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Synthetic and Structural Investigations On Cyclic Acetals

A Thesis submitted by

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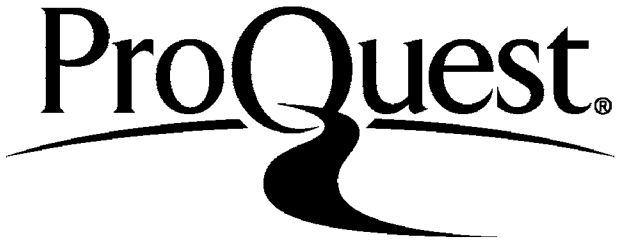

A B S T R A C T

I. Acid catalysed formation of butylidene acetals of certain polyols and D-galactose was studied.

i) Galactitol afforded the 1,3-O-butylidene and 2,3-O-butylidene monoacetals without any kinetically controlled product.

ii) 1-Deoxy-D-galactitol (L-fucitol) produced 4,6-O-butylidene-1-deoxy-D-galactitol as main product together with a stereoisomeric mixture of 2,3-monoacetals and a pure 4,5-monoacetal.

iii) Galactitol under stronger conditions initially produced a complex mixture from which was isolated 2,3:4,5-di-O-butylidene acetal and another dibutylidene acetal with the probable structure of 2,4:5,6-di-O-butylidene acetal in small yields and 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol and 1,3:4,6-di-O-butylidenegalactitol in moderate yields. Longer reaction times afforded the 1,3:4,6-di-O-butylidenegalactitol as the main product with a considerable amount of 1,3:2,4:5,6-triacetal.

iv) 3-O-Methyl-D-glucitol afforded a stereoisomeric mixture of 2,4:5,6-di-O-butylideneacetal as the only diacetal.

v) 1-Deoxy-D-glucitol gave the 2,4:5,6-di-O-butylidene derivative as the main diacetal.

vi) 2-Deoxy-D-glucitol gave an unidentified kinetically controlled product and 1,3:4,6-di-O-butylideneacetal as the thermodynamically controlled diacetal.

vii) D-Galactose afforded the 4,6-O-butylidene derivative as the main monoacetal.

II. A new method for separating the five and six-membered cyclic acetals of polyols on basic resin Dowex-1 x 8 (OH^-) is described.

III. Nuclear magnetic resonance spectroscopy and mass spectrometry were used for characterisations and structural analysis of the butylidene acetals.

IV. The possibility of utilization of J_{H-C-OH} type vicinal coupling constants in deriving structural information about cyclic acetals is discussed.

To my wife

ACKNOWLEDGEMENTS

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CONTENTS

I. INTRODUCTION

Cyclic acetals are the condensation products of polyhydroxy compounds with aldehydes and ketones. The reaction usually requires an acid catalyst. The most commonly used acids are the mineral acids and some Lewis acids such as zinc chloride.

The mechanism for the cyclic acetal formation is usually represented as shown below (Fig. I-1).[1]

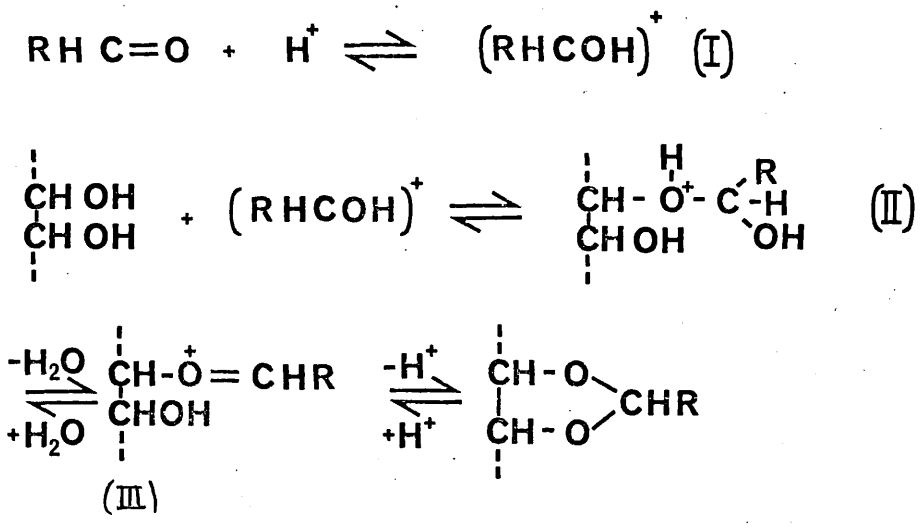
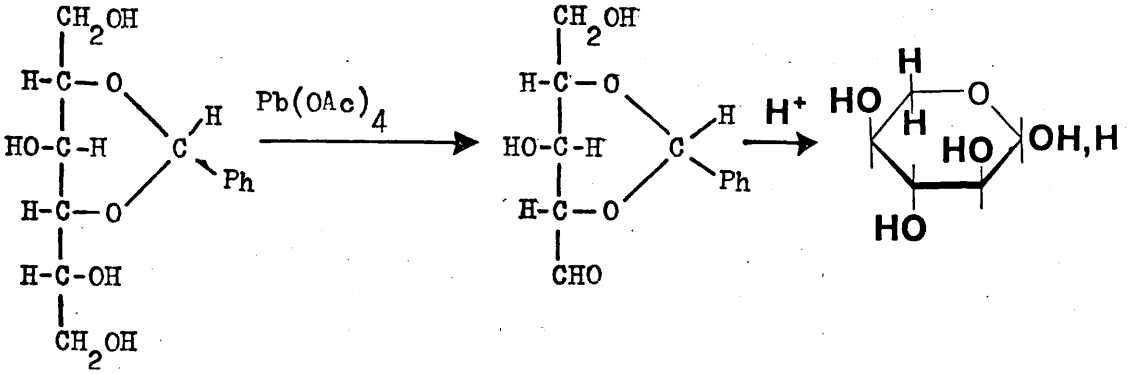


Fig. I-1

First step is the formation of a conjugated acid(I) which reacts with one of the nucleophilic hydroxyl group oxygens, to form a hemi-acetal(II) and then the intermediate(III) reacts with the second hydroxyl group forming an acetal ring. The hemi-acetal formation in simple triols preferentially occurs on the primary hydroxyls[2] but this situation is complicated in the case of the higher polyhydric alcohols such as D-glucitol. In 1-deoxy derivative of D-glucitol, initial formation of intermediate products suggests that hemi-acetal formation does not involve the primary hydroxyl group. This is probably

because, the deoxy group enhances the nucleophilicity of the adjacent hydroxyl group.[1]

The most important industrial use of acetals is in the resins field. Some of the polymeric products have been patented.[3, 4] It has also been observed that some methylated 2,4-monoacetals of D-glucitol provide protection against carbon tetrachloride induced liver damage in rats.[5] The importance of cyclic acetal derivatives as protecting groups in carbohydrate chemistry is well recognised.[6] This arises from the fact that cleavage of the acetal group under mild acid conditions does not result in a change of the stereochemistry of the original carbohydrate molecule. Isopropylidene derivatives are usually used for this purpose, because they can be easily synthesised and removed under very mild conditions. Isopropylidene and other ketals favour the formation of five-membered acetal rings but aldehydes tend to yield six-membered rings,[3] therefore when the protection of alternate hydroxyl groups is required, benzylidene acetals are more commonly used. The role of acetal protection in synthetic carbohydrate chemistry can be demonstrated as follows in preparation of L-xylose from D-glucitol (Fig. I-2).[7]



2,4-O-Benzylidene-D-glucitol L-Xylose

Fig. I-2

For a given hydroxy compound, the number of theoretically possible isomers can be very high. Normally, in practice, the structural isomers formed during an acetalation reaction is far less than that expected from theoretical considerations. For example, although eight and nine-membered cyclic acetals are possible, such structures have never been observed. Even the seven-membered acetal rings are rarely observed. The most common acetal rings are the six-membered 1,3-dioxane rings, possibly because the rings can take the stable chair conformations (Fig. I-3).[8]

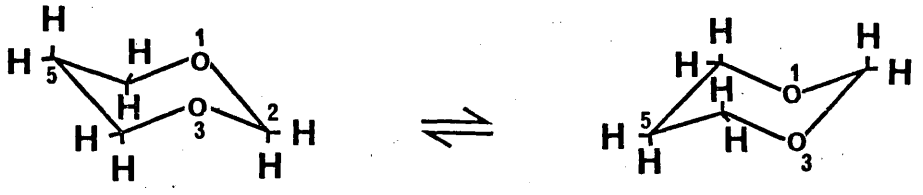


Fig. I-3

Five-membered acetal rings are also quite common. These are in fact the derivatives of 1,3-dioxolane, therefore they are named as 1,3-dioxolane derivatives, e.g. 1,2-O-alkylideneglycerol or 2-alkyl-4-hydroxymethyl-1,3-dioxolane (Fig. I-4).[9]

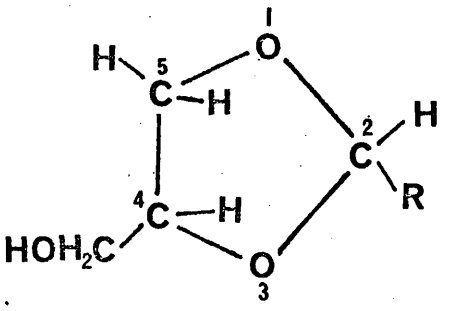


Fig. I-4

Pre-knowledge of types of structural isomers obtainable from a given acetalation reaction is desirable. The rules of Barker and Bourne[3,10] are extremely useful for this purpose. In these rules the Greek letters α, β and γ are used to indicate the relative positions of the hydroxyl groups involved in the acetal formation. An α-ring represents a five-membered ring (1,3-dioxolane), a β-ring represents a six-membered ring (1,3-dioxane) and a γ-ring represents a seven-membered ring (1,3-dioxepane). The letters (T) and (C) represent the relative stereochemistry of hydroxyl groups in a polyol. According to the Fischer projection formula, the hydroxyl groups which are on the same side of the carbon chain are called cis (C) and those which are on the opposite side of the carbon chain called trans (T). Later trans (T) and cis (C) were replaced by threo and erythro respectively.[11]

The Barker and Bourne rules are as follows:

(i) β-Erythro-rings are the most preferred ones in the formation of cyclic acetals, in which large groups at positions 2, 4 and 6 are equatorial. (Fig. I-5).

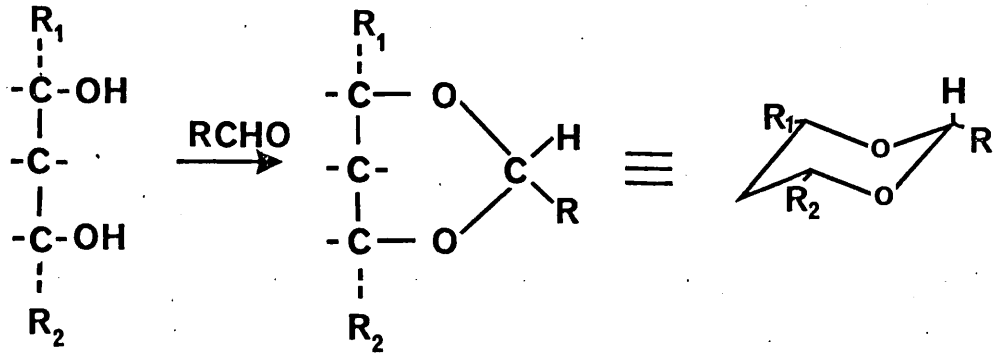


Fig.I-5

(ii) The second preference is for β-rings in which one of the primary hydroxyl groups of the polyol is involved in the acetal formation (Fig. I-6).

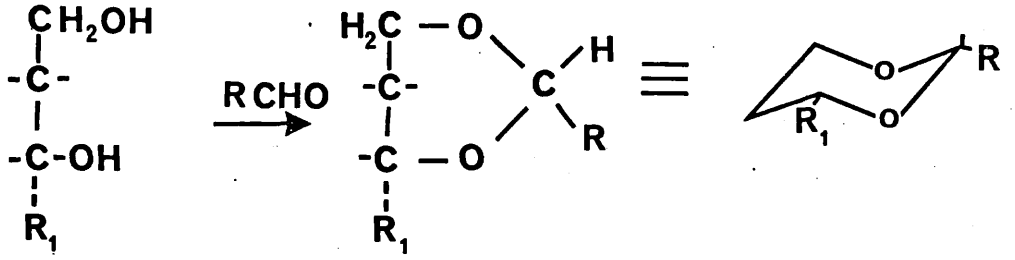


Fig. I-6

(iii) The third preference is for α, α-threo, β-threo and γ-threo rings. The α-threo rings are formed from two neighbouring secondary hydroxyl groups in threo configuration (Fig. I-7).

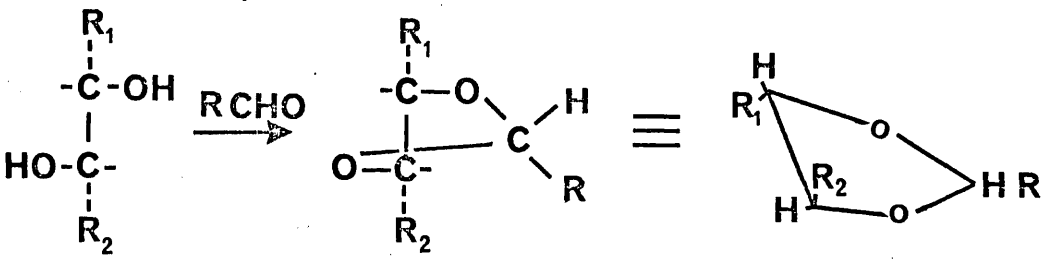
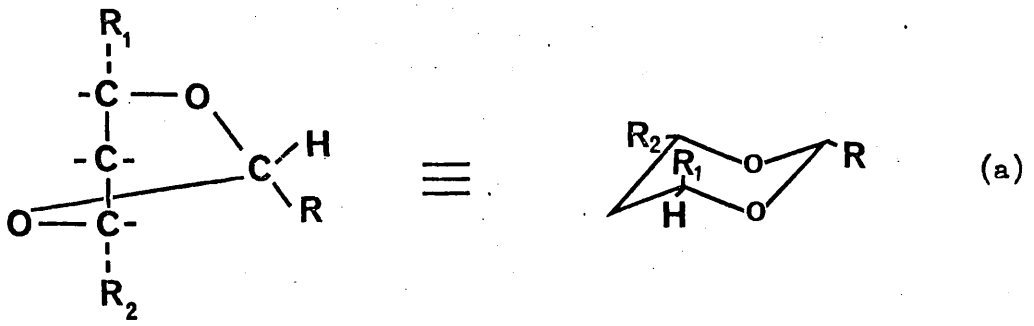


Fig. I-7

The β-threo rings involve two alternate secondary hydroxyl groups in threo configurations (Fig. I-8, a) and α-erythro rings are formed from neighbouring secondary hydroxyl groups in erythro configuration (Fig. I-8,b).



