6-di-O-benzylidene galactitol, i.e. β, β. These authors considered that the diacetal should have been the product of these reactions not the triacetal. Consequently, it was claimed that the rules of Barker and Bourne[12] were invalid. However, modifications of these rules applied when polyols were partially substituted [see rule (iv)].

These above reactions were acetal exchange reactions, which were not considered in Barker and Bourne's[12] rules. Also the di-O-isopropylidene derivative was a ketal, and these were not considered in Barker and Bourne's[12] rules. Overall, these rules applied to cyclic acetal formation from a polyol, only.

Finally, the Barker and Bourne[12] rules considered mono acetal formation, although they form the basis for more substituted

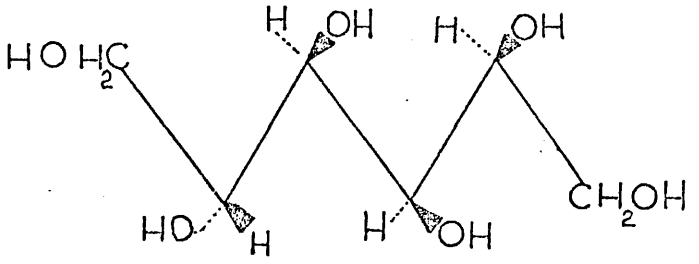
acetals. If this assumption was incorrect then the most thermodynamically stable triacetal of galactitol would be expected to possess the 1,3:2,5:4,6 structure, i.e. β, γC , β not the 1,3:2,4:5,6 structure, since the 1,3:4,6 diacetal structure was the immediate precursor.

Despite the fact that Haworth[16] introduced the term conformer into carbohydrate chemistry many years previously, two explanations were offered to account for the validity of the rules governing acetal formation. Both of these explanations were subsequently shown to be based upon conformational analysis principles.

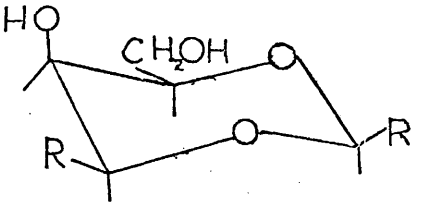
In conjunction with Whiffen[17] an explanation was rendered by the originators for these rules. If polyols were considered to exist in planar zig-zag[18] conformations, then substituents on adjacent carbon atoms were in fully staggered conformations. This conformation for a polyol entailed that the distance between adjacent groups was just greater than their van der Waal radii, hence non-bonded interactions were minimised. Barker et al[17] correlated the required internuclear distances between ring forming oxygens with the actual distances in polyhydric alcohols. Consequently, it was found that a βC disposition of hydroxyl groups (in the Fischer projection formula) would form an acetal ring with relative ease, and little strain.

The explanations offered by this assumption were found to be in agreement with the experimental observations.

Consider D-glucitol in its planar zig-zag form :-



In this configuration, the hydroxyl groups on carbon atoms C_2 and C_4 were stereochemically orientated for cyclic acetal formation. Consequently, assuming the βC compound, when formed, to exist in a chair form, this would be stabilised by equatorial substituents on carbon atoms C_2,C_4 and C_6 of the 1,3-dioxane ring.



A crystal structure analysis of unsubstituted polyols by Jeffrey and Kim[19] has revealed that these compounds adopted a planar zig-zag conformation only if this conformation does not lead to a 1,3 steric interaction between oxygen atoms. These authors also proposed that polyols in solution were governed by the same conformational factors as in the solid state. However, a nuclear magnetic resonance spectroscopic study[20] of fully acetylated polyols detected the planar zig-zag conformation for the arabino and manno configurations only, whereas other polyols were found to be mixtures of conformers.

Jeffrey and Kim[19] have detected the planar zig-zag conformation in the solid state for DL-arabinitol,[21] galactitol,[22] and D-mannitol,[23] none of which possessed parallel 1,3 interactions. Conversely, bent conformations have been detected for ribitol,[24] xylitol,[25] D-glucitol[26] and D-iditol:[27] all would possess 1,3-interactions in a zig-zag conformation.

Bonn et al[14] commented on the occurrence of zig-zag conformations only if interactions of 1,3 eclipsed orientated oxygen atoms were absent; i.e. for galactitol and D-mannitol only.

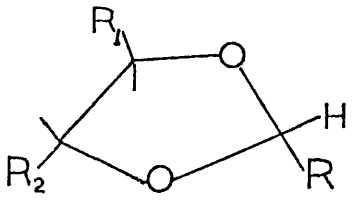
Hence the assumption of planar zig-zag conformations for polyols, made by Barker et al,[17] causing the predominance of certain acetal products has subsequently shown to be valid only in certain instances. Horton et al[28] in agreement, have stated that the equilibrium between the various possible acetals could only be a function of the free-energy content of each acetal, and not identifiable with the conformation of the parent polyol.

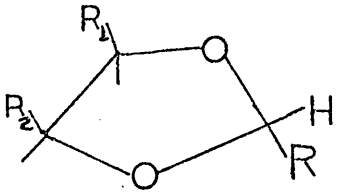
Mills[29] considered that a conformational examination of the acetal would offer an alternative explanation for acetal formation.

Five, six and seven membered acetal rings could be equated to their cyclic hydrocarbon analogues. Hence the stability of the acetal formed could be compared to the preferred conformation for the parent polyol.

When 1,3-dioxolane ring compounds were formed, it was found that the polyol with the αT configuration formed a more stable

acetal than the polyol with the αC configuration.

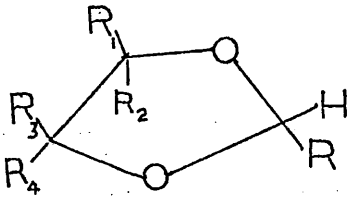


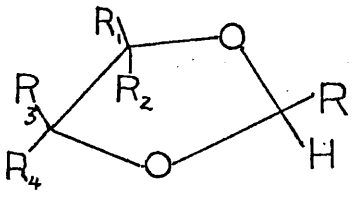


This was a reflection of the destabilisation of the 1,3-dioxolane ring caused by non-bonded interactions between αC substituents. Hence the αT compound would have less interactions than the αC compound and less internal energy.

It has been shown by Raman[30] and nuclear magnetic resonance spectroscopy[31] that 1,3-dioxolane was slightly distorted, but not enough to deviate far from a planar ring. Therefore cis substituents would be expected to cause a small dihedral angle, but not trans substituents. This entailed greater interactions in the cis isomer.

If R_1 and R_2 were not equivalent for a compound containing a 1,3-dioxolane ring, then the configuration at the acetal carbon (C_2) would be expected to give rise to diastereomeric ring forms.



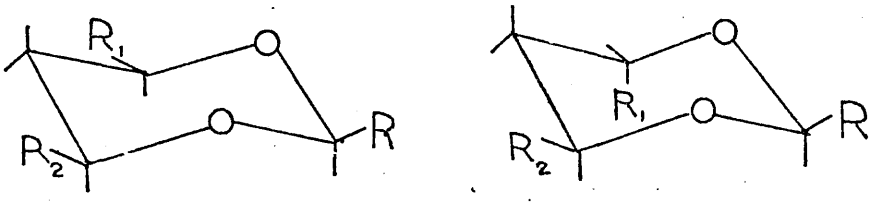


The 1,3-dioxane ring could be postulated to exist in the chair conformation. However, the carbon-oxygen bonds were about 10%

shorter than the carbon-carbon bonds, thus giving a slight puckering in the O_1-C_2-O_3 region and a flattening in the rest of the molecule in the C_4-C_5-C_6 [32]. Ring substituents at C_4 and/or C_6 which have an equatorial orientation would minimise the internal energy of the molecule.

The cis isomer (βC ring) would contain two large substituents in an equatorial orientation, but the trans isomer would contain one bulky grouping in an energetically unfavoured axial orientation.

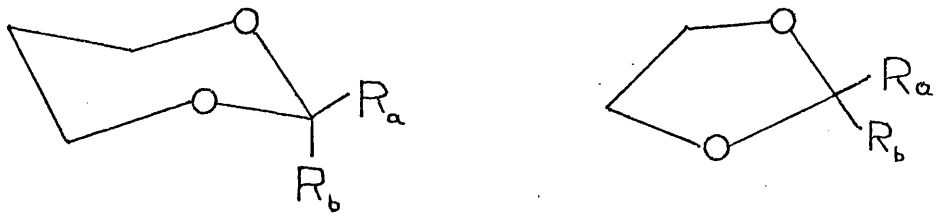
Hence 1,3 interactions would be present in the βT compound but not the βC compound.



The alkyl or aryl acetal grouping was assumed to adopt an equatorial orientation.

These conformational factors accounted for the stability of βC and β compounds.

This explanation also accounted for the preference of ketals to exist as five membered not six membered rings. A six membered ketal ring contained an unfavoured axial group at C_2.



Again, like 1,3-dioxolanes, diastereomeric forms were possible for 1,3-dioxanes. Like ketals, alkyl or aryl groups in an axial orientation would not be stable enough to exist in acid solution.

All compounds so far encountered containing the 1,3-dioxepane (ɣ) ring have involved D-mannitol. In a series of recently published work, Stoddart and Szarek[33,34,35] have given an account of the differing conformers for this ring form. At the time of Mills[29] publication, very scant conformational data existed for this ring form, although 2,5-O-methylene mannitol[36] had been synthesised. However conformational evidence by comparison with cycloheptane has enabled an interpretation of this ring size. A detailed n.m.r. study of conformations of the 1,3-dioxepane ring has been made for 2,5-O-methylene-D-mannitol and some related compounds. An examination of this acetal with methylene or benzylidene acetals spanning the 1,3 and 4,6 positions has unequivocably proven the methylene protons, spanning the 2,5 position, to be equivalent. This has been interpreted as the 1,3-dioxepane ring being in the twist conformation rather than a rapid ring-inversion process. Hence the methylene acetal protons were in a magnetically equivalent environment. Therefore, twist chair

conformers predominated, but evidence suggested that a 1,3-dioxane ring fused trans to the 1,3-dioxepane ring gave rise to a twist boat conformation.

By a consideration of the foregoing rules and the reasons which accounted for them, it should be possible to predict with reasonable accuracy the product formed by a specific polyol and an aldehyde.

Classically, the structures of these ring compounds were determined by periodate oxidation,[37] coupled with formic acid and formaldehyde determinations. After oxidation, the fragments of the acetal could be isolated and further characterised. Methylation of an acetal followed by acidic hydrolysis then periodate oxidation would again afford more structural information. These two techniques, periodate oxidation and methylation, should enable the positions of free hydroxyl groups in the molecule to be located. Periodate oxidation determined the number of vicinal hydroxyl groups in a molecule. The formation of the per-O-methyl ether was essential, since this was the most available derivative which was inert to both acid and base.

However, the basic assumption in this method of structural determination was for the non-migration of acetal rings during these reactions. It has been shown[38] that acetal rings could migrate upon chemical reaction. Alternatively acetal ring isomerisation could occur.

A limitation which arose in these techniques was encountered in fused or adjacent ring diacetal structures, e.g. consider the 1,3:2,4-diacetal of D-glucitol. The previously discussed techniques

would identify free hydroxyl groups at positions C_5 and C_6: no evidence was available for the size or stereochemistry of the rings spanning C_1-C_4.

Two techniques have evolved which have been successfully applied to acetal chemistry and found to be particularly amenable to this problem. These techniques were nuclear magnetic resonance spectroscopy (n.m.r.) and mass spectrometry: both afforded structural data.

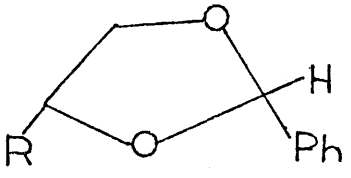
For n.m.r. two nuclei were available in acetals: ^{1}H and ^{13}C. Instrumentally ^{1}H spectra were more readily obtained and conformationally more diagnostic. Since ^{13}C was about 1.1% naturally abundant, it was possible to produce spectra without further enrichment.

In order to clarify the total data presented in a proton n.m.r. spectra, three main parameters have to be understood. If the chemical shifts, multiplicities and coupling constants of the signals were correctly interpreted then a large volume of structural and conformational data was available. In conjunction with the integrals for the signal areas, spin-decoupling experiments and computing techniques, assignments could be made with reasonable certainty.

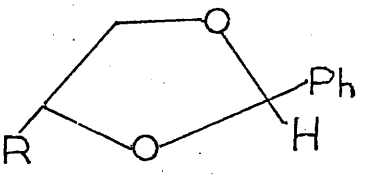
For acetals, the proton on C_2 (the acetal carbon) would be relatively deshielded, due to its electronegative environment, and hence would resonate at low field with respect to most other proton

signals in the molecule. Often the position of this resonance could give information on the size of the ring forms present.

Baggett et al[39] have studied a wide range of benzylidene acetals, i.e. 4-alkyl 2-phenyl 1,3-dioxolanes and the corresponding 1,3-dioxane analogues. Evidence has been offered for the size of the ring under consideration and the existence of diastereoisomers. In these compounds, the proton on C_2 has been observed as a singlet in a region of the spectrum free from other signals. In a series of 4-substituted 2-phenyl 1,3-dioxolanes, singlets were observed in the regions τ 4.46-4.52 and τ 4.62-4.67 and assigned to the following diastereoisomers.



τ = 4.62-4.67



τ = 4.46-4.52

For the series of 2-phenyl 1,3-dioxanes examined a singlet was observed at $\tau \sim 4.9$. Hence benzylidene protons of 1,3-dioxolanes resonated at lower applied fields than for the corresponding 1,3-dioxanes.

For the 1,3-dioxolanes the occurrence of the signal at a relatively low field was indicative of the deshielding of the proton on C_2 by the adjacent two oxygen atoms. Since a 1,3-dioxolane acetal proton resonated at a lower field than the analogous 1,3-dioxane compound, the deshielding experienced in a 1,3-dioxolane was greater than that for a 1,3-dioxane ring. Consequently the unshared electrons of the

1,3-dioxolane ring were in orbitals eclipsed with the C_2-H bond[40].

A subsequent examination[41] of some butylidene acetals of D-mannitol has enabled 1,3-dioxolane, 1,3-dioxane and 1,3-dioxepane ring forms to be distinguished.

Riddell et al[42] have made a study of 1,3-dioxane rings by ^{13}C. The existence of non-chair forms has been detected.

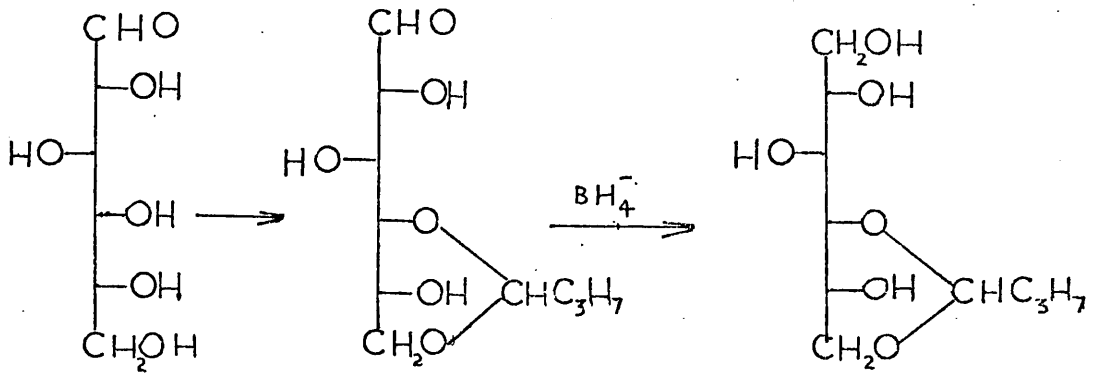
Mass spectrometry of acetals was pioneered by Marshall and Williams[43]. A systematic examination of 1,3-dioxolane compounds enabled an interpretation of their fragmentation patterns.

These facts were enlarged and extended to a knowledge of the fragmentation patterns for the acetals of sugars[44]. A later study[45] of benzylidene acetals of polyols and some substituted derivatives has led to the half-ion ("h-rupture") mechanism to be proposed.

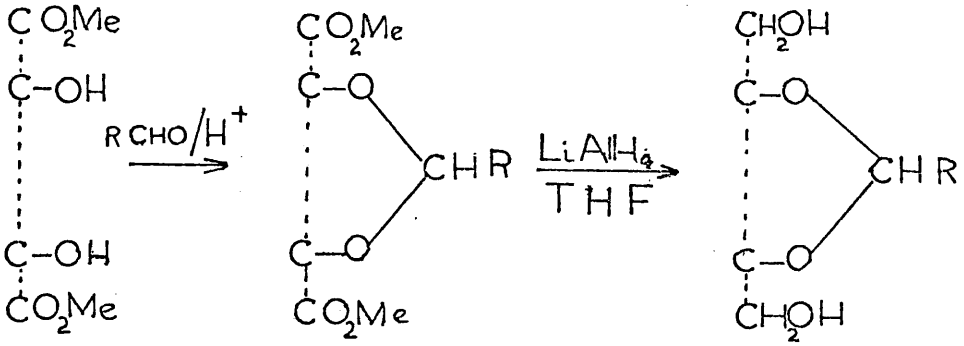
A knowledge of the mass spectrum and n.m.r. for an acetal should reveal much structural data. However unlike n.m.r., mass spectrometry was not usually stereo-specific. Consequently it would be expected to obtain similar spectra for the same alkylidene 2,4-mono acetal of allitol or D-glucitol.

In this introductory section, the reaction of a polyol with an aldehyde has been discussed. However alternative syntheses could give rise to polyol acetals:—

a) from a monosaccharide , e.g. 4,6-O-butylidene-D-glucitol [46].



b) from the diester of a saccharic acid [47].



c) acetal exchange reactions [48].

An attempt to account for the existence and stability of certain ring forms[49] in acetal chemistry has been offered. This discussion will be expanded and expounded in this text as these problems arise.

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SECTION B

RESULTS AND DISCUSSION

B. RESULTS AND DISCUSSION

Many organic reactions are influenced by kinetic parameters in the initial stages. This is in direct contrast to the equilibrium position which, when attained is governed by thermodynamic parameters.

Several acetalisation reactions[1] are directly comparable to this situation. The initial formation of a kinetic acetal occurs during the preliminary course of the reaction[2] which isomerises to a different product at thermodynamic equilibrium. A kinetic product, which is thermodynamically unstable, is governed by the activational energetics of the reaction, whereas a thermodynamic product is influenced by the free energy of the products.

Hann and Hudson[3], when considering the reactions of polyhydric alcohols with acidified formaldehyde, envisaged a succession of reactions. It was postulated that some of these reactions might be in competition causing a "state of reversible equilibrium" to exist, involving a number of acetals. However, if one of the acetals crystallised from the reaction mixture during this acetalisation process, then the equilibrium conditions may cause this solid phase to be the predominant product, e.g. in the reaction of D-glucitol and formaldehyde in conc.hydrochloric acid the crystallisation of 1,3:2,4:5,6 tri-O-methylene D-glucitol occurs as the major product.

In previous work[4] the acid hydrolysis of 2,4-O-butylidene-D-glucitol was investigated polarimetrically. When the synthesis of this acetal

from D-glucitol and n-butyraldehyde was followed by polarimetry (i.e. the reverse process to hydrolysis) the reaction was characterised by a decline in the optical rotation of the reaction mixture, initially, after which this value increased to a constant positive value at equilibrium.

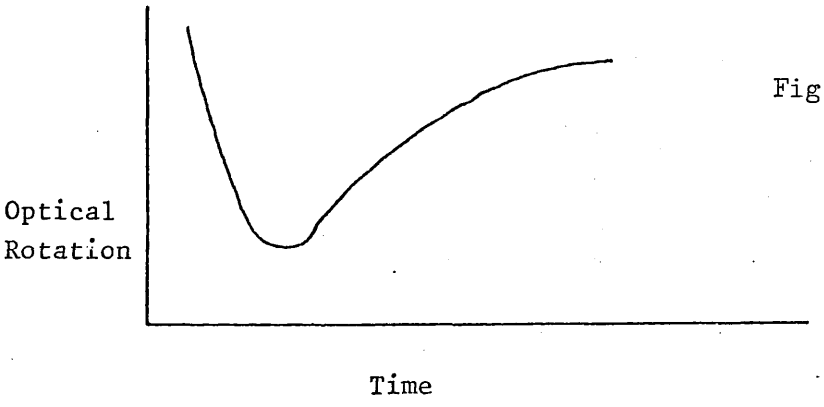


Fig (i)

This observation was interpreted as the initial formation of a kinetic acetal which isomerised to a different product at thermodynamic equilibrium.

Since hemi-acetal formation was considered to occur at a primary hydroxyl group[5], and 4,6-O-butylidene-D-glucitol was a known compound with a large negative value for its specific rotation[6], this observation was interpreted as the initial formation of the 4,6 acetal which isomerised to 2,4-O-butylidene D-glucitol at thermodynamic equilibrium. This assumed that hemi-acetal formation had occurred at C_6 of D-glucitol.

A later investigation[7] into this reaction enabled the detection of the kinetic acetal and its subsequent isomerisation to the thermodynamic product[8] to be monitored by gas liquid chromatography. When this

reaction was repeated on a macro scale and neutralised at the maximum concentration of kinetic product (i.e. at the minimum on the graph, Figure (i)), then the kinetic acetal could be isolated by adsorption chromatography. An analysis of this product by periodate oxidation, in conjunction with methylation studies, confirmed the structure to be 2,3-O-butylidene-D-glucitol, not the 4,6 mono acetal. Consequently, kinetic control in this reaction had formed a compound from the αT configuration of D-glucitol. This product had a low preference in the Barker and Bourne rules (see Section A).

i.e. D-glucitol $\rightleftharpoons$ 2,3-O-butylidene-D-glucitol

$+nC_3H_7CHO$ in NHCl $\not\rightleftharpoons$ 4,6-O-butylidene-D-glucitol

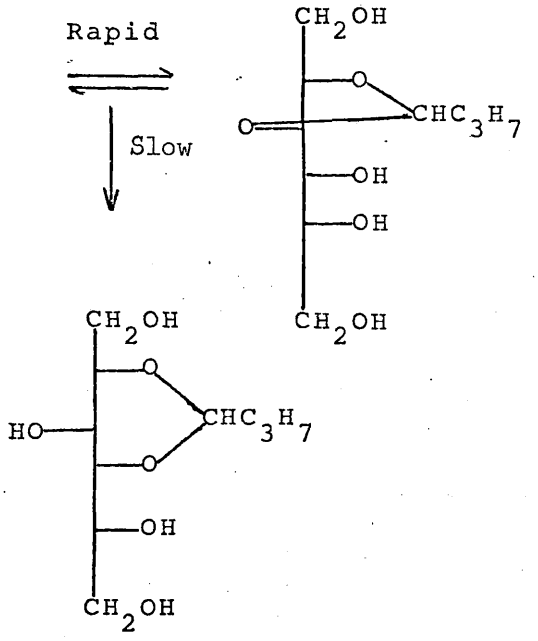
Since the 2,3-acetal (i.e. αT ring form) was identified as the kinetic product it must be reasoned why this product and not the 4,6-acetal was formed, and was the rearrangement to the 2,4-acetal inter or intra molecular?

Evidence for the rearrangement to the 2,4-acetal has been obtained from studies of the acidic hydrolysis of the 2,3 acetal[9]. The hydrolysis rate for the 2,3-acetal was considerably greater than that for the 2,4-acetal in N aqueous hydrochloric acid. The only product of this hydrolysis was D-glucitol: no other acetals were observed. Hence the rapid hydrolysis of the 2,3-acetal with only the polyol and n-butyraldehyde being produced, enabled the 2,4-acetal to

occur slowly. Therefore the formation of the thermodynamic product did not proceed principally via an intramolecular ring migration reaction.

Capon et al[10] have commented on the latter statement. They argued that the hydrolysis experiment indicated rapid equilibrium between D-glucitol and n-butyraldehyde only, and this made it impossible to deduce from which side of the equilibrium other acetals were being formed.

i.e. D-glucitol + n-C_3H_7CHO in N HCl

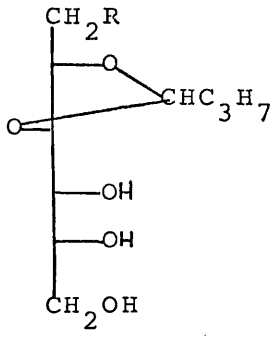


As a consequence of this work on D-glucitol , the acetalisation reactions were examined for various substituted analogues of D-glucitol and n-butyraldehyde.

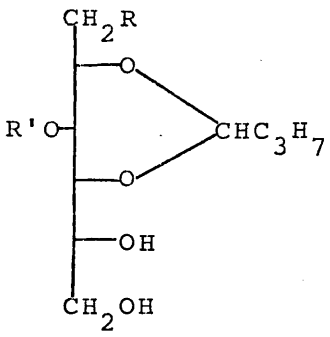
The deoxy polyols, 1 and 2-deoxy-D-glucitol and 3-O-methyl-D-glucitol were considered.

1-Deoxy-D-glucitol[11] was comparable to D-glucitol. Kinetic control was exhibited by this acetalisation reaction. 2,3-O-Butylidene

1-deoxy-D-glucitol (I, R=H) was isolated as the kinetic acetal and 2,4-O-butylidene-1-deoxy-D-glucitol (II, R=H) as the thermodynamic product. (n.b. D-glucitol I and II, R=OH).

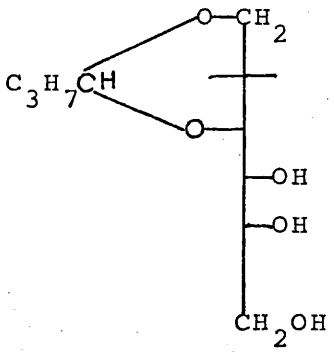


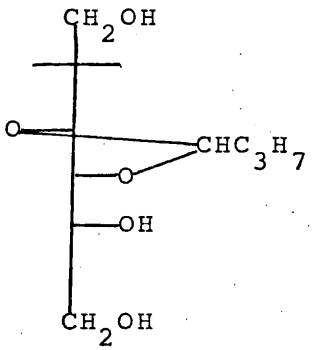
I



II

Again, 2-deoxy-D-glucitol[11] and n-butyraldehyde in acid solution were governed by kinetic control. However, the kinetic product was 1,3-O-butylidene 2-deoxy-D-glucitol which isomerised to the 3,4-acetal at equilibrium. Overall, this process involved the sequence:-

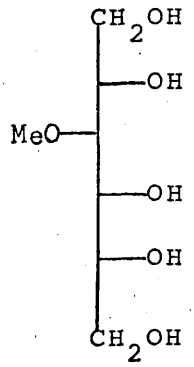


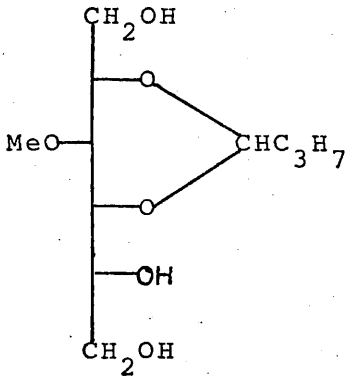


1,3 mono (β ring) ⟶ 3,4 mono (αT ring).

This observation was in direct contrast to Barker and Bourne's rules. The formation of a β ring would have been postulated as the thermodynamic acetal (either the 1,3 or 4,6 mono acetals). Also, the previous work on D-glucitol and its 1-deoxy analogue has shown that an αT compound, i.e. the 2,3 acetal, was formed as the kinetic acetal. Since 2-deoxy-D-glucitol was synonymous with 2-deoxy-D-mannitol, it was obvious that this deoxy polyol was functioning as neither a D-glucitol nor a D-mannitol derivative.

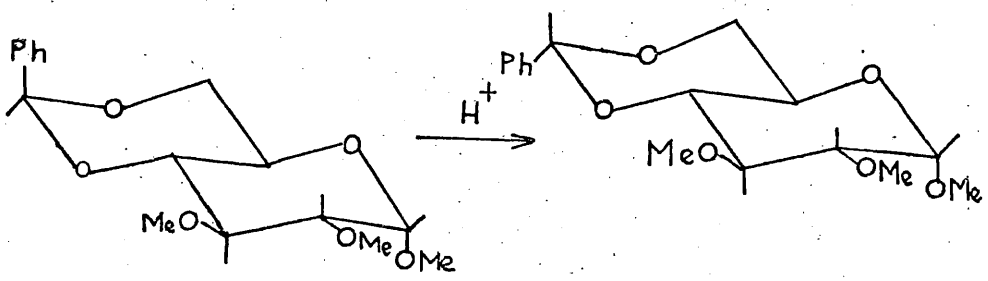
For 3-O-methyl-D-glucitol[11] no evidence for kinetic control was afforded by polarimetric and glc. studies. The βC ring compound was isolated as the thermodynamic product, i.e. 2,4-O-butylidene-3-O-methyl-D-glucitol. Hence it may be considered that the absence of an αT hydroxyl grouping in this molecule inhibited the formation of a kinetic acetal.





An acetalisation reaction of a different type was investigated by nuclear magnetic resonance.

Since it has been illustrated that acid catalysed acetalisation reactions proceed to a state of thermodynamic equilibrium, the formation of the more stable diastereoisomer predominates.[12] In the formation of methyl 4,6-O-benzylidene hexopyranosides[13] only the isomer with the phenyl group equatorial was encountered. However, when the acetal ring was introduced under conditions of kinetic control the two diastereoisomers were obtained, e.g. methyl 2,3-di-O-methyl α-D-glucopyranoside reacted with benzylidene bromide in potassium tertiary butoxide to give the diastereomeric 4,6 acetals. However, this reaction differed since acetalisation was occurring in a basic media. The least thermodynamically stable diastereoisomer was converted into the other upon treatment with acids. The most thermodynamically stable isomer contained the phenyl group in an equatorial position.

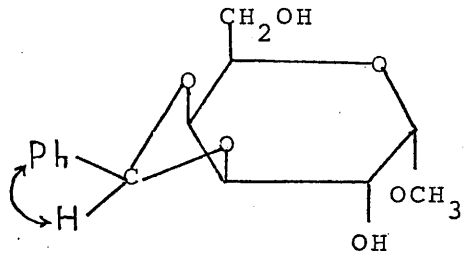


Methyl 2,3-Di-O-Methyl 4,6-O-Benzylidene α-D-Glucoside.

Similar observations to the above were encountered with the corresponding D-galactose series.

The conversion of the axial phenyl compound to the equatorial compound accounted for the formation of one diastereoisomer with acidic catalysis.

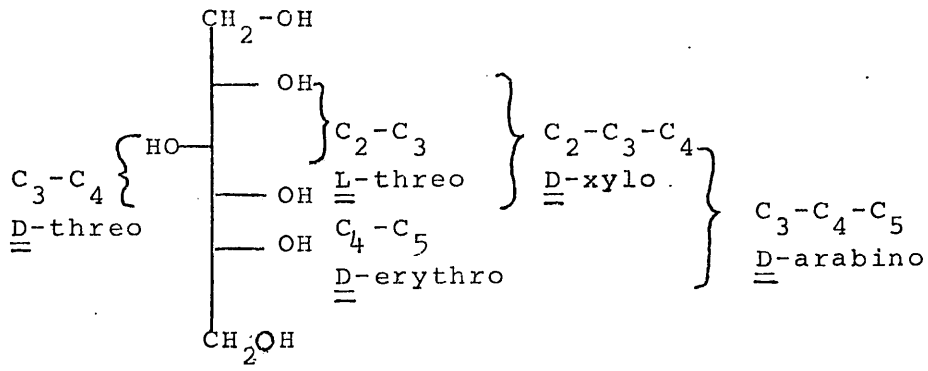
However, when the benzylidenation reactions of methyl α-D-galactopyranoside was followed in homogenous acid conditions[13], n.m.r. gave evidence for the formation of diastereomeric 3,4-O-benzylidene acetal as the kinetic product.



In the work considered in this thesis an examination has been presented of the reactions of various polyols and n-butyraldehyde in acidic media. The observations have been compared and contrasted to the previous work accumulated on D-glucitol and its substituted derivatives.

In the Fischer projection formula the adjacent secondary hydroxyl groups of D-glucitol may be envisaged to comprise of small polyol fragments.

viz:



Hence the presence of the above configurations are readily identifiable in the D-glucitol molecule. Hence the reaction of these polyols and n-butyraldehyde have been examined and the observations related to the previous work on D-glucitol.

B.1. Synthesis and Structure of the Butylidene Tetritols

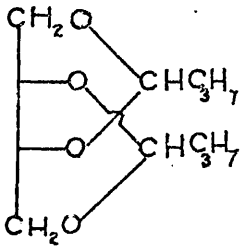
Erythritol:-

Since erythritol was optically inactive its reaction with n-butyraldehyde in N hydrochloric acid was monitored by glc. With the polyol and aldehyde both at 0.25 m, in N hydrochloric acid, aliquots of the reaction mixture were taken and neutralised. After evaporation of this solution, the residue was extracted with hot ethanol and the resulting extracts converted to their trimethyl silyl ethers. By this technique, the presence of only one mono acetal could be detected. When the neutralised and extracted reaction aliquots were examined by thin layer chromatography (MEK saturated with water) again the presence of one mono acetal could be detected. Hence the existence of a kinetic acetal for this reaction was deduced to be absent.