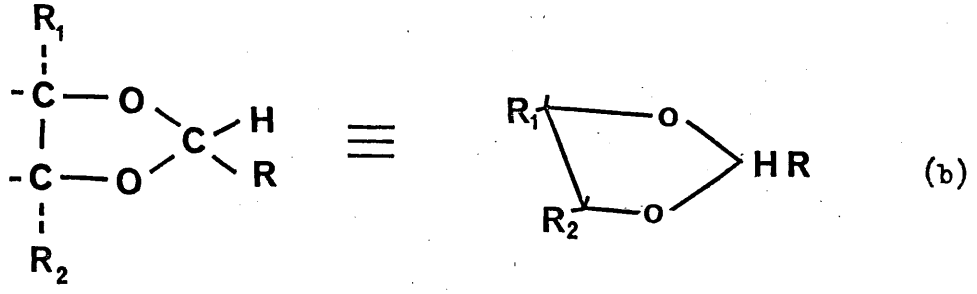


Fig. I-8

A γ-threo ring usually adopts a skew conformation (Fig. I-9).[12]

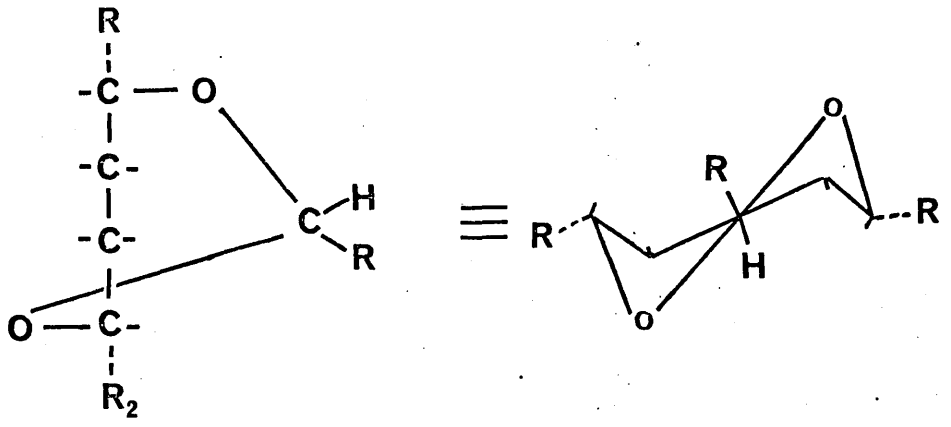
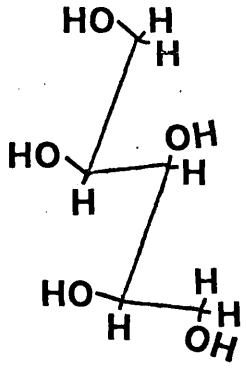


Fig. I-9

At equilibrium, the reaction mixture usually contains the isomers with β-erythro and β-rings in higher yields, as the thermodynamically stable products. But in the early stages of acetalisation, relatively less stable acetals can be the chief products.

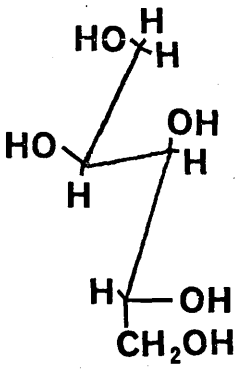
It is known that polyols normally adopt planar zig-zag conformations in the crystalline state when 1,3-diaxial interactions are not present.[13, 14] However in solution, these polyols can adopt several twisted conformations[14] which may partly explain the formation of kinetically controlled products during the initial stages of an acetalation reaction. At equilibrium, products with the lowest free energy are dominant regardless of the original conformation of the polyol.

It will be profitable to reconsider some of the factors that may affect the acetalation reactions in the light of the latest discovered conformational facts. It is now known that in solution, acyclic derivatives of polyols with the xylo configuration of hydroxyl groups will exist in a twisted conformation about the carbon-carbon bonds which carry the hydroxyl groups in syn-axial positions.[14, 15] Distortion is caused by syn-axial interactions of hydroxyl groups (Fig. I-10).



a) Fully extended coplanar zig-zag conformation of xylitol.

Calculated non-bonded interaction energy 24 kcal mol^{-1}.



b) Conformation a) rotated about C_3-C_4 bond by 120°.

Calculated non-bonded interaction energy 1.8 kcal mol^{-1}.

Fig. I-10

D-Glucitol has been shown to exist as a bent molecule[15] in the crystalline state. Figure I-11 shows the syn-axial interactions in this polyol, when the carbon chain is in the planar zig-zag conformation.

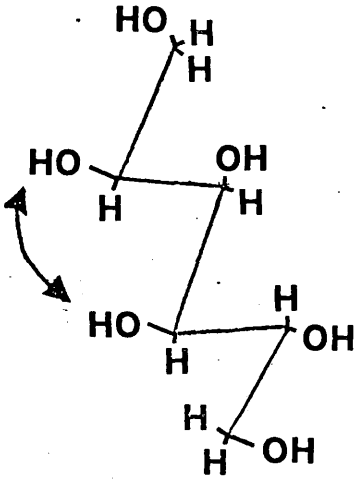


Fig. I-11

The bent-conformation of D-glucitol can partially explain the kinetically controlled formation of 2,3-monoacetals of this polyol and its derivatives.[16, 17] The polyols with bent conformations must be energetically less stable than non-bent molecules because in the latter case the carbon chain possess a stable zig-zag conformation in which the syn-axial interactions are non existent. The carbon chain in D-glucitol can regain its zig-zag conformation with the formation of 2,4-monoacetal derivatives (Fig. I-12) and with the elimination of syn-axial interactions in this molecule. This could probably be another reason for the thermodynamic stability of this type of ring in D-glucitol.

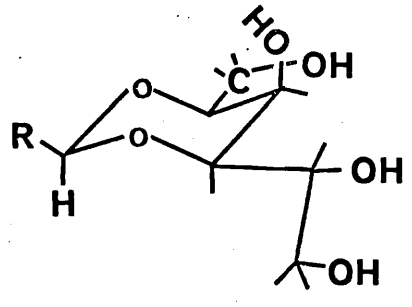
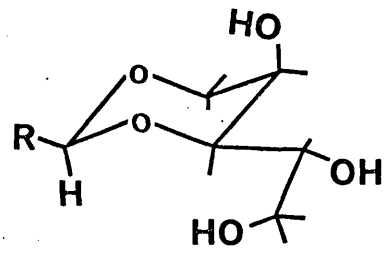
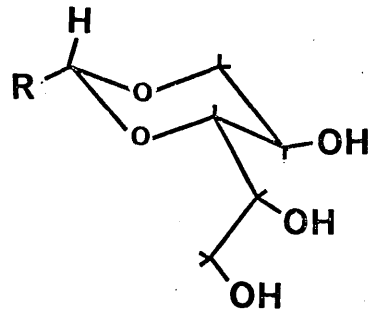


Fig. I-12

It has been pointed out by J.A. Mills[18] that an axial hydroxyl group on a six-membered acetal ring may be preferred to the equatorial one. Thus the benzylidenation of arabinitol favoured the formation of a 1,3-monoacetal[19] where the hydroxyl group on C-2 is axial to the ring, and not the formation of a 3,5-monoacetal in which the hydroxyl group occupies the equatorial position (Fig. I-13).





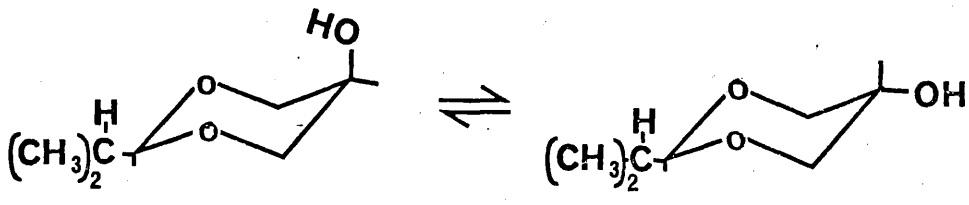
1,3-monoacetal of D-arabinitol 3,5-monoacetal of D-arabinitol

Fig. I-13

Similarly D-glucitol favours the formation of 2,4-acetal rings[17] and galactitol affords the stable 1,3:4,6-dimethylene[20] and benzylidene[21] acetals.

Also during the methylenation of D-glycero-D-gluco-heptitol which contains 2,4- and 4,6-hydroxyl groups in β-erythro configuration, the 2,4-acetal ring was formed preferentially because the 4,6-ring contains an equatorial hydroxyl group.[22]

Latest quantitative studies[23, 24] on 5-hydroxy-2-isopropyl-1,3-dioxane showed that when equilibrated in cyclohexane, the axial hydroxyl is preferred by a free energy difference of 0.9 kcal mol^{-1} over the isomer with an equatorial hydroxyl group, and by a difference of 0.5 kcal mol^{-1} in isopropyl alcohol or t-butyl alcohol (Fig. I-14).



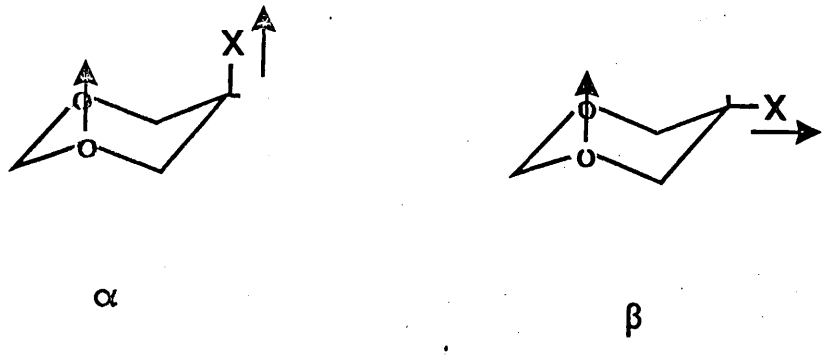
cis trans

$\Delta G_{80^\circ} = +0.9$ kcal mol^{-1}

Fig. I-14

It was suggested that electron withdrawing substituents at the 5-axial position could decrease the stability of cis form due to dipole-dipole

repulsions (Fig. I-15) unless an opposite force, like intramolecular hydrogen bonding, compensates for this effect.[25] Electronegative substituents such as chlorine X = Cl (Fig. I-15,β) and bromine X = Br (Fig. I-15,β) prefer the equatorial positions.



α β

Fig. I-15

However in 5-fluoro-1,3-dioxane, it was found that the fluorine atom preferred the axial position X = F (Fig. I-15,α).[25] This phenomenon was recently explained by L. Phillips[26] who suggested that the so-called, "Gauche effect" [27,28] predominates when the electronegativity of X is increased.

The "gauche effect" rule was defined as a tendency of a compound to adopt a structure which has the maximum number of gauche interactions between the adjacent electron pairs and/or polar bonds.[27] It was later suggested that this rule only applies for very electronegative substituents and for oxygen functions, but it is only reliable when the molecules are in solution.[26] This rule especially applies to the 1,2-disubstituted ethanes. These suggestions together with the hydrogen bond formation explain the preference of a hydroxyl group for axial positions.

In the light of these arguments the 1,3:4,6-diacetals of D-mannitol containing the hydroxyl groups at equatorial positions (Fig. I-16), are expected to be relatively unstable, but on the

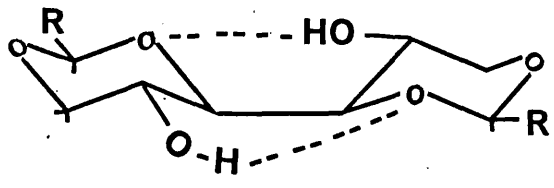


Fig. I-16

contrary these acetals are obtained easily and in good yields.[29, 30] 1,3:4,6-Di-O-butylidene-2-deoxy-D-mannitol was also obtained in good yield as described in this thesis (Section VI). It is probably reasonable to suggest that, the stabilities of these acetals are increased by the energy lowering effect of intramolecular hydrogen bonding of equatorial hydroxyl groups to the neighbouring ring oxygens (Fig. I-16).

D-Arabinitol does not give the 3,5-monoacetals (β-ring) in which the equatorial hydroxyl group cannot form intramolecular hydrogen bonds with the acetal ring oxygens.[18, 19] Thus the Barker and Bourne rules do not distinguish between the stabilities of the two possible β-rings which may be different due to equatorial or axial disposition of the hydroxyl groups.

It is now possible to say that a β-ring or a β-threo ring in a chair conformation with an axial hydroxyl group which is capable of forming intramolecular hydrogen bonds with the acetal ring oxygens, and has gauche carbon-oxygen bond dipole interactions with the ring oxygens, is more favoured than a β-ring or a β-threo-ring with an equatorial hydroxyl group which has only trans carbon-oxygen bond dipole interactions and cannot form hydrogen bonds.

The gauche effect can indeed be an important factor in the formation of cyclic acetals. It was pointed out[26,31] that theoretically, arabinitol can afford both cis and trans fused ring isomers (Fig. I-17),

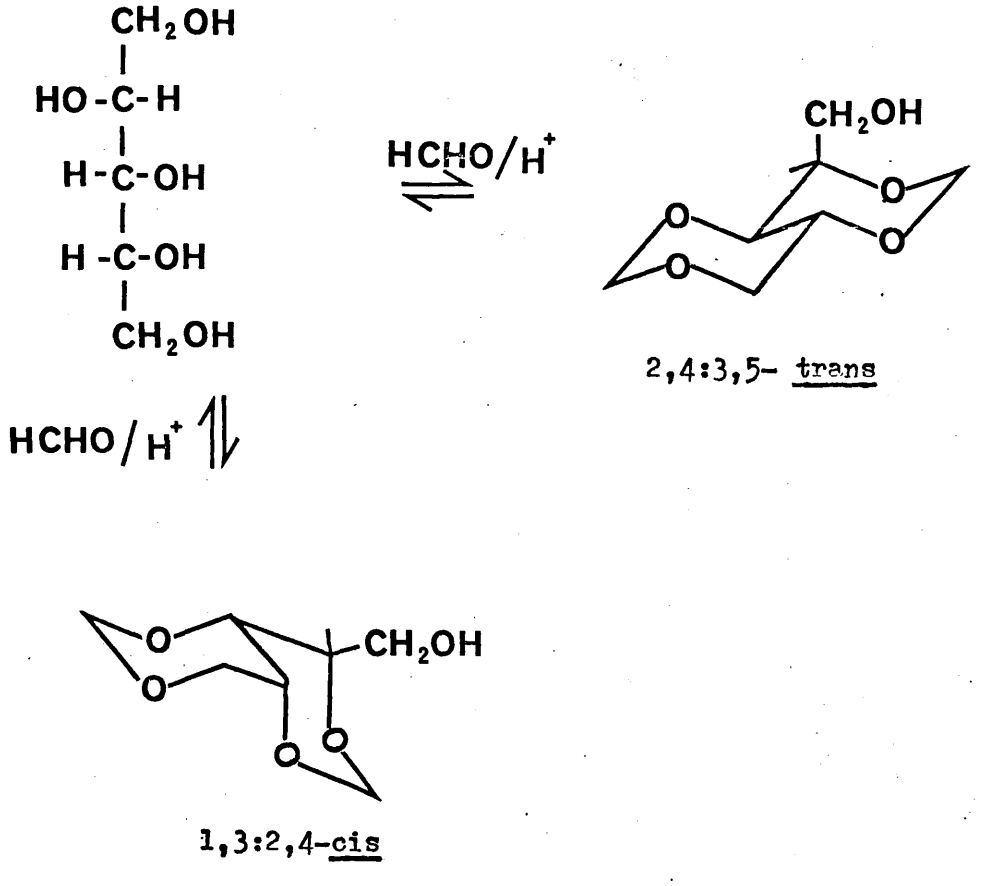


Fig. I-17

but in practice only the cis isomer has been observed, although the non-bonded interactions favour the trans isomer. This situation can be explained by the effect of carbon-oxygen bond dipole interactions between the ring oxygens which have 1,2-disubstituted ethane type relations.[26] The trans isomer has three trans carbon-oxygen bond dipole interactions while the cis isomer has only the gauche carbon-oxygen bond dipole interactions.