This reaction was repeated on a larger scale and left for 20 hours at room temperature to attain equilibrium; a diacetal had crystallised from the reaction mixture. This was filtered off and recrystallised from ethanol to give white plate-like crystals (m.p. 76-77^{o}). The remaining reaction solution was neutralised with sodium hydrogen carbonate, evaporated to dryness and the residue exhaustively extracted with hot benzene. The extracts on cooling deposited crystals of a mono acetal (m.p. 99-101^{o}). These two acetals analysed for a di and mono butylidene tetritol, respectively,

and both were hydrolysed by acid to give erythritol.

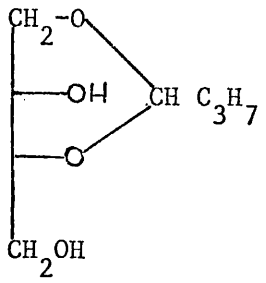
Hydroxyl groups were shown to be absent in the di-acetal. A subsequent physico-chemical examination of this compound showed it to be 1,3:2,4-di-O-butylidene erythritol.



The mono acetal was characterised as its crystalline per-benzoate and phenyl boronate. An attempt to prepare a mono trityl ether resulted in a syrupy product. However, this syrup could be readily acetylated to give 2-O-acetyl 1,3-O-butylidene 4-O-trityl erythritol.

The mono acetal did not consume periodate, hence the presence of vicinal hydroxyl groups in the molecule were absent.

The mono acetal was fully methylated by methyl iodide-silver oxide to give a syrupy product. Hydrolysis of this methylated acetal gave a syrupy product which again failed to consume periodate. Hence vicinal hydroxyl groups were absent in the methylated polyol. This determined the structure of the mono acetal to be 1,3-O-butylidene-DL- erythritol.



L-Threitol:-

When the reaction of equimolar (0.25 m) amounts of L-threitol and n-butyraldehyde in N hydrochloric acid was examined polarimetrically, an initial decline in the optical rotation, with time, was observed. After this minimum had been passed, the optical rotation gradually increased to reach a positive equilibrium value after 3 hours. In previous work this change in optical rotation with time has been interpreted as being indicative of kinetic control in acetalisation reactions. However, attempts to observe kinetic control, and confirm the former deduction, by glc on a variety of column packing (APK, PPE or OV225) for TMS or acetate derivatives were unsuccessful. The presence of one peak was observed. Consequently glc was inadequate to resolve these mono acetals. However the presence of two mono acetals in this reaction could be illustrated by TLC on silica (MEK saturated with water).

When this reaction was repeated on a macro scale and left for 20 hours at room temperature, crystals of a di-acetal had separated.

These were filtered off and recrystallised from light petroleum to give white needle-like crystals (m.p. 67°).

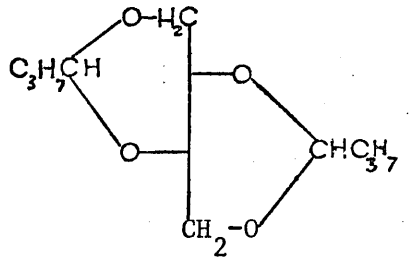
The remaining solution was neutralised with sodium bicarbonate and evaporated to dryness. The residue was extracted with hot ethanol. The evaporated extracts were chromatographed on a column of silica, eluting with MEK saturated with water. However, this separated the two mono acetals from the unreacted polyol. Subsequent attempts to separate these mono acetals on alumina or silica with a variety of solvents were unsuccessful. However, a separation was achieved by ion-exchange chromatography. Dowex OH^- resin was utilised, eluting with carbon dioxide-free water. The mono acetal which had the smaller Rf value on silica tlc (eluting with MEK), and was subsequently shown to be the thermodynamic acetal containing a 1,3-dioxane ring, was eluted first. The kinetic acetal was eluted secondly. This had the larger Rf value and was later shown to possess a 1,3-dioxolane ring.

When the relevant fractions were evaporated, the thermodynamic acetal was obtained as a solid which was recrystallised from ethanol (m.p. 54-54.5°; $[\alpha]_D$ = + 5.6° in H_2O). However the kinetic acetal was obtained as a syrup ($[\alpha]_D$ = -19.2° in H_2O) which could not be induced to crystallise.

The diacetal and two mono acetals gave satisfactory elemental analyses for a di- and mono-butylidene tetritols. The acid hydrolysis

of these acetals afforded L-threitol only, as identified by paper chromatography.

The absence of hydroxyl groups in the diacetal was shown by infra-red spectroscopy. An examination of this diacetal subsequently showed it to be 1,3:2,4-di-O-butylidene-L-threitol.



As a consequence of this work by n.m.r. spectroscopy the above compound was shown to exist in the "O-inside" conformation (see Section C).

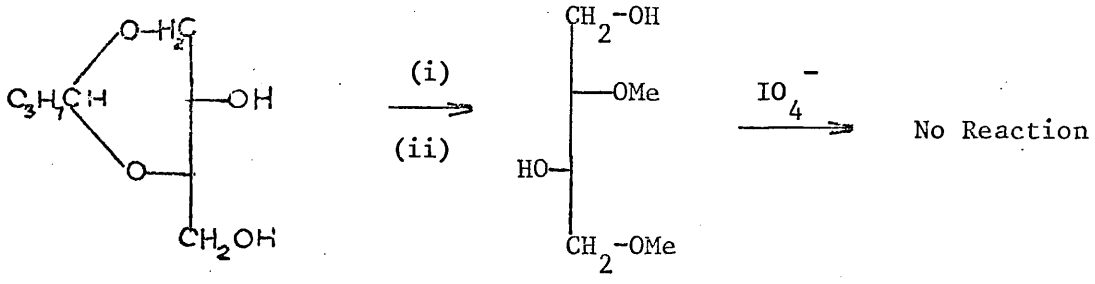
The thermodynamic mono acetal was characterised as a crystalline per benzoate and a crystalline phenyl boronate. However attempts to prepare a crystalline derivative for the kinetic mono acetal e.g. benzoate, acetate, tosylate, were unsuccessful.

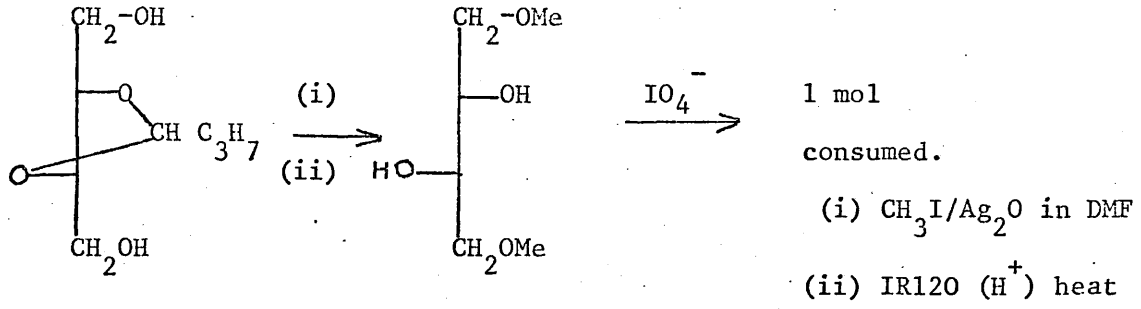
Neither mono acetal consumed periodate, hence vicinal hydroxyl groups were absent in both molecules.

Methylation of both acetals gave syrupy di-O-methyl mono butylidene L-threitols. After acidic hydrolysis each residue was treated with periodate. The residual syrup resulting from the thermodynamic acetal failed to consume periodate, whereas that resulting from the kinetic

acetal consumed 1 mol of periodate.

These observations fixed the structure of the thermodynamic acetal as 1,3-O-butylidene-L-threitol and the kinetic acetal as 2,3-O-butylidene-L-threitol.





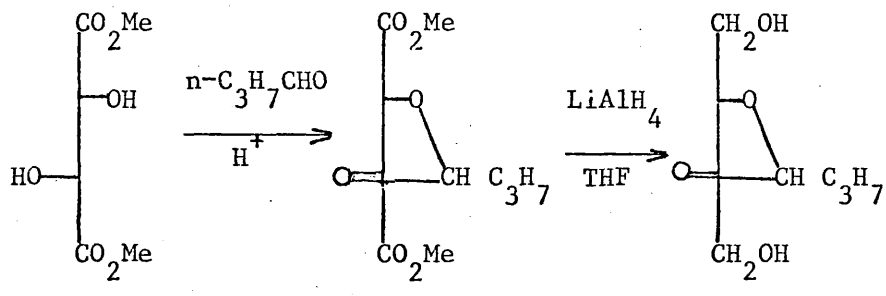
The structure of 2,3-O-butylidene-L-threitol could be shown by an independent synthesis from (+)-tartaric acid.

Dimethyl (+)-tartrate, used in the synthesis of L-threitol, was refluxed with n-butyraldehyde in light petroleum with toluene-p-sulphonic acid, as a catalyst. The water produced in this reaction being removed azeotropically by the Dean and Stark technique. Evaporation of the reaction mixture after 14 hours gave 2,3-O-butylidene di-O-methyl (+) tartrate. This ester was reduced to 2,3-O-butylidene L-threitol upon

treatment with lithium aluminium hydride in tetra hydrofuran.

The syrup, which resulted after removal of excess hydride and inorganic matter, could not be crystallised, like 2,3-O-butylidene-L-threitol synthesised directly from L-threitol. However this acetal failed to consume periodate and behaved identically to 2,3-O-butylidene-L-threitol on tlc on silica (MEK saturated H_2O).

This mono acetal had a favourable specific rotation ($[\alpha]_D = -17.5^o$ in H_2O) and gave comparable n.m.r. (in D_2O) and infra-red spectra.



B.2. Synthesis and Structure of the Butylidene Pentitols

Ribitol:-

When the reaction of equimolar concentrations (0.25 m) of ribitol and n-butyraldehyde in N hydrochloric acid was monitored, the presence of one mono acetal could be observed for this reaction. The gradual increase in concentration of this product could be observed with time. This reaction, when repeated and monitored by tlc on silica plates in MEK saturated with water, again showed the presence of one mono acetal. These two observations were deduced as being diagnostic for the absence of the formation of a kinetic acetal for this reaction.

This reaction was repeated on a larger scale and allowed to reach equilibrium. By neutralisation, evaporation, extraction and chromatographic separation, a mono and diacetal were obtained. The yield of diacetal was improved by repeating the reaction using 1.5 mol of n-butyraldehyde to 1 mol of ribitol. The diacetal separated from the reaction mixture and was filtered off after 24 hours. After washing thoroughly with water, the diacetal was dried and recrystallised from ethanol to give white crystals (m.p. 60-61°).

The remaining reaction mixture was neutralised and extracted. Chromatography on silica gel, eluting with methyl ethyl ketone saturated with water, gave the mono acetal. This was obtained as a pale yellow syrup which could not be crystallised.

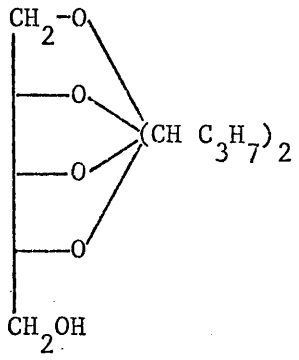
These acetals analysed satisfactorily for a di and mono butylidene pentitol.

The diacetal gave a crystalline mono benzoate. Methylation of the diacetal gave a syrupy product which was hydrolysed by acid. Periodate oxidation on the residual syrup liberated 1 mol of formaldehyde and 2 mols of formic acid, with 3 mols of periodate consumed. Consequently the free hydroxyl group may be located at C_5 (equivalent to C_1).

An attempt to prepare a trityl ether was unsuccessful and gave triphenyl carbinol (m.p. 160°).

Despite the fact that the free hydroxyl group was fixed at C_5,

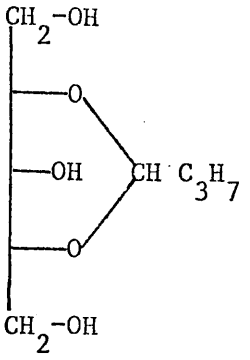
the nature of the two acetal rings spanning C_1-C_4 could not be ascertained by this method.



However, a subsequent examination of this diacetal by n.m.r. spectroscopy has enabled the structure to be determined as 1,3:2,4 di-O-butylidene ribitol.

The mono acetal of ribitol readily afforded several crystalline derivatives : a tri-benzoate, a phenyl boronate and a di-tritylate. Selective benzoylation with 2 mols of benzoyl chloride gave a di-O-benzoate. This product was later identified as 2,4-O-butylidene 1,5-di-O-benzoyl ribitol. The formation of the di-tritylate and di-benzoate suggested two free primary hydroxyl groups.

The mono acetal upon treatment with periodate failed to be oxidised. Hence the presence of vicinal hydroxyl groups in the molecule were absent. This reaction was unique since only one structure was possible for this acetal i.e. 2,4-O-butylidene ribitol (βC ring compound). Hence the structure was uniquely defined.



Xylitol:-

The reaction of equimolar amounts of xylitol and n-butyraldehyde (0.25 m) in N hydrochloric acid was monitored by glc analysis. No evidence for the existence of a kinetic acetal was obtained. A tlc examination of the same reaction system supported this observation.

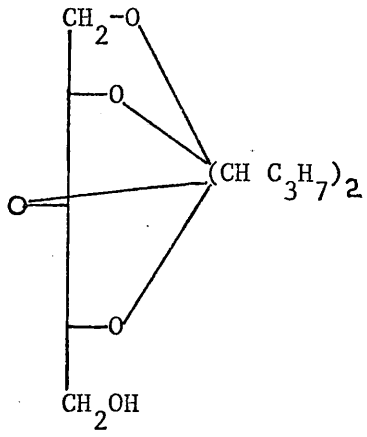
This acetalisation when repeated on a gramme scale and left to equilibriate for 24 hours, gave oily droplets in the reaction mixture. The reaction mixture was neutralised, evaporated and extracted. A syrup remained after evaporation of the extracts. This syrup was introduced onto the top of a column of silica gel and a di and mono acetal separated.

The diacetal was obtained as a syrup which could not be crystallised. The mono acetal was isolated as a white solid, which was recrystallised from ethanol to give the pure product (m.p. 115-117°).

Each acetal gave a satisfactory elemental analysis. The diacetal yielded a crystalline benzoate. Methylation of the diacetal gave a syrupy mono-methyl ether. After acid hydrolysis, this ether was treated with periodate by the usual technique. Three mols of periodate

were consumed, with 2 mols of formic acid and 1 mol of formaldehyde liberated.

Hence like ribitol, the free hydroxyl group could be located at C_5, but no information was available concerning the acetal rings from C_1-C_4.

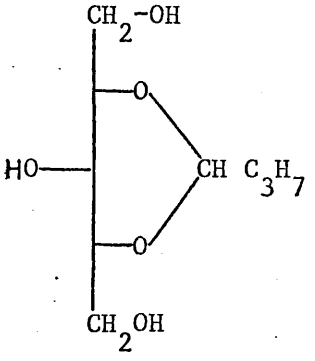


Again like di-O-butylidene ribitol, an attempt to prepare a mono-tritylate only resulted in triphenyl carbinol. Hence the primary hydroxyl group was hindered for this etherification reaction.

The structure of the diacetal was later fixed as 1,3:2,4 di-O-butylidene xylitol, by physico-chemical methods.

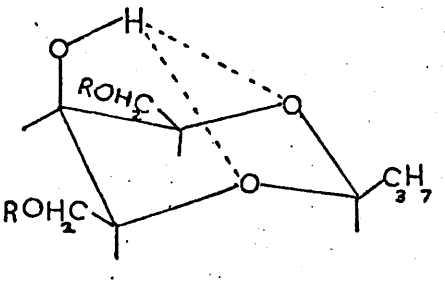
The mono acetal of xylitol was less reactive than the mono acetal of ribitol. Tri-benzoylation of the acetal resulted in the isolation of a crystalline di-benzoate, only. A crystalline phenyl boronate could not be obtained, but a crystalline di-O-trityl ether was yielded. These derivatives suggested two free primary hydroxyl groups in the molecule.

Treatment of this mono acetal with periodate, resulted in the consumption of no oxidising agent. Hence vicinal hydroxyl groups were absent in this acetal. Again, like mono-butylidene ribitol, this reaction was characteristic for 2,4-O-butylidene xylitol i.e. the βC compound.



Hence the formation of a di-benzoate would be expected to involve C_1 and C_5, with C_3 not benzoylated. However, the free hydroxyl was readily acetylated in pyridine to give a crystalline product.

A later study of this di-benzoate by infra red spectroscopy has shown the presence of intramolecular hydrogen bonding (see Section C), thus inferring the following conformation:-



D-Arabinitol:-

As D-arabinitol was optically active, its reaction with n-butyraldehyde was amenable to a study by polarimetry. Equimolar amounts of this polyol and n-butyraldehyde (0.25 m) in N hydrochloric acid when examined by polarimetry gave a curve which progressed through a maximum before declining and reaching thermodynamic equilibrium. However this curve was the exact reverse of that normally encountered in these reactions i.e. usually a minimum was initially encountered which increased to a positive equilibrium value. (In this observation, the Hg 365 nm line was employed, since the Na-D line resulted in only small changes in optical rotation). Nevertheless, this curve was interpreted as being characteristic for kinetic control occurring in this reaction. This observation was confirmed by glc, and the maximum concentration of kinetic acetal was after 20 minutes.

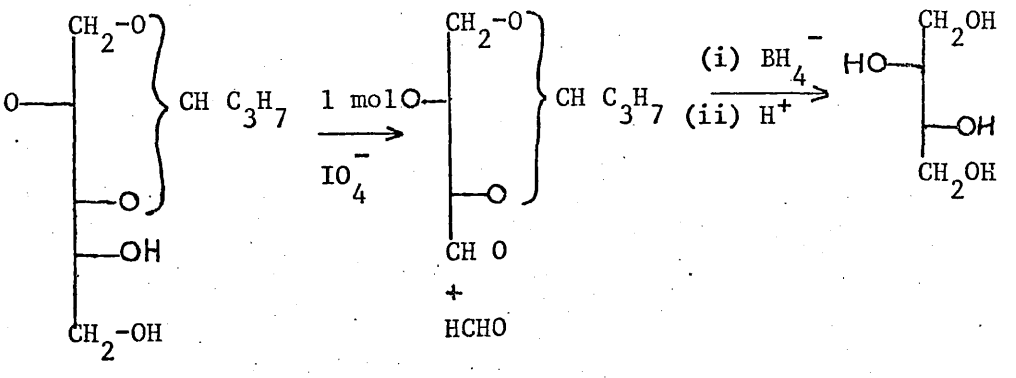
This reaction when repeated on a larger scale, with the usual 'work-up' procedure enabled the isolation of two mono acetals. These mono acetals were separated on Dowex OH^- resin, eluting with carbon dioxide-free water. Again, like the mono acetals of L-threitol, the acetal later shown to possess the 1,3-dioxane type ring and the smaller Rf was eluted firstly, with the 1,3-dioxolane type ring compound eluted lastly.

Both acetals were obtained as white crystalline solids, after recrystallisation from ethanol (firstly eluted acetal m.p. 94-95°,

lastly eluted acetal m.p. 88-89°).

Both acetals were characterised as their respective tri-benzoates.

Both acetals were treated with periodate. One mol of oxidant was consumed and one mol of formaldehyde liberated. Therefore one pair of vicinal hydroxyl groups was present in each acetal and since formaldehyde was liberated, these must have both incorporated a primary hydroxyl grouping. Two possibilities existed for each acetal: C_1 and C_2, or C_4 and C_5. The fragments of oxidation were isolated by continuous extraction with chloroform. The respective fragments were reduced with borohydride and hydrolysed with acid. The resultant solutions were examined by paper chromatography and compared with erythritol and L-threitol standards. Subsequently, threitol not erythritol was identified for each acetal. This could only have arisen from C_2-C_3, considering the initial periodate oxidation result. Hence both acetals must have had the free vicinal hydroxyl groups at C_4-C_5.



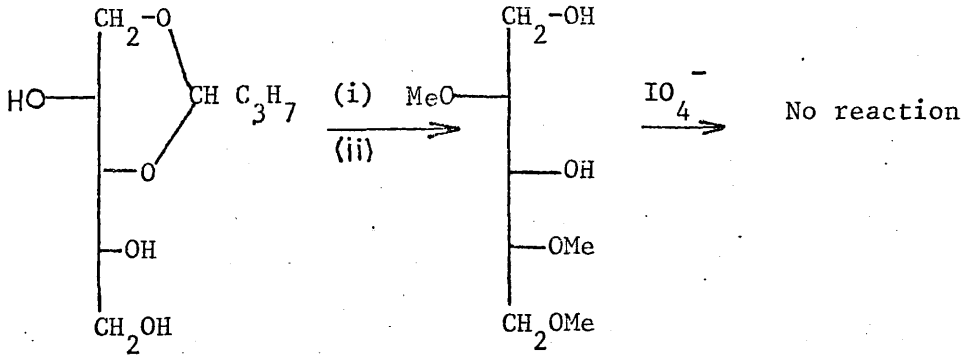
The ultimate proof of the structures of the kinetic and thermodynamic

acetal was furnished by methylation.

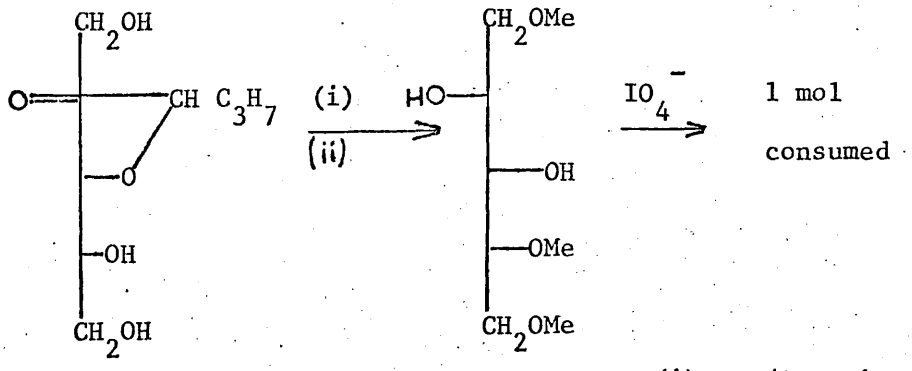
Each acetal was fully methylated to give a syrupy tri-O-methyl ether. These were hydrolysed by acid, to remove the acetal rings, and treated with periodate.

The tri-O-methyl ether resulting from the thermodynamic acetal failed to consume periodate, hence methylation had blocked C_2, C_4 and C_5. This enabled the structure to be ascertained as 1,3-O-butylidene-D-arabinitol. However, the product of the kinetic acetal consumed 1 mol of periodate. Consequently the kinetic acetal could be attributed the structure 2,3-O-butylidene-D-arabinitol.

Thermodynamic:



Kinetic:



(i) MeI/Ag_2O in DMF

(ii) IR120 (H^+) - heat

The reaction of D-arabinitol with a threefold molar excess of n-butyraldehyde in 5N hydrochloric acid gave a complex mixture of reaction products. A mixture of diacetals was obtained by chloroform extraction of these products. However, all attempts to separate these products were unsuccessful.

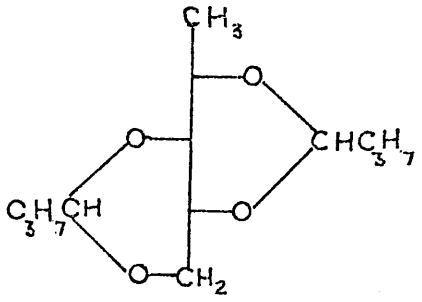
B.3. Synthesis and Structure of the Butylidene Deoxy Polyols

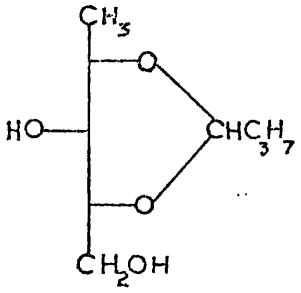
1-Deoxy-D-Xylitol:-

Despite the fact that this polyol was optically active, an opaque solution was produced in N hydrochloric acid with equimolar amounts of n-butyraldehyde. Consequently, it was not possible to examine the reaction of this polyol with n-butyraldehyde by polarimetry. Hence the reaction of this polyol and n-butyraldehyde (both 0.25 m) in N hydrochloric acid was monitored by glc. No evidence was afforded for kinetic control: only one mono acetal could be detected. Examination of this reaction by tlc confirmed these observations.

A macro scale examination of this reaction enabled the isolation of a di and mono acetal at thermodynamic equilibrium. The acetals were separated by chromatography on silica eluting initially with chloroform, then MEK saturated with water.

A syrupy diacetal was obtained ($[\alpha]_D = -16.19^{o}$ in $CHCl_3$) which could not be crystallised. Proton n.m.r. showed this compound to be 1-deoxy 2,4:3,5-di-O-butylidene-D-xylitol.



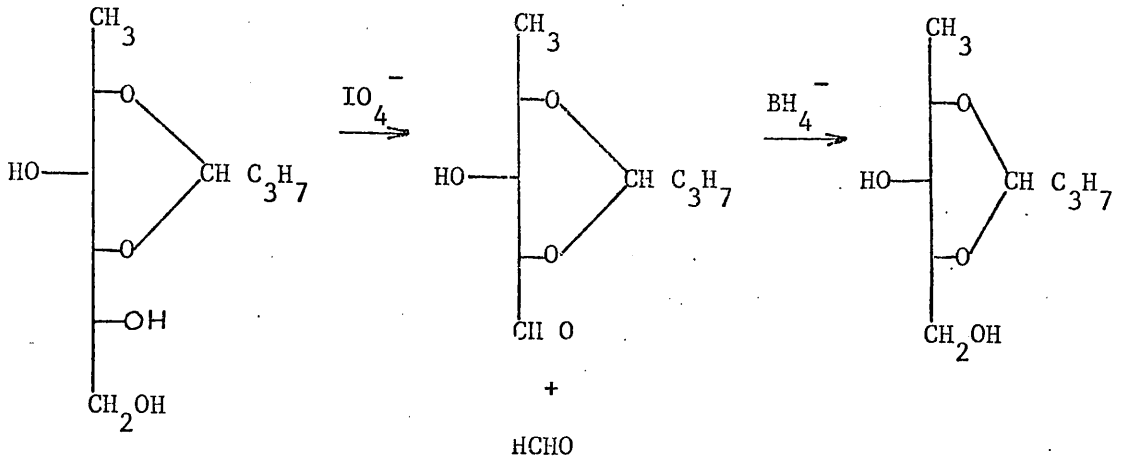


The mono acetal was obtained, after recrystallisation from ethanol, as white crystals (m.p. 85-87° $[\alpha]_D \simeq -4.4°$ in H_2O).

The mono acetal was not oxidised by periodate, but this observation was not unique in determining the structure, like xylitol.

However, the acetal was comparable in melting point, mixed melting point and specific rotation to a sample of 2,4-O-butylidene-1-deoxy-D-xylitol synthesised indirectly.

The reaction of 1-deoxy-D-glucitol with n-butyraldehyde in N hydrochloric acid gave 2,4-O-butylidene 1-deoxy-D-glucitol (I). Treatment of this acetal with sodium meta periodate afforded 2,4-O-butylidene-5-deoxy aldehydo-L-xylose (II). When this fragment was reduced with borohydride and the product isolated: 2,4-O-butylidene 1-deoxy-D-xylitol (III) (m.p. 86-87° $[\alpha]_D = -3.9°$ in H_2O) resulted.



I II III

6-Deoxy-D-Glucitol:-

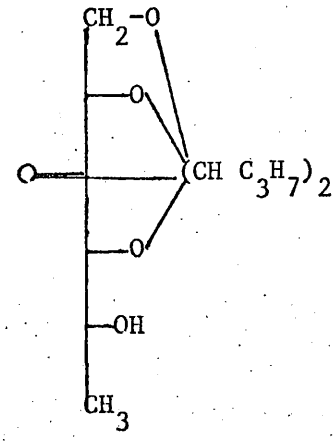
The reaction between this polyol and n-butyraldehyde (both 0.25 m) was monitored polarimetrically in N hydrochloric acid. A characteristic decline in optical rotation with time was observed initially, passing through a minimum and then a gradual increase to a positive equilibrium value. This was attributed to the formation of a kinetic acetal which subsequently isomerised to a thermodynamic product. The existence of kinetic control was confirmed by glc. The occurrence of a kinetic acetal and its rearrangement was readily observed for TMS- derivatives.

This reaction was repeated using large amounts of reactants to isolate the products. After 24 hours crystals of a diacetal had separated. These crystals were filtered off, washed with water and recrystallised from ethanol to give off-white crystals (m.p. 114-116° $[\alpha]_D$ = 0.7° in $CHCl_3$). The remaining reaction solution was neutralised, evaporated and extracted. The combined extracts were evaporated to

give a syrup. A mixture of two mono acetals was separated by chromatography on a column of silica gel, eluting with MEK saturated with water. The mixture of mono acetals was separated by chromatography on Dowex OH^- resin eluting with CO_2 free water. The first acetal eluted had the smaller Rf on silica in MEK saturated with water and was later shown to contain a 1,3-dioxane ring. This was the thermodynamic product. Evaporation yielded a white solid which was recrystallised from ethanol to give white crystals (m.p. 152-153° $[\alpha]_D = -5.2°$ in water). The kinetic acetal was eluted lastly. A syrup was obtained which could not be crystallised.

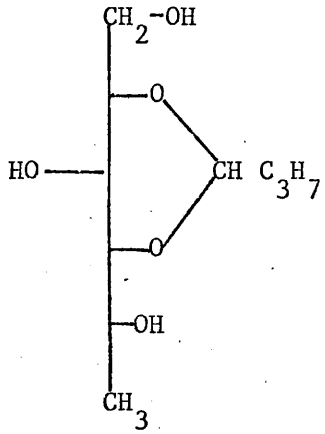
Satisfactory elemental analyses were obtained for the di and two mono butylidene 6-deoxy D-glucitols.

The diacetal was methylated to give a syrupy product. After acid hydrolysis, the resultant syrup was treated with periodate. Three mols of periodate were consumed with one mol of formaldehyde and two mols of formic acid liberated. Hence the hydroxyl group at C_5 had been methylated in the acetal. Hence C_1-C_4 were involved in the two acetal rings.



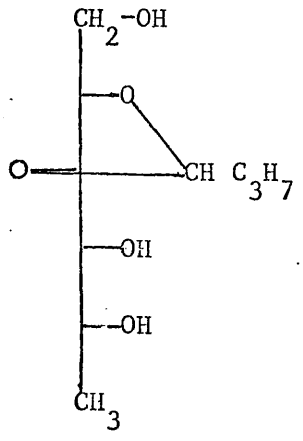
An examination of the n.m.r. spectra for this compound inferred the structure to be 1,3:2,4-di-O-butylidene-6-deoxy-D-glucitol.

The thermodynamic mono acetal was treated with periodate: no consumption of the oxidising agent resulted. Hence vicinal hydroxyl groups were absent in this molecule. This reaction uniquely defined the structure as 2,4-O-butylidene-6-deoxy-D-glucitol i.e. the only structure possible which would not react with periodate.



The kinetic acetal was treated with periodate: one mol of oxidant was consumed with no formaldehyde nor formic acid liberated. Hence one pair of vicinal hydroxyl groups was present in the molecule. The solution after oxidation was extracted continuously with hot chloroform. The extracted fragment was treated with borohydride and hydrolysed with IR120 (H^+) resin. The resultant compound was examined by paper chromatography with L-threitol and erythritol standards. The fragment was shown to give threitol. Hence this must have arisen from C_2-C_3. However, this acetal could have been the 1,3 or 2,3 structure. However,

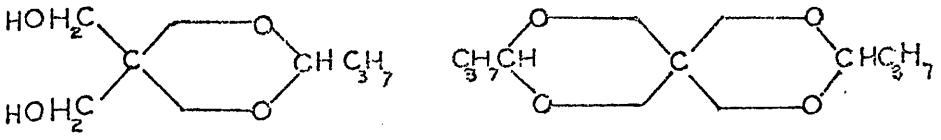
a n.m.r. study showed the presence of a five-membered ring enabling the structure to be deduced as 2,3-O-butylidene-6-deoxy-D-glucitol.



B.4. Synthesis and Structure of Some Miscellaneous Butylidene Acetals

Pentaerythritol:-

A mono and diacetal of penta erythritol were synthesised by allowing equimolar amounts (0.25 m) of the polyol and n-butyraldehyde in N hydrochloric acid to react overnight. Crystals of di-O-butylidene penta erythritol had separated. These were filtered off, washed with water and recrystallised twice from ethanol to give white plate-like crystals (m.p. 63-64°).

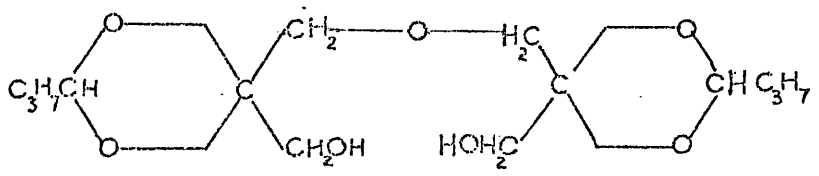


The remaining reaction mixture was neutralised, evaporated and extracted. The combined extracts gave a syrupy product after evaporation. Unreacted polyol was removed by chromatography on silica gel eluting with MEK saturated with water. Mono butylidene pentaerythritol was isolated as a white solid which was recrystallised from ethanol to give white crystals (m.p. 75-76^{o}).

The stereo chemistry of the diacetal was investigated and analysed by n.m.r. spectroscopy.

Dipentaerythritol:-

The reaction of this polyol and n-butyraldehyde in N hydrochloric acid was heterogeneous, hence it was necessary to shake the reaction mixture mechanically overnight. The reaction mixture was extracted with chloroform and the extracts washed thoroughly with water. After evaporation of the chloroform, a syrup of di-O-butylidene dipentaerythritol remained. This could not be crystallised.



The remaining reaction mixture was neutralised and examined by thin layer chromatography. Only unreacted polyol could be detected: no trace of any mono acetals was observed.

Methyl α-D-Glucoside:-

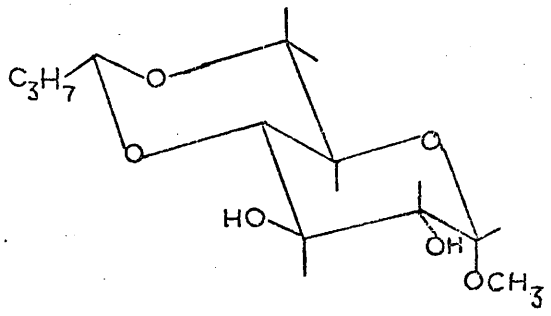
Equimolar amounts of the glucoside and n-butyraldehyde were examined polarimetrically in N hydrochloric acid. No evidence for kinetic control was obtained. The optical rotation decreased with time and had not reached equilibrium after five hours. Paper chromatography and tlc inferred the presence of D-glucose but no acetal formation.

The polarimetric reaction was repeated using a solution of hydrogen chloride in anhydrous dimethyl formamide (DMF). Again, as above, no acetal formation was observed, only hydrolysis.

When the reaction was repeated using toluene-4-sulphonic acid in anhydrous DMF, acetal formation was observed, but no evidence for

kinetic control was furnished. A mono acetal was extracted from the residue and recrystallised from ethanol (m.p. 108-109° $[\alpha]_D$ = 106.3° in H_2O).

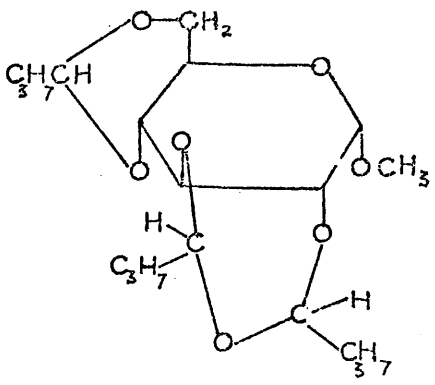
The acetal was treated with periodate but no consumption had occurred after 3 hours. Hence vicinal hydroxyl groups were originally thought to be absent. However, after 14 hours, one mol of periodate had been consumed with no formaldehyde nor formic acid liberated. Therefore one pair of vicinal hydroxyl groups was present in the molecule. The acetal was deduced as having the 4,6-ring structure. It gave a syrupy dimethyl ether and a crystalline dibenzoate.



A fully benzoylated derivative was obtained.

The reaction of methyl α-D-glucoside with three mols of n-butyraldehyde in the presence of conc. hydrochloric acid (after shaking for 3 hours) gave a solid product, after the addition of water. This product was filtered off and recrystallised from ethanol to give white crystals (m.p. 103-104° $[\alpha]_D$ = 69.9° in $CHCl_3$). This compound did not analyse for a di-O-butylidene acetal of methyl α-D-glucoside but $C_{19}H_{34}O_7$.

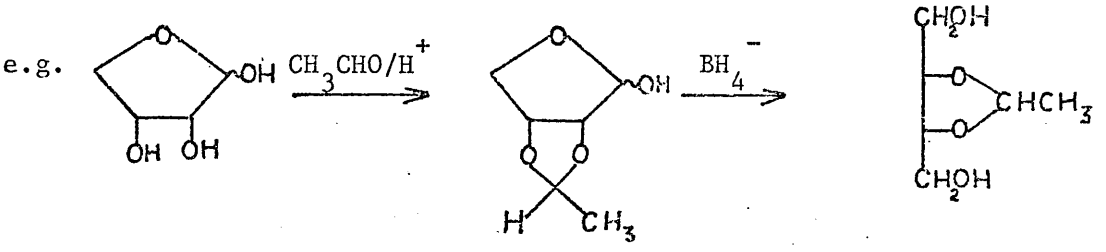
An infra red spectrum showed the absence of hydroxyl groups in the molecule. The structure of this compound was shown to be methyl 2,3 oxido di-n-butylidene 4,6-O-butylidene-α-D-glucoside.



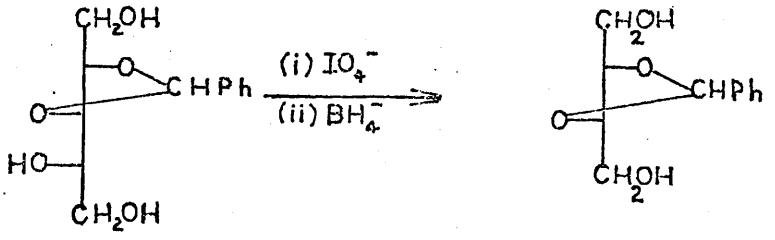
Discussion

For the tetritols, erythritol and L-threitol, it would be expected from the discussion in Section A that the thermodynamically most stable mono acetal would contain the β ring, i.e. the 1,3-O-mono acetal. This has been observed for both of these polyols with a variety of aldehydes. No published work has been offered for any other mono acetal ring forms from direct reaction of these polyols and an aldehyde under acidic conditions.

However previous work has shown that synthetic techniques could be employed to obtain both the αC acetal for erythritol[14,15] and the αT acetal of L-threitol[16] by indirect routes:-



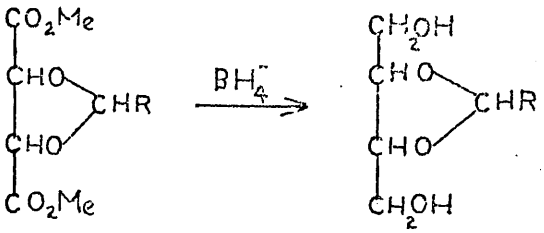
2,3-O-ethylidene erythritol



2,3-O-benzylidene-L-threitol

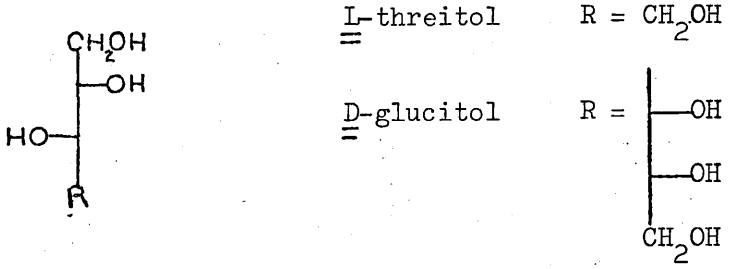
Feit[17] has synthesised similar compounds by the reaction of the dimethyl esters of different isomers of tartaric acid and aldehydes in acidic solution: borohydride reduction of this cyclic interim

product would give the 2,3 acetal of the polyol.



In the reaction between either erythritol or L-threitol and n-butyraldehyde in N hydrochloric acid the 1,3-mono-butylidene acetal was isolated as the thermodynamic product in both instances. However, in the acetalisation reaction of L-threitol and n-butyraldehyde a kinetic acetal was isolated and subsequently shown to be 2,3-O-butylidene L-threitol i.e. the αT compound. This was the first time that this ring form had been identified for the reaction between L-threitol and an aldehyde.

The configuration of threitol was comparable to D-glucitol from C_1 to C_3, as both molecules contained an αT configuration of hydroxyl groups.



Since D-glucitol exhibited a kinetic acetal with several aldehydes[8] and the reaction occurred at C_2-C_3 a similar reaction was envisaged with L-threitol. Both kinetic acetals involved the 2,3 ring form.

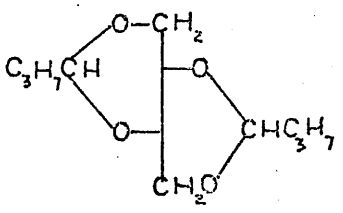
However D-glucitol could form the 2,4 compound as the thermodynamic product.

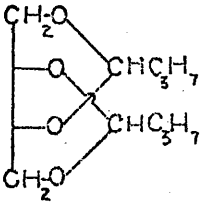
The values of a negative specific rotation for the kinetic acetal and a positive value for the thermodynamic acetal correlated with the polarimetric graph of the reaction between L-threitol and n-butyraldehyde.

The absence of the formation of a kinetic acetal for erythritol was to be predicted by comparison with D-glucitol. The equivalent erythro configuration existed at C_4-C_5: no acetal formation has been detected at these hydroxyl groups.

Both erythritol and L-threitol formed the 1,3:2,4 di-O-butylidene acetal, i.e. two β rings, as would have been predicted by previous theory.

These compounds both contained two 1,3-dioxane rings.





Both of these fused ring systems contained two chair forms and the conformations are discussed more fully in Section C.

The di-O-butylidene acetal of L-threitol was shown to exist in the "O inside" conformation by n.m.r. spectroscopy. A similar conclusion has been deduced regarding the structures of the

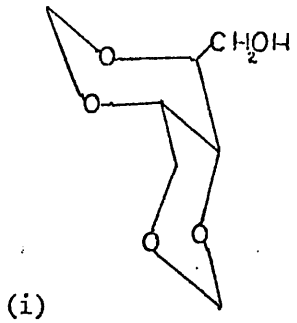
di-O-methylene[18] and di-O-benzylidene[19] acetals of L-threitol.

An examination of the structures of ribitol and xylitol would predict that the 2,4 mono acetal, i.e. βC compound, would be obtained as the thermodynamic product resulting from acetalisation. Also since xylitol and D-glucitol have similar structures from C_1-C_4 it would be logical to suppose that xylitol, like D-glucitol, would form a kinetic acetal involving an αT ring.

However, an acetalisation reaction with D-arabinitol would be more complex. The formation of the βC ring compound for this polyol was not possible. However a β ring could be formed and two possibilities: the 1,3 or 3,5 mono acetal as the thermodynamic acetal. Again D-arabinitol possessed an αT configuration of hydroxyl groups, suggesting that kinetic contrcl might have been expected.

When diacetal structures were considered, the prediction of the 1,3:2,4 compound, i.e. β and βC rings, was considered likely for ribitol and xylitol. Again, the formation of a diacetal for D-arabinitol appeared more complex than for the other two pentitols. Two general possibilities existed: either 1,3:2,4 or 2,4:3,5 - both of these compounds contained one β and one βT ring.

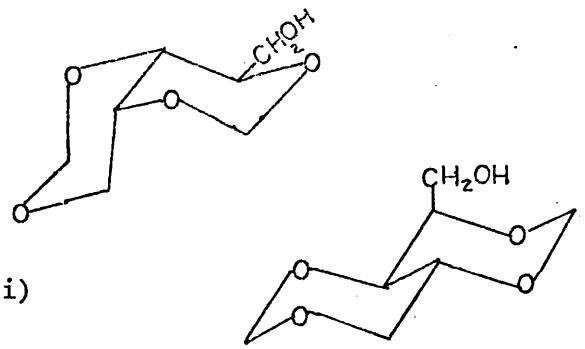
In a recent publication on vicinal polar bonds[20] the reaction of D-arabinitol with formaldehyde was considered. The two possible products are illustrated.



(i)

A

(cis fused 1,3:2,4)



(ii)

B

(trans fused 2,4:3,5)

From a consideration of molecular overcrowding and steric considerations the trans fused system (B) should be more stable. Experimentally, at thermodynamic equilibrium, the cis fused product (A) was obtained. This observation was attributed to the isomer (B) having three trans disposed carbon-oxygen bonds whilst isomer (A) can adopt conformer (A(i)) with only gauche oxygen-oxygen interactions. In solution the gauche arrangement predominates for vicinal oxygen substituents.

Stoddart[21] has arrived at the same conclusions by a different reasoning. By considering the thermodynamic equilibrium the relative free energy of the system would determine the product. Although it has been predicted that the 2,4:3,5 diacetal was 0.7 kcal $mole^{-1}$ more stable than the 1,3:2,4 isomer, the latter product predominated.

When the reactions of either ribitol or xylitol with n-butyraldehyde were examined, the 2,4 acetal was obtained as the thermodynamic product, as previously predicted. No evidence for

kinetic control was obtained for either of these polyols, rather surprisingly for xylitol. This was feasible for ribitol,but xylitol contained two αT hydroxyl groupings at C_2-C_3 and C_3-C_4 which had been previously shown to facilitate kinetic control in D-glucitol and some of its substituted analogues.

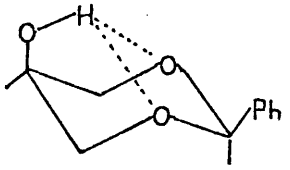
However the ribo configuration was not present in D-glucitol. The formation of several crystalline derivatives was readily accomplished for the mono acetal of ribitol. However analogous reactions with 2,4-O-butylidene xylitol failed to give a fully substituted benzoate and failed to yield a crystalline phenyl boronate.

The dibenzoate product obtained from attempted trimolar benzoylation showed the presence of intra molecular hydrogen bonding by infra red spectroscopy. Despite the fact that this hydroxyl group was readily acetylated it differed in reactivity from that of the dibenzoate of ribitol. The formation of a ditritylate for 2,4-O-butylidene xylitol showed the unreacted hydroxyl group to be in the 3 position.

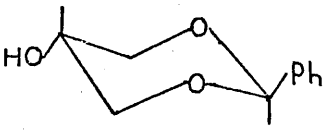
Much work has been focussed on the selective esterification[22] reactions of this type of system. In a study on cyclohexanols Eliel et al[23] have demonstrated that axial hydroxyl groups were acetylated far less readily than equatorial hydroxyl groups. The same conclusion has also been observed for the benzoylation of several glycosides[24]: in all instances equatorial hydroxyl groups were esterified with a greater ease than axial hydroxyl groups.

Hence, overall, reactivity towards esterification was shown to be dependent upon conformation.

An alternative study was made on the rate of esterification of cis and trans 5-hydroxyl 2 phenyl 1,3-dioxane (i.e. cis and trans 1,3-O-benzylidene glycerol)[25]. A preliminary study of these compounds by infra red spectroscopy showed the presence of intra-molecular hydrogen bonding in the cis isomer giving conformation (A), whereas the trans isomer showed absorptions for both bonded and free hydroxyl groups, suggesting conformation (B).



A (cis)



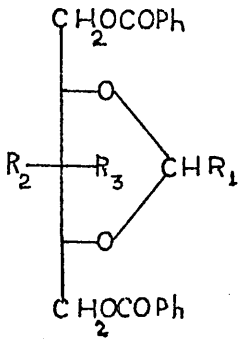
B (trans)

Kinetic esterification studies with substituted benzoyl chlorides showed the ratio of the rate constants to be:-

cis : trans = 5.6:1, in direct contrast to the 4-phenyl cyclo hexanols cis : trans = 1:6.6. Hence the reactivity of the hydroxyl group in cis 5-hydroxyl 2-phenyl 1,3-dioxane was increased markedly, meaning hydrogen bonding was important in the esterification of this compound. In an inert solvent e.g. carbon tetrachloride, acetylation proceeded at a greater rate for trans 4-phenyl cyclohexanol than for the cis isomer[25]. Conformational reasoning[26] would have predicted that the trans isomer was more stable.

A later investigation into the esterification of alcohols with acetic anhydride[27] showed no rate enhancement due to intra molecular hydrogen bonding.

The most recent publication on this problem has been made by Sugihara and co-workers[28]. 1,5-Di-O-benzoyl 2,4-O-alkylidene pentitols were kinetically examined upon esterification. The pentitols considered were ribitol and xylitol with methylene or benzylidene acetal groups.



I. 1,5-di-O-benzoyl 2,4-O-methylene
$[R_1 = R_2 = H \quad R_3 = OH]$ ribitol

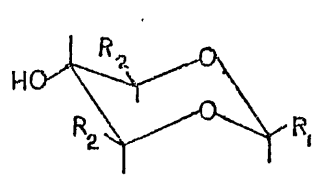
II. 1,5-di-O-benzoyl 2,4-O-methylene
$[R_1 = R_3 = H \quad R_2 = OH]$ xylitol

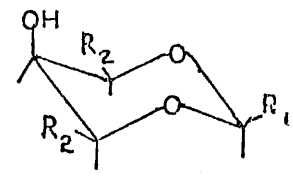
III. 1,5-di-O-benzoyl 2,4-O-benzylidene
$[R_1 = Ph; R_2 = H; R_3 = OH]$ ribitol

IV. 1,5-di-O-benzoyl 2,4-O-benzylidene
$[R_1 = Ph; R_2 = OH; R_3 = H]$ xylitol

Hudson[29] found compound IV to be the only product obtained in an attempt to fully benzoylate 2,4-O-benzylidene xylitol, but compounds I, II and III readily yielded tribenzoates.

Overall, the ribitol compounds I and III, with an equatorial hydroxyl group were more reactive than the corresponding xylitol compounds, II and IV, with an axial hydroxyl group.



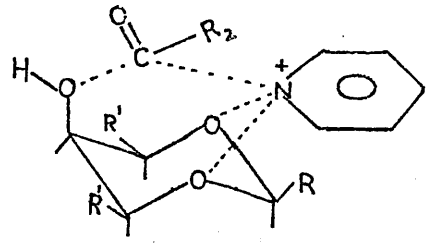


R_1 = H or Ph

R_2 = $C_6H_5CO_2CH_2$

Ribo Xylo

The greater reactivity of the benzylidene compounds was consistent with esterification data presented with acid anhydrides, although conformational changes were limited. The differences were smaller because of increased reactivity and less selectivity of acid chlorides. Sugihara et al[28] proposed the following intermediate for esterification in pyridine for the xylitol compounds.



R^1 = CH_2OCOPh

Therefore it appears that the benzoylated product of 2,4-O-butylidene xylitol may be compared to 1,5-di-O-benzoyl 2,4-O-benzylidene xylitol, in being inert to benzoylation at the hydroxyl group at C_3.

The formation of 1,3-O-butylidene-D-arabinitol as the thermodynamic acetal for n-butyraldehyde and D-arabinitol was in agreement with the product isolated from other aldehydes and this polyol. In

these latter examples the 1,3 acetal[30] was always obtained, never the 3,5. However kinetic control was detected in the initial stages of this reaction and subsequently 2,3-O-butylidene-D-arabinitol was isolated as the kinetic product. This was the first occurrence of this acetal.

Again the D-arabino configuration occurred in D-glucitol, from C_3-C_5. Despite the fact that this configuration contained an αT hydroxyl diol grouping at C_2-C_3, the corresponding site in D-glucitol, C_3-C_4, has not been shown to facilitate kinetic control. However the thermodynamic product contained the 1,3(β)ring which must have been more stable than the 3,5(β) ring since only the former product was obtained.

Hann et al[16] have synthesised 1,3 and 2,3-mono-benzylidene D-arabinitol which were subsequently oxidised and reduced to give the analogous D-threitol compounds.

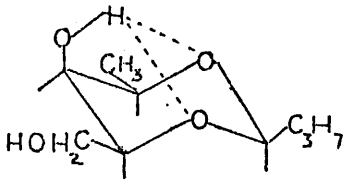
Ribitol and xylitol readily afforded their respective 1,3:2,4-di-O-butylidene acetals, i.e. a β and a βC ring. Foster et al[31] have isolated 1,3:2,4-di-O-benzylidene-D-arabinitol as well as the 1,3-mono acetal from the reactions of the polyol and benzaldehyde. For the butylidene analogues the ring structures were determined by physical techniques, whereas Foster proved the structures of the benzylidene diacetal by chemical techniques. However, an attempt to synthesise di-O-butylidene acetals for D-arabinitol resulted in a mixture of at least two products which could not be

separated by conventional techniques. Nevertheless, perhaps with the advent of liquid chromatography an amenable technique will present itself for the separation of these diacetals and future inseparable compounds.

As previously mentioned, xylitol was unique in not forming a kinetic acetal since it contained part of the 'reactive' D-glucitol configuration. Hence a study of acetalisation of xylitol blocked specifically at one hydroxyl group was considered. 1-Deoxy-D-xylitol was conveniently synthesised. Earlier work on this polyol by Richtmyer et al[32], with either formaldehyde or benzaldehyde enabled the isolation of a di-O-methylene, di-O-benzylidene diacetal, as well as 2,4-O-methylene 1-deoxy-D-xylitol indirectly. The di-O-methylene acetal could be assigned the 2,4:3,5 structure.

In this investigation 1-deoxy-D-xylitol behaved analogously to xylitol. Neither compound exhibited kinetic control. Like xylitol, 1-deoxy-D-xylitol gave the 2,4 mono acetal as the thermodynamic product, i.e. the βC compound.

The occurrence of this compound was directly comparable to xylitol. An infra red spectrum of this molecule showed the presence of intra molecular hydrogen bonding. Conformationally, the terminal methyl group would be expected to adopt an equatorial orientation, preferentially, enabling the axial OH at C_3 for 1-deoxy-D-xylitol to form an intra molecular hydrogen bond.



The isolation of these mono acetals for both xylitol and 1-deoxy-D-xylitol was directly analogous to D-glucitol, which also formed the βC compound as its thermodynamic mono acetal. However, it must be regarded as being irregular that neither xylitol nor its 1-deoxy analogue exhibited kinetic control since the xylo configuration had been shown to facilitate kinetic control in D-glucitol.

The diacetal which was isolated was analogous structurally to the di-O-methylene acetal and probably the di-O-benzylidene acetal mentioned before.

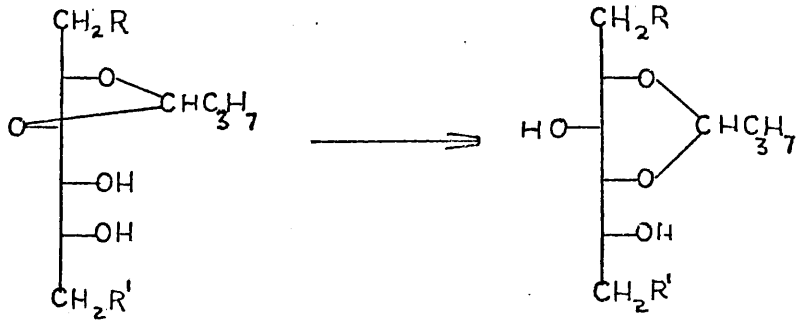
This acetal was attributed to the 2,4:3,5 structure, which was expected to be conformationally similar to 1,3:2,4-di-O-butylidene L-threitol and 1,3:2,4-di-O-butylidene xylitol.

In the pioneering work of Hann and Hudson[33] on the relationship of acetal structure and the parent polyol, 6-deoxy-D-glucitol was synthesised from 1,3:2,4-di-O-methylene D-glucitol, via 6-deoxy 1,3:2,4-di-O-methylene D-glucitol.

Like D-glucitol[7] and 1-deoxy-D-glucitol[11] it was predicted that 6-deoxy-D-glucitol would form the βC compound as its thermodynamic mono acetal, and possibly exhibit kinetic control. Experimentally, 2,4-O-butylidene-6-deoxy-D-glucitol was obtained

as the thermodynamic acetal. Kinetic control was exhibited and a syrupy kinetic acetal isolated. Although inadequate acetal was available for a complete structural analysis, all the evidence favourably inferred the 2,3 structure, i.e. 2,3-O-butylidene-6-deoxy-D-glucitol.

Hence the following pictorial relationship can be shown between D-glucitol, 1-deoxy-D-glucitol and 6-deoxy-D-glucitol.



Kinetic Acetal Thermodynamic Acetal

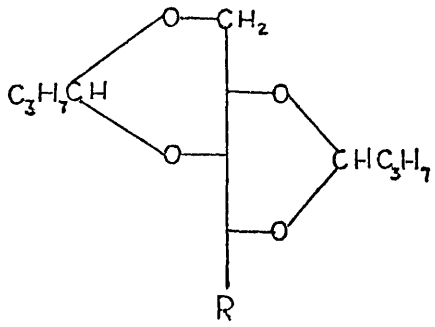
D-glucitol R = R^1 = OH

1-deoxy-D-glucitol R = H R^1 = OH

6-deoxy-D-glucitol R = OH R^1 = H

The di-O-butylidene acetal isolated from this reaction was found to possess the 1,3:2,4 structure.

Again this structure was directly comparable to 1,3:2,4 di-O-butylidene-D-glucitol and 1,3:2,4-di-O-butylidene xylitol. Indeed very similar features were observed for the ^{1}H n.m.r. spectra of these compounds (see Section C).



xylitol R = CH_2OH

D-glucitol R = $-CH(OH)-CH_2OH$

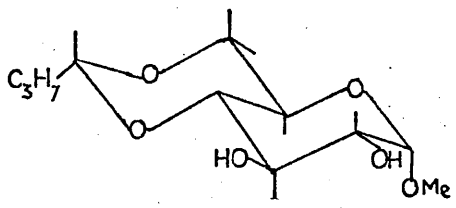
6-deoxy-D-glucitol R = $-CH(OH)-CH_3$

Since similar mono acetals (both kinetic and thermodynamic) have been isolated for D-glucitol, 1-deoxy-D-glucitol and 6-deoxy-D-glucitol, the substitution of a hydroxy methyl group at C_1 or C_5 for a methyl group has not affected acetalisation reactions from C_2 - C_4 in these polyols.

In this work, the separation of the kinetic and thermodynamic mono acetals for L-threitol, D-arabinitol and 6-deoxy-D-glucitol has been achieved on Dowex OH^- resin. This resin has been previously employed for the separation of anomeric glycosides[34]. An explanation has been offered considering the respective acidities of different hydroxyl groups in the molecule. A strong acidic hydroxyl group would be retained on the resin in preference to a weakly acidic hydroxyl group. In this work a six-membered 1,3-dioxane acetal ring has been eluted preferentially to a five-membered 1,3-dioxolane acetal. Consequently, 1,3-dioxane ring compounds must be less acidic than the isomeric 1,3-dioxolane acetals.

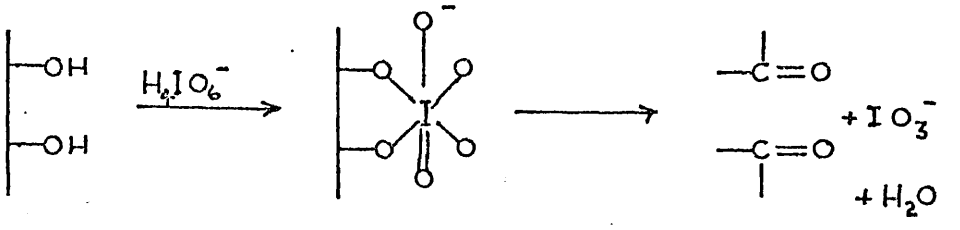
The reaction of most aldohexoses or aldohexosides with an

aldehyde has given the 4,6-mono acetal as the major product isolated. This work has been adequately reviewed by de Belder[35]. For methyl glycosides, the 4,6 acetal has always been isolated, with the anomeric methyl group still retained in the product, i.e. anomeric hydrolysis has not occurred. In this work the reaction of methyl α-D-glucoside and n-butyraldehyde was examined, and methyl 4,6-O-butylidene α-D-glucoside was obtained, in agreement with previous work. However, in the structural elucidation of this molecule, the initial periodate oxidation result, after two hours, was firstly misconstrued, but interpreted later, and given a conformational significance. After complete oxidation, one mol of periodate had been consumed, whereas no oxidation had occurred after 3 hours. The intermediate which has been postulated in periodate oxidation, depends upon a suitable orientation for the reacting hydroxyl groups. Hence if an unfavourable stereochemical orientation exists, oxidation is very slow.



In the expected conformation for this acetal the hydroxyl groups available for oxidation at C_2 and C_3 were in a di-equatorial orientation.

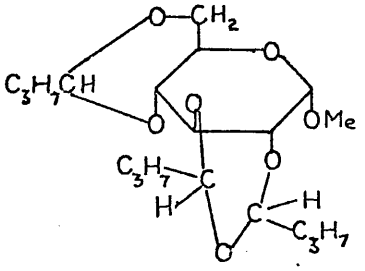
In contrast, the oxidative cleavage of a diol grouping may be depicted[36].



In the octahedral complex, four groupings are in one plane. In order to achieve this structure for methyl 4,6-O-butylidene-α-D-glucoside a change in the above conformation has to occur. Methylation of the 4,6-acetal with dimethyl sulphate and aqueous sodium hydroxide gave a syrup which had a similar infra red spectrum to the syrupy product obtained by methylation of the 4,6-acetal of methyl α-D-glucoside. In neither spectrum was it possible to determine the nature of the anomeric linkage, as the solvent (carbon tetrachloride) has an absorption band near the region (900-800 cm^{-1}) of interest, but methylation of the 4,6-acetal of α-D-glucose should have given mainly the β-anomer[37].

Diacetal formation for methyl α-D-glucoside has never been observed. Consequently, the reaction of methyl α-D-glucoside with three moles of n-butyraldehyde in concentrated hydrochloric acid gave methyl 2,3-oxido di-n-butylidene α-D-glucoside. The ethylidene compound has previously been synthesised by an analogous

technique[37]. The stereochemistry of this molecule has been examined and it appears that some deviation from the $^4C_1$ chair conformation has occurred.

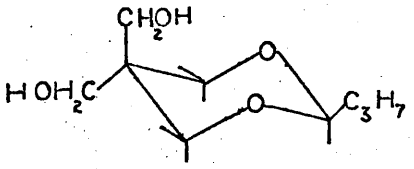


Hence, stereochemically methyl α-D-glucoside cannot form a diacetal. The internal energy which has to be overcome must be too great. In both of these compounds of methyl α-D-glucoside retention of the anomeric grouping has resulted. This was in direct contrast to the initial polarimetric work on this glycoside, when aqueous or anhydrous hydrochloric acid hydrolysed the anomeric grouping.

Lastly, the formation of butylidene acetals for pentaerythritol and dipentaerythritol was considered.

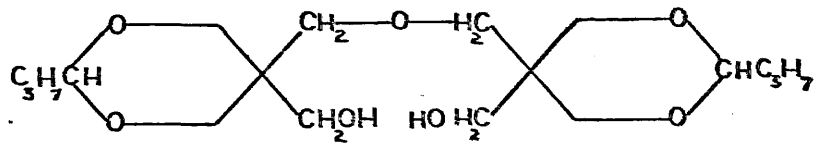
For pentaerythritol a mono and diacetal were obtained. The diacetal had previously been reported by a Russian worker[38], but with a lower melting point.

Stereochemically mono butylidene pentaerythritol was postulated as in a chair conformation.



However, the stereochemistry and conformational aspects of di-O-butylidene pentaerythritol were far more complex. This molecule will be discussed more fully in Section C.

For dipentaerythritol, only a diacetal was produced. Very little information was available for acetal formation on the acetals of this molecule. However, a symmetrical structure was proposed for di-O-butylidene dipentaerythritol.



Overall the results of this discussion can be summarised:-

	Kinetic Mono	TD Mono	Di
Erythritol	-	2,4	1,3;2,4
L-Threitol	2,3	1,3	1,3;2,4
Ribitol	-	2,4	1,3;2,4
Xylitol$^{\phi}$	-	2,4	1,3;2,4
D-Arabinitol	2,3	1,3	?
1-Deoxy-D-Xylitol	-	2,4	2,4;3,5
6-Deoxy-D-Glucitol	2,3	2,4	1,3;2,4
Me α-D-Glucoside	-	4,6	2,3;4,6*
Penta erythritol	-	✓	✓
Dipenta erythritol	-	-	✓

*Me 2,3 oxido di-n-butylidene 4,6-O-butylidene α-D-glucoside

$^{\phi}$Kinetic control has been detected for xylitol[39].

SECTION B. REFERENCES

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SECTION C

APPLICATION OF PHYSICAL TECHNIQUES TO STRUCTURAL DETERMINATIONS OF ACETALS

SECTION C. APPLICATION OF PHYSICAL TECHNIQUES TO THE CHEMISTRY OF ACETALS

Classically, the structures of acetals were determined by chemical techniques. However, these methods were limited and restricted by two factors. Primarily, the basic assumptions were the non-migration of acetal rings upon chemical reaction, an assumption which was generally valid. Also, more importantly, the fact remained that these techniques only allowed the location of the position of free hydroxyl groups in an acetal molecule: no evidence was rendered for the size or stereochemistry of fused or adjacent acetal rings. For the latter technique graded acidic hydrolysis was employed. However, since an acetal was synthesised under acidic conditions competing equilibria could result.

Hence, since the advent of physical techniques and instrumental methods to this class of compound, a large volume of structural, configurational and conformational data could be readily accumulated.

Three physical techniques will be discussed with respect to the above: infra red spectroscopy (i.r.), mass spectroscopy (m.s.) and nuclear magnetic resonance spectroscopy (n.m.r.).

Infra Red Spectroscopy:—

The infra red spectra of acetals, like most carbohydrates were complex and hence not very readily fully interpretable. Nevertheless,

these spectra may be utilised for:

(i) the identification of functional groups (or, conversely the absence of functional groups e.g. absence of OH in acetylation product).

(ii) visual comparison with known standards or compounds of a similar class or the "finger printing" of spectra.

(iii) correlating information on conformational, configurational or structural data.

(iv) monitoring chemical reactions kinetically: qualitatively or quantitatively.

This work has utilised infra red of acetals and related compounds in the formation of derivatives, e.g. after benzoylation, methylation or acetylation, products have been checked for the absence of hydroxyl groups.

Acetals and derivatives which were not fully substituted have been examined to determine the nature of the free hydroxyl group[1] present.