This stability of cis fused ring systems was first recognised by Mills.[18] In later years 1,3:2,4:5,6-tri-O-benzylidenegalactitol was synthesised.[32] In this thesis it is also shown that a tri-O-butylidene-galactitol with the same structure is formed in moderate yield. The formation of 1,3:2,4-rings in galactitol acetals can be explained using the same arguments as for 1,3:2,4-diacetals of arabinitol. It can be seen clearly that in 1,3:2,4:5,6-triacetals of galactitol, all carbon-oxygen bond dipole interactions between the ring oxygens of the fused rings are of the gauche type (Fig. I-18).

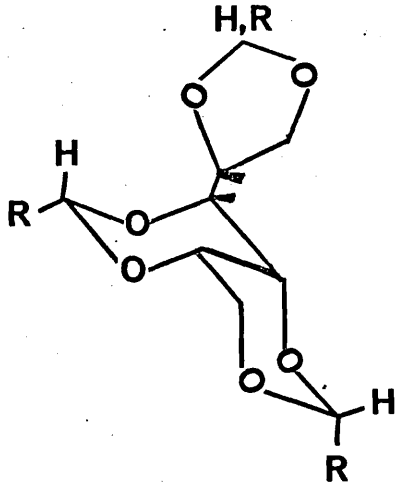
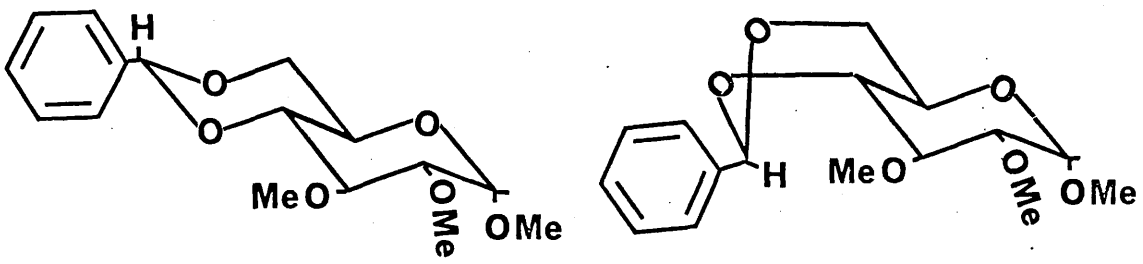


Fig. I-18

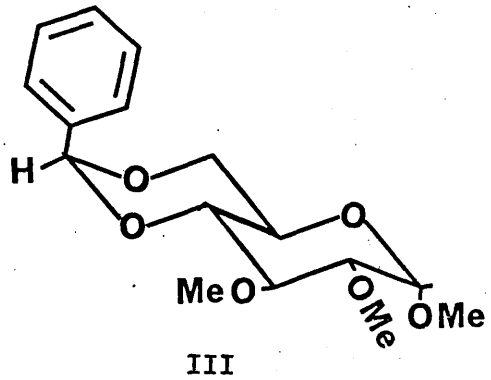
In 1965 Foster et al observed two stereoisomeric methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranosides.[33] The structures (I) and (II) were offered for these compounds (Fig. I-19).



I II

Fig. I - 19

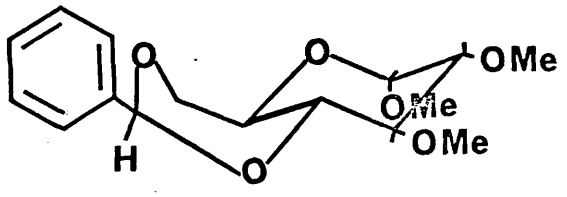
One of the isolated isomers (m.p. 125.5-127°) was converted to the other isomer smoothly with hydrogen chloride in carbon tetrachloride. For this reason conformation (II) was assigned to the unstable isomer. Recently an alternative conformation (III) was suggested (Fig. I-20) for the unstable isomer.[31]



III

Fig. I-20

However, in the structure (III), the phenyl group on the acetal carbon is axial to the acetal ring. This situation is very likely to cause instability. Therefore it is not likely that, in solution, this compound exists mainly in conformation (III). An equilibrium may exist between the conformation (III) and another conformation which contains acetal ring in the boat form. An alternative conformation could be (IV), in which the acetal ring is in a pseudo twist-boat form and contains the phenyl group in the equatorial position.



IV

Fig. I-21

The free energy of a twist boat form is less than that of a boat conformation. Unlike the structure (II), the conformation (IV) contains one carbon-oxygen bond which has gauche type dipole interactions with the carbon-oxygen bond dipole of the sugar ring which may be another stabilisation factor. Thus, it seems possible that, in solution an equilibrium exists between the conformations (III) and (IV).

The above acetal (Fig. I-20,III) is the only example reported,in which a large group at position 2 of the 1,3-dioxane ring occupies an axial configuration. It is well established that the large substituents on the acetal carbon of a six-membered ring prefer the equatorial positions simply because of the destabilisation effects arising from the 1,3-diaxial interactions between the axial substituent and the ring-protons.

The preference of the substituents on the acetal carbon for axial or equatorial positions is also dependent on the electronegativity of the substituent. Increased electronegativity favours the axial isomers.[34] This phenomenon is known as "the anomeric effect".[23, 25] Thus for example, the alkoxy groups prefer the axial position. In the following synthesis of 2-alkoxy-1,3-dioxane (Fig. I-22), the axial isomer was favoured by about 2:1 over the equatorial one under equilibrium conditions.[23, 35]

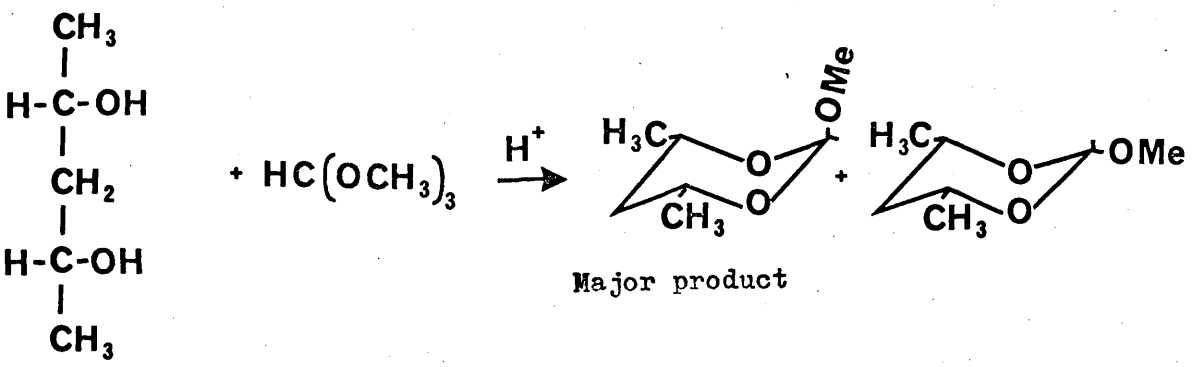


Fig. I-22

In the axial position the alkoxy group can avoid the "rabbit-ear interactions" of the syn-axial electron pairs on the hetero atoms.

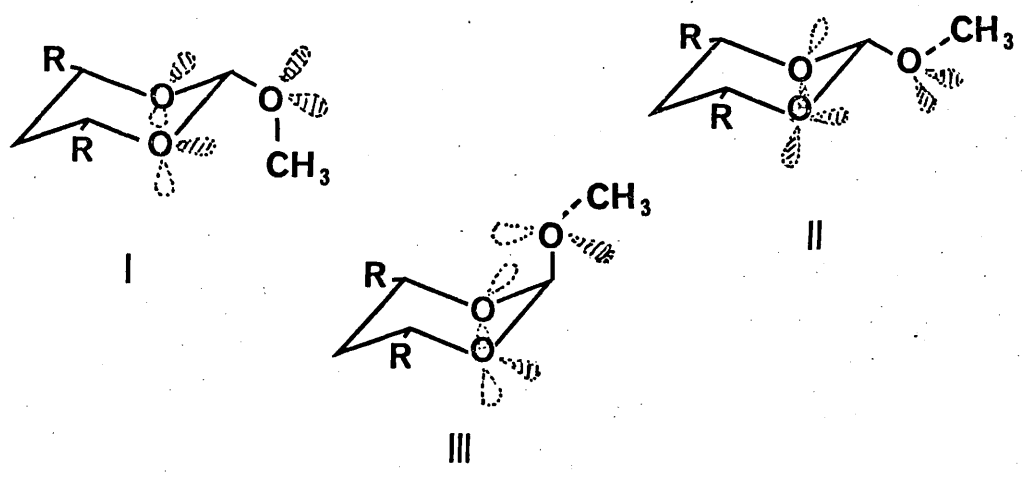


Fig. I-23

The figure I-23 shows that in (I) and (II) the dipole repulsions due to the orientations of the unshared p electron lobes are at maximum (rabbit-ear orientation), whereas in (III) there is a minimum number of dipole repulsions.

The above discussions could point out the reasons for the preferential formation of 5-membered 1,3-dioxolane rings in the trichloroethylidene acetals of D-glucose.[36] In the hypothetical acetal, 2-trichloroethylidene-1,3-dioxane, the trichloroethylidene group is directed to the axial position by the "anomeric effect". However this creates strong 1,3-diaxial interactions between the axial trichloroethylidene group and the ring protons causing instability in the acetal ring (Fig. I-24). Therefore, it is reasonable to

expect the reactions of polyhydroxy compounds with trichloro-acetaldehyde, to afford five-membered acetal rings in which these interactions may be avoided.

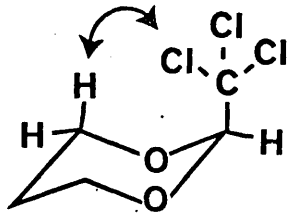


Fig. I-24

In six-membered acetals, stereoisomerism on the acetal carbon is not common due to the effects discussed above. However, this type of isomerism is quite common amongst the five-membered acetals. The substituent on the acetal carbon of 1,3-dioxolane can be either on the same side or on the opposite side of the mean plane of the ring as the substituent at position C-4 or C-5, and these are usually called cis and trans isomers respectively. Figure I-25 shows the cis and trans isomers of 1,2-O-alkylidene glycerol.

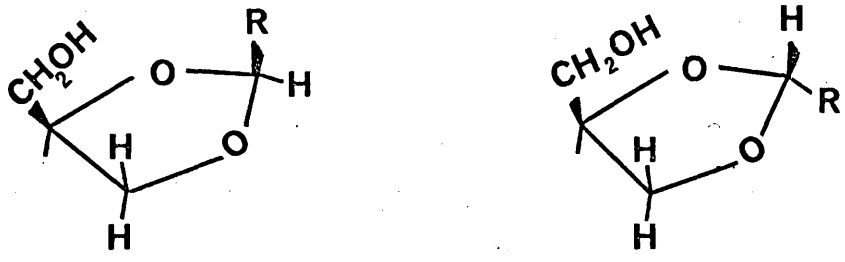


Fig. I-25

The cis configuration is not a favoured one, because of the interactions of the large groups. The more stable 1,3-dioxolane derivatives are those in which the large groups are trans (Fig. I-25,b).

In the literature, there are several examples of this type of isomerism, obtained from polyols as well as sugars. For example, two of the four possible isomers of 2,3:4,5-di-O-benzylidenegalactitols were obtained.[37, 38] An example of this in sugars is the formation of the isomeric trichloroethylidene acetals of D-glucose. Reaction of this sugar with chloral hydrate in the presence of sulphuric acid afforded two monoacetals, namely, α- and β-1,2-O-trichloroethylidene-α-D-glucofuranoses, differing only in their configurations at acetal carbon atoms, and four isomeric 1,2:5,6-di-O-trichloroethylidene-α-D-glucofuranoses,[36] two of which are shown in the figure I-26.

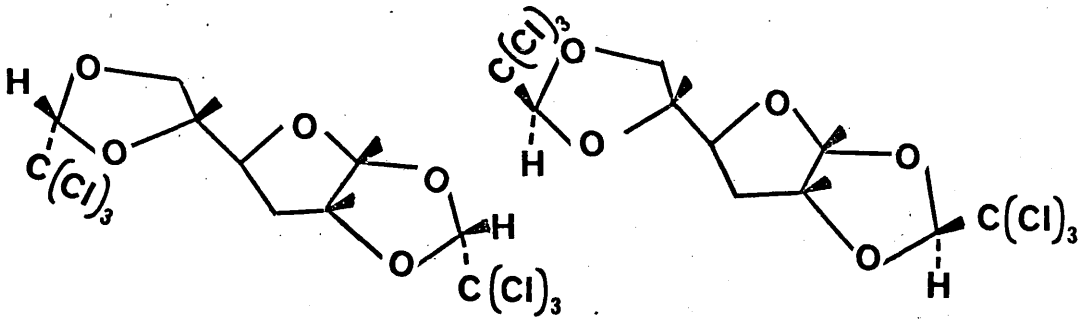


Fig. I-26

II.A Cyclic Acetals of Galactitol

i) Introduction

The crystal-structure analysis of galactitol has shown that the planar zig-zag conformation is adopted in the solid state, by this compound (Fig. II-1).[14,15]

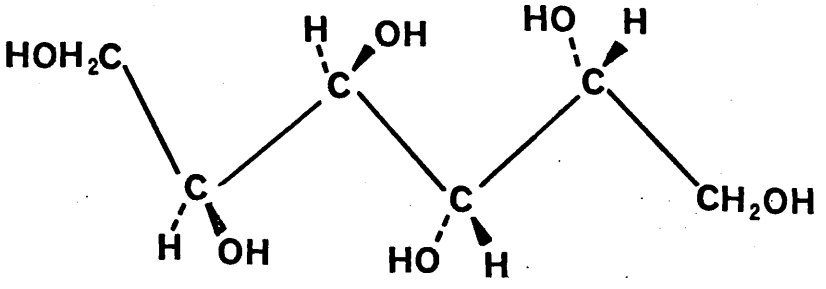


Fig. II-1

It was also suggested that, the absence of the 1,3-interactions in this molecule, allows the planar zig-zag conformation also to exist in solution.[14] Galactitol molecules also undergo thermal movements about a centrosymmetrical structure when the constraint of the crystal field has been eliminated by dissolution.[14]

The known reactions of galactitol with several aldehydes showed that galactitol acetals generally favour the 1,3-dioxane rings with the axial hydroxyl substituents on the C-2 and C-5. Thus the reaction of galactitol with benzaldehyde afforded 1,3:4,6-di-O-benzylidenegalactitol in 93% yield.[21] The reaction with formaldehyde again gave 1,3:4,6-di-O-methylenegalactitol in good yield. These results conform with the rules of Barker and Bourne.