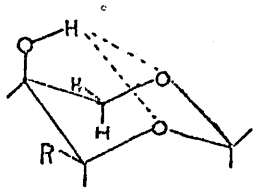
i.e.	primary	1080 - 1000	cm^{-1}
	secondary	1130 - 1080	cm^{-1}
	tertiary	near 1140	cm^{-1}

Cyclic acetals do not give highly characteristic absorption bands, but instead show 4 or 5 stretching vibrations in the range 1200-1020 cm^{-1}. In like fashion, the C-O-C asymmetric stretch of an ether at 1150-1070 cm^{-1} is only of partial value in structure studies. The propyl chain in butylidene acetals and the CH groups in the polyol chain both give stretching vibrations in the range 3000-2850 cm^{-1} but the information is of limited interpretative use. On the other hand, benzoates and acetates have strong characteristic C = O bond stretching vibrations at 1748-1724 cm^{-1}.

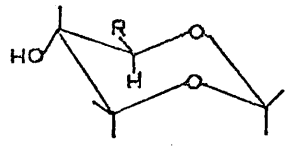
Conformationally, the presence of inter, intra moleculary bonded or free hydroxyl groups can afford much information. For this work spectra were recorded as dilute solutions (less than 0.005 m) in carbon tetrachloride solution. Fundamentally, the hydroxyl grouping absorbed at 3600 cm^{-1}. However, this figure was shifted to a lower wave number when the hydroxyl group was hydrogen bonded: as a general rule, the lower the frequency, the greater the strength of the hydrogen bond.

The reaction of L-arabinitol with formaldehyde could yield either the 1,3 or 3,5 acetal i.e. both β rings. Experimentally, as discussed in the previous section, the 1,3 ring was produced[2]. The preferred conformer had an axial hydroxyl group at C_2, which could

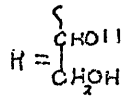
form a hydrogen bond with the two oxygen atoms of the 1,3-dioxane ring, thus stabilising this structure.



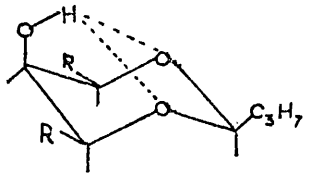
1,3



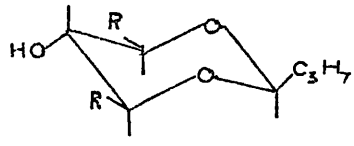
3,5



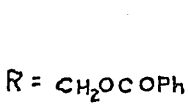
The benzoylation of 2,4-O-butylidene xylitol produced the 1,5-dibenzoate only. The infra red spectrum of this product showed the presence of intra molecular hydrogen bonding absorbing at 3580 cm^{-1}. Hence the conformation with an axial hydroxyl group at C_3 was inferred. The corresponding 2,4-O-butylidene 1,5-di-O-benzoyl ribitol showed no such bonding.



xylo



ribo



However, in direct contrast 1,3-O-butylidene L-threitol, which would be expected to form a similar hydrogen bonded structure, afforded a fully benzoylated product.

Mass Spectrometry:-

This analytical technique involves the fragmentation of a molecule by electron impact and the separation of the fragments, both radicals and ions, on the basis of mass. It is possible to extend this to a gas

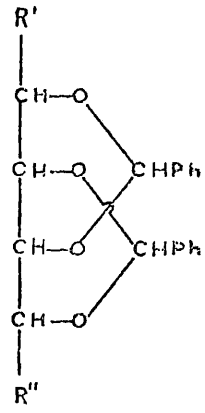
liquid chromatographic separation e.g. polysaccharide analysis, hence enabling much structural information to be made available from mg amounts. Mass spectrometry may be applied to acetals for the determination of molecular weight, elemental analysis or structural determinations of the molecule.

In general, a substance must have a vapour pressure of 10^{-2} mm Hg (approx.), to enable a mass spectrum to be produced. However, if the substance is not this volatile, it has to be converted into a suitably volatile derivative e.g. trimethyl silyl ether, methyl ether or acetate derivatives are often employed. Consequently acetals with many free hydroxyl groups were converted to one of the above derivatives.

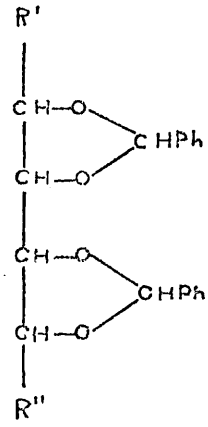
Early work on carbohydrates by Kochetkov et al[3] involved a study of the mass spectra of methyl glycosides, both fully methylated and some deuterated analogues. A later investigation by Marshall and Williams[4] of 1,3-dioxolane compounds enabled a fragmentation pattern to be assembled.

However, Chizhov et al[5] examined many fused ring and adjacent ring type acetals. A half ion type mechanism was proposed[6,7].

Molecules of the type I and II were examined.



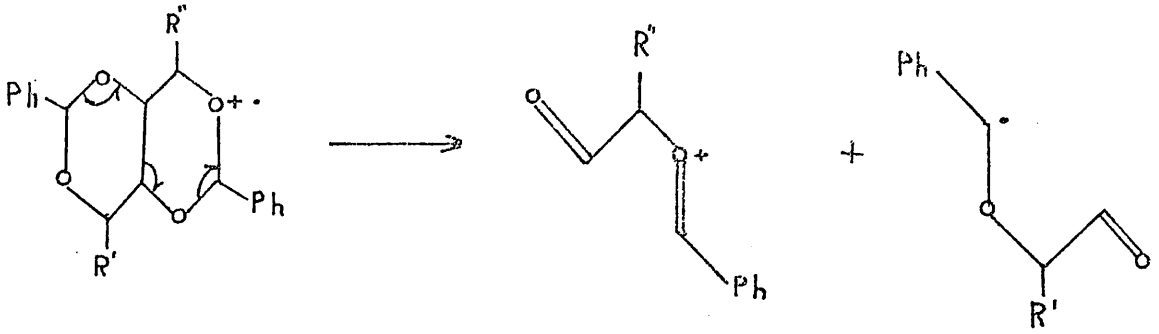
I



II

All molecules of type I (1,3,6,8-tetraoxo bicyclo 4.4.0 decanes) gave mass spectra with intense peaks having a mass number equal to one half of the molecular weight for symmetrically substituted compounds e.g. $R_1 = R_2$; 1,3;2,4-di-O-benzylidene erythritol. When R_1 and R_2 were not equal then a pair of peaks were produced whose sum total was equal to the molecular weight e.g. 1,3; 2,4-di-O-benzylidene ribitol. These ions were designated "half ions" and the overall process "h-rupture".

An explanation for this process entailed the fission of three bonds to give two very stable fragments, the h-ion and the h-radical n.b. only one fragment was charged.



h - ion h - radical

e.g. for 1,3:2,4-di-O-benzylidene ribitol (molecular weight 328).

h-ion m/e 149

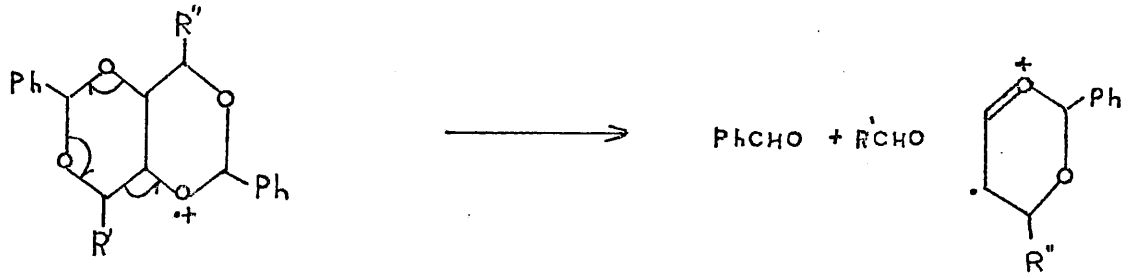
h-radical m/e 179

$\therefore$ (h-ion + h-radical) = 328

(h-radical - h-ion) = 30

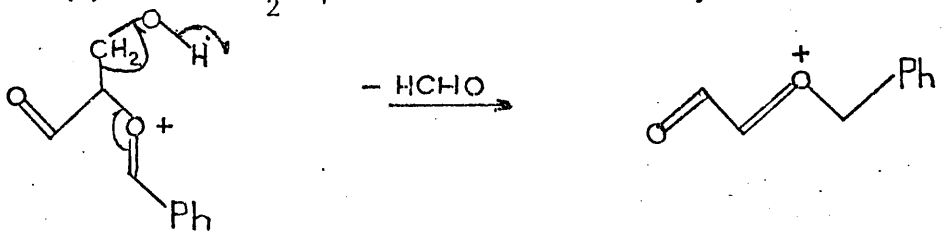
$\equiv$ (CH_2—OH - H) = 31-1 = 30

Also the formation of the ion where m/e equals one 1,3-dioxane ring was explained, viz.



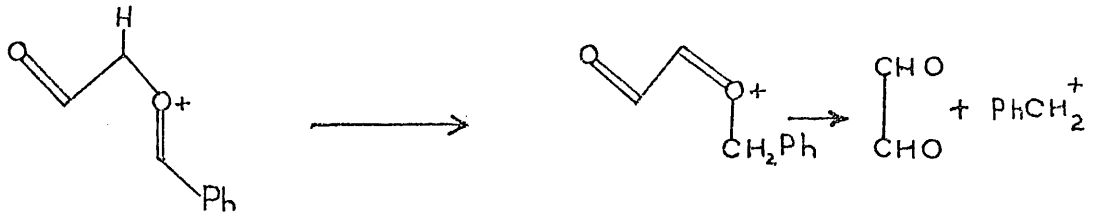
The h-ion can undergo two transformations:

(i) if R = CH_2OH, 1 molecule of formaldehyde can be lost



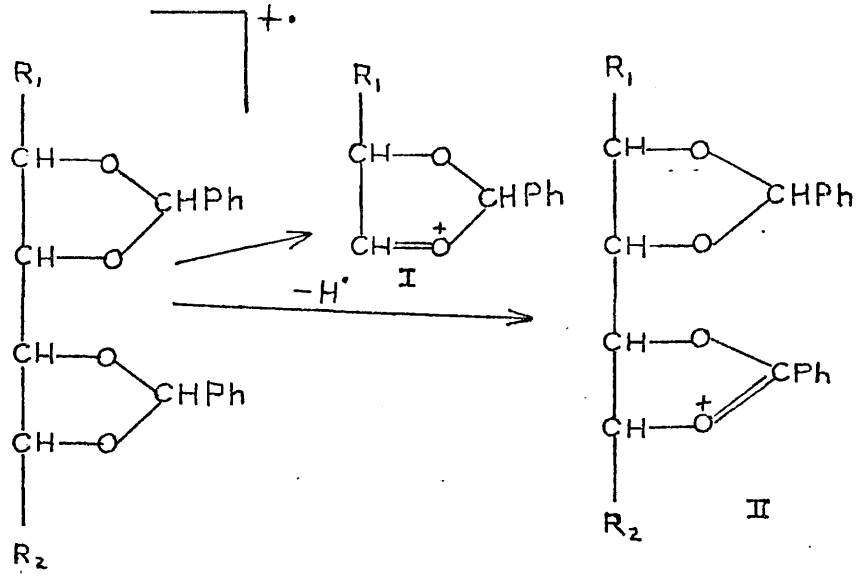
m/e 179 m/e 149

(ii) if R = H then an isomerisation can occur.



This fragmentation has been supported by meta-stable ions of suitable m/e values.

Compounds of type II (4,4' -bis-1,3-dioxolane) gave a different fragmentation pattern to the isomeric 1,3-dioxane type acetals.



The above fragment (I) was the most abundant in the spectra: all others were of low intensity. As shown by Marshall et al[4] the molecular ion could lose a hydrogen atom. This fragment could then lose benzaldehyde and benzoic acid.

Consequently, a knowledge of the mass spectra of acetals has

been employed for structural and to a lesser extent stereochemical determinations.

Mass spectra of cyclic butylidene acetals showed several characteristic features. The molecular ion M^+ and the ion $(M-1)^+$ were encountered. The loss of the side-chain group C_3H_7 has been observed: this has resulted in the appearance of the ion $(M-43)^+$, this is in direct contrast to Chizhov's work where the C-Ph bond was extremely resistant to electron impact.

However, for mono acetals it was not possible to account for spectral differences in structural isomeric acetals of the same polyol, e.g. 1,3-(or 2,3)-O-butylidene-D-arabinitol nor for isomeric structures of different polyols e.g. 2,4-O-butylidene ribitol (or xylitol).

Considering the diacetals examined, the following characteristic fragments were observed (m/e values).

	M^+	$(M-1)^+$	$(M-43)^+$	h-ions
1,3:2,4-di-O-butylidene erythritol) 1,3:2,4-di-O-butylidene-L-threitol)	230	229	187	115
1,3:2,4-di-O-butylidene ribitol) 1,3:2,4-di-O-butylidene xylitol)	260	259	217	115, 145
1-deoxy 2,4:3,5-di-O-butylidene-D-xylitol	244	243	201	115, 129
6-deoxy 1,3:2,4-di-O-butylidene-D-glucitol	284	283	241	115, 169

All of the diacetals examined belonged to the 1,3,6,8-tetraoxobicyclo (4.4.0) decane class.

Nuclear Magnetic Resonance Spectroscopy:—

For a specific nucleus the spin quantum number, I, may be integral, half integral or zero. Nuclei which have spin possess a magnetic moment enabling them to be studied by nuclear magnetic resonance (n.m.r.) spectroscopy.

Acetals, like all carbohydrate derivatives possess two nuclei which are amenable for a n.m.r. study: the proton (^{1}H, $I = \frac{1}{2}$) and a carbon isotope (^{13}C, $I = \frac{1}{2}$). However, the difference in isotopic abundances of these nuclei gives rise to different spectral features.

Proton magnetic resonance spectroscopy (p.m.r.) on high resolution instruments can reveal much structural data e.g. configurational, conformational, anomeric character and the nature of the linkage for polysaccharides.

In order to interpret a first order p.m.r. spectrum fully, three fundamental parameters have to be understood.

a) Chemical shift (δ in ppm): the resonance of a particular proton from a standard compound (e.g. tetramethyl silane, $\delta = 0$). These values may be converted to a τ scale where $10 - \delta = \tau$. A proton in the vicinity of an electron with-drawing group will be relatively deshielded and will resonate at a lower applied field. Usually anomeric and acetal protons resonate at a lower applied field than other protons for carbohydrates. Hence these features may be readily identified. Overall, the value of the chemical shift may be utilised in functional

group identification.

b) Multiplicity : this gives an indication of the number of protons (n) to which a particular proton resonance is coupled.

$$\text{Multiplicity} = 2nI + 1, \quad \text{but } I = \tfrac{1}{2} \text{ for } {}^{1}H$$

$$= n + 1$$

The intensities of signals in a multiplet are in accord with a Binomial Expansion i.e. triplet 1:2:1, quartet 1:3:3:1

e.g. a triplet may be derived from a signal coupled to a CH_2 group. However, the coupling of a signal to two independent groups may be the same, giving rise to multiplicities less than that theoretically expected.

c) Coupling constant (JHz): a measure of the stereochemical environment of adjacent coupled protons. The magnitude of the coupling constant affords information on the dihedral angle for adjacent protons. (J is a maximum value when the dihedral angle equals 180°).

However, if the value of $\Delta\delta$ approximates to J, then these features can overlap and the spectrum is termed second-order i.e. for a first order spectrum $\Delta\delta > J$, where $\Delta\delta$ = shift difference between two protons.

However, the data furnished by n.m.r. only apply in solution and only for that solvent at that temperature. Different spectral features may be observed in different solvents at different temperatures. Also

different conformations may exist in the crystalline state, here X-ray crystallography has to be employed .

N.m.r. may be conveniently applied for the anomeric configuration, conformation and general ring stereochemistry of mono-saccharides.

Baggett et al[8] examined several benzylidene acetals and determined the stereochemistry at C_2 (the acetal carbon atom) as well as the ring size.

More recently Hall et al[9] have incorporated the use of complexing reagents to form chelates ~ usually rare earth compounds termed lanthanide shift reagents. The use of these reagents has considerably simplified spectra in several cases. Nevertheless, conformers which occur in these complexes, may be different from those in normal solutions or the crystalline state.

Methylated or acetylated derivatives have enabled much more spectral simplification.

When the cyclic butylidene acetals of D-mannitol were examined[10], a relationship between ring size and the resonance of the acetal proton was obtained. Since the acetal proton occurred as a triplet (i.e. coupled to an adjacent CH_2 group), the position of this triplet was indicative of ring size. A 1,3-dioxolane ring triplet resonated at 4.85-5.00 τ, a 1,3-dioxane at 5.4-5.5 τ and a 1,3-dioxepane ring intermediate between these two values. These values have been recorded for many acetals and shown to be valid.

An examination of the cyclic butylidene acetals has enabled the following features to be assigned for the aliphatic butylidene acetal chain:-

(i) the shift of the protons of the terminal methyl group occur as a triplet at $\tau = 9.1$ ($J = 6$ Hz).

(ii) the protons of the two methylene groups do not occur as first order features, but as a multiplet at 8.5 τ (approx.). However, at 220 MHz these two groups exist as separate multiplets at 8.4 and 8.7 τ, but neither are first order.

(iii) the acetal proton occurs as a triplet, τ values previously discussed ($J = 5$ Hz).

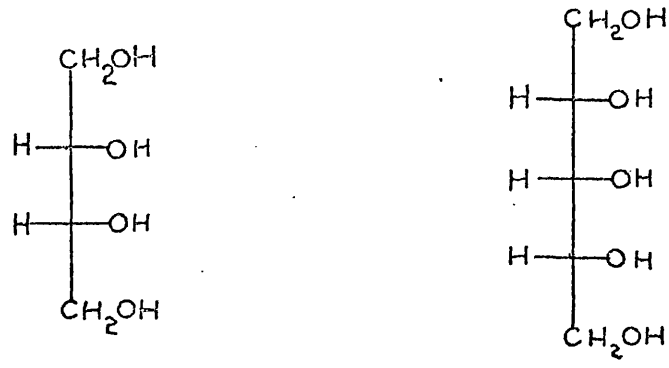
These features confirm that n-butyraldehyde does not rearrange upon acetalisation reaction, i.e. n-C_3H_7 present in acetal.

For terminal deoxy polyol acetals a doublet exists at 8.7 τ ($J = 6$ Hz).

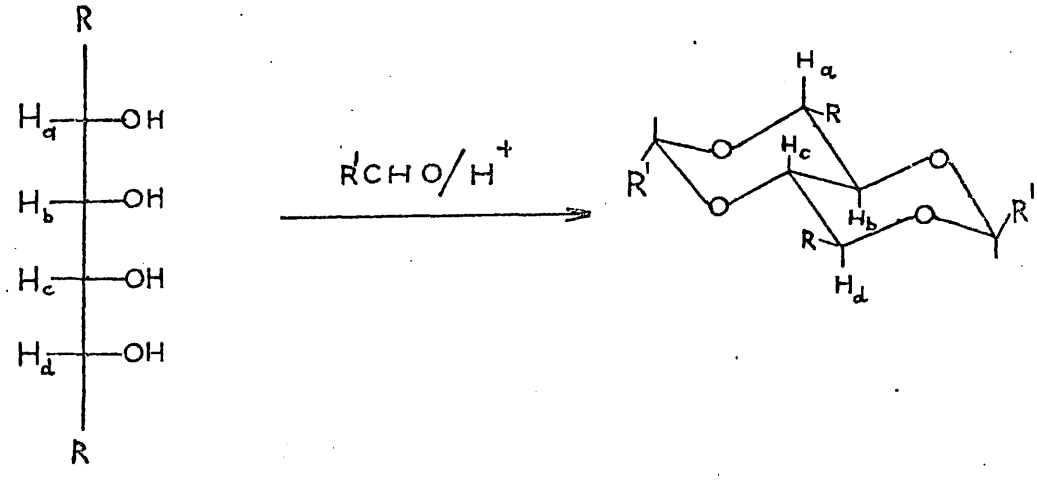
Spectra for mono acetals with free hydroxyl groups do not reveal much conformational data.

However, this study was more concerned with diacetal structures.

For a cis-cis tetritol system one conformer is obtained,

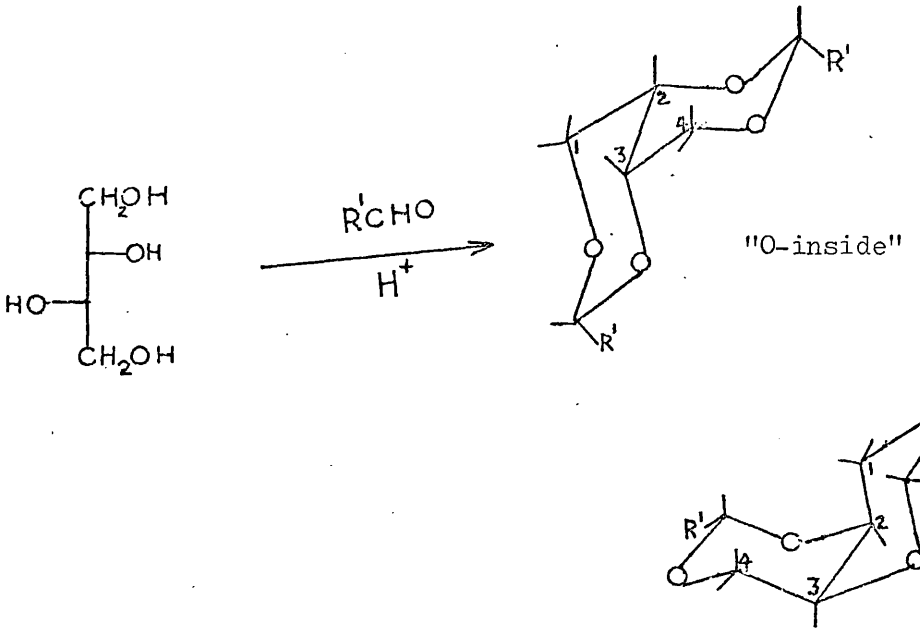


n.b. H_a, H_b, H_c and H_d all adopt axial conformations



e.g. diacetals of erythritol and ribitol.

However, the presence of a threo configuration can give more than one conformer e.g. L-threitol.



Hence compounds with this type of configuration e.g. L-threitol xylitol and 6-deoxy-D-glucitol diacetals fall into this category.

Experimentally, Lemieux and Howard[11] have illustrated by n.m.r., as well as dipole moment measurements, that the "O-inside" conformation was favoured for 1,3:2,4-di-O-methylene L-threitol. The same conclusion has been reached by Foster et al[12] when considering 1,3:2,4-di-O-benzylidene L-threitol. Graded acidic hydrolysis gave 1,3-O-benzylidene L-threitol, a compound whose structure and conformation had been shown previously. Hence the conformer of the mono acetal could be related to the diacetal.

Resonance positions of Butylidene Acetal Protons at 100 MHz

	Solvent	τ	J (Hz)
1,3-O-butylidene-DL-erythritol	D_2O	5.40	5.0
1,3:2,4-di-O-butylidene erythritol	$CDCl_3$	5.40	4.9
1,3-O-butylidene-L-threitol	D_2O	5.24	5.0
2,3-O-butylidene-L-threitol	D_2O	4.88	5.0
1,3:2,4-di-O-butylidene-L-threitol	$CDCl_3$	5.48	5.0
2,4-O-butylidene ribitol	D_2O	5.47	5.0
1,3:2,4-di-O-butylidene-DL-ribitol	$CDCl_3$	5.40 ; 5.28	4.75
2,4-O-butylidene xylitol	D_2O	5.45	4.8
1,3:2,4-O-butylidene-DL-xylitol	$CDCl_3$	5.45 ; 5.38	5.0
1,3-O-butylidene-D-arabinitol	D_2O	5.36	5.0
2,3-O-butylidene-D-arabinitol	D_2O	4.88	4.8
2,4-O-butylidene-1-deoxy-D-xylitol	D_2O	5.23	5.0
2,4:3,5-di-O-butylidene 1-deoxy-D-xylitol	$CDCl_3$	5.48 ; 5.44	5.0
2,4-O-butylidene 6-deoxy-D-glucitol	D_2O	5.24	5.0
2,3-O-butylidene 6-deoxy-D-glucitol	D_2O	4.90	4.9 (approx.)
1,3:2,4-di-O-butylidene 6-deoxy-D-glucitol	$CDCl_3$	5.42 ; 5.40	5.0
Mono butylidene pentaerythritol	D_2O	5.37	4.9
di-O-butylidene-RS-pentaerythritol	$CDCl_3$	5.53	5.0
di-O-butylidene dipenta erythritol	$CDCl_3$	5.58	4.65
Methyl 4,6-O-butylidene α-D-glucoside	D_2O	5.28	5.0
Methyl 2,3-oxido di-n-butylidene 4,6-O-butylidene α-D-glucoside	$CDCl_3$	5.45 (4.97 and 4.91 acetal protons of oxido ring)	5.0

Every acetal synthesised was examined by n.m.r. Initially a spectrum was recorded at 60 MHz on a "bench top" instrument. A more detailed spectrum was obtained at 100 or 220 MHz.

The spectra of mono acetals recorded in D_2O contained a broad band at 5.6 - 5.7 τ attributable to HDO, due to isotopic exchange. However when the spectra were recorded at a slightly elevated temperature (40-45°), the position of this peak was shifted to a slightly higher field (approx. 6.2 τ) enabling signals previously under this band to be revealed.

As observed from the table, the positions of the acetal triplets were in good agreement with the values predicted for the particular ring sizes, as previously discussed. Assignments were verified by double resonance techniques: irradiation of the $(CH_2)_2$ multiplet caused the triplets each to collapse to a singlet.

N.m.r. spectroscopy has been utilised primarily to aid the elucidation of diacetal structures. Spectra obtained for individual compounds will now be considered:-

For di-O-butylidene erythritol (Fig.1) the acetal triplet which integrated for two protons occurred at 5.40 τ (for $CDCl_3$ solution at 100 MHz). This was interpreted as two magnetically equivalent 1,3-dioxane type rings, i.e. the 1,3:2,4 diacetal structure. The other signals were produced for the protons of the polyol skeleton, neither of which were first order. A multiplet resonating at 5.90 τ integrating for two protons was attributed to the equatorial

Fig. 1 1,3:2,4-Di-O-Butylidene Erythritol in $CDCl_3$; 100MHz, 250Hz expansion

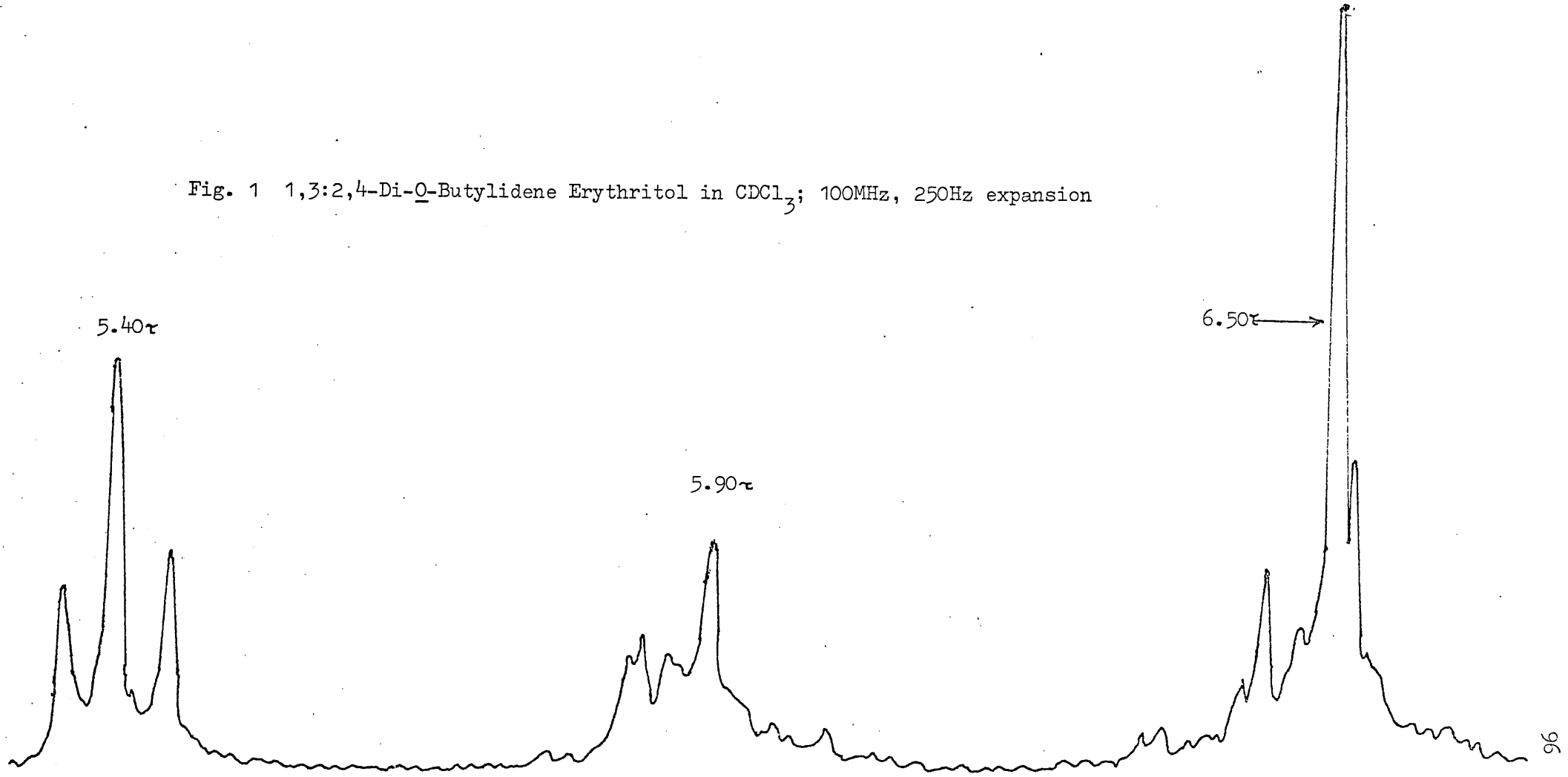
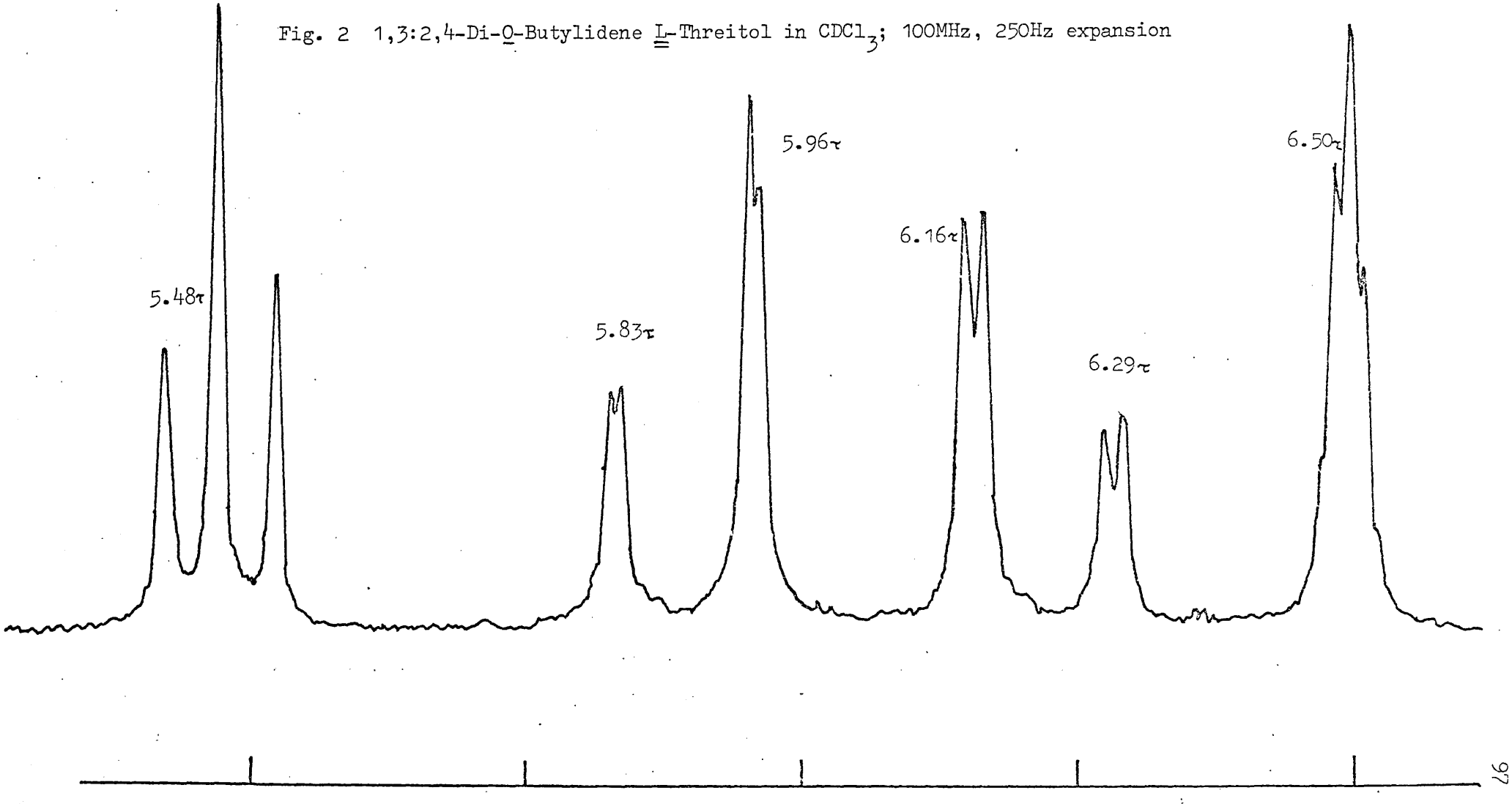
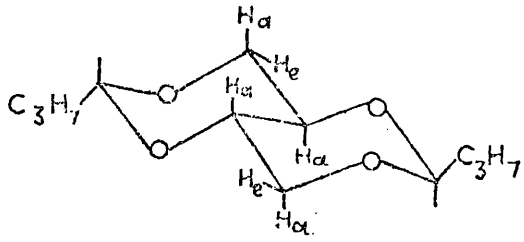


Fig. 2 1,3:2,4-Di-O-Butylidene L-Threitol in $CDCl_3$; 100MHz, 250Hz expansion

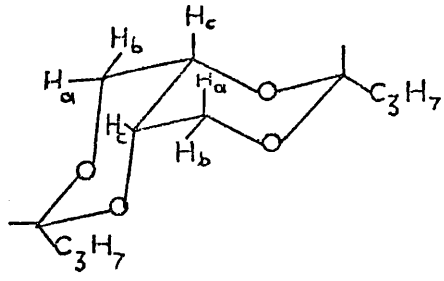


protons H_e and a multiplet at 6.50τ which integrated for four protons was assigned to the axial protons H_a.



Di-O-butylidene L-threitol (Fig.2) showed a triplet at 5.48 τ integrating for two protons, which was assigned to the acetal protons in this molecule. Hence two equivalent six membered rings were present; this enabled the 1,3: 2,4-diacetal structure to be assigned. However, as previously discussed, molecules of this type could exist in two possible conformations: the "O-inside" and "H-inside" conformers.

However, the evidence from this spectrum indicated that this molecule existed in the "O-inside" conformation at room temperature in $CDCl_3$.



The following signals were obtained and analysed on a first order basis.

τ	Multiplicity	J(Hz)
5.83	doublet	0.75
5.96	doublet	0.75
6.16	doublet	2
6.29	doublet	2
6.50	distorted quartet	3.5

Irradiation of the signal at highest field (i.e. the distorted quartet at 6.50 τ) caused the remaining doublets to each collapse to a singlet. Hence this signal was attributed to the bridge-head protons H_c, since it integrated, also, for two protons.

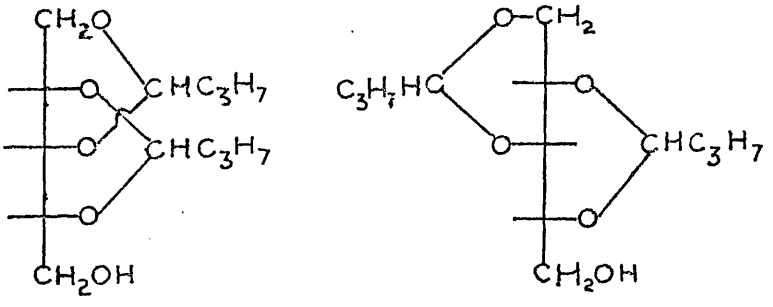
The doublets centred at 5.83 and 5.96 τ were assigned a quartet which was assigned to the equatorial protons H_b. The remaining quartet (i.e. doublets centred at 6.16 and 6.29 τ) was assigned to the axial protons, H_a. The value of the coupling constant J_{bc} = 2 Hz agreed with the value predicted for this conformation: a value of J_{bc} = 10 Hz would be expected for the "H inside" conformation. These assignments were confirmed by double resonance techniques.

A value for the geminal coupling J_{ab} = 12 Hz could also be obtained from this spectrum.

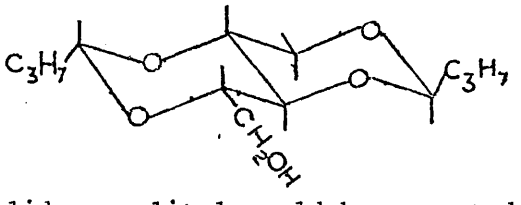
Overall, this spectrum was analysed on the basis of a 'double ABM' type where A = H_a protons, B = H_b protons and

M = H_c protons: Lemieux[11] has previously termed di-O-methylene -L-threitol $A_2M_2X_2$.

An examination of the spectra of both di-O-butylidene ribitol (Fig.3) and di-O-butylidene xylitol (Fig.4) showed the presence of two non-equivalent six membered rings, i.e. both exhibited two triplets each integrating for one proton. Hence it was logical to assign the 1,3:2,4 structure to both of these compounds. However, the remaining signals were not readily assigned.



Conformationally the ribitol diacetal could exist in one conformer.



However, di-O-butylidene xylitol would be expected to be analogous to 1,3:2,4-di-O-butylidene L-threitol existing in the "O-inside"conformation, but this could not be confirmed by p.m.r.

1-Deoxy-di-O-butylidene-D-xylitol (Fig.5) gave two separate triplets, each integrating for one proton, indicating two 1,3-dioxane type rings in this molecule. This fixed the structure of this compound as 1-deoxy 2,4:3,5-di-O-butylidene-D-xylitol.

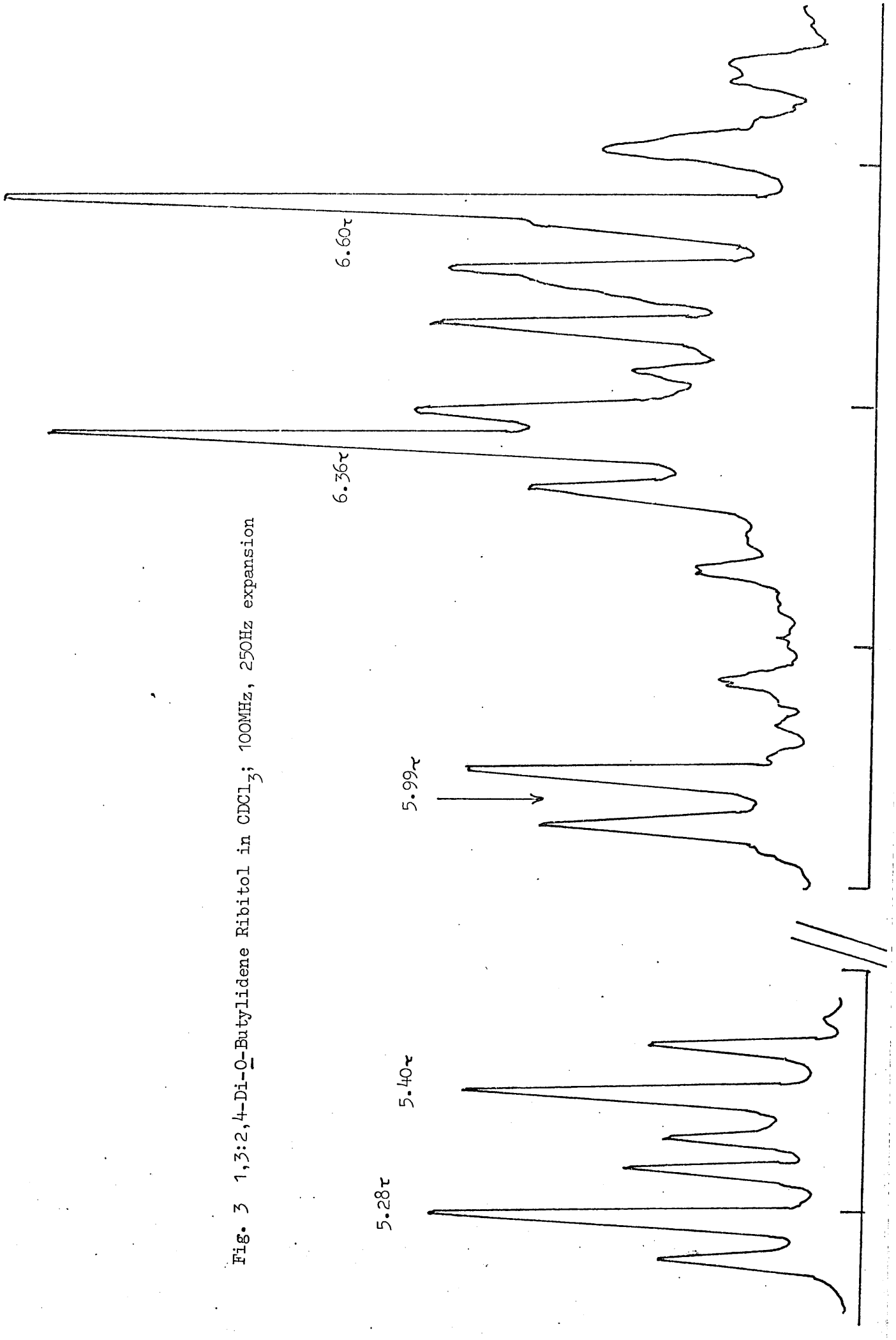


Fig. 3 1,3:2,4-Di-O-Butylidene Ribitol in $CDCl_3$; 100MHz, 250Hz expansion

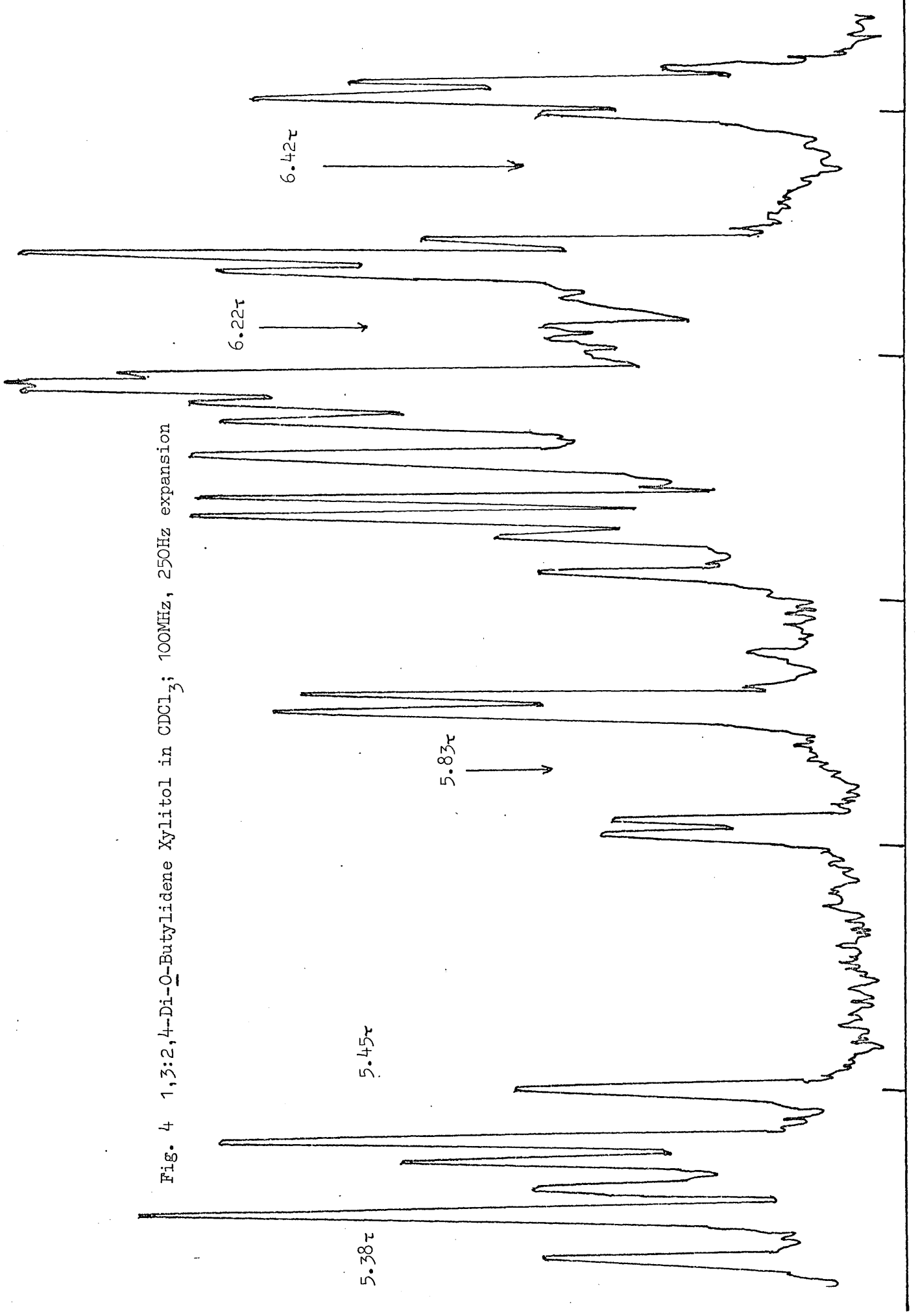
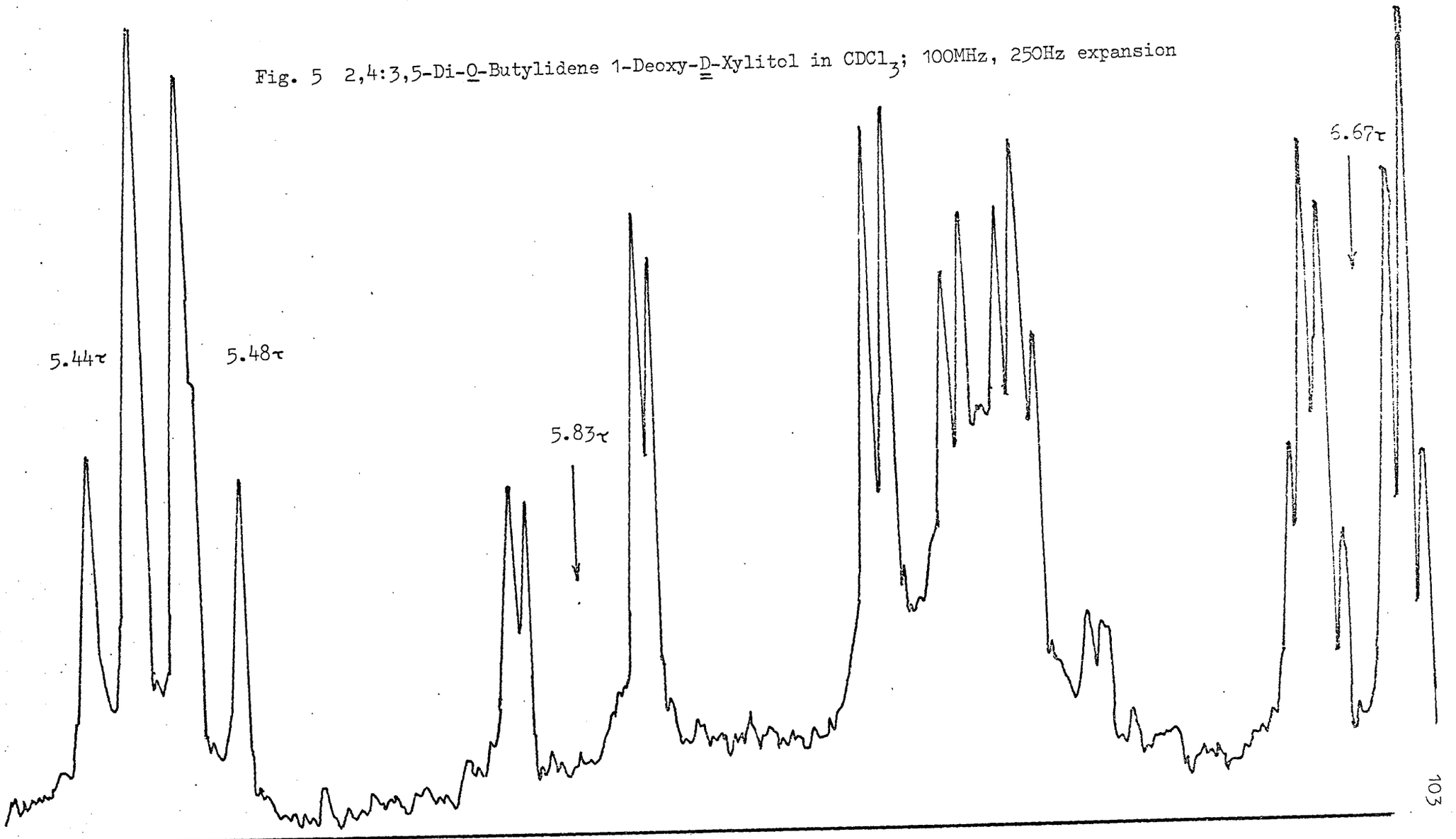
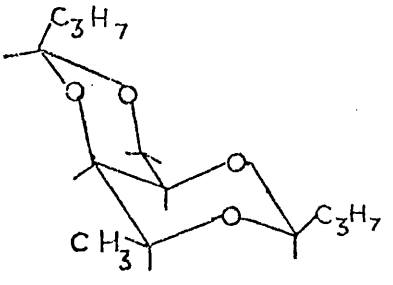


Fig. 4 1,3:2,4-Di-O-Butylidene Xylitol in $CDCl_3$; 100MHz, 250Hz expansion

Fig. 5 2,4:3,5-Di-O-Butylidene 1-Deoxy-D-Xylitol in $CDCl_3$; 100MHz, 250Hz expansion



Again, conformationally, this compound would be expected to exist in the "O-inside" conformation, with the terminal methyl group occupying an equatorial orientation.



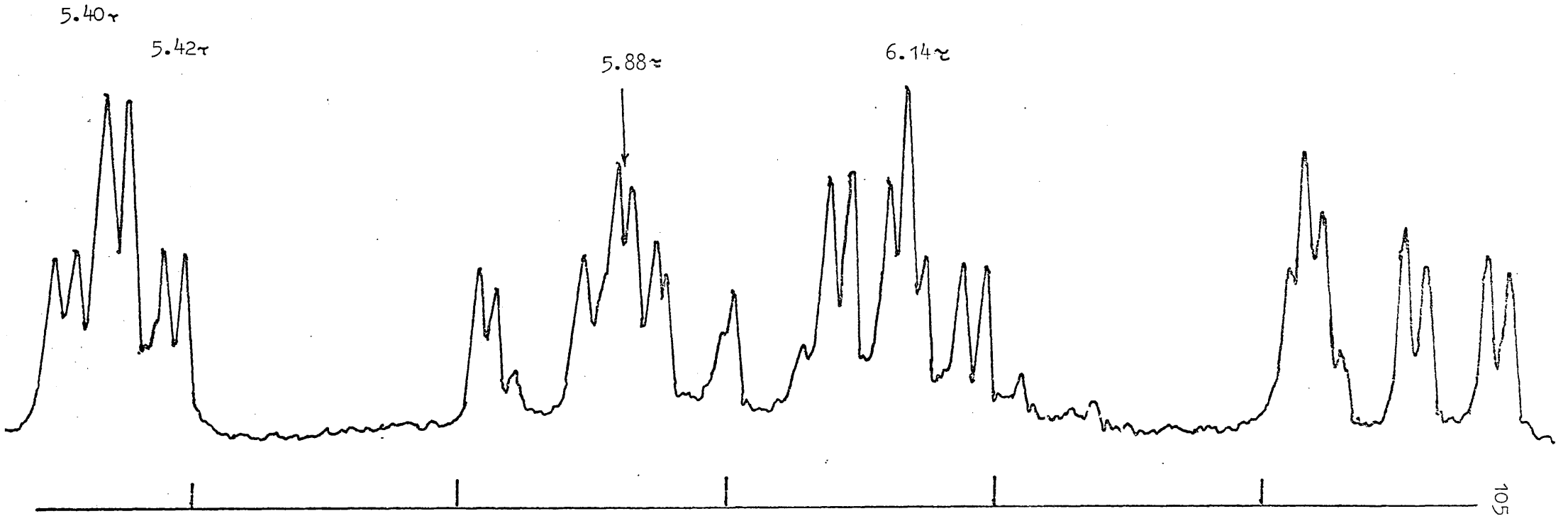
A doublet was observed for the terminal methyl group at 8.72 τ (J = 6 Hz).

An AB quartet could be observed for the geminal methylene grouping. A value of J_{ab} = 12 Hz and J_{bc} = 1.5 Hz were obtainable from the spectrum.

6-Deoxy di-O-butylidene-D-glucitol ($CDCl_3$; 100 MHz) showed two triplets at 5.42 and 5.40 τ, characteristic for two non-equivalent 1,3-dioxane rings (Fig.6). This enabled the 1,3:2,4 diacetal structure to be assigned to this molecule. A doublet for the terminal deoxy group was observed at 8.7 τ. A singlet at 7.96 τ, integrating for one proton, was assigned to the one free hydroxyl group in the molecule.

The 1,3:2,4 diacetal structure was proved by the comparable similarities of this spectrum with the spectra of both 1,3:2,4-di-O-butylidene-D-glucitol and 1,3:2,4-di-O-butylidene xylitol

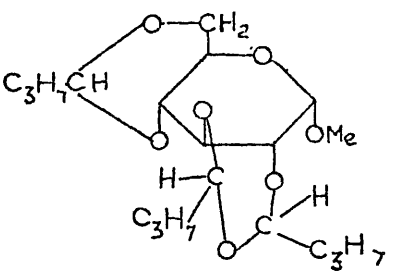
Fig. 6 1,3:2,4-Di-O-Butylidene 6-Deoxy-D-Glucitol in $CDCl_3$; 100MHz, 250Hz expansion



(both in $CDCl_3$ at 100 MHz).

Very scant data was furnished from the spectrum recorded of methyl 4,6-O-butylidene α-D-glucoside (in D_2O at 100 MHz). An acetal triplet was observed at 5.28 τ, indicating a six membered ring, and an anomeric doublet at 5.18 τ (J = 3 Hz). An intense singlet was observed at 6.52 τ integrating for three protons, and was assigned to the anomeric methoxy group.

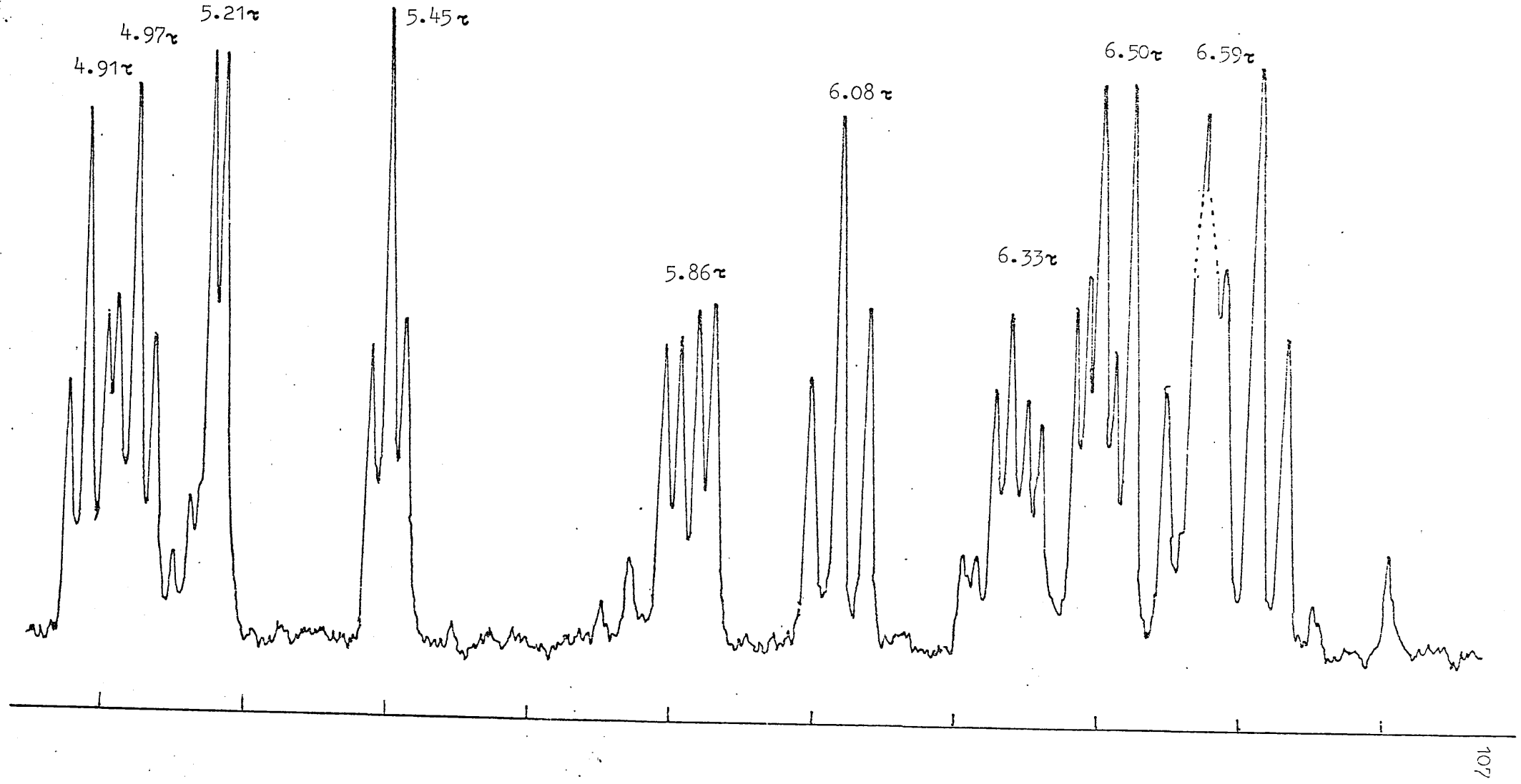
When the spectrum of methyl 2,3 oxido di-n-butylidene 4,6-O-butylidene-α-D-glucoside (in $CDCl_3$ at 220 MHz) was examined, regular features were revealed but these could not be fully assigned (Fig.7).

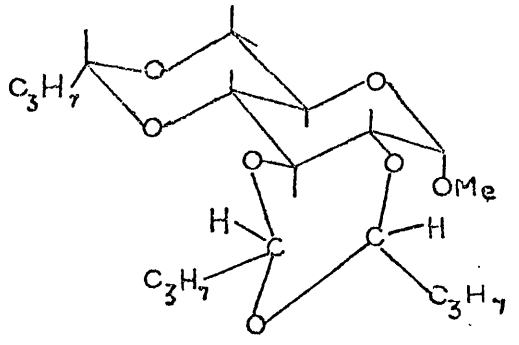


An acetal triplet at 5.45 τ (J = 5 Hz) was observed for the acetal proton, H_a. Two other triplets were observed at 4.91 and 4.97 τ (both J = 5 Hz) and were assigned to the acetal protons, H_b and H_c. The anomeric OCH_3 group was observed as a singlet at 6.59 τ. An anomeric doublet was identified at 5.21 τ (J = 4 z).

The triplet at 6.08 τ was tentatively assigned to H_3, and since this possessed a large J value (9 Hz), it was assigned to a diaxial coupling (a quartet was expected from a first order analysis). However this could be assigned to the $^4C_1$ conformation.

Fig. 7 Methyl 2,3-Oxido-(di-n-butylidene) 4,6-O-Butylidene-α-D-glucoside in $CDCl_3$; 220MHz, 500Hz expansion



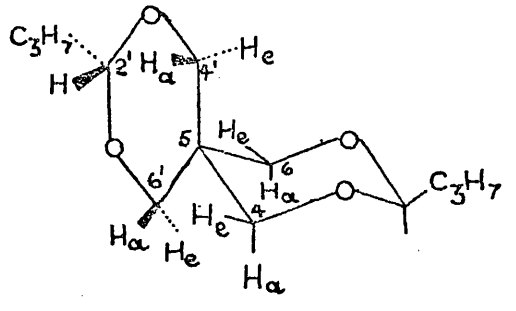


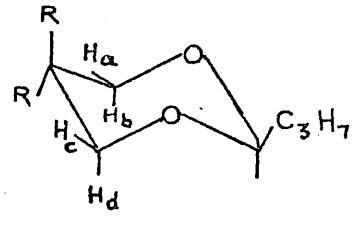
However, molecular models showed that some deviation from the normal $^4C_1$ conformation had to occur. The stereochemistry of the seven membered ring could not be determined.

The spectra of the butylidene acetals of pentaerythritol were analysed on a first order basis (Figs.8 and 9).

The acetal triplet for the mono acetal (in D_2O at 100 MHz) was identified at 5.37 τ (J = 4.9 Hz).

The C-H protons of the hydroxymethyl groups at C_5 gave two singlets at 6.18 and 6.60τ, hence the protons bound to the carbon in each group were magnetically equivalent.



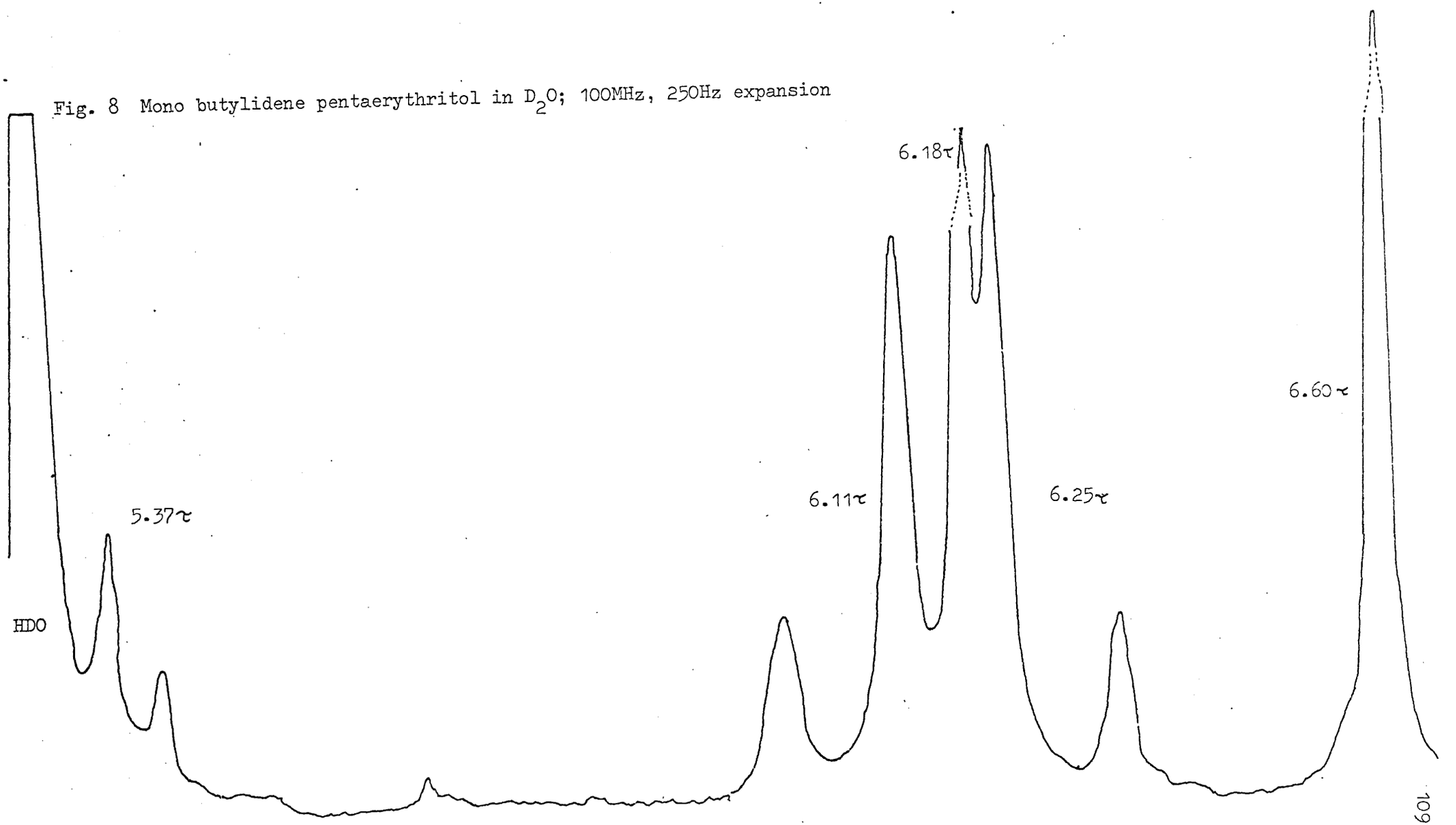


R =CH_2OH

The remaining four protons were observed at 6.11 and 6.25 τ as doublets.

The equatorial protons H_a and H_c constituted the doublet at lower field (6.11 τ), and the axial protons (H_b and H_d) the remaining doublet (6.25 τ).

Fig. 8 Mono butylidene pentaerythritol in D_2O; 100MHz, 250Hz expansion



The diacetal of pentaerythritol (Fig.9) could only contain two 1,3-dioxane type rings. However the spectrum for the di-O-butylidene acetal (in $CDCl_3$ at 220 MHz) was unexpectedly complex. A triplet integrating for two protons existed at 5.53 τ and was assigned to the two acetal protons.

Evidence for the interpretation of the rest of the spectrum came from double resonance experiments.*

The signals at 5.46 τ involved two protons in a deshielded environment and were assigned to the 6e, 4'e protons. A coupling constant of J = 11 Hz was obtained as well as a smaller coupling of J = 2.4 Hz for 4e, 6e (equivalent to 4'e, 6'e).

A similar value (J = 11 Hz) was obtainable for 4e and 6'e, and was located centred at 6.45 τ.

Large couplings centred at 6.49 τ (J = 11.5 Hz) and 6.67 τ (J = 12 Hz) were assigned to $H_{4'a}$, H_{6a} and H_{4a}, $H_{6'a}$ respectively.

The spectrum of di-O-butylidene dipentaerythritol (in $CDCl_3$ at 100 MHz) was extremely complex (Fig.10). However, a triplet integrating for two protons was identified at 5.58 τ and assigned to the acetal protons of two six membered acetal rings.