In the galactitol molecule, two types of six-membered rings are possible, namely β- and β-threo rings. According to the above mentioned rules, the β-ring is the most stable acetal ring possible for this molecule. The second possible favourable acetal ring for galactitol is α-threo ring. It has been shown that, the acetalation of 1,6-disubstituted galactitols affords α-threo rings.[37,38]

In a recent work, the reaction of dimethylgalactarate with paraformaldehyde and concentrated sulphuric acid was found to give the 2,3:4,5- and 2,5:3,4-di-O-methylene acetals in 2 to 1 ratio. These were both reduced by lithium aluminium hydride to 2,3:4,5-di-O-methylenegalactitol and 2,5:3,4-di-O-methylenegalactitol respectively.[39] The structural evidence for these compounds was supplied by mass spectrometry and n.m.r. spectrometry.[40]

ii) Butylidene Monoacetals of Galactitol

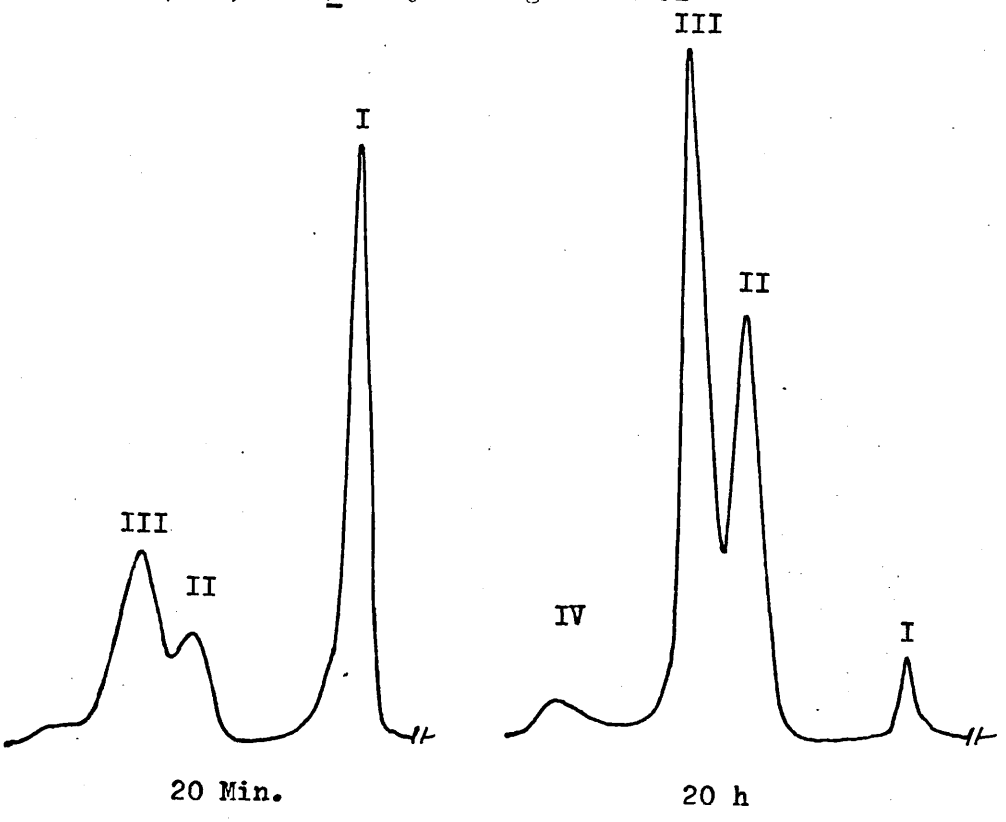
Some optically active monoacetals of galactitol are known.[41, 42] For example, the 1,3-O-ethylidene-L-galactitol was obtained by the reduction of the 4,6-O-ethylidene-D-galactose.[42] But in the literature no report on the direct formation of monoacetals of galactitol has appeared.

It was decided to investigate the formation of the monoacetals of this polyol and to compare its results with those obtained from the similar reactions of D-glucitol. In this polyol 2,3-monoacetal rings are formed under kinetically controlled conditions. The formation of an intermediate product was indicated by a minimum on the curve of change of rotation with time of this reaction.[16] In the case of galactitol, polarimetric studies were not possible because of its optical inactivity and therefore g.l.c. was used in monitoring the reaction (Fig. II-2).

The initial formation of two monoacetals was observed from the reaction of galactitol with n-butyraldehyde in 0.5N-hydrochloric acid but no kinetic preference was observed for either of the monoacetals.

The reaction of approximately equimolar quantities of galactitol and n-butyraldehyde in 0.5N-hydrochloric acid gave an optically-inactive fraction after 48 h. This mixture contained mainly two monoacetals. Some diacetal, present in the mixture, was extracted with chloroform. The syrupy monoacetal fraction, thus obtained was crystallised on standing at 5°, but it could not be separated into its components by chromatography on silica gel or by fractional

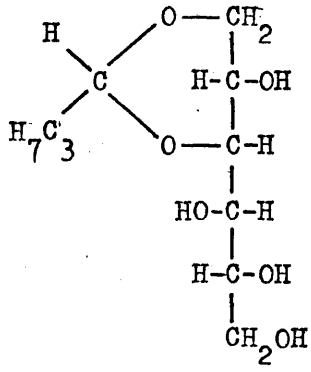
I-Galactitol
II-2,3-O-Butylidene-DL-galactitol
III- 1,3-O-Butylidene-DL-galactitol
IV- 1,3:4,6-Di-O-butylidenegalactitol



(Pye-104 ; Apiezon-K ; temperature 180°)

Fig. II-2

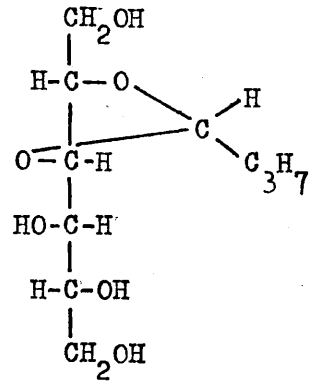
crystallisation, although it was possible to recrystallise it as a mixture from ethanol-ether. The monoacetals were separated by column chromatography on Dowex-1 X8 ($\overline{OH}$) resin. The compounds separated in this manner, were shown to be a crystalline 1,3-O-butylidene-DL-galactitol (Fig. II-3,I) and a crystalline 2,3-O-butylidene-DL-galactitol (Fig. II-3,II).



1,3-O-butylidene

(4,6-O-butylidene)-DL-galactitol

I



2,3-O-butylidene

(4,5-O-butylidene)-DL-galactitol

II

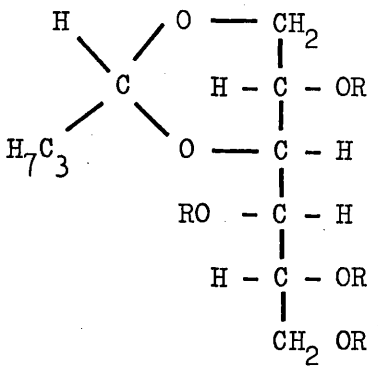
Fig. II-3

It was shown that after 48 h, the reaction mixture contained the 1,3-monoacetal in higher yield, however a considerable amount of 2,3-monoacetal also existed. The only diacetal which could be isolated from this reaction mixture in small yield was 1,3:4,6-di-O-butylidene-galactitol.

iii) The Structural Analysis of 1,3-O-Butylidene-DL-galactitol

The monoacetal (Fig. II-4,I) was characterised as its crystalline tetra-acetate (Fig. II-4,II) and tetra-benzoate (Fig. II-4,III) derivatives. Methylation of the free hydroxyl groups of this compound, using methyl iodide and silver oxide in dimethylformamide, gave two crystalline products. The main product was the fully methylated 1,3-O-butylidene-DL-galactitol (Fig. II-4,IV). This compound was characterised by its n.m.r. and mass spectrum. The infrared spectrum (nujol mull) did not show any hydroxyl peaks.

The other product, isolated in very small amount, was shown to be a trimethyl-1,3-monoacetal.



(I) R = H

(II) R = Ac

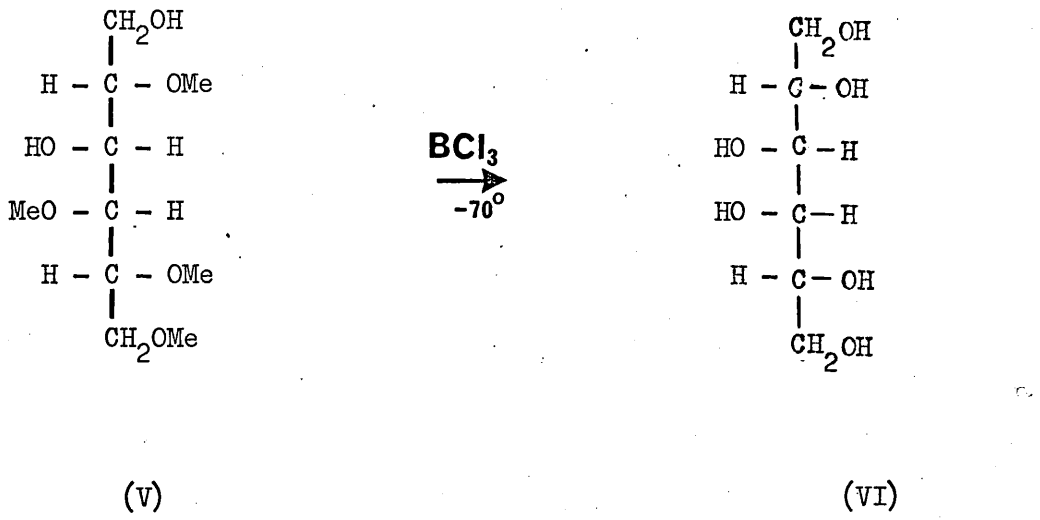
(III) R = Bz

(IV) R = Me

Fig. II-4

The trimethyl 1,3-monoacetal was also characterised by its n.m.r. and mass spectrum. The infrared (nujol and KBr disc) and n.m.r. showed the presence of a hydroxyl group in the molecule but the position of the hydroxyl group was not located.

Quantitatively, the monoacetal (Fig. II-4,I) consumed 2.04 mol of periodate ion and liberated 1.12 mol formaldehyde and 0.91 mol formic acid. The acetal group of (IV) was removed in the presence of the acidic resin Amberlite -120(H^+), to give a crystalline tetra-O-methylhexitol (Fig. II-5, V). When (V) was treated with boron trichloride at -70°, galactitol (VI) was obtained.



(V) (VI)

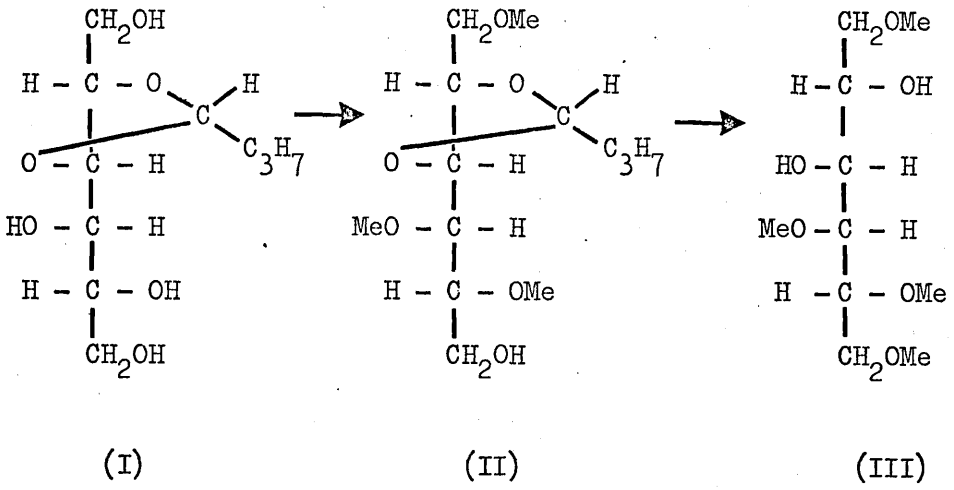
Fig. II-5

The structure of tetra-O-methylgalactitol (V) was derived as follows. It did not consume any periodate ion showing the absence of vicinal hydroxyl groups. Tritylation gave a crystalline monotrityl derivative indicating the presence of only one free primary hydroxyl group. These results indicate the structure of this compound to be 2,4,5,6-tetra-O-methyl-DL-galactitol (V).

The tetra-O-methylgalactitol was further characterised by the mass spectrum of its acetate derivative.

iv) The Structural Analysis of 2,3-O-Butylidene-DL-galactitol

The monoacetal (Fig. II-6,I) was characterised as its crystalline tetra-acetate derivative. The acetal consumed 2.05 mol of periodate ion and liberated 1.08 mol of formaldehyde and 1.00 mol of formic acid. On methylation, the acetal (I) gave a syrupy tetramethyl ether (II).

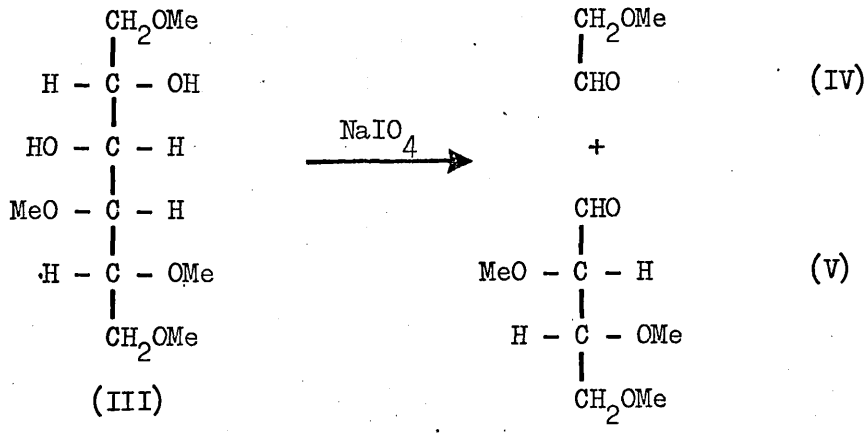


(I) (II) (III)

Fig. II-6

The hydrolysis of (II) by the acidic resin Amberlite -120(H^+) gave a tetra-O-methylhexitol , which on demethylation with boron trichloride produced galactitol.