The use of computers for aiding the assignments of signals in n.m.r. spectra has been widely applied[13]. In this work a substituted mono acetal was recorded on a high resolution instrument, analysed and the findings verified by use of a computer.

*Irradiation at 6.49τ collapsed the signals at 5.46 τ to a singlet.

Fig. 9 Di-O-Butylidene Pentaerythritol in $CDCl_3$; 220MHz, 500Hz expansion

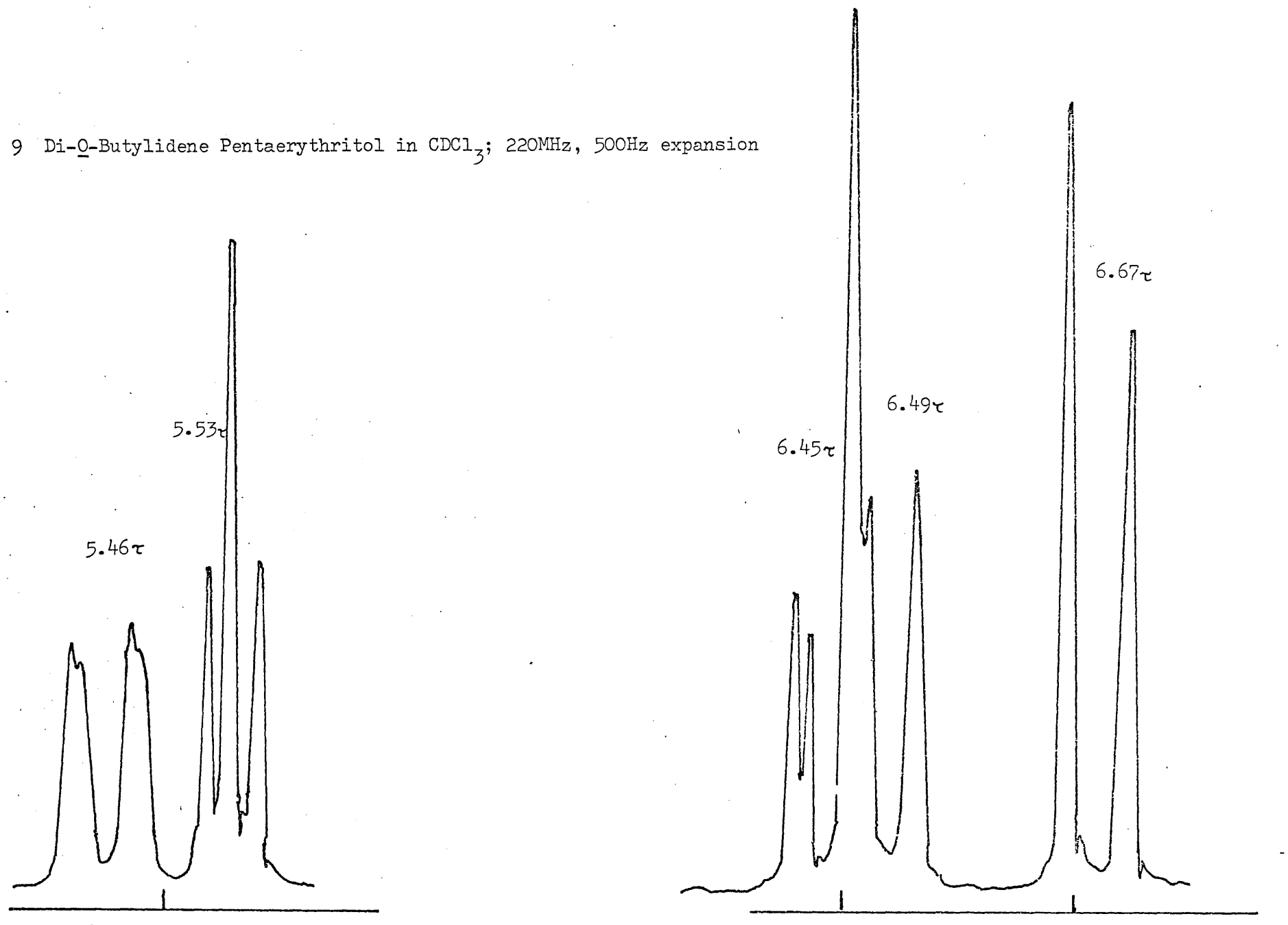
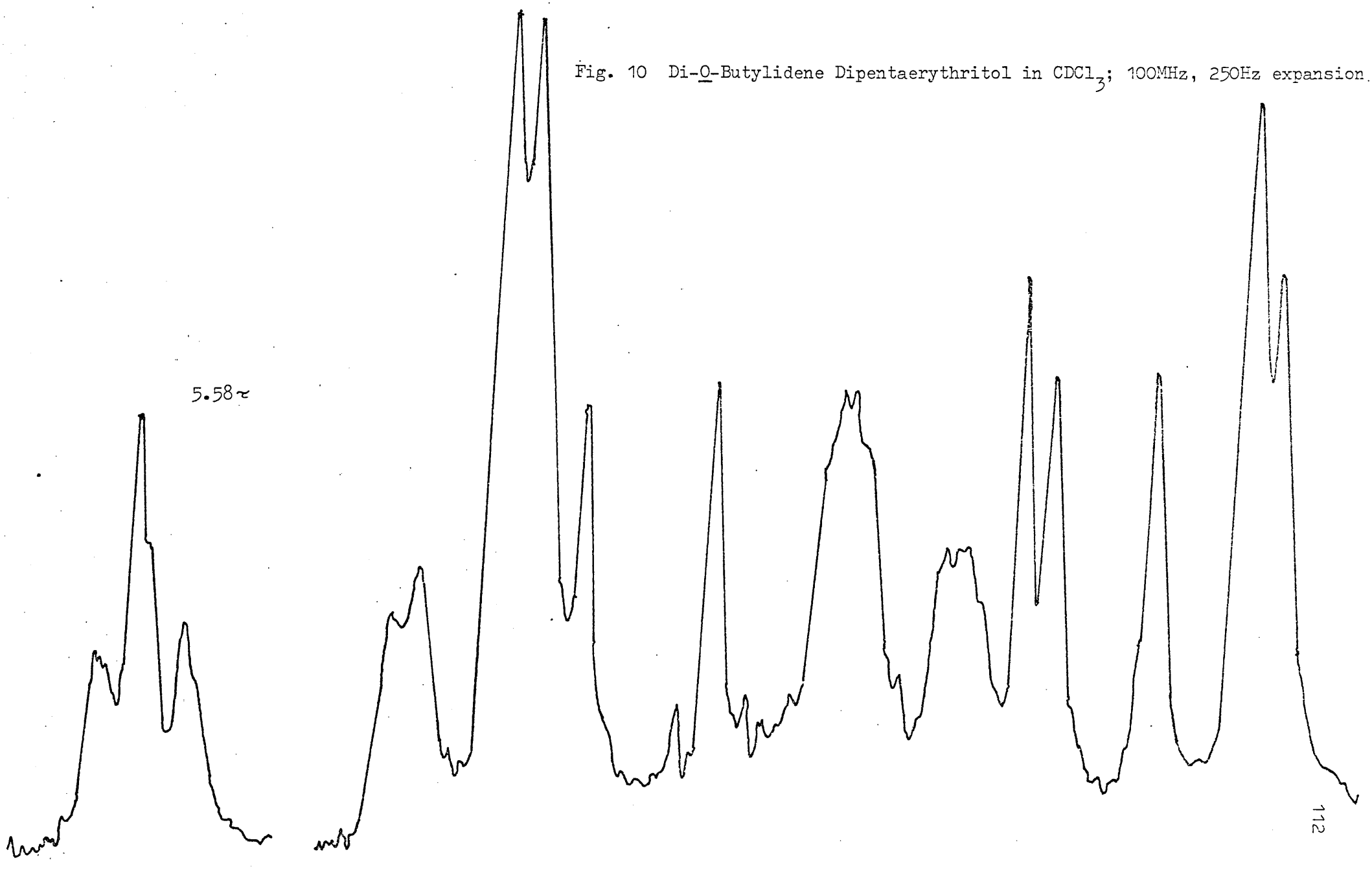
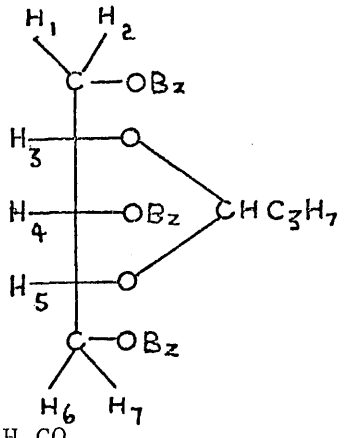


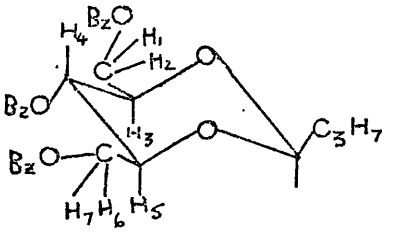
Fig. 10 Di-O-Butylidene Dipentaerythritol in $CDCl_3$; 100MHz, 250Hz expansion.



The spectrum of 2,4-O-butylidene 1,3,5 tri-O-benzoyl ribitol was recorded in $CDCl_3$ at 220 MHz.

The following assignments were made, suggesting the illustrated conformation.





Bz = C_6H_5CO

The acetal triplet and the C_3H_7- chain were not concerned with this study.

The triplet at lowest field (4.67 τ; J = 9.6 Hz) was assigned H_4. The large value of J denoted a diaxial coupling. A triplet was obtained for this proton instead of a quartet (expected from first order) since the magnitude of $J_{H_4-H_5}$ must have equalled J_{H3-H4}.

The quartets centred at 5.47 and 5.62 τ were attributable to the protons on the carbons of the primary hydroxyl groups. The signals at 5.47 τ were assigned to H_1 and H_6 and the signals at 5.62 τ to H_2 and H_7. The following coupling constants were available:

$$J_{H_1-H_2} = J_{H_6-H_7} = 12.2 \text{ Hz}$$

$$J_{H_2-H_3} = J_{H_5-H_6} = 3.5 \text{ Hz}.$$

A multiplet, not first order, centred at 5.92 τ (J = 5.6 Hz approx.) was assigned to H_3 and H_5.

These values were computed using the UEA NMR BASIC Programme[14,15], as seven independent nuclei, utilising the shifts (from TMS) and coupling constants (both in Hz).

The result was an approximate reproduction of the spectrum (when plotted). A better and more accurate computed spectrum was obtained by applying this data to the UEA NMR ITERATIVE[16] Programme.

These programmes utilised the Atlas computer[17].

After six iterations the following refined parameters were produced:

	Experimental Spectrum		Refined Parameters
H_1	5.62 τ	963.9 Hz	963.900 Hz
H_2	5.47	997.5 Hz	997.306 Hz
H_3	5.92 τ	898.8 Hz	898.606 Hz
H_4	4.67	1172.5 Hz	1172.306 Hz
H5	5.92 τ	898.8 Hz	898.606 Hz
H_6	5.62	963.9 Hz	963.900 Hz
H_7	5.47	997.5 Hz	997.306 Hz
$J_{1,2}$		12.2 Hz	12.58 Hz
$J_{2,3}$		3.5 Hz	3.500 Hz
$J_{2,3}$		5.6 Hz (approx.)	6.181 Hz
$J_{3,4}$		9.6 Hz	10.080 Hz
$J_{4,5}$		9.6 Hz	10.080 Hz

$J_{5,6}$	5.6 Hz (approx.)	6.181 Hz
$J_{5,7}$	3.5 Hz	3.500 Hz
$J_{6,7}$	12.2 Hz	12.200

These agreed with the values obtained experimentally, and thus illustrate the validity of this technique for this compound.

The carbon nuclear magnetic resonance spectra (cmr) have been obtained for most of the acetals synthesised. Information has been accumulated concerning the magnetic and stereochemical environment of the carbon 'backbone' of these compounds.

The same general principles apply in cmr as in pmr[18]. Each nucleus in a separate magnetic environment will give rise to a signal. These resonances may be related to a standard compound and carbon chemical shift data compiled. Originally the standard employed in these determinations was carbon disulphide, but this carbon resonance has overlapped with carbonyl resonances. Consequently, like pmr, spectra have been related to TMS (δ = 0 ppm) or TSP (δ = 0 ppm for D_2O). The relationship between CS_2 and TMS may be depicted:

$$\delta_{CS_2} = \delta_{TMS} + 194.1 \text{ ppm.}$$

However, two fundamental differences arise in cmr, which do not occur in pmr, both of which are attributed to the natural abundance of ^{13}C (n.b. ^{13}C = 1.1% ^{1}H = 100%).

This low natural abundance makes the detection of carbon-carbon

coupling (i.e. $^{13}C-^{13}C$) impossible to observe, hence multiplet signals are not obtained. Therefore coupling constants (J_{C-C} Hz) cannot be measured, and stereochemical relationships between carbon nuclei cannot be observed.

In general, pmr is recorded for 5% solutions whereas 50% solutions are required for cmr.

The absence of multiplicity causes spin decoupling double resonance techniques to be invalid. Nevertheless, assignments and structural data may be aided by "off-centre" resonance techniques. The sample is irradiated with a second radio frequency field which causes the spectrum to change from singlets to intense multiplets. These multiplets derive from the respective carbon atoms coupling with the protons which are bonded to them. The following signal multiplicity will be produced:-

Methyl Carbon - Quartet

Methylene Carbon - Triplet

Methine Carbon - Doublet

Quaternary Carbon - Singlet

Hence, the appearance of these features under "off-centre" resonance conditions can aid structural determinations.

Carbon nuclear magnetic resonance has been generally applied to carbohydrate chemistry[19]. Studies have concerned glycosides[20], aldoses[21,22] and inositols[23]. Like p.m.r. the use of lanthanide shift reagents[24] has

been employed as well as the INDOR technique[25], to help clarify spectra. Rules have been formulated to aid structural assignments.

Voelter et al[26] have examined series of polyols and formulated the following set of rules:-

(i) a terminal methyl or a methylene group of deoxy polyols occurs at high field.

(ii) hydroxyl groups exert a strong inductive effect on carbon atoms, causing a greater down field shift in cmr than observed in p.m.r. for the hydrogen atom of the C-H bond.

(iii) shifts of primary hydroxyl carbon atoms in vicinal polyols occur at higher fields than for secondary hydroxyl carbon atoms.

(iv) signals for symmetrical polyols (configurationally) e.g. xylitol, are found in pairs, i.e. C_1 equivalent to C_5, C_2 equivalent to C_4. Polyols with an asymmetric configuration e.g. D-arabinitol, give one signal for each carbon atom.

Limited studies have been made for cmr of acetals[27]. In the introduction it was mentioned that Riddell[28] showed the existence of non-chair forms in 1,3-dioxanes by c.m.r.

In the spectra produced by butylidene acetals, the n-propyl side chain was only slightly deshielded relative to TMS. The terminal methyl and two methylene carbon atoms of this grouping were readily

identified by off-centre resonance as a quartet and two triplets, respectively. The terminal methyl group occurred at 13.5-16.2 ppm and the two methylene groups at 17.3-20.4 ppm and 36.1-39.4 ppm, respectively.

Initially, the spectra of some known mono-butylidene acetals of D-glucitol were recorded in D_2O.

The values are tabulated below, excluding the C_3H_7 side chain (all values in ppm).

Isomer	CH_2 (pri)		CH (sec)				Acetal Carbon
2,3	62.78	64.50	72.05	73.35	77.98	79.93	107.32
2,4	62.77	63.96	63.64	70.11	79.82	81.33	103.55
3,4	64.07	64.28	72.48	72.92	77.45	80.14	105.92
4,6	63.53	71.19	61.59	69.79	73.99	81.65	103.23

The signals which occurred at lowest field for these acetals were observed as doublets by off-centre resonance techniques and were assigned to the acetal carbon atoms. The position of the acetal carbon resonance was at a lower field for the 1,3-dioxolane type compounds (2,3 and 3,4 acetals) than for the 1,3-dioxane type compounds (2,4 and 4,6 acetals). This was comparable to the observations made for p.m.r. of butylidene acetals[10]: the acetal proton of five membered ring acetals resonated at a lower field than that for six membered ring acetals.

The remaining six signals were attributed to the D-glucitol "skeleton" of the acetal. Two signals near high field occurred

as triplets by off-centre resonance, whereas the remaining signals were observed as doublets by the same technique. These resonances were assigned to the primary hydroxyl carbon atoms (C_1 and C_6) and secondary hydroxyl carbon atoms (C_2-C_5), respectively, as generalised for the parent polyols. Unfortunately, it was not possible to assign these features to the actual individual carbon atoms in the D-glucitol framework.

^{13}C spectra were recorded for most acetals synthesised, if sufficient compound was available.

Assignments were confirmed by off-centre resonance techniques. The chemical shifts and assignments are tabulated.

Individual spectra are now discussed, excluding the butylidene acetal grouping.

For the mono-butylidene tetritols only 1,3-O-butylidene-DL-erythritol was examined. Four resonances were observed for the erythritol portion. The signals at 63.85 and 72.81 ppm occurred as triplets under off-centre resonance conditions and were assigned to the primary hydroxyl carbon atoms. By an analogous technique, the signals at 64.07 and 84.56 ppm were observed as doublets and subsequently assigned to the secondary hydroxyl carbon atoms. Therefore, carbon atoms of primary hydroxyl groups were less deshielded than carbon atoms for secondary hydroxyl groups, only in part.

However, the 1,3:2,4-di-O-butylidene tetritols were spectrally significantly different. Di-O-butylidene erythritol gave two

Carbon Atom Resonances of Cyclic Butylidene Acetals at 22.63 MHz (all values in ppm)

		C_3H_7			Polyol						Acetal Carbon		
		CH_3	CH_2	CH_2	CH_2		CH						
1,3-O-Butylidene-DL-Erythritol	D_2O	16.18	20.06	38.50	63.85	72.81	64.07	84.56			105.06		
1,3:2,4-Di-O-Butylidene Erythritol	$CDCl_3$	16.83	20.38	39.37	71.41		76.58				105.70		
1,3:2,4-Di-O-Butylidene-L-Threitol	$CDCl_3$	13.81	17.47	36.89	69.68						101.82		
2,4-O-Butylidene Ribitol	D_2O	14.56	18.44	36.89	62.24		63.10	82.08			103.01		
1,3:2,4-Di-O-Butylidene-DL-Ribitol	$CDCl_3$	13.91	17.37	36.35	61.59	68.38	72.59	74.10	78.42		102.25	102.79	
2,4-O-Butylidene Xylitol	D_2O	14.67	18.34	37.32	62.67		64.83	81.22			103.55		
1,3:2,4-Di-O-Butylidene-DL-Xylitol	$CDCl_3$	13.81	17.47	36.78	61.69	69.57	70.11	78.31			101.50		
2,3-O-Butylidene-D-Arabinitol	D_2O	16.05	19.49	37.82	Assignments not possible						106.78	107.36*	*Diastereoisomers
1,3-O-Butylidene-D-Arabinitol	D_2O	15.86	19.56	38.54	65.19	74.35	64.99	71.75	80.46		104.96		
6-Deoxy 1,3:2,4-Di-O-Butylidene-D-Glucitol	$CDCl_3$	13.84	17.54	36.65	69—70 (approx.)		65.64	69—70		81.82	101.64		19.95 (deoxy)
2,4-O-Butylidene 1-Deoxy-D-Xylitol	D_2O	13.90	17.60	36.70	62.30		66.60	76.60	80.70		102.70		16.70 or 17.60 (deoxy)
1-Deoxy 2,4:3,5-Di-O-Butylidene-D-Xylitol	$CDCl_3$	13.84	17.48	36.78	69.67		70.45	71.94	74.35		101.84	101.71	15.92 (deoxy)

(continued overleaf)

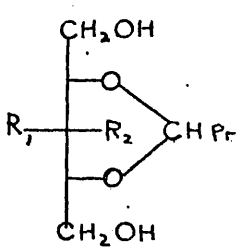
		C_3H_7			Polyol					Acetal Carbon	
		CH_3	CH_2	CH_2	CH_2	CH					
Di-O-Butylidene-RS-Pentaerythritol	$CDCl_3$	13.97	17.09	36.84	70.25 70.70					102.70	32.36 (quaternary)
Di-O-Butylidene Dipentaerythritol	$CDCl_3$	13.97	17.22	36.84	Not Assigned					102.50	39.18 (quaternary)
Me 4,6-O-Butylidene-α-D-Glucoside	D_2O	15.72	19.36	38.01	70.38	65.05	72.85	74.60	82.79	105.20	57.84 (OCH_3) 102.60 (anomeric)
Me 2,3-Oxido-di-n-Butylidene-4,6-O-Butylidene-α-D-Glucoside	$CDCl_3$	13.84	17.42 17.61 18.20	36.24 37.30	68.69	62.39	78.83	79.03		?	55.24 (OCH_3) 98.85 Anomeric 102.68 Acetal 98.97 7 Membered Ring Acetal 99.17

resonances for the polyol fragment, at 71.41 and 76.58 ppm, and these appeared as a triplet and doublet respectively, under off-centre resonance conditions, and were assigned to the primary hydroxyl carbon atoms and the secondary hydroxyl carbon atoms.

However, only one resonance was observed for di-O-butylidene-L-threitol and this appeared as an overlapping triplet and doublet under "off-centre" resonance conditions. Hence this resonance at 69.68 ppm was assigned to the two primary and two secondary hydroxyl carbon atoms. Therefore equal deshielding was encountered by the primary, and secondary hydroxyl carbon atoms.

The mono and di-butylidene acetals of ribitol and xylitol may be conveniently considered together.

Both 2,4-O-butylidene mono acetals gave a resonance at low field (103.01 ppm for ribitol, and 103.55 for xylitol) which occurred as doublet under off-centre resonance conditions, and was assigned to the acetal carbon atom. The remaining five atoms occurred as three signals (see table). The primary hydroxyl carbon atoms occurred at highest field as one resonance and the three secondary hydroxyl carbon atoms at a lower field, as two resonances. This was accounted for by the symmetry of both of these molecules.



R_1 = H; R_2 = OH 2,4-O-butylidene ribitol

R_1 = OH; R_2 = H 2,4-O-butylidene xylitol

However, the diacetals differed slightly in the resonance of their acetal carbon atoms: 1,3:2,4-di-O-butylidene ribitol gave two resonances at 102.25 ppm and 102.79 ppm, whereas 1,3:2,4-di-O-butylidene xylitol showed only one resonance for the acetal carbon atoms at 101.5 ppm. The acetal rings for the di-butylidene ribitol acetal contained two carbon nuclei which were not magnetically equivalent, whereas the acetal carbon atoms for di-O-butylidene xylitol were equivalent.

As for pmr[10] the mono butylidene-D-arabinitols gave resonances which differed according to ring size. The 1,3-mono acetal gave an acetal carbon resonance at 104.96 ppm whereas the 2,3 acetal gave two resonances for the acetal carbon atom at 106.78 ppm and 107.36 ppm, indicating diastereoisomers. These findings were analogous to the mono acetals of D-glucitol: a 1,3-dioxolane acetal ring carbon atom resonated at a lower applied field than the isomeric 1,3-dioxane compound.

Hence for both cmr and pmr 1,3-dioxolane rings were more deshielded than 1,3-dioxane rings for the same polyol.

Unfortunately, insufficient compound was available for this to be illustrated for the kinetic and thermodynamic acetals of both L-threitol and 6-deoxy-D-glucitol.

For the three deoxy polyols examined, the terminal methyl group of the polyol fragment was observed at 17.5 ppm (approx.). This was confirmed as a quartet under off-centre resonance conditions.

2,4-O-Butylidene-1-deoxy-D-xylitol gave five resonances for the polyol fragment. The terminal deoxy grouping was identified as above. The signal at highest field of the remaining four signals was assigned to the primary hydroxyl carbon atom. The remaining three resonances were assigned to the secondary carbon atoms.

Hence, the substitution of a terminal methyl group into 2,4-O-butylidene xylitol to give the 1-deoxy analogue has caused the secondary carbon atoms to lose their magnetic equivalence.

The diacetal of 1-deoxy-D-xylitol gave two resonances for the acetal carbon atoms: therefore both rings were not magnetically equivalent. The remaining signals were readily assigned to the polyol fragment. The resonances in order of decreasing field were attributed to the terminal deoxy group carbon atom, the primary carbon atom and lastly the three secondary carbon atoms (excluding the propyl and acetal carbon resonances).

In contrast, 6-deoxy 1,3:2,4-di-O-butylidene-D-glucitol gave only one resonance for the two acetal carbon atoms. The remaining signals were readily assigned to the deoxy, primary and secondary carbon atoms.

For di-O-butylidene pentaerythritol the quaternary carbon atom was readily identified as one signal at 32.36 ppm (no coupling occurred for this signal under off-centre resonance conditions). Only one signal was observed for the two acetal carbon atoms at 102.7 ppm.

This suggested both 1,3-dioxane rings to be magnetically equivalent. However, two resonances were observed for the remaining four primary carbon atoms.

Equivalently, di-O-butylidene dipentaerythritol gave only one resonance for the quaternary carbon atoms(39.18 ppm) and acetal carbon atoms (102.5 ppm). The remaining signals were attributable to the primary carbon atoms.

The butylidene acetals of methyl α-D-glucoside were considered. Here, two resonances, each occurring as doublets under off-centre resonance conditions, occurred. The signal at lowest field (105.2 ppm) was assigned to the acetal carbon atom and the other signal (at 102.6 ppm) to the anomeric carbon atom. Evidence from the pmr spectra of this compound was utilised: since the acetal proton was at a slightly higher field than the anomeric proton, it was argued that the carbon resonances would be of the same order of deshielding. The glycoside glycon (OCH_3) was identified at 57.84 ppm (quartet for off-centre). The primary carbon atom and secondary carbon atoms were assigned as before: primary 70.38 ppm, secondary 65.05, 72.85, 74.60, 82.79 ppm.

The spectrum for methyl 2,3-oxido di-n-butylidene 4,6-O-butylidene glucoside was extremely complex. One signal was observed for the methyl group and two signals for each methylene group comprising the n-propyl side chain. The anomeric-OCH_3 was identified at 55.24 ppm. The signal at 68.69 ppm was assigned to the primary hydroxyl carbon and

the remaining four signals (62.39 ppm → 78.60 ppm) to the secondary carbon atoms (not including the anomeric carbon atom).

The remaining signals were attributable to the three acetal carbon atoms and the anomeric carbon atom. Actual individual assignment was not possible since each signal occurred as a doublet under off-centre resonance conditions.

Possible assignments could be :

4,6 acetal carbon 98.25 ppm

Seven membered acetal ring carbon 98.97 and 98.85 ppm

Anomeric carbon atom 102.68 ppm

These have been assigned, tentatively, by comparison to the p.m.r. spectrum of this compound.

In this section the values of p.m.r. and c.m.r. have been illustrated for structural assignments. For a given polyol different ring sizes can be distinguished. Both p.m.r.[10] and c.m.r. identify an acetal proton or carbon atom for a 1,3-dioxolane ring at a lower field than the isomeric 1,3-dioxane ring.

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SECTION D

EXPERIMENTAL

GENERAL TECHNIQUES AND INSTRUMENTATION

All evaporations were carried out under reduced pressure (water bath temperature less than 50°). Melting points are uncorrected.

Paper Chromatography

Descending chromatography was used on Whatman No.1 paper.

The following solvent systems were used (v/v):

Butan-1-ol-Ethanol-Water (40:11:19).

Methyl ethyl ketone saturated with water.

Ethyl Acetate - Acetic Acid - Formic Acid - Water (18:3:1:4).

Butanol-Acetone-Water (3:5:2)[1] - used for separation of erythritol and threitol. A tungstate impregnated paper was used (Whatman No.1 paper was dipped in an aqueous solution of sodium tungstate dihydrate (5% w/v) and allowed to air-dry).

Chromatograms were developed by silver nitrate in acetone solution followed by ethanolic sodium hydroxide, as pioneered by Trevelyan et al[2]. Fixing was achieved with aqueous sodium thiosulphate soln. (5%).

Thin Layer Chromatography

Silica gel coated glass plates were utilised.

Acetals were separated by methyl ethyl ketone saturated with water.

Toluene-methanol (9:1 or 6:4) was used for fully substituted acetals or derivatives e.g. per-O-acetates.

Rf values have not been reported owing to their variation with temperature, as well as the uncertain composition of the former solvent.

Chromatograms were developed by iodine vapour, as yellow spots, or ethanolic sulphuric acid (10%) followed by heating at 120°, as charred black spots. (The latter method was the most sensitive by far).

Gas Liquid Chromatography

A Perkin Elmer F11 and Pye 104 instruments were used. The following columns were used: Apiezon-K (7.5%), OV-17 (7.5%) or m-bis(m-phenoxy phenoxy) benzene (5%) on Celite.

With the exception of fully substituted polyol derivatives, compounds were converted to their trimethyl silyl ethers, according to the method of Sweeley et al [3].

Optical Rotations

These were obtained on a Perkin Elmer 141 instrument in 1 decimetre glass or silica cells using the sodium-D or mercury 365 lines. Specific rotations are quoted at ambient temperature, as recommended by Collins et al [4].

Infra Red Spectroscopy

A Perkin Elmer 257 instrument was employed over the range 4000 - 625 cm^{-1}. Samples were recorded as solutions in dry carbon tetrachloride, or if insoluble as nujol mulls or rock salt discs.

Optical Densities

The Unicam SP 1800 instrument with 1 cm silica cells was used.

Nuclear Magnetic Resonance Spectroscopy

Proton n.m.r. were recorded initially on a Varian E.M. 360 instrument. More detailed spectra were obtained on a Varian HA-100 or HR-220 instrument at P.C.M.U., Harwell.

Carbon n.m.r. were recorded on a Brucker 90 MHz instrument jointly at Q.M.C. (University of London) and P.C.M.U. Harwell.

Spectra were recorded in deuterated solvents:-

for $CDCl_3$: tetra methyl silane (TMS) was used as the internal standard whereas in D_2O : 2,2-dimethyl-2-silapentane-5-sulphonate (TSP) was utilised.

P.m.r. spectra were recorded as 5% solutions : c.m.r. spectra as 50% solutions.

Mass Spectroscopy

Spectra were recorded by the University of London Intercollegiate Research Service (School of Pharmacy).

Solvents

Pyridine was dried by refluxing over sodium hydroxide pellets and distilling, collecting the pure fraction.

Dimethyl Formamide was distilled and the pure component stored over 4A molecular sieve.

Tetrahydrofuran was refluxed over calcium hydride, and distilled.

Diethyl ether was dried with sodium wire.

Anhydrous methanol was obtained by the method of Vogel [5].

n-Butyraldehyde was freshly distilled prior to usage.

Elemental Analyses

These were determined by Alfred Bernhardt, Mülheim, Ruhr, Germany.

D.1. Synthesis of Polyols

Erythritol, ribitol and xylitol were commercial samples obtained from B.D.H., Poole, England. The purities of these polyols were checked by melting points, gas liquid chromatography (tms. derivatives on a PPE stationary phase column) and paper chromatography.

L-Threitol, D-arabinitol, 1-deoxy-D-xylitol, 1-deoxy-D-glucitol and 6-deoxy-D-glucitol had to be obtained by synthetic methods.

(i) L-Threitol

The borohydride reduction of the dimethyl ester of (+)-tartaric acid afforded this polyol.

A mixture of (+)-tartaric acid (60g), Amberlite IR120(H^+) resin (50 ml), methanol (100 ml) and benzene (200 ml) were refluxed for 10 hours, the water produced in the reaction being removed azeotropically using the Dean and Stark method. The distillate, although not a clear liquid was removed periodically, and further amounts of methanol (2 x 25 ml) added at convenient intervals.

After refluxing, the reaction mixture was cooled, filtered and the resin washed with methanol. The combined filtrates were evaporated under reduced pressure to yield a clear syrup. This residual syrup was distilled under reduced pressure to give the di-O-methyl ester of (+)-tartaric acid.

b.p. 182-186° (at 58 mm Hg)

yield 68.0 g (95%)

The syrup solidified, after prolonged cooling, to give a translucent solid which could not be recrystallised.

A solution of dimethyl tartrate (27.5 g) in dry methanol (250 ml) was added slowly to a vigorously stirred suspension of potassium borohydride (25 g) in dry methanol (250 ml). After complete addition, the mixture was heated at 70° with stirring for 7 hours. The mixture was cooled, treated with acetone-water (1:1, 50 ml) to give a sticky precipitate. The supernatant liquid was decanted and the residue dissolved in the minimum amount of water. These two solutions were combined and deionised with Amberlite IR120 (H^+) resin to remove potassium ions, and boron subsequently removed as volatile methyl borate by successive evaporations from methanol.

The syrupy product was crystallised from butan-1-ol and water to yield white needle crystals of L-threitol.

m.p. 87° (lit 88-89°)

yield 9.7 g (52%)

$[\alpha]_D$ -3.28° (c = 1 in H_2O; lit = -4.0°; c = 7 in H_2O[6])

(ii) D-Arabinitol

The reduction of D-arabinose with potassium borohydride gave D-arabinitol.

A solution of D-arabinose (10 g) in deionised water (150 ml) was treated with potassium borohydride (0.5 g) in small amounts, over a period of 30 minutes. The reaction mixture was left for 12 hours.

After this time, potassium and boron were removed as in the previous reduction.

The syrupy residue was crystallised from acetone and recrystallised from ethanol.

m.p.	98-99°	(lit 99-101°)
yield	8.9 g	(89%)

(iii) 1-Deoxy-D-xylitol

Treatment of the tosyl hydrazone of D-xylose with potassium borohydride yielded syrupy 1-deoxy-D-xylitol.

Toluene-4-sulphonyl hydrazide (10 g) was dissolved in hot ethanol (80 ml) and added to a solution of D-xylose (8 g) in a hot mixture of water (10 ml) and glacial acetic acid (10 ml).

The reaction mixture was allowed to cool, and left for 12 hours,

during which time the crystalline tosyl hydrazone separated. This was removed by filtration, washed with cold ethanol and then ether. The white crystals of D-xylose tosyl hydrazone were allowed to dry in air.

m.p.	149-150°	(lit 149°)[7]
yield	16.1 g	

A suspension of D-xylose tosyl hydrazone (10 g) in dry methanol (200 ml) was treated with potassium borohydride (10.0 g) in small amounts over a period of 14 hours. When the addition was completed, the reaction mixture was heated for 14 hours at 50°. Potassium and boron were removed by the same techniques as previously described. The residual syrup, when examined by paper chromatography 40/11/19 contained 1-deoxy-D-xylitol (R.f. = 0.47) and D-xylitol (R.f.= 0.26). Chromatography of the syrup on a column of cellulose (100 x 4 cm), with elution by buton-1-ol saturated with water afforded pure 1-deoxy-D-xylitol as a pale yellow syrup.

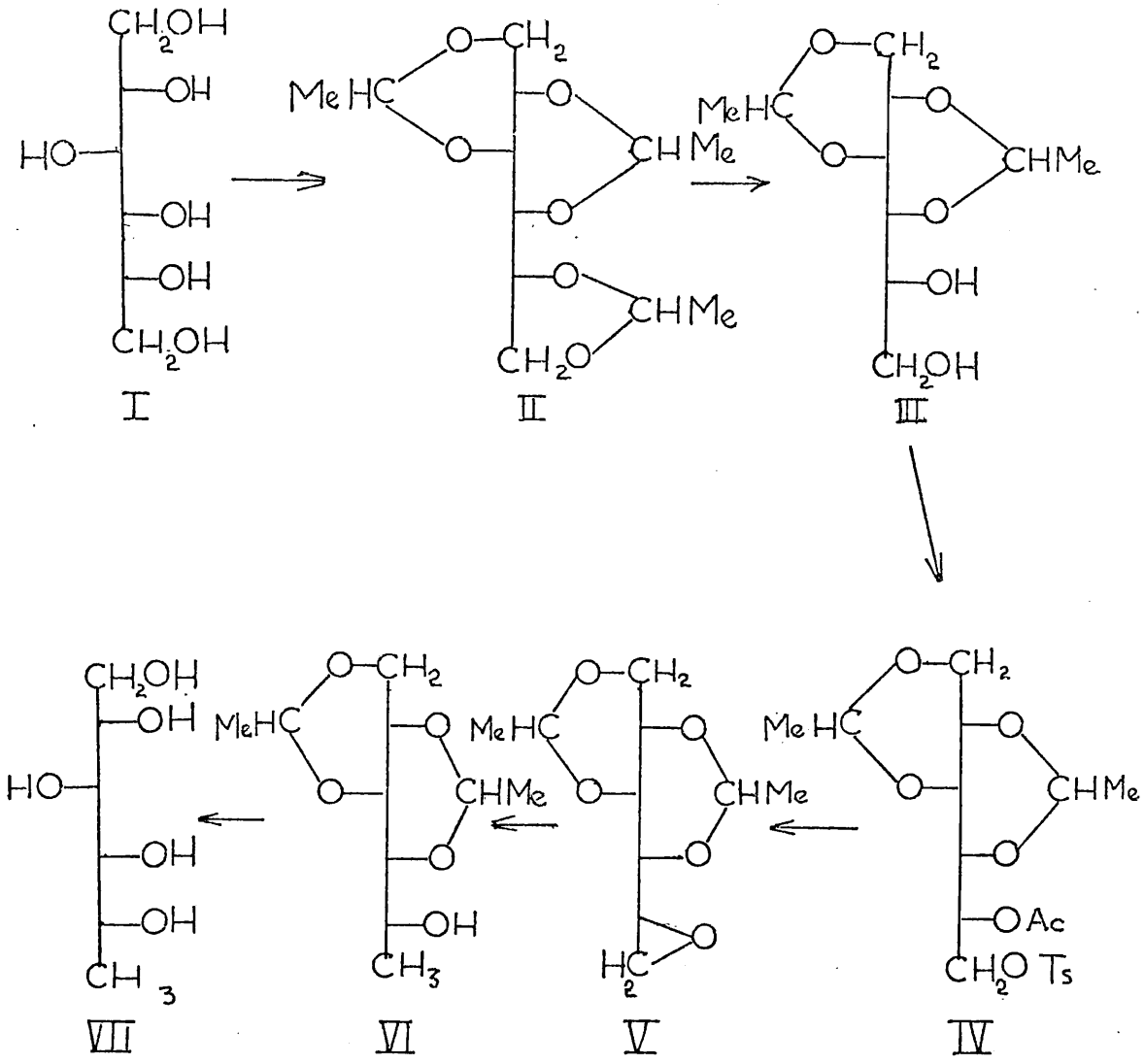
yield	1.6 g	(40%)
$[\alpha]_D$	2.76°	(C = 1.01 in H_2O)

1-Deoxy-D-xylitol was characterised as its di-O-benzylidene acetal, by the method of Richtmyer et al[8].

m.p.	170-172°	(lit 175-176°)
$[\alpha]_D$	- 34°	(C = 0.5 in $CHCl_3$: lit -34.5° C = 0.4 in $CHCl_3$)

(iv) 6-Deoxy-D-glucitol

A multi-stage synthesis starting from D-glucitol (I) gave 6-deoxy-D-glucitol (VII).



A mixture of D-glucitol (I; 75 g), paraldehyde (225 ml) and hydrobromic acid (48%, 30 ml) were shaken mechanically overnight in a stoppered flask. The yellow reaction mixture was shaken with chloroform (250 ml) and water (100 ml). The chloroform layer was separated, washed with 5% sodium bicarbonate, then water, and

evaporated under reduced pressure to yield syrupy 1,3:2,4:5,6-tri-O-ethylidene-D-glucitol (II)[9].

The syrupy acetal (90 g) was hydrolysed to the di-acetal by heating at 80° with 50% acetic acid (300 ml), for 50 minutes in an open flask. Evaporation of the hydrolysate followed by the addition of ethanol and re-evaporation afforded a partially solid product. Crystalline 1,3:2,4-di-O-ethylidene-D-glucitol (III) was precipitated by the addition of diethyl ether (150 ml), followed by vigorous shaking for 30 seconds and storing in a refrigerator for 24 hours. The crude product was recrystallised from ethanol.

m.p. 203-205° (lit 212-214°)[10]

yield 37 g

The di-acetal (III, 15g) in dry pyridine (60 ml) was cooled in an ice-salt bath and treated with toluene-p-sulphonyl chloride (12.8 g, 1.05 mol), added portionwise during 1 hour. The reaction mixture was left for 12 hours at room temperature, during which time crystals of pyridine hydrochloride separated. Redistilled acetic anhydride (12 ml) was added and the reaction mixture left for a further 2 hours at room temperature. The mixture was poured onto crushed ice and the resultant solution extracted with chloroform (2 x 50 ml). The extracts were washed with water and evaporated under reduced pressure.

The syrupy residue was dissolved in hot ethanol (20 ml) and light

petroleum (13 ml) added. 5-O-Acetyl 1,3:2,4 di-O-ethylidene-6-O-p-tosyl-D-glucitol (IV) separated, on storing at a low temperature, as white crystals.

m.p. 130-135° (lit 140°)[11]

yield 22.0g

5,6-Anhydro 1,3:2,4-di-O-ethylidene-D-glucitol(V) was obtained by shaking 5-O-acetyl-6-O-p-tosylate(IV) (15 g) in dry chloroform (150 ml), with sodium (1.7 g) previously dissolved in dry methanol (30 ml), in a separating funnel for 20 minutes. Water (25 ml) and chloroform (75 ml) were added and the chloroform layer separated and washed with water (2 x 20 ml), then dried with anhydrous magnesium sulphate. After evaporation of the organic solvent, the solid residue was recrystallised from ethanol to yield 5,6-anhydro di-O-ethylidene-D-glucitol (V).

m.p. 130-133° (lit 136°)[11]

yield 6.7 g

The anhydro compound (7.0 g) was added in small amounts to a vigorously stirred suspension of lithium aluminium hydride (1.0 g) in freshly distilled anhydrous tetrahydrofuran (60 ml). After 45 minutes, excess lithium aluminium hydride was destroyed by the cautious dropwise addition of water (1.0 ml), followed by 15% sodium hydroxide (1.0 ml) then water (3.0 ml). (This process involved adding the aqueous solutions dropwise through a double surface condenser). A granular precipitate was produced, which was filtered off and washed

with warm tetrahydrofuran, then hot chloroform. The combined filtrates were evaporated to dryness and crystallised from warm ethanol to give 6-deoxy 1,3:2,4-di-O-ethylidene-D-glucitol(VI) as a white granular solid.

m.p. 176-177° (lit 178-179°)[12,9]

yield 5.6 g.

The di-O-ethylidene-D-glucitol (5.5 g) was boiled in an open flask with ethanol (22 ml), water (22 ml) and 5N hydrochloric acid (11 ml) for 15 minutes. After evaporation of the solution, the residue was neutralised with 0.88 ammonia. The solution was evaporated and ethanol added and re-evaporated. The syrupy residue was chromatographed on a column of silica (60 x 3.5 cm), eluting initially with methyl ethyl ketone to remove mono acetals present in the hydrolysis product, then with methyl ethyl ketone saturated with water to elute 6-deoxy-D-glucitol. The deoxy polyol was obtained as a pale brown syrup, which could not be recrystallised.

yield 2.5 g (60%)

$[\alpha]_D$ -11.76° (C = 1.1 in H_2O)

(v) 1-Deoxy-D-glucitol

An adaptation of the synthesis via D-glucose tosyl hydrazone described by de Belder and Weigel[13] afforded this polyol.

A solution of toluene-p-sulphonylhydrazide in hot ethanol (80 ml) was mixed with a solution of D-glucose in hot aqueous acetic acid

(1:1, water:acetic acid,60 ml). The mixture was allowed to cool to room temperature and left overnight. White crystals of D-glucose tosyl hydrazone had precipitated. These were filtered off, washed with ethanol, then ether and air dried.

m.p. 167-169° (lit 170°)[7,14]

yield 40.1 g (85.3%)

A stirred suspension of D-glucose tosyl hydrazone (25.0 g) in dry methanol (700 ml) was treated with potassium borohydride (15.0 g) in small amounts over a period of 48 hours. The reaction mixture was refluxed for 24 hours. Methanol was removed by evaporation under reduced pressure. The residue was dissolved in water (400 ml) and de-ionised with Amberlite IR120 (H^+) resin to remove all potassium. Boron, present as boric acid, was removed by successive evaporations from methanol.

Part of the residual syrup was purified on a cellulose column (4.5 x 70 cm.) eluting with n-butanol saturated with water. The respective fractions were collected. The remaining residual syrup was purified in the same manner. The combined extracts were evaporated to give a syrup which was crystallised and recrystallised from ethyl acetate to give pure 1-deoxy-D-glucitol as white crystals.

m.p. 126-127° (lit 128-129°)[13]

yield 8.8 g (75%)

D.2. Reaction of the Tetritols with n-Butyraldehyde

(i) Erythritol

A solution of erythritol (7.5 g) in N hydrochloric acid (250 ml) was mixed with n-butyraldehyde (4.5 g, 1 mol). The reaction flask was stoppered, shaken vigorously then left for 20 hours at room temperature. During this time crystals of di-acetal separated in the reaction flask. These were filtered off, washed with water and recrystallised from ethanol to give 1,3:2,4-di-O-butylidene erythritol.

m.p. 76-77°

yield 1.5 g

Analysis:

Found C = 62.56 % ; H = 9.56%

$C_{12}H_{22}O_4$ requires C = 62.58 % ; H = 9.63%

The remaining solution was neutralised 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 exhaustively extracted with hot benzene to give plate-like crystals of 1,3-O-butylidene-DL-erythritol on cooling.

m.p. 99-101°

yield 6.6 g

Analysis:

Found C = 54.75% ; H = 9.46%

$C_8H_{16}O_4$ requires C = 54.53% ; H = 9.15%

1,3-O-Butylidene 2,4-Di-O-Benzoyl Erythritol

The acetal (0.5 g) in dry pyridine (10 ml) was cooled in an ice bath and treated dropwise with redistilled benzoyl chloride (0.8 ml, 2.4 mol). The reaction mixture was left for 24 hours at room temperature then poured onto crushed ice. The syrup, which was deposited, was separated by decanting the upper layer, washed with water and crystallised and recrystallised from ethanol to give 1,3-O-butylidene 2,4-di-O-benzoyl erythritol.

m.p. 56-57°

yield 0.72 g (66%)

Analysis:

Found C = 68.65% ; H = 6.37%

$C_{22}H_{24}O_6$ requires C = 68.73% ; H = 6.29%

2-O-Acetyl 1,3-O-Butylidene-4-O-Trityl Erythritol

The acetal (0.5 g) in dry pyridine (15 ml) was treated with purified triphenyl methyl (trityl) chloride (0.87 g, 1.1 mol) and left for 2 days at room temperature. The reaction mixture was poured onto crushed ice and an oil separated. This was isolated and washed with water: however, attempts to crystallise this compound failed. Hence the syrup was redissolved in dry pyridine (5 ml) and treated

with redistilled acetic anhydride (2 ml), then left for 2 hours. After pouring into water, the reaction yielded a syrup which was separated and crystallised from ethanol.

m.p. 74.5-75°

yield 0.9 g (69%)

Analysis:

Found C = 75.67% ; H = 7.10%

$C_{29}H_{32}O_5$ requires C = 75.62% ; H = 7.00%

1,3-O-Butylidene 2,4-O-Phenyl Boronate Erythritol

The acetal (0.5 g) in water (0.5 ml) was mixed with phenyl boronic anhydride (0.29 g, 1 mol) in warm methanol (4.5 ml), and left in a refrigerator for 24 hours.

The solid product was filtered off and recrystallised from toluene. A spectro photometric estimation of boron gave a content of 4.2%.

m.p. 56-57°

yield 0.55 g (77.5%)

Analysis:

Found C = 63.97% ; H = 7.12% ; B = 4.01%

$C_{14}H_{19}BO_4$ requires C = 64.15% ; H = 7.31% ; B = 4.12%

(ii) L-Threitol

A solution of L-threitol (5 g) in N hydrochloric acid (165 ml) was mixed with n-butyraldehyde (3 g, 1 mol) and left for 20 hours at room temperature.

Needle crystals of 1,3:2,4-di-O-butylidene-L-threitol had separated and these were filtered off, washed with water and recrystallised from light-petroleum.

m.p. 67^{o}

yield 1.5 g

$[\alpha]_D$ 40.38^{o} (C = 2.54 in $CH\ Cl_3$)

Analysis:

Found C = 62.63% ; H = 9.68%

$C_{12}H_{22}O_4$ requires C = 62.58% ; H = 9.63%

The remaining acidic reaction mixture was neutralised with sodium bicarbonate, evaporated to dryness and extracted with hot ethanol (3 x 30 ml). An examination of the combined extracts by TLC, using MEK saturated with water, on silica plates, showed the presence of two mono acetals, as well as some unreacted polyol. The mono acetals were separated from the polyol by chromatography on a column of silica (50 x 3.5 cm), eluting with MEK saturated with water. Attempts to separate these two acetals by conventional adsorption chromatography, failed with a wide variety of solvents.

However a separation was achieved on a Dowex OH^- resin column

(60 x 3.5 cm) eluting with carbon dioxide-free water.

1,3-O-Butylidene-L-threitol was eluted firstly i.e. the slower spot on the thin layer chromatogram. Evaporation of the relevant fractions yielded a clear syrup, which was crystallised from ethanol.

m.p. 54-54.5°

yield 1.8 g

$[\alpha]_D$ 5.6° (C = 1 in H_2O)

Analysis:

Found C = 54.44% ; H = 9.23%

2,3-O-Butylidene-L-threitol was eluted secondly from the column. Evaporation of the relevant fractions yielded a pure yellow syrup, which could not be induced to crystallise by a wide range of solvents.

yield 0.4 g

$[\alpha]_D$ - 19.2° (C = 1 in H_2O)

Analysis:

Found C = 54.28% ; H = 8.96%

$C_8H_{16}O_4$ requires C = 54.53% ; H = 9.15%

1,3-O-Butylidene 2,4-O-di-Benzoyl-L-Threitol

The 1,3-O-mono acetal (0.35 g) was dissolved in dry pyridine and treated with redistilled benzoyl chloride (0.56 ml, 2.1 mol). The same process for extraction was used as for 1,3-O-butylidene-DL-erythritol. The product was crystallised from ethanol.

m.p. 52-53°

yield 0.5 g (66%)

Analysis:

Found C = 68.76% ; H = 6.44%

$C_{22}H_{24}O_6$ requires C = 68.73% ; H = 6.29%

1,3-O-Butylidene 2,4-O-Phenyl Boronate L-Threitol

The acetal (0.35 g) in water (0.75 ml) was mixed with phenyl boronic anhydride (0.208 g, 1 mol) in methanol (5 ml).

The reaction flask was left in a refrigerator for 24 hours. After this period, the product had crystallised and was filtered off. Purification was effected by recrystallisation from toluene. Spectrophotometrically a value of 3.8% was obtained for the boron analysis.

m.p. 96°

yield 0.4 g (77%)

Analysis:

Found C = 64.01% ; H = 7.19% ; B = 3.97%

$C_{14}H_{19}BO_4$ requires C = 64.15% ; H = 7.31% ; B = 4.12%

The Synthesis of 2,3-O-Butylidene-L-Threitol from Dimethyl Tartrate

Dimethyl tartrate (see page 134) (10 g), n-butyraldehyde (3.7 g, 1 mol), p-toluene sulphonic acid (0.5 g) and light petroleum (100 ml) were refluxed overnight with the azeotropic removal of the water produced in the reaction by a Dean and Stark apparatus. The reaction mixture was neutralised with sodium hydrogen carbonate and evaporated to dryness. The residue was shaken with chloroform (3 x 50 ml), the combined extracts washed with water (2 x 10 ml), and dried with anhydrous magnesium sulphate. TLC of the extracts in MEK saturated with water, chloroform or ethyl acetate showed the absence of any diester and the presence of one product only. Evaporation of the chloroform extracts afforded a pale yellow syrup of 2,3-O-butylidene dimethyl tartrate.

yield 11.7 g (90%)

The 2,3-O-butylidene diester (7 g) in dry tetrahydrofuran (70 ml) was added dropwise to a vigorously stirred suspension of lithium aluminium hydride (3 g) in tetrahydrofuran (250 ml). The reaction was refluxed overnight with stirring. Excess lithium aluminium hydride was destroyed by the sequential addition of water (3 ml), then 15% sodium hydroxide (5 ml) followed by water (9 ml), dropwise down the condenser of the reaction apparatus. A granular precipitate was obtained which was filtered off and washed thoroughly with hot ethanol. The combined

filtrates were evaporated under reduced pressure to yield a pale yellow syrup of 2,3-O-butylidene-L-threitol, which could not be crystallised. This syrup was chromatographically pure and spectrophotometrically equivalent (IR and NMR, in D_2O) to the previously obtained 2,3-O-butylidene-L-threitol, prepared directly from the polyol.

yield	4.5 g	(85%)
$[\alpha]_D$	-17.5°	(C = 1 in H_2O)

D.3. Reaction of the Pentitols with n-Butyraldehyde

(i) Ribitol

In equimolar amounts, the reaction between ribitol and n-butyraldehyde yielded the mono acetal with a trace of di-acetal. Hence the molar ratio of n-butyraldehyde to ribitol was increased in order to obtain better yields of the diacetal.

Ribitol (10 g 0.5 M) in N hydrochloric acid (135 ml) was mixed with n-butyraldehyde (7.1 g, 1.5 mol) and left in a stoppered flask for 24 hours. Crystals of 1,3:2,4-di-O-butylidene ribitol had separated. These were removed by filtration and recrystallised from ethanol.

m.p. 60-61°

yield 3.4 g

Analysis:

Found C = 59.83% ; H = 9.28%

$C_{13}H_{24}O_5$ requires C = 59.97% ; H = 9.29%

The remaining aqueous acidic solution was neutralised with sodium hydrogen carbonate, evaporated to dryness and extracted with hot ethanol-ethyl acetate (1:1, 3 x 50 ml). The combined extracts were evaporated to dryness and the 2,4-O-mono acetal separated by column chromatography on silica (50 x 3.5 cm) with methyl ethyl ketone saturated with water as the elutant. Evaporation of the relevant fractions gave 2,4-O-butylidene ribitol as a pale yellow syrup which could not be crystallised.

yield 6.5 g

Analysis:

Found C = 52.24% ; H = 8.62%

$C_9H_{18}O_5$ requires C = 52.41% ; H = 8.70%

1,3:2,4-Di-O-Butylidene-5-O-Benzoyl Ribitol

The diacetal (0.75 g) in dry pyridine (15 ml) was treated with redistilled benzoyl chloride (0.41 ml; 1.2 mol) and left for 24 hours at room temperature. The reaction was poured onto ice and the oil which deposited extracted with chloroform. The chloroform extracts were washed with water, dried with anhydrous sodium sulphate and evaporated to yield the mono-benzoate which was crystallised from ethanol.

m.p. 69-70°

yield 0.85 g (81%)

Analysis:

Found C = 65.81% ; H = 7.61%

$C_{20}H_{28}O_6$ requires C = 65.91% ; H = 7.74%

2,4-O-Butylidene 1,3,5-Tri-O-Benzoyl Ribitol

The mono acetal (0.5 g) in dry pyridine (10 ml) was cooled in ice and treated with benzoyl chloride (1.1 ml, 3.05 mol). The reaction mixture was left for 24 hours, poured onto ice and the product extracted as for the previously mentioned di-O-acetal. The product was

crystallised and recrystallised from ethanol.

m.p. 83.5-84.5°

yield 0.9 g (72%)

Analysis:

Found C = 69.63% ; H = 5.95%

$C_{30}H_{30}O_8$ requires C = 69.48% ; H = 5.83%

2,4-O-Butylidene 1,5-Di-O-Benzoyl Ribitol

The acetal (0.5 g) in dry pyridine (10 ml) was cooled in ice and treated with benzoyl chloride (0.68 ml, 2.4 mol) as above. The di-benzoate was extracted, by the previous technique, as a syrup. Crystallisation and recrystallisation was effected by ethanol.

m.p. 83-84°

yield 0.7 g (70%)

Analysis:

Found C = 66.31%; H = 6.44%

$C_{23}H_{26}O_7$ requires C = 66.65%; H = 6.33%

2,4-O-Butylidene 1,5-Di-O-Trityl Ribitol

The mono acetal (0.25 g) in dry pyridine (5 ml) was cooled in ice and treated with purified trityl chloride (0.67 g, 2 mol). The reaction mixture was left for 2 days at room temperature, poured onto ice and the solid product which separated, filtered off and recrystallised

from ethanol-water (4:1).

m.p. 99-100°

yield 0.3 g (36%)

Analysis:

Found C = 81.97%; H = 6.50%

$C_{47}H_{46}O_5$ requires C = 81.71%; H = 6.71%

2,4-O-Butylidene 1,3-O-Phenyl Boronate Ribitol

A solution of the mono acetal (0.3 g) in water (0.7 ml) was mixed with a solution of phenyl boronic anhydride (0.15 g, 1 mol) in methanol (4 ml) and left overnight. The reaction mixture was evaporated to dryness and the residue recrystallised from toluene.

m.p. 72-73°

yield 0.3 g (71%)

Analysis:

Found C = 61.85% ; H = 7.31% ; B = 3.66%

$C_{15}H_{21}BO_5$ requires C = 61.66% ; H = 7.25% ; B = 3.70%

(ii) Xylitol

A solution of xylitol (7.6 g), n-butyraldehyde (3.6 g, 1 mol) in N hydrochloric acid (300 ml) was shaken vigorously and left for 24 hours at room temperature. The reaction mixture was neutralised with sodium hydrogen carbonate, evaporated to dryness and extracted with

hot chloroform (3 x 75 ml). Evaporation of the chloroform yielded a syrup, which was chromatographed on silica (75 x 3.5 cm) eluting initially with chloroform to give 1,3:2,4-di-O-butylidene xylitol as a pale yellow syrup after evaporation of appropriate fractions.

Analysis:

Found C = 60.12% ; H = 9.02%

$C_{13}H_{24}O_5$ requires C = 59.97% ; H = 9.29%

When the solvent was changed to methyl ethyl ketone saturated with water, the mono acetal was eluted. Evaporation of these fractions yielded a syrup which was crystallised from ethanol to give 2,4-O-butylidene xylitol as white crystals.

m.p. 115-117°

yield 4.5 g

Analysis:

Found C = 52.04% ; H = 8.51%

$C_9H_{18}O_5$ requires C = 52.41% ; H = 8.70%

1,3:2,4-Di-O-Butylidene 5-O-Benzoyl Xylitol

The diacetal (0.5 g) in dry pyridine (10 ml) was treated with benzoyl chloride (0.3 ml, 1.3 mol) after cooling in ice. The reaction mixture was left for 24 hours at room temperature, poured onto crushed ice and the product extracted as in the previous benzoylations.

The benzoate was crystallised from aqueous ethanol.

m.p. 78-79°

yield 0.5 g (71%)

Analysis:

Found C = 65.78% ; H = 7.58%

$C_{20}H_{28}O_6$ requires C = 65.91% ; H = 7.74%

2,4-O-Butylidene 1,5-Di-O-Benzoyl Xylitol

2,4-O-Butylidene xylitol (0.5 g) in pyridine (10 ml) was cooled in ice and treated with redistilled benzoyl chloride (1.02 ml, 3.6 mol) and left 24 hours at room temperature. The reaction mixture was poured onto crushed ice and the product extracted with chloroform. The extracts were dried with anhydrous sodium sulphate, evaporated to dryness andthe syrupy product crystallised from ethanol to yield a white powder.

m.p. 134-135°

yield 0.65 g (65%; for dibenzoate)

Analysis:

Found C = 66.40% ; H = 6.50%

$C_{23}H_{26}O_7$ requires C = 66.65% ; H = 6.32%

3-O-Acetyl 2,4-O-Butylidene 1,5-Di-O-Benzoyl Xylitol

The di-O-benzoate of the mono acetal (0.25 g) in dry pyridine (5 ml) was treated with redistilled acetic anhydride (1.5 ml) and the reaction mixture left for 6 hours at room temperature. The reaction mixture was poured onto ice and the oil which was deposited separated by decantation and crystallised from ethanol.

m.p. 82-83.5°

yield 0.2 g (74%)

Analysis:

Found C = 65.91% ; H = 6.01%

$C_{25}H_{28}O_8$ requires C = 65.77% ; H = 6.18%

2,4-O-Butylidene 1,5-Di-O-Trityl Xylitol

The mono acetal (0.4 g) in dry pyridine (10 ml) was treated with triphenyl methyl chloride (1.15 g, 2 mol). The reaction mixture was left for four days at room temperature, poured onto crushed ice and the sticky solid which separated, recrystallised from alcohol, with a trace of water.

m.p. 88-92°

yield 0.4 g (30%)

Analysis:

Found C = 81.45% ; H = 6.57%

$C_{47}H_{46}O_5$ requires C = 81.71% ; H = 6.71%

(iii) D-Arabinitol

A solution of D-arabinitol (8 g) in N hydrochloric acid (210 ml) was mixed with n-butyraldehyde (3.8 g, 1 mol) and left for 20 hours at room temperature. The reaction mixture was neutralised with sodium hydrogen carbonate, evaporated to dryness and the residue extracted with hot ethanol (3 x 50 ml). Tlc showed the presence of two mono acetals, as well as some unreacted polyol. The mixed mono acetals were separated from the polyol by chromatography on silica (column 100 x 5 cm.) eluting with MEK saturated with water. The mixed mono acetals were separated on a column of Dowex OH^- resin, eluting with CO_2 free water. 1,3-O-Butylidene-D-arabinitol was eluted firstly from the column. When the eluate was removed, a white solid remained which was recrystallised from ethanol.

m.p. $94\text{-}95^{o}$

yield 2.3 g

$[\alpha]_D$ -14.7^{o} (C = 1.105 in H_2O)

Analysis:

Found C = 52.22%; H = 8.63%

2,3-O-Butylidene-D-arabinitol was eluted secondly from the column. The relevant fractions were evaporated to leave a white powder, which was recrystallised from ethanol.

m.p. 88-89°

yield 0.75 g

$[\alpha]_D$ 2.85° (C = 1.05 in H_2O)

Analysis:

Found C = 52.20% ; H = 8.61%

$C_9H_{18}O_5$ requires C = 52.41% ; H = 8.70%

Both acetals were characterised as their respective per-benzoates.

The acetal (0.5 g) in dry pyridine (10 ml) was cooled to -5°C. Benzoyl chloride (1.03 g, 3 mol) was added dropwise and the reaction mixture allowed to reach room temperature, and left for two days.

The mixture was poured onto crushed ice, extracted with chloroform (2 x 10 ml) and the extracts washed with water. Removal of the chloroform afforded a syrup, in both cases, which was crystallised and recrystallised from ethanol:-

1,3-O-butylidene 2,4,5-tri-O-benzoyl-D-arabinitol

m.p. 109-110°

yield 1.0 g (80%)

Analysis

Found C = 69.29% ; H = 5.22%

2,3-O-butylidene 1,4,5-tri-O-benzoyl-D-arabinitol

m.p. 117-118°

yield 0.9 g (72%)

Analysis:

Found C = 69.37% ; H = 5.30%

$C_{30}H_{30}O_8$ requires C = 69.48% ; H = 5.83%

D.4. Reaction of Some Deoxy Polyols with n-Butyraldehyde

(i) 1-Deoxy-D-Xylitol

A mixture of 1-deoxy-D-xylitol (3 g) in N hydrochloric acid (90 ml) was mixed with n-butyraldehyde (1.6 g, 1 mol) and the reaction mixture left for 20 hours at room temperature. After neutralisation with sodium hydrogen carbonate, the mixture was evaporated to dryness and the residue extracted with chloroform (3 x 50 ml). The combined chloroform extracts were evaporated to dryness and chromatographed on a column of silica (75 x 3.5 cm) eluting initially with chloroform to give 1-deoxy 2,4; 3,5-di-O-butylidene-D-xylitol as a pale yellow syrup.

yield 0.8 g

$[\alpha]_D$ -16.19° (C = 1.025 in $CHCl_3$)

Analysis:

Found C = 63.76% ; H = 9.76%

$C_{13}H_{24}O_4$ requires C = 63.90% ; H = 9.90%

The introduction of 5% ethanol into the chloroform elutant afforded 2,4-O-butylidene-1-deoxy-D-xylitol. After removal of the solvent the product was recrystallised from ethanol, as white needles.

m.p. $85-87^\circ$

yield 1.2 g

$[\alpha]_D$ $-4{\cdot}4^\circ$ (C = 1 in H_2O)

Analysis:

Found C = 56.90% ; H = 9.38%

$C_9H_{18}O_4$ requires C = 56.80% ; H = 9.47%

Periodate Oxidation of 2,4-O-Butylidene-1-Deoxy-D-Glucitol

A solution of 2,4-O-butylidene-1-deoxy-D-glucitol (1 g) in deionised water (50 ml) was treated with sodium periodate (1.02 g, 1.05 mol) and the reaction flask stored in a dark place for 2 hours. After this period, the pH of the solution was checked and made slightly alkaline with N/100 sodium hydroxide solution to pH 8-8.5. The reaction mixture was continuously extracted with chloroform overnight. The chloroform extract was washed with water (5 ml) and evaporated under reduced pressure to yield a syrup of 2,4-O-butylidene 5-deoxy-L-xylose.

yield 0.8 g (94%)

This syrup in deionised water (25 ml) was treated with potassium borohydride (0.5 g) for 6 hours at room temperature. Potassium and boron were removed as for previous borohydride reductions by the use of Amberlite IR 120 (H^+) and methanol respectively. After removal of the solvent, the syrupy residue was crystallised and recrystallised from ethanol to give 2,4-O-butylidene 1-deoxy-D-xylitol.

m.p. 86-87°

yield 0.75 g (93%)

$[\alpha]_D$ -3.9° (C = 1.1 in H_2O)

(ii) 6-Deoxy-D-Glucitol

A solution of 6-deoxy-D-glucitol (5.0 g) in N hydrochloric acid (120 ml) was mixed with n-butyraldehyde (2.2 g, 1 mol) and left for 24 hours at room temperature. After this period had elapsed crystals of di-acetal had separated. These were filtered off, washed with water and crystallised from ethanol to give buff-coloured crystals of 1,3: 2,4-di-O-butylidene-6-deoxy-D-glucitol.

m.p. 114-116°

yield 0.9 g

$[\alpha]_D$ -0.7°. (C = 1 in $CHCl_3$)

Analysis:

Found C = 61.40% ; H = 9.40%

$C_{14}H_{36}O_5$ requires C = 61.29% ; H = 9.55%

The remaining reaction mixture was neutralised with sodium hydrogen carbonate, evaporated to dryness and extracted with warm ethanol (3 x 50 ml). The combined extracts, after evaporating to dryness, were chromatographed on a column of silica eluting with methyl ethyl ketone saturated with water. This step separated the two mono acetals from the unreacted polyol.