The structure of tetra-O-methylhexitol (III) was proved as follows. It consumed 1.06 mol of periodate ion and its periodate oxidation products gave methoxy acetaldehyde (Figs. II-7, IV) and tri-O-methyl-DL-threose (Figs. II-7, V). The former was characterised as its known,[43] crystalline p-nitrophenylhydrazone and the latter was characterised by its n.m.r. and mass spectrum and elemental analysis.



(III) (IV) (V)

Fig. II-7

II-B Formation and Some Reactions of Di- and Triacetals of Galactitol

i) Results and Discussion

The reaction of 1 mol galactitol with approximately 2 mol n-butyraldehyde in 5N-hydrochloric acid was studied. G.l.c. analysis of the reaction mixture at certain time intervals showed the initial formation of several products (Fig. II-8). It is known from previous work on acetalation of galactitol that, either 1,3:4,6-diacetal[20, 21] or 1,3:2,4:5,6-triacetal[32] is obtained depending on the reaction conditions. In this work, a mixture of acetals containing a triacetal in highest yield was obtained, after 14 h. This reaction also gave some 1,3:4,6-di-O-butylidenegalactitol but in low yield. The remaining products consisted of a complex mixture of several diacetals. No monoacetals were detected. It was possible to separate the various groups of products by solvent extraction or by column chromatography on alumina. The butylidene triacetals were soluble in light petroleum, therefore they could be extracted directly from the syrupy mixture. At the same time 1,3:4,6-di-O-butylidenegalactitol precipitated out on addition of light petroleum and was removed by filtration. Although light petroleum first dissolved all the products except 1,3:4,6-diacetal, on standing in a cool place, the mixture of diacetals was deposited as a syrup. The triacetals thus remained in the light petroleum. The syrupy mixture of dibutylidene galactitols was shown to be free from the triacetals and 1,3:4,6-di-O-butylidenegalactitol by t.l.c. in solvent benzene-methanol (9:1). The remaining syrupy mixture was expected to contain mainly the structural and stereoisomeric forms of 1,3:4,5- and 2,3:4,5-diacetals (Fig. II-9) from theoretical considerations. It was not possible to isolate any of the isomers of the former.

I - 1,3:4,6-Di-O-butylidenegalactitol
II - 2,3:4,5-Di-O-butylidenegalactitol
III - 2,4:5,6-Di-O-butylidene-DL-galactitol
IV - 1,3:2,4:5,6-Tri-O-butylidene-DL-galactitol

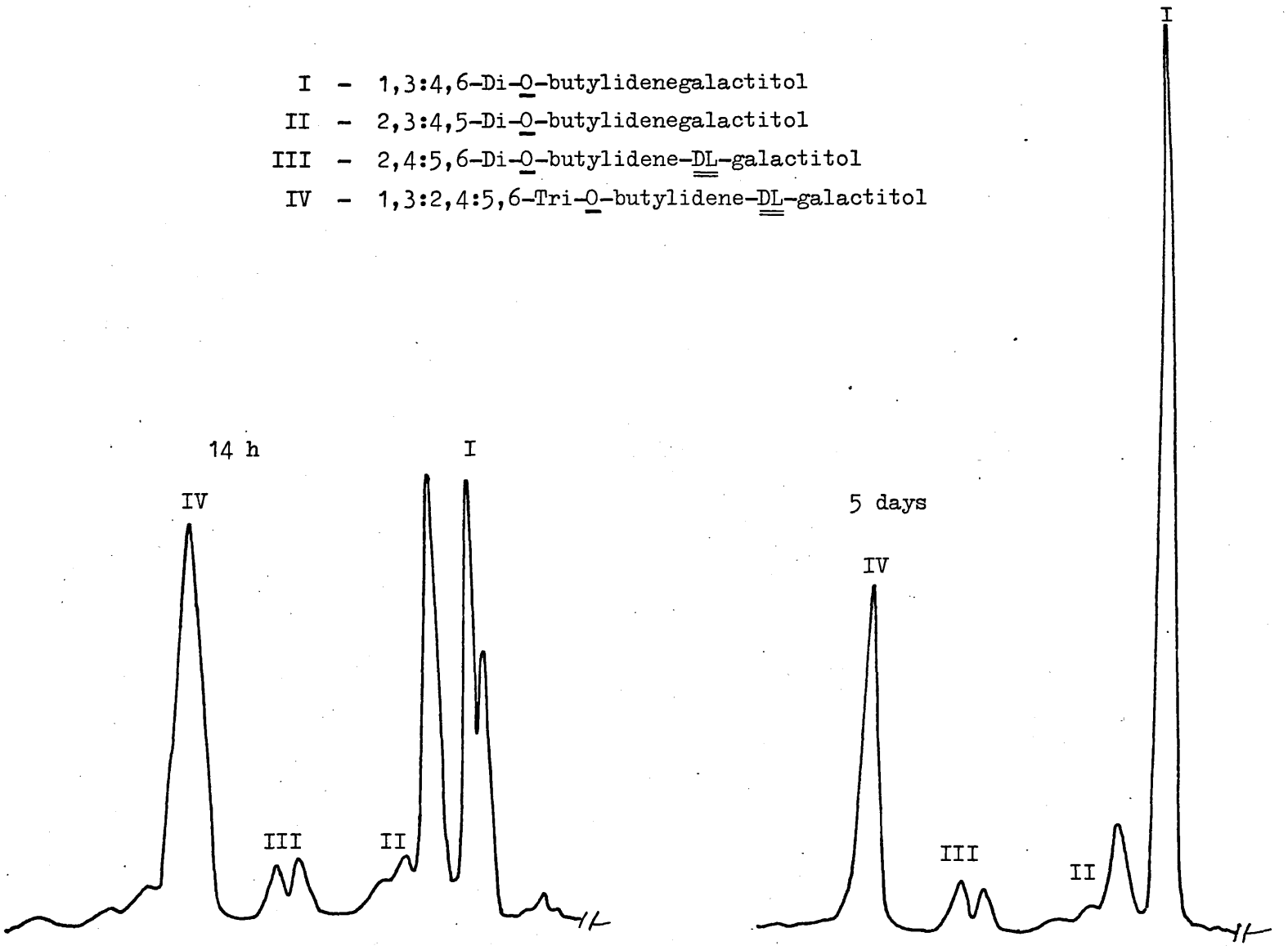
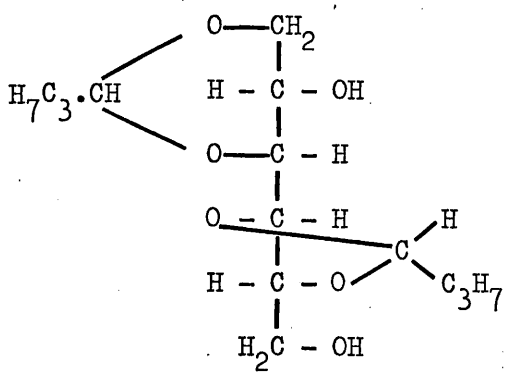
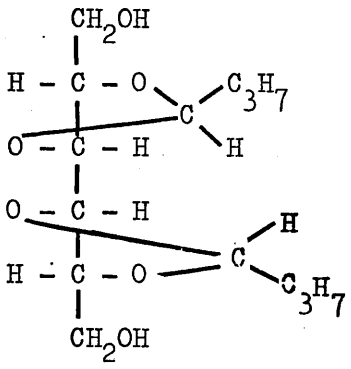


Fig. II-8 The reaction of galactitol (ca. 1 mol) with n-butyraldehyde (ca. 2 mol). in 5N-Hydrochloric acid, monitored by g.l.c. (Pye-104; Apiezon-K, 7.5%; temperature 180°).



1,3:4,5-di-O-butylidenegalactitol
(D-form)



2,3:4,5-di-O-butylidenegalactitol
(meso-form)

Fig. II-9

Several attempts to resolve the diacetal mixture failed. However column chromatography on neutral alumina gave two crystalline diacetals in very small yields, when diethyl ether containing 2% methanol was used as eluent.

One of the diacetals, thus obtained showed variable m.p. on several recrystallisations from carbon tetrachloride. All the various crystalline fractions of this product showed a slightly broadened triplet at τ 4.95 in their 60 MHz n.m.r. spectra. This broad triplet was partially resolved into three overlapping triplets by the 220 MHz spectrometer.

The absence of the higher field triplets on n.m.r. spectra suggested that the diacetal contained only five-membered rings.[29] The highest m.p. obtained for this product was 83°. The acetal behaved like a single substance on t.l.c. and g.l.c. A correct elemental analysis was obtained as a dibutylidene galactitol. The correlation of the n.m.r. spectrum with its structure will be discussed later. Sufficient product was not obtained to conduct further structural analysis using the usual chemical

methods but there is good evidence from n.m.r. studies to assign the structure of 2,3:4,5-di-O-butylidenegalactitol (Fig. II-9), to this product which is a stereoisomeric mixture on the acetal carbon atoms.

The other crystalline fraction from the alumina column was also recrystallised from carbon tetrachloride. As for the above diacetal, chemical methods for structural analysis could not be used and therefore the predicted structure of this compound was based on its n.m.r. and mass spectra, which will be discussed in later sections. Thus, the unexpected structure of 2,4:5,6-di-O-butylidenegalactitol (Fig. II-10), was assigned to this compound. It is rather unusual to obtain an acetal of galactitol containing a β-threo ring, but this product apparently existed in the reaction mixture, in a very small amount (Fig. II-8). The insignificant yield and easy decomposition at room temperature indicated its structural instability.

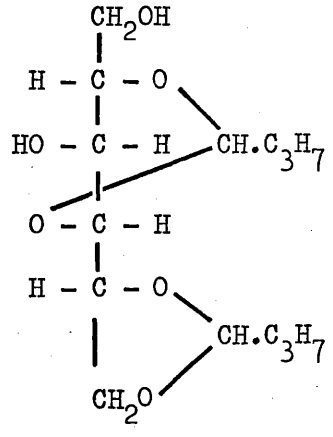


Fig. II-10

The g.l.c. of the reaction of galactitol with n-butyraldehyde (Fig. II-8), suggested that most of the products which existed in the reaction mixture after 20 h, disappeared after a reaction time of four days. After five days at room temperature the reaction mixture solidified. The products isolated at this stage consist only of the 1,3:4,6-di-O-butylidene acetal and the 1,3:2,4:5,6-triacetal. The 1,3:4,6-diacetal was obtained in higher yield but no other diacetals were observed in significant amounts. These results suggested that at initial stages several diacetals were formed which gradually converted into the thermodynamically stable acetal, 1,3:4,6-di-O-butylidenegalactitol, together with the slightly less stable 1,3:2,4:5,6-triacetal. However shorter reaction times produced a higher yield of the triacetal, suggesting that, even this compound gradually converted to the 1,3:4,6-diacetal. Very high yields were also reported[20, 21] for other 1,3:4,6-diacetals of galactitol, using hydrogen chloride as catalyst, which also suggest the higher stability of the 1,3:4,6-diacetals compared to the 1,3:2,4:5,6-triacetals under stronger conditions.

ii) Structural Analysis of 1,3:4,6-Di-O-butylidenegalactitol

The 1,3:4,6-di-O-butylidene acetal (Fig. II-11) was obtained in good yield from the reaction in 5N-hydrochloric acid, after a long reaction time, and also in smaller yield in 0.5N-hydrochloric acid (II.A-ii). These two compounds were identical as shown by their n.m.r. spectra and mixed m.p. The diacetal could be recrystallised from ether, carbon tetrachloride or methanol giving the pure compound which melted at 135°. It gave the diacetate and dibenzoate derivatives in

good yield. On methylation the acetal produced a dimethyl ether (Fig. II-11,II). Hydrolysis of this with the acidic resin IR-120(H^+) gave a di-O-methyl hexitol (III), which on demethylation produced galactitol.

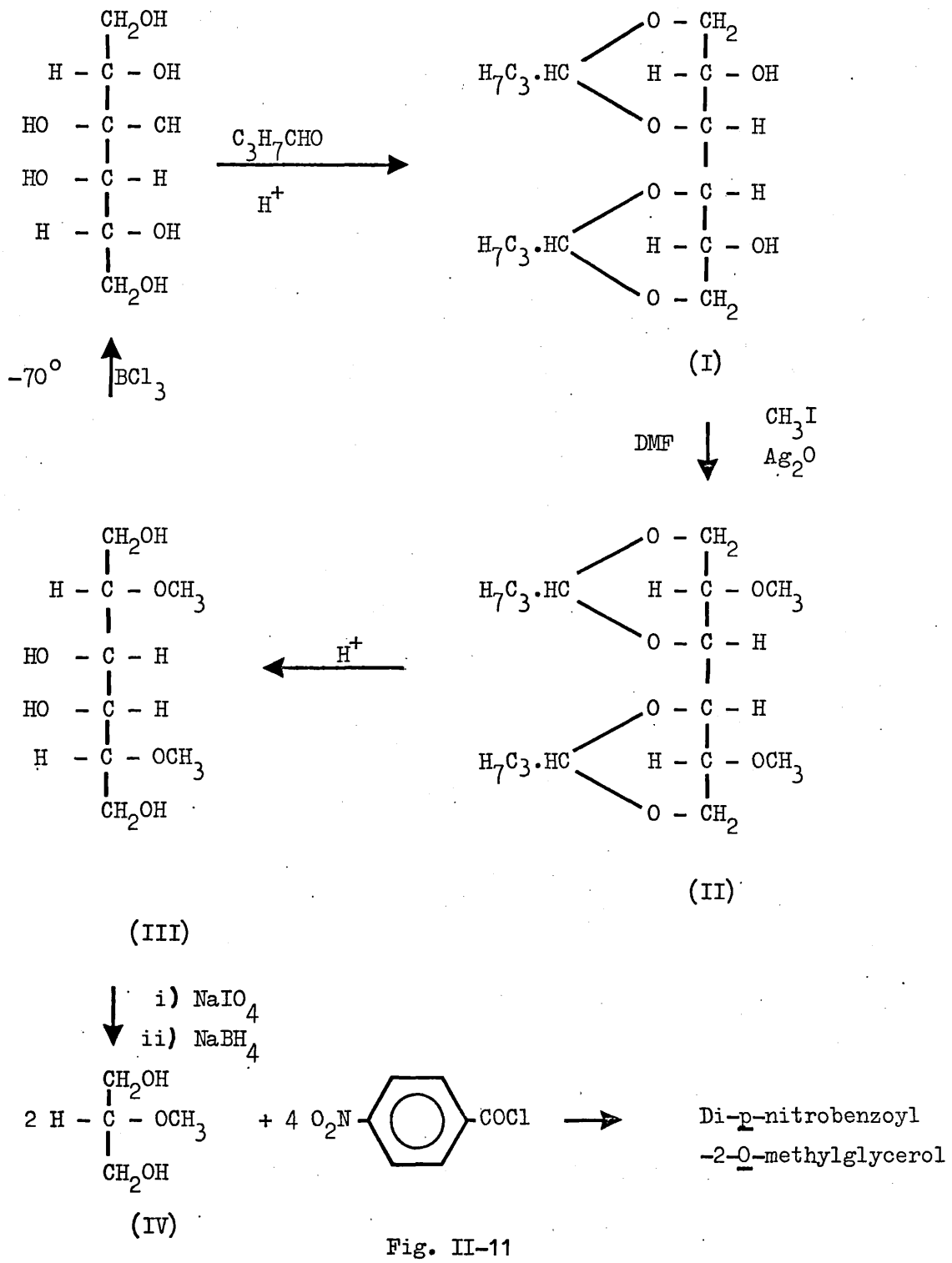


Fig. II-11

The di-O-methylgalactitol (II) consumed 1.07 mol of periodate ion (after 24 h) and liberated no formaldehyde and formic acid. The reported[44] m.p. of 2,5-di-O-methylgalactitol is 183.5°. In our hands, the m.p. could only be raised up to 176-177.5° and the tetra-acetate of this compound had m.p. 148° (reported by Painter as 88.5°).[44] Periodate oxidation of di-O-methylgalactitol followed by borohydride reduction as used by Painter, gave 2-O-methylglycerol, characterised as its known crystalline di-p-nitrobenzoate.[44] From these results, we can assume that, 2,5-di-O-methylgalactitol and its tetra-acetate are dimorphic.