The two mono acetals were separated on a column of Dowex OH^- resin eluting with carbon dioxide-free water. Initially 2,4-O-butylidene-6-deoxy-D-glucitol was eluted. After removal of the water, the 2,4 acetal was crystallised from ethanol.

m.p. 152-153°

yield 1.1 g

$[\alpha]_D$ -5.2° (c = 0.8 in H_2O)

Analysis:

Found C = 54.42% ; H = 8.98%

Secondly 2,3-O-butylidene-1-deoxy-D-glucitol was eluted. A syrup was obtained after removal of the water: this could not be crystallised.

yield 0.4 g

Analysis:

Found C = 54.40% ; H = 9.26%

$C_{10}H_{20}O_5$ requires C = 54.52% ; H = 9.15%

D.5. Reaction of some Miscellaneous Polyhydroxy Compounds with n-Butyraldehyde

(i) Pentaerythritol

A mixture of pentaerythritol (10 g) in N hydrochloric acid (295 ml) was mixed with n-butyraldehyde (5.3 g, 1 mol) and the reaction mixture left for 14 hours at room temperature. Crystals of diacetal had separated. These were filtered off, washed with water and recrystallised twice from ethanol, as white plates.

m.p. 63-64° (lit 60.5°)[15]

yield 8 g

Analysis:

Found C = 64.06% ; H = 9.84%

$C_{13}H_{24}O_4$ requires C = 63.90% ; H = 9.90%

The remaining acid solution was neutralised with sodium hydrogen carbonate, evaporated to dryness and extracted with ethanol. The ethanol extracts were evaporated to yield a syrup. This syrup was introduced into a silica column (25 x 3.5 cm) and mono-butylidene pentaerythritol eluted by methyl ethyl ketone saturated with water. The relevant extracts were evaporated to give a solid which was crystallised from ethanol.

m.p. 75-76°

yield 1.2 g

Analysis:

Found C = 57.10% ; H = 9.32%

$C_9H_{18}O_4$ requires C = 56.82% ; H = 9.53%

(ii) Dipentaerythritol

A hetereogeneous mixture of dipentaerythritol (10 g) in N hydrochloric acid (160 ml) was mixed with n-butyraldehyde (4.3 g) and shaken mechanically overnight.

The resulting mixture was extracted with chloroform (3 x 50 ml) and the combined chloroform extracts washed thoroughly with water (3 x 15 ml). Removal of the solvent under reduced pressure yielded di-O-butylidene dipentaerythritol as a colourless syrup.

yield 10.2 g

Analysis:

Found C = 59.49% ; H = 9.40%

$C_{18}H_{34}O_7$ requires C = 59.64% ; H = 9.45%

(iii) Methyl α-D-Glucoside

a) A solution of methyl α-D-glucoside (10 g), n-butyraldehyde (3.8 g, 1 mol) and anhydrous toluene-4-sulphonic acid (0.5 g) in anhydrous dimethyl formamide (200 ml) were shaken mechanically for 15 hours. After neutralisation with 5% sodium hydrogen carbonate, the mixture was evaporated to dryness and the residue extracted with hot ethyl acetate (3 x 30 ml). The combined extracts were examined by thin layer chromatography in MEK saturated with water and toluene - methanol (9:1) and shown to contain only one product. The extracts were evaporated to dryness to yield a syrup which was crystallised

from ethanol to yield methyl 4,6-O-butylidene α-D-glucoside as white crystals.

m.p. 108-109°

yield 3.5 g

$[\alpha]_D$ 106.30° (C = 1.1 in H_2O)

Analysis:

Found C = 53.26% ; H = 8.21%

$C_{11}H_{20}O_6$ C = 53.21% ; H = 8.12%

b) A mixture of methyl α-D-glucoside (10 g), n-butyraldehyde (11.1 g) and conc. HCl (0.5 ml) was shaken mechanically for 3 hours. Water (10 ml) was added and a solid separated. This was filtered-off, washed thoroughly with cold water and recrystallised from ethanol - water (9:1) to give methyl 2,3-oxido di-n-butylidene 4,6-O-butylidene -α-D-glucoside as white plate-like crystals.

m.p. 103-104°

yield 8.6 g (45%)

$[\alpha]_D$ 69.90° (C = 1.07 in $CHCl_3$)

Analysis:

Found C = 61.08% ; H = 9.09%

$C_{19}H_{34}O_7$ requires C = 60.94% ; H = 9.15%

Methyl 2,3-O-Benzoyl 4,6-O-Butylidene-α-D-Glucoside

The mono acetal (0.4 g) in dry pyridine (12 ml) was treated with purified benzoyl chloride(0.46 g, 2 mol) and left at room temperature for 24 hours. The reaction mixture was poured onto crushed ice, the resulting solution extracted with chloroform. Evaporation of the chloroform afforded the syrupy product which was crystallised from ethanol.

m.p. 98-99°

yield. 0.5 g (68%)

Analysis:

Found C = 65.55% ; H = 6.06%

$C_{25}H_{28}O_8$ requires C = 65.77% ; H = 6.18%

General Methods used in Structural Analysis

(i) Periodate Oxidation with Estimation of Liberated Formaldehyde and Formic Acid

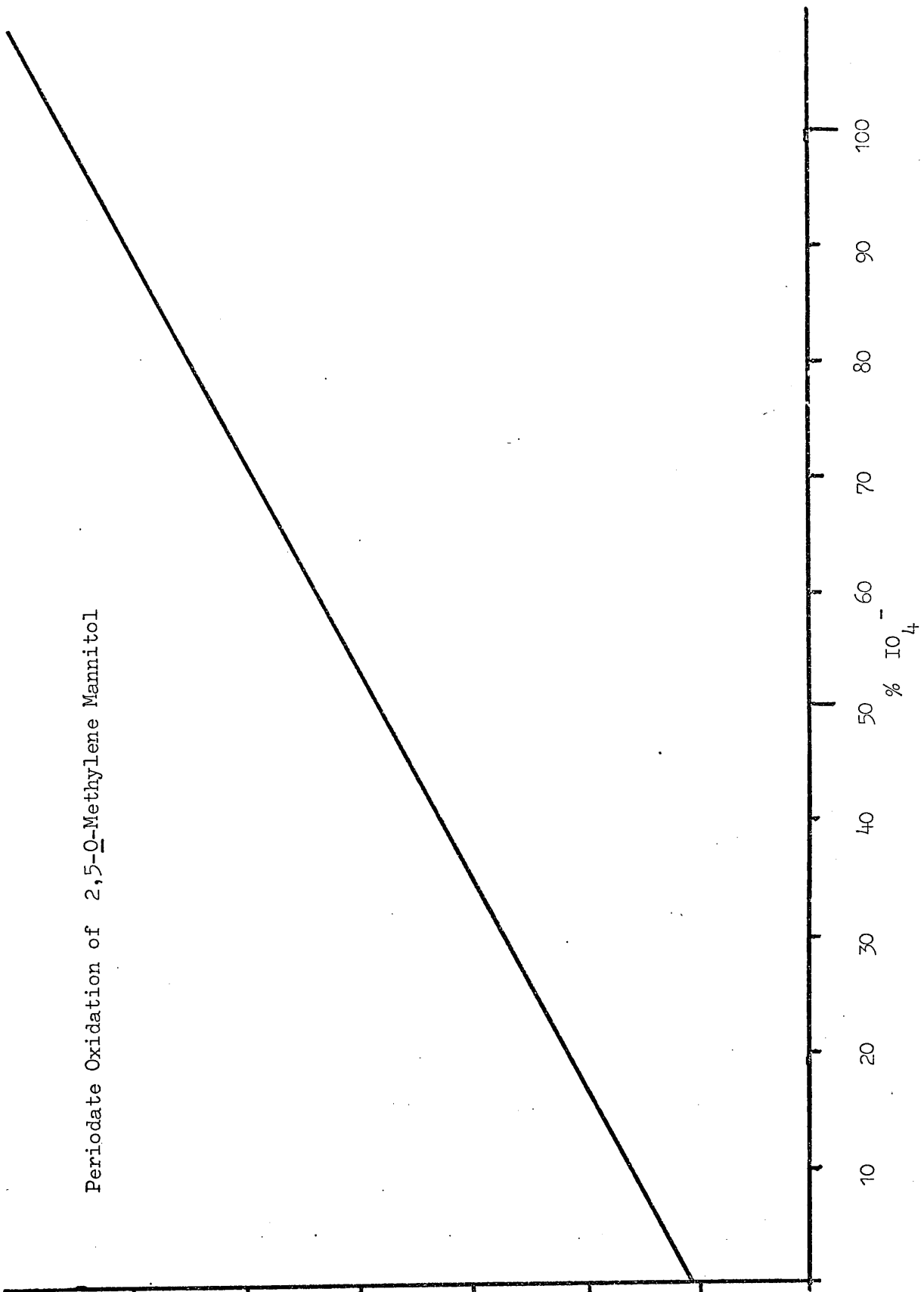
a) Oxidation[16]

Equimolar solutions of sodium meta periodate and potassium iodate were used in this analysis. The periodate solution was taken to be 100% whilst the iodate solution was taken as 0% with respect to concentration of periodate.

Solutions of sodium meta periodate (0.321 g in 100 ml. of water: 0.015M) and potassium iodate (0.321 g in 100 ml. of water: 0.015M) were freshly prepared. Aliquots of both solutions (1 ml) were diluted to 250 ml with water. A further aliquot of both solutions (1 ml of both) was combined and diluted to 500 ml with water.

The solutions diluted to 250 ml were taken to contain 100% and 0% of periodate. The solution diluted to 500 ml contained 50% periodate. The optical densities of these three solutions were measured at 223 nm in 1 cm silica cell, with water as a blank. A linear calibration graph was constructed from these readings.

Samples of the compounds (0.01 g) were dissolved in 0.015 M sodium meta periodate (10 ml) and aliquots (1 ml) were withdrawn periodically, diluted 250 times with water and the optical densities recorded at 223 nm. The concentration of periodate present in the oxidation mixture was determined from the calibration graph. Aliquots were recorded at ½ hour intervals until a constant value was obtained,


Periodate Oxidation of 2,5-O-Methylene Mannitol
Optical Density at 223 nm
0.7
0.6
0.5
0.4
0.3
0.2
0.1
10
20
30
40
50
60
70
80
90
100
% IO_4^-

usually 2-3 hours for the acetal of a polyol.

This method was checked by simultaneously oxidising 2,5-O-methylene mannitol (0.01 g), a compound which consumed 1 mol of periodate.

b) Liberated Formaldehyde

A spectrophotometric determination of formaldehyde was used by its colour reaction with chromotropic acid reagent[18].

Reagent: Sodium salt of chromotropic acid (0.2 g) dissolved in water (20 ml) and mixed with 12.5M sulphuric acid (80 ml); i.e. water (1 part) + concentrated sulphuric acid (2 parts).

The solutions of compounds and 2,5-O-methylene mannitol in 0.015 M periodate from the initial oxidation were employed.

After 20 hours, aliquots (1 ml) of 2,5-O-methylene mannitol solution were diluted to 10 ml, 20 ml and 50 ml with water. An aliquot of each diluted solution (1 ml) was placed in individual stoppered tubes. A blank, comprised of water (1 ml) was similarly prepared. Each of the four tubes was treated with 20% sodium sulphite solution (0.1 ml) and chromotropic acid reagent (8.4 ml).

Simultaneously, an aliquot of the sample solution (1 ml) was diluted with water (15 ml) and treated as above with sodium sulphite and chromotropic acid reagent.

The five tubes were stoppered and heated on a boiling water bath for 1 hour, during which time violet colour developed. After

cooling aqueous thiourea (0.4%, 0.5 ml) was added and the optical densities for the solutions recorded at 570 nm.

A linear calibration graph was obtained from the readings of the 2,5-O-methylene mannitol solutions.

Hence the amount of formaldehyde produced by the compound could be calculated.

c) Liberated Formic Acid[17]

A known weight of compound (0.01 g) was dissolved in 0.015M sodium periodate solution (10 ml) and left to oxidise for four hours. An aliquot (5 ml) was withdrawn, treated with ethylene glycol to destroy excess periodate, diluted with water (10 ml) and titrated against standard sodium hydroxide (0.02N). A blank titre was also taken without any compound present.

(ii) Isolation of Fragments of Oxidation

The pH of the solution after oxidation was adjusted until it was just alkaline, with sodium hydrogen carbonate. The solution was continuously extracted in a liquid extractor with hot chloroform (100 ml) overnight.

The extract was washed with water (10 ml), dried over sodium sulphate and evaporated to dryness to yield a syrup.

This syrup, in methanol, was reduced with potassium borohydride to give the corresponding polyol.

Acetal rings were removed from the fragment if required, by heating an aqueous solution with Amberlite 1R 120 (H^+) resin on a boiling waterbath for six hours.

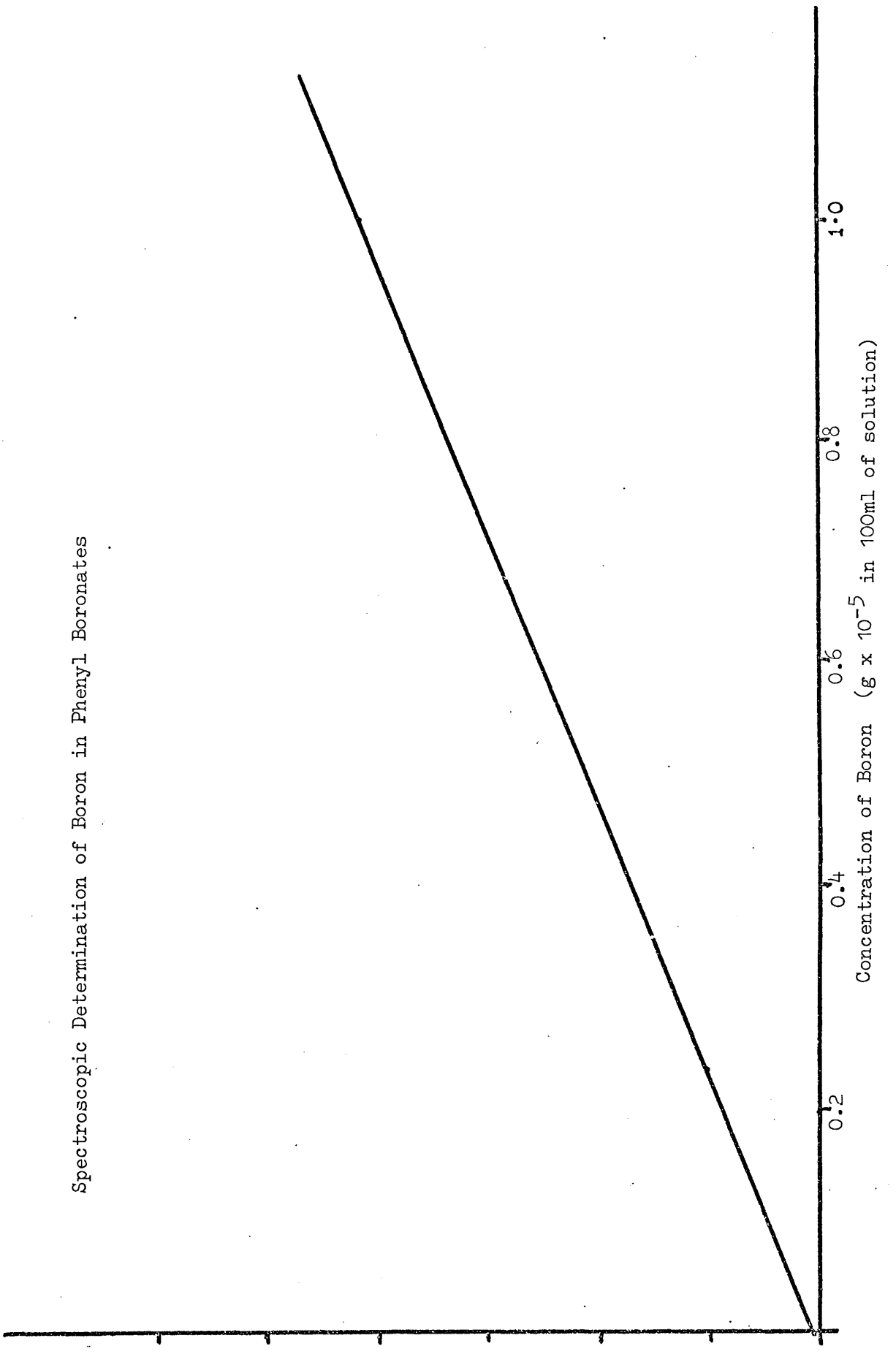
(iii) Spectroscopic Estimation of Boron in Phenyl Boronates of Acetals

Phenyl boronates were hydrolysed in aqueous ethanol solution, and the liberated phenyl boronic acid determined spectrophotometrically at 219 nm[19].

Phenyl boronic anhydride (0.25 g) was dissolved in water-ethanol (1:1, 50 ml). An aliquot of this solution (10 ml) was diluted to 100 ml with aqueous ethanol and aliquots of this solution (1,2,3,4 and 5 ml respectively) were diluted to 100 ml with aqueous ethanol. The optical densities of these solutions were measured at 219 nm.

A calibration graph of optical density against concentration of boron was plotted.

The acetal phenyl boronate (0.1 g) was dissolved in the same aqueous ethanol solution. An aliquot of this solution (20 ml) was diluted to 100 ml and a further aliquot (20 ml) of the diluted solution diluted to 100 ml with the aqueous ethanol solution. Finally an aliquot of this solution (10 ml) was diluted to 20 ml with aqueous ethanol.


Spectroscopic Determination of Boron in Phenyl Boronates
Optical Density at 219 nm
1.2
1.0
0.8
0.6
0.4
0.2
0.2
0.4
0.6
0.8
1.0
Concentration of Boron (g x 10^{-5} in 100ml of solution)

(iv) Methylation of Acetals[20]

The method of Kuhn *et al*[21] was used.

The acetal (1 g) was dissolved in anhydrous dimethyl formamide (25 ml). Methyl iodide (3 equivalents per hydroxyl group) and silver oxide (2 equivalents per OH group) were added and the mixture stoppered and stirred mechanically overnight in a vessel protected from light. After 24 hours, the mixture was filtered and the filtrate evaporated, using a vacuum pump, to give a solid residue. Chloroform (75 ml) was added and the mixture refiltered. The chloroform extract was washed with water (3 x 10 ml) and evaporated to dryness to give a syrupy product.

Complete methylation was checked for by IR (in dry CCl_4 solution) and by tlc on silica plates (using toluene/methanol 9:1).

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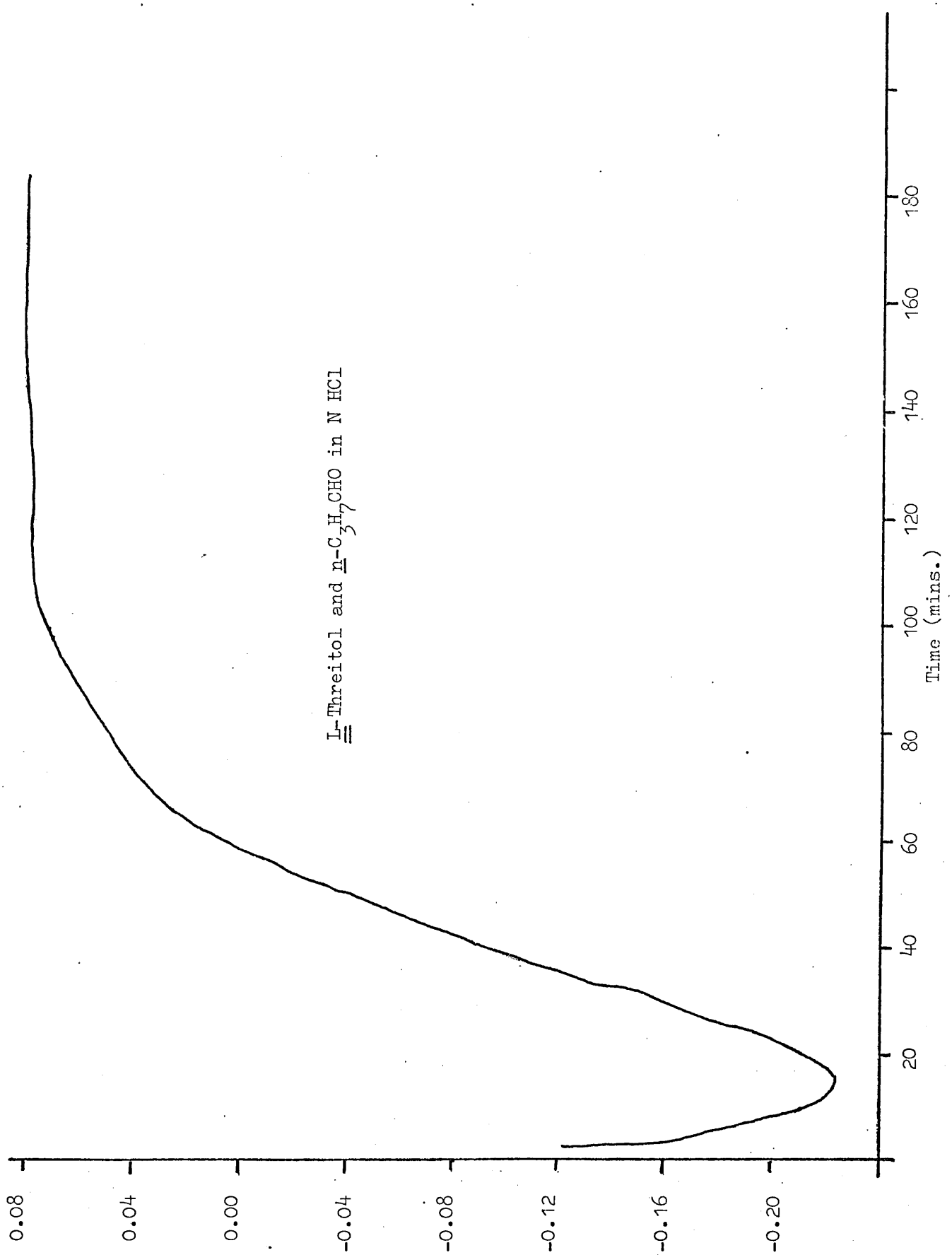
APPENDIX

Polarimetric Investigation of the Reactions of Polyols with n-Butyraldehyde

a) L-Threitol (both at 0.25 M in N hydrochloric acid)

Sodium D-line : 1 dm glass cell.

Time (mins.)	Optical Rotation(α^{o})	Time (mins.)	Optical Rotation (α^{o})
3	- 0.125	25	- 0.185
4	- 0.160	26	- 0.182
5	- 0.173	27	- 0.181
6	- 0.176	28	- 0.172
7	- 0.190	29	- 0.165
8	- 0.195	30	- 0.160
9	- 0.204	32.5	- 0.143
10	- 0.212	35	- 0.124
11	- 0.217	37.5	- 0.106
12	- 0.219	40	- 0.092
13	- 0.223	42.5	- 0.078
14	- 0.225	45	- 0.066
15	- 0.224	47.5	- 0.050
16	- 0.226	50	- 0.040
17	- 0.221	55	- 0.018
18	- 0.220	60	0.006
19	- 0.218	70	0.034
20	- 0.214	80	0.047
21	- 0.212	90	0.062
22	- 0.209	105	0.075
23	- 0.203	120	0.074
24	- 0.196	180	0.085

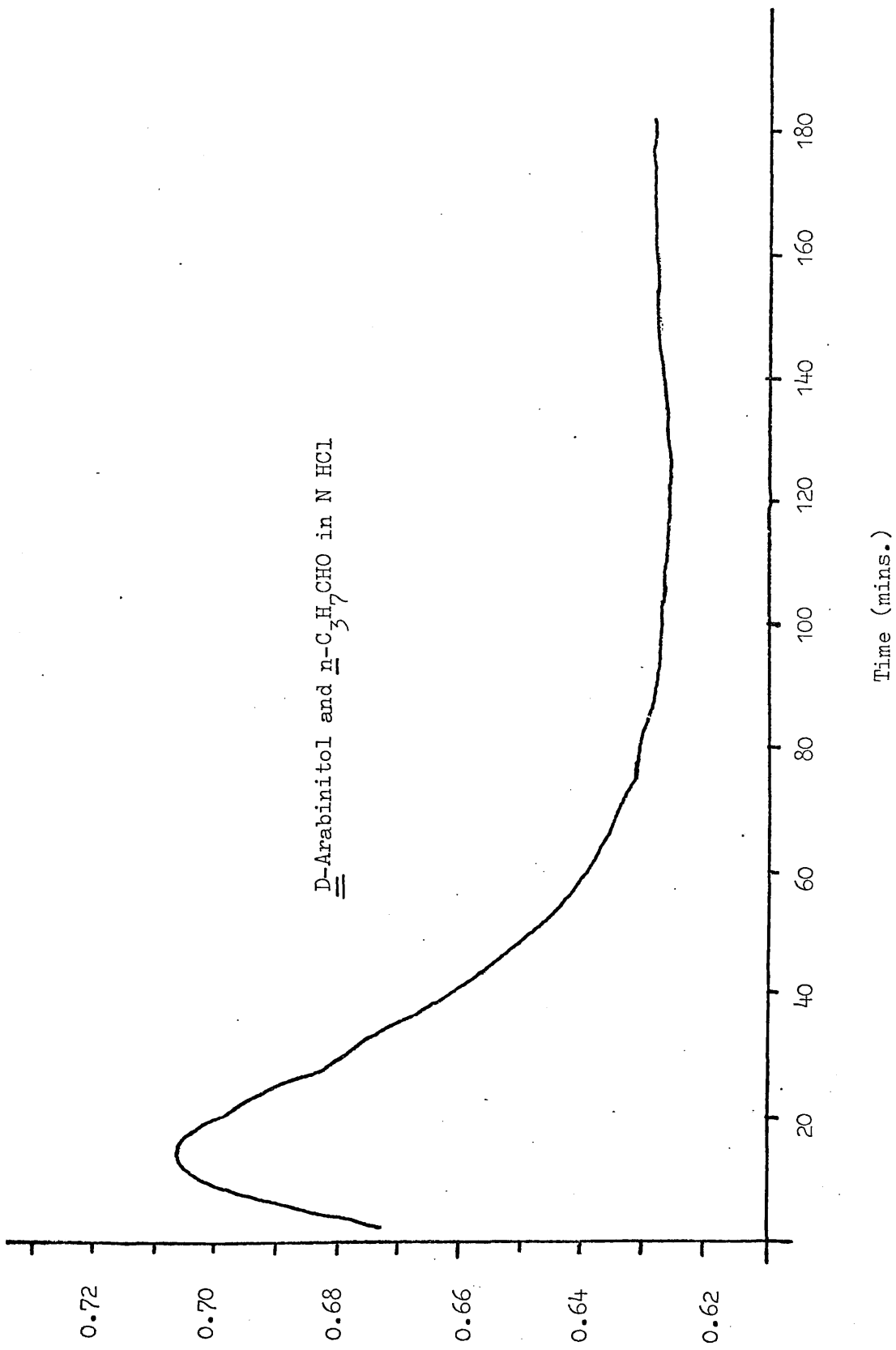

L-Threitol and n-C_3H_7CHO in N HCl
Optical Rotation (α°)
0.08
0.04
0.00
-0.04
-0.08
-0.12
-0.16
-0.20
20
40
60
80
100
120
140
160
180
Time (mins.)

b) D-Arabinitol (both at 0.25 M in N hydrochloric acid)

Mercury 365 line : 1 dm silica cell.

Time (mins)	Optical Rotation (α^{o})
3	0.674
4	0.679
5	0.686
6	0.691
7	0.694
8	0.696
9	0.700
10	0.701
11	0.704
12	0.704
13	0.706
14	0.705
15	0.705
16	0.705
17	0.705
18	0.704
19	0.701
20	0.700
21	0.699
22	0.696
23	0.695

Time (mins)	Optical Rotation (α^{o})
24	0.694
25	0.692
26	0.688
27	0.686
28	0.685
29	0.681
30	0.681
33	0.676
36	0.670
39	0.664
42	0.660
45	0.655
50	0.649
55	0.643
60	0.640
70	0.634
80	0.631
90	0.628
105	0.627
120	0.626
150	0.628
180	0.628

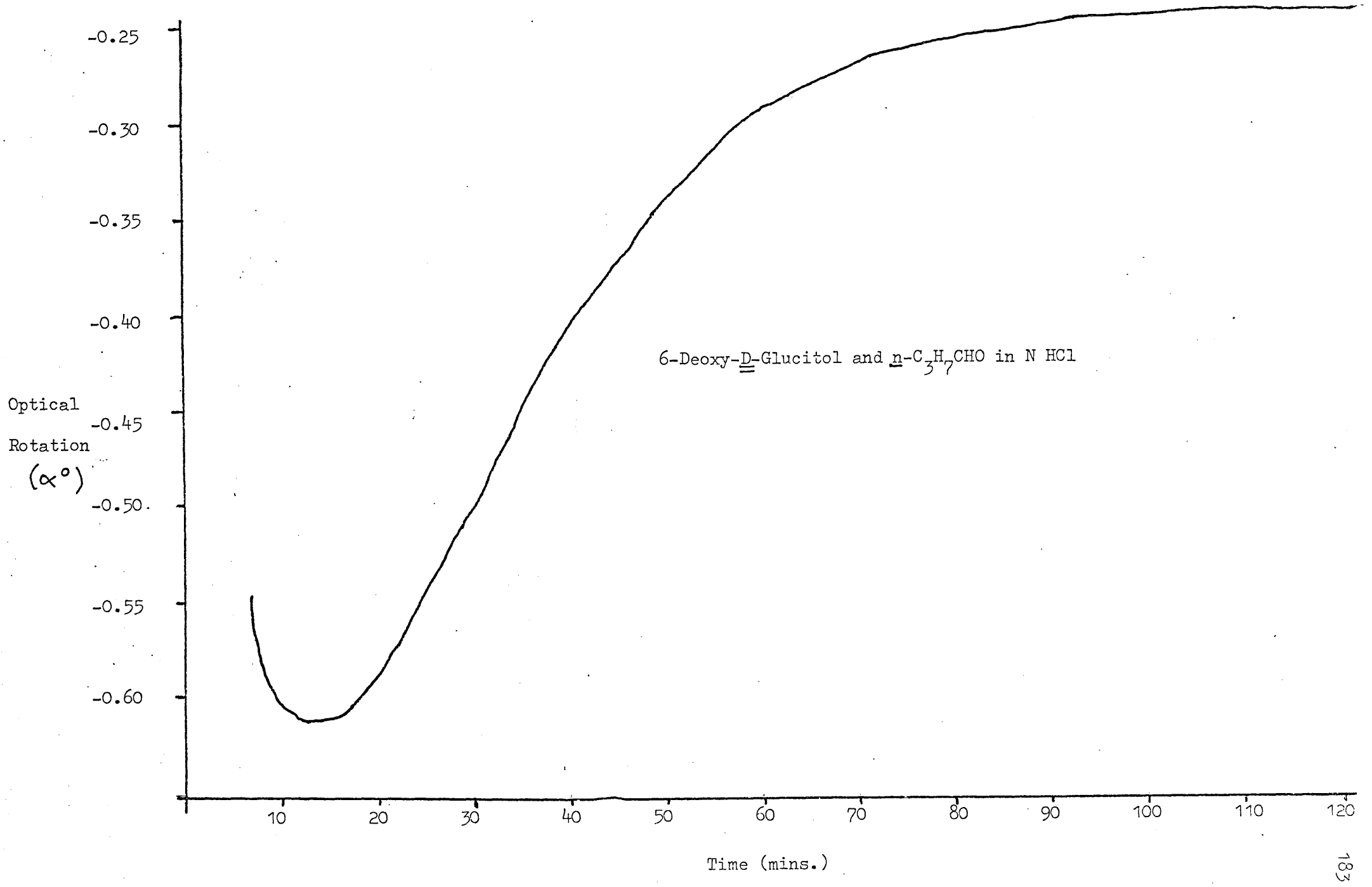

D-Arabinitol and n-C_3H_7CHO in N HCl
Optical Rotation (α°)
0.72
0.70
0.68
0.66
0.64
0.62
20
40
60
80
100
120
140
160
180
Time (mins.)

c) 6-Deoxy-D-Glucitol (both 0.25 M in N hydrochloric acid)

Sodium D line : 1 dm glass cell

Time (mins)	Optical Rotation (α^{o})
7	- 0.548
8	- 0.584
9	- 0.595
10	- 0.602
11	- 0.607
12	- 0.611
13	- 0.611
14	- 0.611
15	- 0.610
16	- 0.608
17	- 0.602
18	- 0.597
19	- 0.591
20	- 0.589
21	- 0.580
22	- 0.572
23	- 0.562
24	- 0.554
25	- 0.541
26	- 0.534

Time (mins)	Optical Rotation (α^{o})
27	- 0.523
28	- 0.518
29	- 0.503
30	- 0.496
32.5	- 0.472
35	- 0.447
37.5	- 0.424
40	- 0.404
42.5	- 0.390
45	- 0.369
47.5	- 0.354
50	- 0.344
55	- 0.312
60	- 0.293
70	- 0.268
80	- 0.254
90	- 0.248
105	- 0.246
120	- 0.245


-0.25
-0.30
-0.35
-0.40
-0.45
-0.50
-0.55
-0.60
Optical Rotation (α°)
6-Deoxy-D-Glucitol and n-C3H7CHO in N HCl
10
20
30
40
50
60
70
80
90
100
110
120
Time (mins.)