On tritylation with 2 mol of trityl chloride, the 2,5-di-O-methylgalactitol gave a crystalline dityrityl derivative (Fig. II-12) also indicating the presence of two unoccupied primary hydroxyl groups in the molecule.

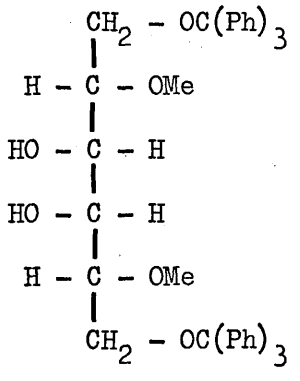


Fig. II-12

The tetra-acetate of 2,5-di-O-methylgalactitol was further characterised by its mass spectrum which will be discussed in section IX.

The formation of 1,6:3,4- and the 1,4:3,6-diacetals is very unlikely due to considerations of ring sizes, therefore it can be safely assumed that, 2,5-di-O-methylgalactitol can only result from a diacetal which has the structure of 1,3:4,6-di-O-butylidenegalactitol.

A detailed study of the n.m.r. spectra, which confirm the assigned structure of the diacetal and its derivatives, will be given in the section VIII.

iii) Isolation and Structure of 1,3:2,4:5,6-Tri-O-butylidene-galactitol

The triacetal fraction formed in the reaction of galactitol with n-butyraldehyde was separated by the light petroleum extraction of the syrupy mixture of acetals. The t.l.c. in benzene-methanol (9:1) showed only one spot and g.l.c. analysis of the semi-crystalline triacetal fraction gave an unresolved peak (a shoulder was detectable), (Fig. II-8). Examination of this fraction by n.m.r. spectroscopy indicated that it was mainly a stereoisomeric mixture of triacetals. A pure triacetal was obtained from the concentrated light petroleum solution as colourless plates, on standing at -5°. The chemical shifts of the acetal-proton signals in the n.m.r. spectrum of this compound could only be explained in favour of the 1,3:2,4:5,6-triacetal. Proton and C^{13} n.m.r. spectra of this compound will be discussed in section VIII. Further evidence for the structure of this triacetal was furnished by mass spectroscopy which is discussed in section IX.

The mother liquor, left from the crystallisation of the 1,3:2,4:5,6-triacetal, contained a very small quantity of another triacetal which could be the diastereoisomer of the isolated product, as well as some polymerisation products[45] of n-butyraldehyde and other triacetals of different structures, as indicated by the presence of extra signals in

the n.m.r. spectra. It was not possible to isolate any other pure acetals from this mixture.

The most common chemical method for the determination of the structures of hexitol triacetals is the partial hydrolysis of the compounds and the identification of the fragments.[46, 47] However because of the possibility of acetal ring migration, this method should be applied with caution. Under mild hydrolysis conditions, and assuming no acetal migration takes place, the 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol is expected to give a mixture of 1,3:5,6-diacetal, 1,3-monoacetal and 1,3:2,4-diacetal. The partial hydrolysis of the above tri-O-butylidenegalactitol was attempted, using trifluoroacetic acid as catalyst. This acid was shown to be a good catalyst for the complete hydrolysis of the benzylidene and isopropylidene acetal groups,[48] but it proved unsatisfactory for the complete hydrolysis of the butylidene acetals.[49] Therefore it was chosen for rapid partial hydrolysis of the triacetal in this work. However, several partial hydrolysis products were obtained amongst which the 1,3:4,6-diacetal and the 1,3-monoacetal were identified by g.l.c. and t.l.c., indicating that acetal migration had taken place.

iv) Acid Catalysed Migration of 2,3:4,5-Di-O-butylidenegalactitol

When some trifluoroacetic acid was added to the solution of 2,3:4,5-di-O-butylidenegalactitol in $CDCl_3$ and the reaction was followed by n.m.r. spectroscopy, a rapid formation of a higher field triplet at τ 5.4 was observed. The position of this triplet was characteristic for a six-membered acetal ring proton. This observation suggested a migration of the five-membered rings to the six-membered rings. The n.m.r. spectra, at certain time intervals of this reaction are shown in Fig. II-13.

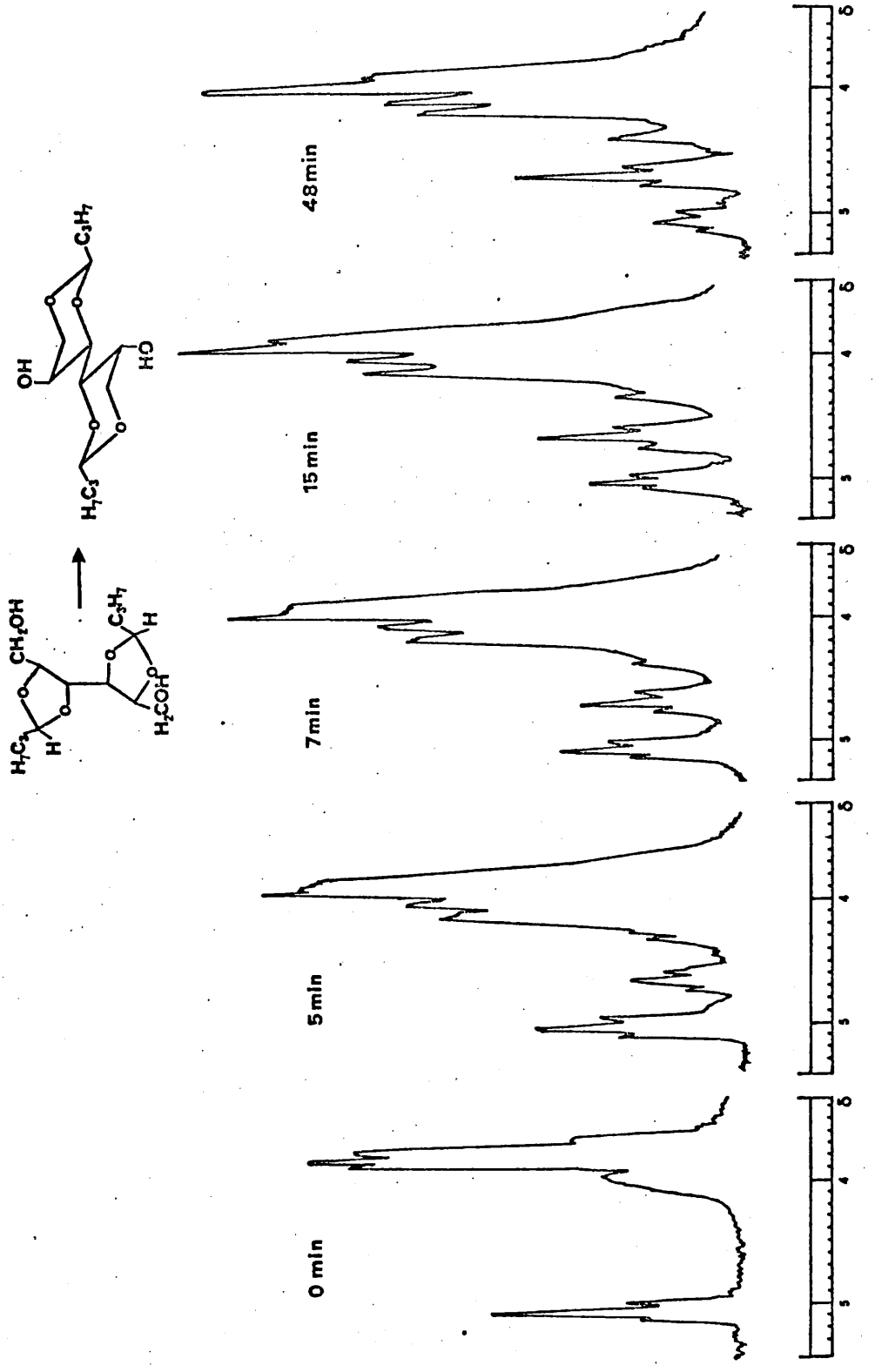


Fig. II-13

These spectra also suggested that there was no noticeable hydrolysis during the migration, since no other triplets due to partial hydrolysis products were observed. If a very rapid hydrolysis of the acetal to the polyol and aldehyde is assumed, then the reformation of other acetals or the formation of another triplet at τ 5.2 due to polymerised butyraldehyde should have been observed.

The product at the end of the reaction was analysed by t.l.c. and it was found to move the same distance as 1,3:4,6-di-O-butylidene-galactitol. The migration was also followed by g.l.c., which confirmed the formation of 1,3:4,6-di-O-butylidene galactitol from 2,3:4,5-di-O-butylidene galactitol in the presence of trifluoroacetic acid (Fig. II-14).

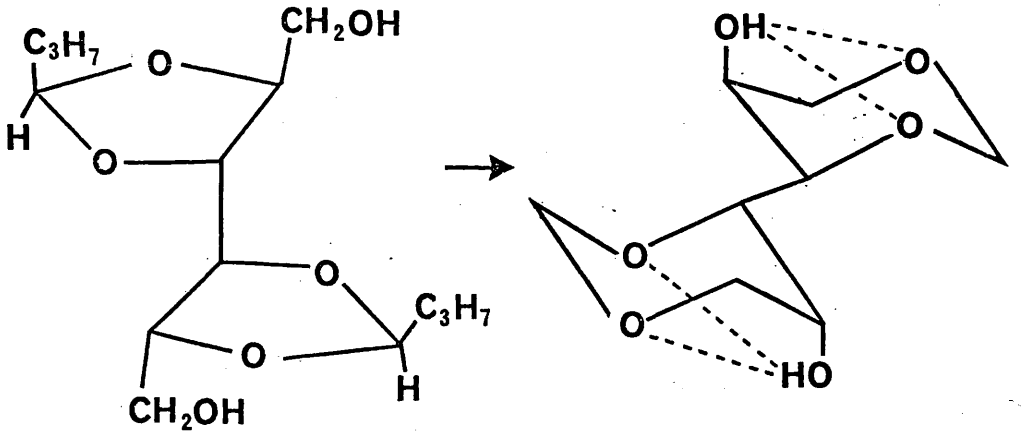
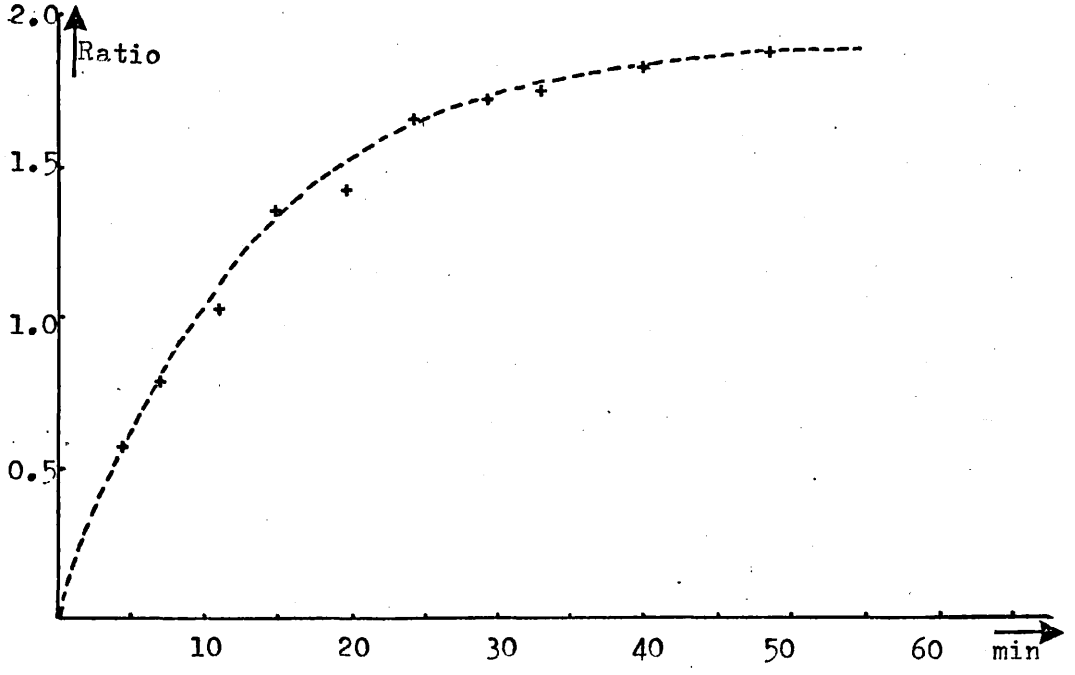


Fig. II-14

The rate of this migration was found to be dependent on the amount of trifluoroacetic acid. The g.l.c. showed much slower reaction because less trifluoroacetic acid was used. A plot of the ratios of the two acetal proton triplet integrals vs. time

is shown in Fig. II-15. The rate of change of the ratios was very fast in the first 10 min. but in $\frac{1}{2}$ h, the reaction slowed down and reached an equilibrium. After a reaction time of 14 h, hydrolysis of the acetals was observed. The position of the triplet in the n.m.r. spectrum of the hydrolysed product was the same as the position of the triplet obtained from the polymeric n-butyraldehyde (τ 5.2).



Change of the ratio of the acetal proton triplets (1,3:4,6-/2,3:4,5-) with time in $CDCl_3$ containing 20% CF_3COOH.

Fig. II-15

These results are not consistent with the results of Rainer Bonn and Ingolf Djong[50] who studied the reaction of 2,3:4,5-di-O-benzylidene galactitol with benzaldehyde and zinc chloride and observed the formation of 1,3:2,4:5,6-tri-O-benzylidene galactitol. These authors claimed that under the light of their result, the rules of Barker and Bourne are valid only if the acetalation of alditols is performed under kinetically controlled conditions.

However, no reaction mechanism was suggested for this product. On considering the Barker and Bourne rules the 1,3:4,6-diacetal was the expected product and in fact this acetal was formed from the 2,3:4,5-dibutylidenegalactitol. It seems that, in the reported reactions of 2,3:4,5-di-O-benzylidenegalactitol with zinc chloride and benzaldehyde, the reactant acetal was first hydrolysed to the polyol or perhaps migrated to the 1,3:4,6-diacetal and then hydrolysed. It is conceivable that these products further reacted with excess benzaldehyde to give the 1,3:2,4:5,6-tri-O-benzylidenegalactitol. The reported yield of the triacetal in this reaction was only 30%. Usually with zinc chloride catalyst, only the kinetically stable acetals are observed.[51] It is known that during acetalation reactions, the catalytic action of zinc chloride is lost after a while, through the formation of the hydrated complex,[51,52] $ZnCl_2(H_2O)_2$ and this results in kinetic control of the reaction.

$$ZnCl_2(PhCHO)_2 + 2H_2O \rightleftharpoons ZnCl_2(H_2O)_2 + 2C_6H_5CHO$$

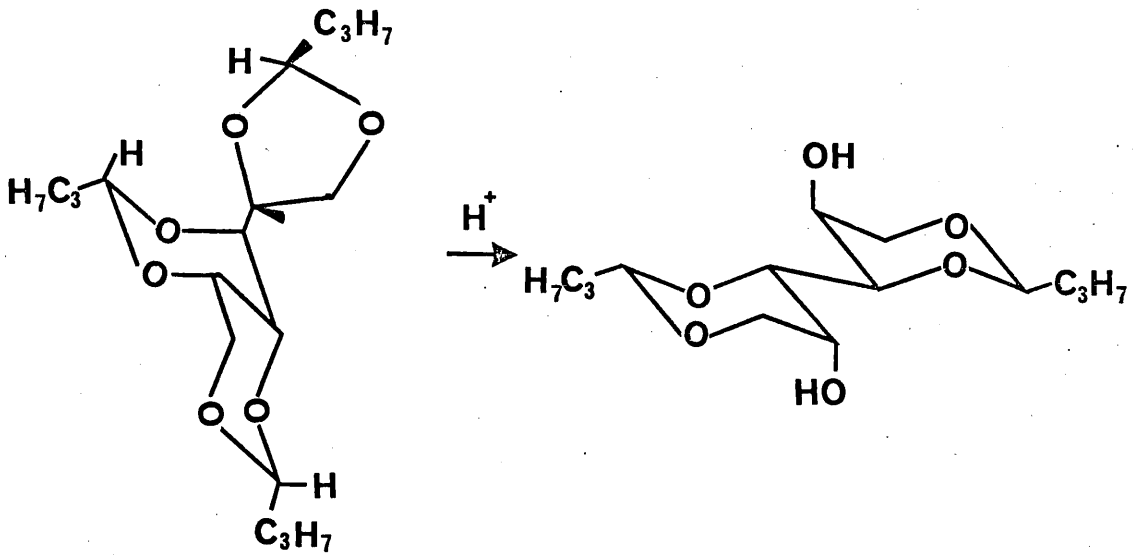
Thus, a thermodynamic stage could not have been reached during the formation of the above mentioned triacetal, under the catalytic action of zinc chloride.

Rainer Bonn and Ingolf Djong[56] discussed the preferential formation of 2,4-rings from D-glucitol by considering the "bent" and zig-zag conformations of this polyol and pointed out that the planar zig-zag conformation of D-glucitol would lead to the optimal O(2)-O(4) distance for β-*erythro* ring closure but in a bent conformation the distance between O(2)-O(4) is *ca.* 4.2Å which is almost twice the distance between these

two atoms when the molecule is in the zig-zag conformation and only a complete turning of 120° would lead to an optimum O(2)-O(4) orientation. Therefore the preference of β-erythro ring should be slight. These arguments in fact support the assumption that the preferential formation of acetal rings under thermodynamically controlled conditions is determined by the free energy content of the products but not by the conformations of the reactants.

These arguments however, do not explain the claims of these authors concerning the Barker and Bourne rules, which were established as a result of investigations carried out on the structures of cyclic acetals isolated under thermodynamically controlled conditions. Hence, contrary to the suggestions of R. Bonn and I. Djong, the Barker and Bourne rules may not be applied to kinetically controlled reactions of polyols; for example under kinetically controlled conditions, the main product of D-glucitol and n-butyraldehyde is the 2,3-monoacetal and not the stable 2,4-monoacetal.

The preceeding discussions were substantiated when some thermodynamically controlled reactions of 1,3:2,4:5,6-tributylidenegalactitol were investigated. As it was pointed out before, the partial hydrolysis of the tributylidenegalactitol resulted in a mixture containing the 1,3:4,6-diacetal. In another reaction of the tributylidenegalactitol in 5N-hydrochloric acid with n-butyraldehyde, the 1,3:4,6-dibutylidene-galactitol was obtained in 35% yield after a reaction of four days (Fig. II-16) indicating that in the reaction of galactitol with aldehydes the triacetal is formed under kinetically controlled conditions, but may undergo gradual hydrolysis and convert to the 1,3:4,6-acetal under thermodynamically controlled conditions.



D-Form

Fig. II-16

III Butylidene Acetals of 1-Deoxy-D-galactitol (L-Fucitol).

i) Introduction

The reactions of 1-deoxy-D-galactitol (Fig. III-1) with aldehydes are expected to be more complicated than the corresponding reactions of galactitol. Galactitol is a symmetrical molecule producing enantiomers, which result in the reduction of the number of possible acetal isomers by half. In 1-deoxy-D-galactitol, the symmetry is removed by the introduction of the deoxy group at C-1. Although this polyol has only five hydroxyl groups, formation of many more different acetals is possible.

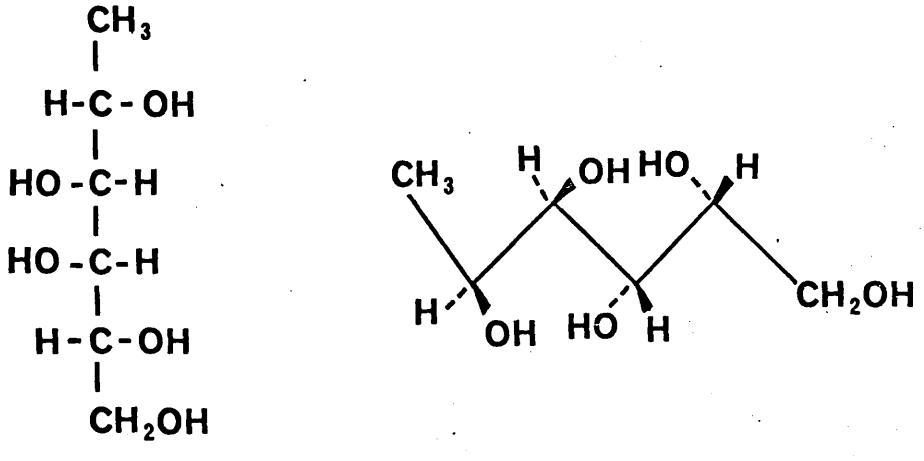


Fig. III-1

Previous studies with n.m.r. showed that some acyclic 1-deoxy-D-galactitol derivatives prefer the planar zig-zag conformation (Fig. III-1) in solution.[53]

Very few examples of acetal formation from this polyol are available in the literature. A dibenzylidene derivative of unknown structure[54] and the 2,3:4,5-di-O-isopropylidene derivative[55] have been reported. No work has been published on the monoacetals of this polyol with the exception of 4,5-di-O-benzyl-1,3-O-benzylidene-6-deoxy-L-galactitol which was prepared from 4,5-di-O-benzyl-1,3-O-benzylidene-L-galactitol.[56]

ii) Results and Discussion

In the reaction of 1-deoxy-D-galactitol with aldehydes, the preferential formation of 2,3-monoacetal in high yield is expected under kinetically controlled conditions, in parallel with the reaction of 1-deoxy-D-glucitol. There is no possibility of formation of other stable acetal rings involving the C-2 hydroxyl group, other than the mentioned 2,3-ring. According to the Barker and Bourne rules, the most stable acetal ring for 1-deoxy-D-galactitol spans 4,6-positions but known reactions of galactitol suggest that the α-threo rings are also possible.

The reaction was monitored by g.l.c. on an Apiezon-K column, at 169°. Samples, taken at certain time intervals were silylated for this purpose. The chromatograms obtained, are represented in Fig. III-2. This suggested that the 2,3-monoacetal (I) was formed as the main product in the early stages of the reaction. After 19 h, the mixture still contained a considerable amount of 2,3-monoacetal unlike the corresponding reaction of 1-deoxy-D-glucitol, in which this monoacetal almost completely disappeared at equilibrium.

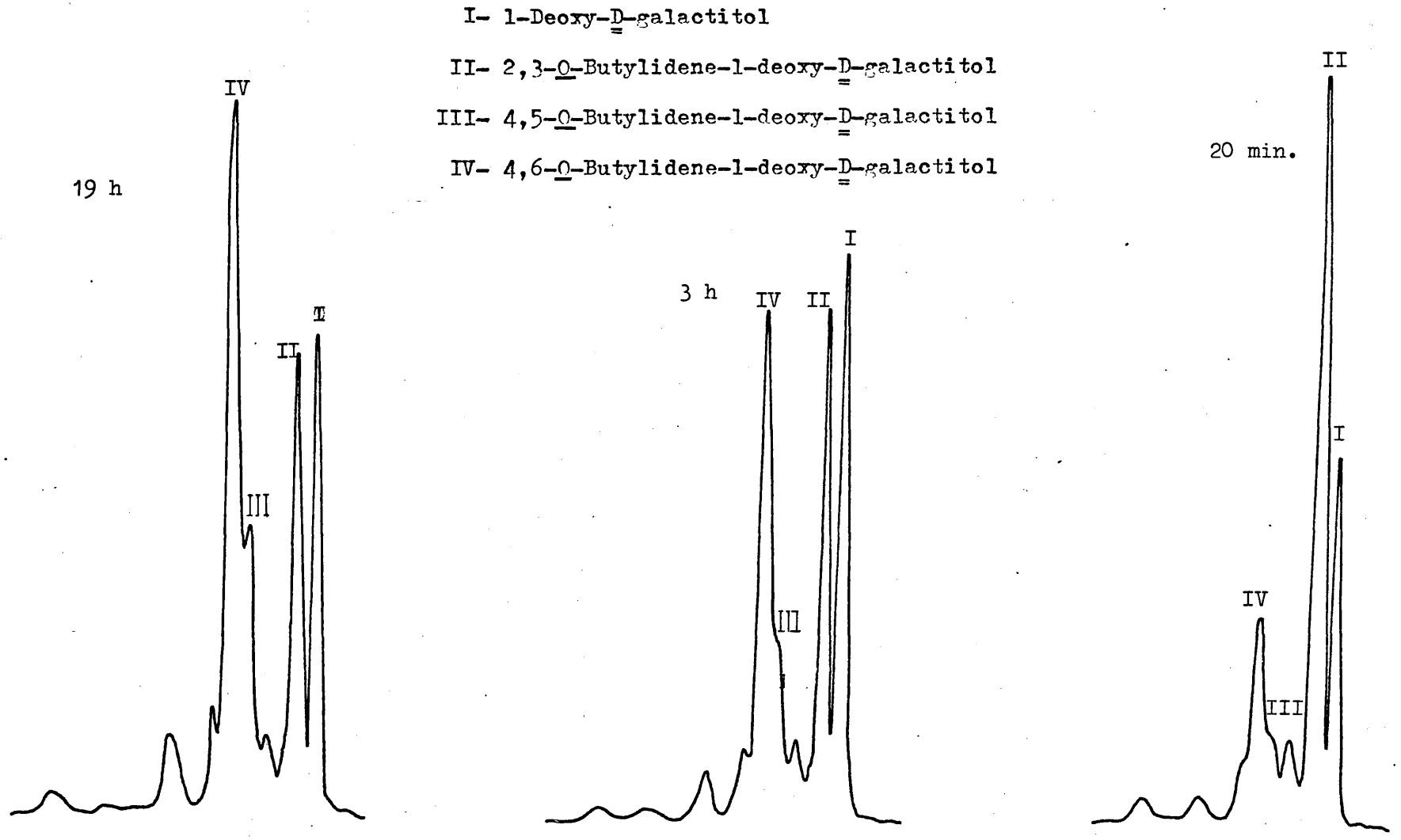
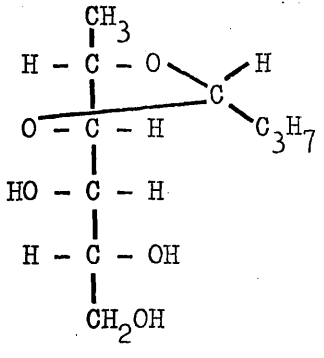


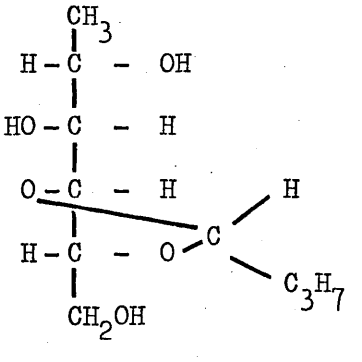
Fig. III-2 The reaction of 1-deoxy-D-galactitol (1 mol) with n-butyraldehyde (1 mol) in N-HCl, monitored by g.l.c. (Pye-104; Apiezon-K 7.5%, temperature 169°).

In all stages of the reaction, quite a large amount of unreacted L-fucitol (1-deoxy-D-galactitol) was also present, again unlike the reactions of 1-deoxy-D-glucitol and galactitol (Fig. III-2).

In accounting for the presence of 4,5- and 4,6-monoacetals, the migration of the 2,3-monoacetal in favour of these products can be ruled out because of the large distances involved. It is therefore more reasonable to accept that the reaction involves the initial fast formation and hydrolysis of the 2,3-monoacetal, together with the slow formation of the 4,5- and 4,6-monoacetals. After two days the 4,6-O-butylidene derivative was obtained in highest yield. The two monoacetals, 2,3-O-butylidene-1-deoxy-D-galactitol (Fig. III-3,I) and 4,5-O-butylidene-1-deoxy-D-galactitol (Fig. III-3,II) were isolated in smaller yields.



I



II

Fig. III-3

The acetalation reaction of galactitol and 1-deoxy-D-galactitol is comparable since both polyols afford acetals with the same type of ring systems. However, when the reaction mixtures are compared at various stages, under similar conditions, the presence of 1-deoxy-D-galactitol after a reaction time of two days may seem unexpected since the activating effect of the deoxy group should have produced a faster reaction. Indeed, as implied by g.l.c. studies, the formation of 2,3-monoacetal in 1-deoxy-D-galactitol is much faster than the formation of the analogous ring from galactitol. The low yield of this product in the former case could be explained if hydrolysis is considered under longer reaction time, whence the position of equilibrium shifts towards the reactants. It is clear from the synthetic and g.l.c. evidence that both galactitol and its 1-deoxy derivative afford β- and α-threo rings in considerable amounts under kinetic and thermodynamic conditions. However, neither of these polyols showed the presence of a truly kinetically controlled intermediate acetal. In comparison, D-glucitol and some of its derivatives produce high yields of kinetically controlled products. This can be explained simply in terms of the high tendency of the formation of the 2,4-rings (β-erythro), which shortens the life time of the 2,3-rings (α-threo). In galactitol and 1-deoxy-D-galactitol 2,4-acetal rings are β-threo type, which is not a favoured conformation, therefore the 2,3-monoacetals of these polyols are obtained in much better yields than the analogous acetals of D-glucitol and its derivatives under thermodynamically controlled conditions.

iii) Synthesis and Structures of Monobutylidene 1-Deoxy-D-galactitols

Although 1-deoxy-D-galactitol can easily be obtained by the reduction of L-fucose with sodium borohydride (Fig. III-4) the method is costly.

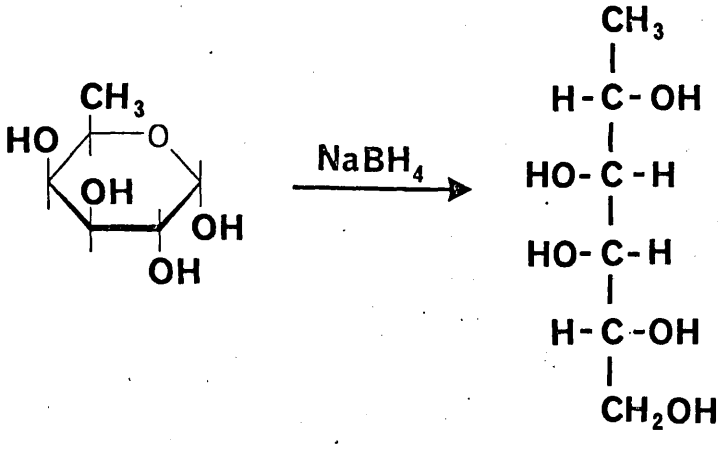
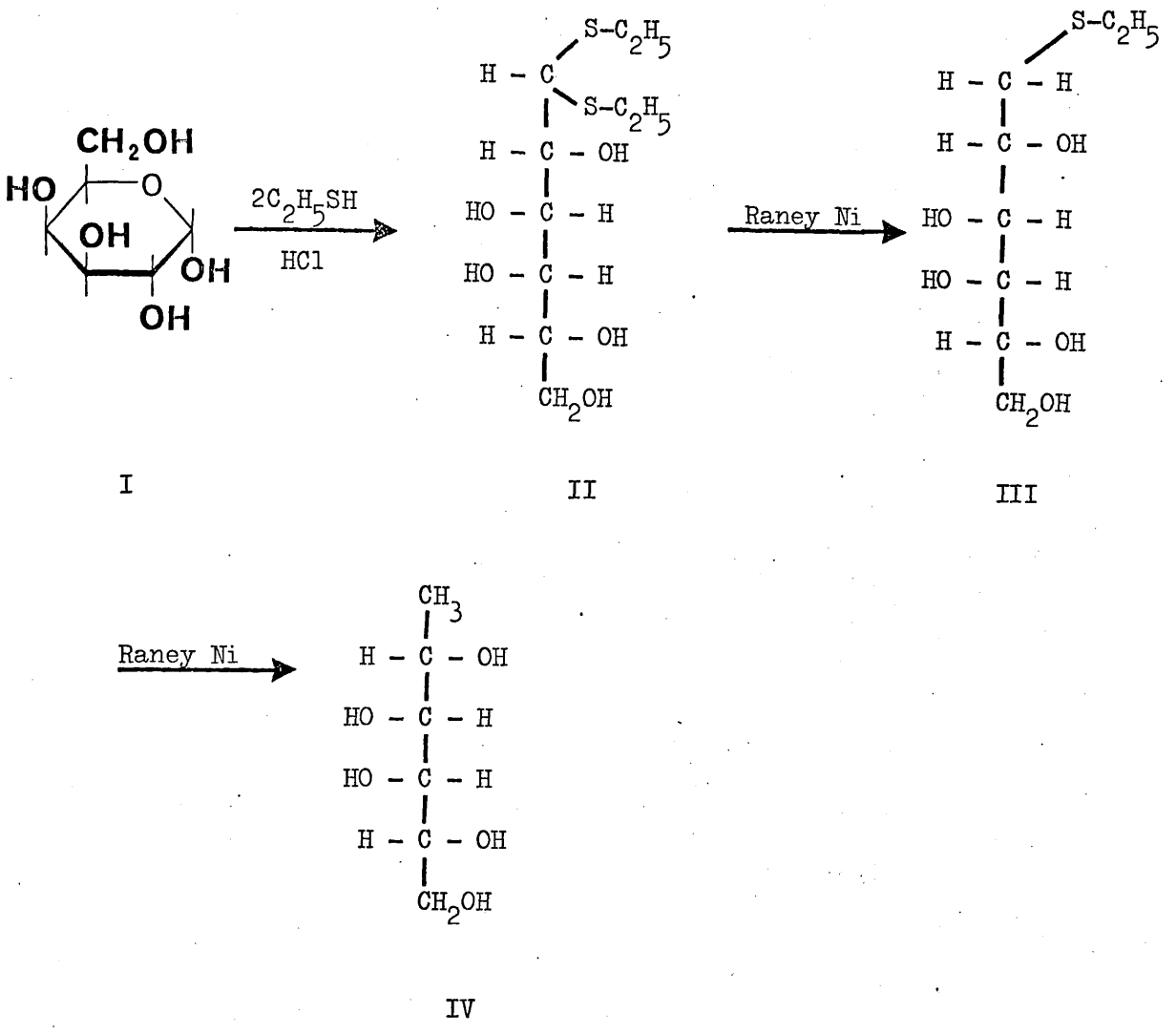


Fig. III-4

It was therefore decided to synthesise the polyol from D-galactose, by desulphurisation of the diethyl mercaptal derivatives with Raney nickel. The method was described by Wolfrom[57] in 1944 and by Jones and Mitchell[58] in 1958. The diethyl thioacetal of D-galactose (II) was easily obtained and purified from the free sugar by recrystallisation. The reduction of the thioacetal by freshly prepared and thoroughly washed Raney nickel gave a reasonable yield of 1-deoxy-D-galactitol (L-fucitol). Fig. III-5 shows the reaction path.



I II III

IV

Fig. III-5

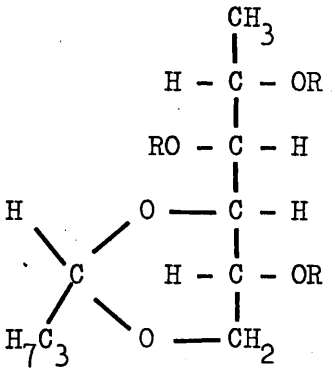
However, when insufficient Raney nickel was used the crystalline monoethyl thioacetal (III) was obtained as reported.[58] The epimerisation of hydroxyl groups by Raney nickel catalyst is known.[59] However the 1-deoxy-D-galactitol which was obtained from D-galactose was identical with the one obtained from L-fucose.

The reaction of this polyol with n-butyraldehyde in N-hydrochloric acid gave a syrupy mixture of several acetals in which the monoacetal component was the main product. A mixture of some diacetals were separated from the monoacetals by extraction with light petroleum (60-80°). T.l.c. of this extract in benzene-methanol (9:1), showed the presence of several diacetals, but none of these could be crystallised from the mixture.

The monoacetal fraction was analysed by t.l.c. in solvent methyl ethyl ketone, saturated with water. This suggested the presence of five and six-membered ring monoacetals. The six-membered monoacetals usually move slightly faster than the five-membered ones in this solvent. The same solvent mixture gives a very distinct separation between mono and diacetals of polyols, therefore it was possible to check the purity of the di- and monoacetal fractions in all the acetal preparations reported in this thesis. However, this solvent mixture is not capable of separating the six-membered monoacetals of different structures from each other. Structural isomers of five-membered monoacetals also are not separated. The reaction mixture also contained some unreacted polyol which did not move on t.l.c. (methyl ethyl ketone-water). The unreacted polyol was crystallised out from the ethanolic solution of the monoacetal fraction. The mixture of monoacetals, thus purified from diacetals and polyol was applied to a column of Dowex-1 X8 (OH^-) resin, as described in section III, iv. The syrupy six-membered monoacetal eluted first and in highest yield. Further fractions from the column contained a mixture of two five-membered ring acetals, namely,

2,3-O-butylidene-1-deoxy-D-galactitol and 4,5-O-butylidene-1-deoxy-D-galactitol which were separated by fractional crystallisation from ethanol. 4,5-O-butylidene-1-deoxy-D-galactitol crystallised out leaving the 2,3-monoacetal in solution, which was crystallised from light petroleum.

The syrupy 4,6-O-butylidene-1-deoxy-D-galactitol (Fig. III, 6, I) was characterised as its crystalline tri-acetate derivative (II). The monoacetal (I) also afforded a crystalline trimethyl ether (III).



(I) R = H

(II) R = Ac

(III) R = Me

Fig. III-6

The yield of the tri-methyl ether of this acetal was low, therefore it was not possible to carry out the usual methylation and hydrolysis procedures in the structural investigations. However periodate oxidation and especially physical methods, such as n.m.r. spectroscopy were extremely useful in this respect.

Thus the monoacetal (I) consumed 0.97 mol of periodate ion and it did not release any acidic fragments. The acetaldehyde released from

this reaction was precipitated as its crystalline 2,4-dinitrophenyl-hydrazone derivative.[60]

The 2,3-monoacetal (Fig. III-3,I) consumed 2.03 mol periodate ion and released 1.2 mol of formaldehyde and 0.97 mol formic acid. Release of formaldehyde from this molecule proves the presence of free hydroxyl groups on C-5 and C-6. This finding limits the possible structures of the acetal to 2,3-, 2,4- and 3,4-monoacetals. The 2,4- and 3,4-monoacetals, however, should not only consume 1 mol of periodate ion and should not release any formic acid. These facts are only compatible with the structure of 2,3-O-butylidene-1-deoxy-D-galactitol.

Further structural evidence derived from the n.m.r. spectrum (discussed in section VIII-iii) shows this material to be a mixture of stereoisomers. The low field triplets (τ 5.10) are characteristic for five-membered acetal ring protons.

The 4,5-O-butylidene-1-deoxy-D-galactitol (Fig. III-3,II) consumed 1.2 mol of periodate ion but it did not produce any formaldehyde nor formic acid. Thus the periodate oxidation alone could not distinguish the structure of this compound from that of the 4,6-monoacetal. But the n.m.r. spectrum of this compound showed an acetal-proton triplet at τ 4.95 (section VIII) which is characteristic for a five-membered ring acetal-proton, whereas the n.m.r. spectrum of the 4,6-O-butylidene-1-deoxy-D-galactitol showed the acetal-proton triplet at τ 5.4, characterising a six-membered ring. Although, the periodate oxidation also does not exclude the possible 3,6-mono and 2,5-monoacetal, higher field acetal-proton signals are expected for seven-membered ring butylidene acetal-protons.[29]

The observation of only one acetal-proton triplet and one deoxy-methyl doublet (section VIII) in the spectrum of 4,5-O-butylidene-1-deoxy-D-galactitol suggested that this was a pure stereoisomer. Only one 4,5-monoacetal was obtained, therefore it was not possible to predict the stereochemistry of the compound on the acetal carbon atom. The 4,5-O-butylidene acetal was also obtained in low yield directly from the concentrated solution of the reaction mixture in chloroform.

Another crystalline fraction was separated out on extraction of the reaction mixture with chloroform after a short reaction time of 20 min. This product was not identified. However, its 60 MHz n.m.r. spectrum indicated it to be a butylidene acetal (m.p. 159°) as suggested by a triplet at τ 4.95. After standing at room temperature for some time it absorbed U.V. light strongly at 223 nm, probably due to elimination of n-butyraldehyde and hence decomposition.

iv) Separation of the Five and Six-membered Ring Monoacetals

The separation of five and six-membered butylidene monoacetals of several polyols have been attempted on silica gel and alumina.[2,61] In some cases a partial separation was achieved but generally the methods did not give satisfactory separations. The same techniques were employed in order to separate the monoacetals of galactitol but they proved unsuccessful. It was then decided to investigate the possible use of a basic ion-exchange resin Dowex-1 X8 (OH^-), which was widely used for the separations of anomeric mixtures of glycosides.[62, 63] The separations achieved in this field were explained by the different acidities of C-2

hydroxyl groups of the α- and β-glycosides.[63] Similarly, the primary and secondary hydroxy groups attached to the five- or six-membered acetal rings usually have different acidities,[2] therefore, it was expected that these compounds would act in the same way on this resin. Indeed a 95% separation of 1,3-O-butylidene-DL-galactitol and 2,3-O-butylidene-DL-galactitol was achieved at the first attempt, using deionised and CO_2-free water as eluent. Later five and six-membered acetals of 1-deoxy-D-galactitol were also successfully separated.

Dowex-1 X8 is an anion exchanger with benzyltrimethyl ammonium active groups. It is supplied in the chloride form and is cross-linked with 8% of divinylbenzene. The resin is converted to the hydroxyl form, by treating with three bed volumes of 4% sodium hydroxide solution.

The separation of the monoacetals on this resin can be explained in terms of the different acidities of the C-1 primary hydroxyl group of 2,3-O-butylidene-DL-galactitol (Fig. III-7,I) and the secondary hydroxyl group on C-2 of the 1,3-O-butylidene-DL-galactitol (Fig. III-7,II) Similarly the hydroxyl group on C-5 of 4,6-O-butylidene-1-deoxy-D-galactitol (Fig. II-7,III) and primary hydroxyl groups on C-6 of 2,3-O-butylidene-1-deoxy-D-galactitol and 4,5-O-butylidene-1-deoxy-D-galactitol (Fig. III-7,IV and V respectively), have different acidities and are resolved on the resin.

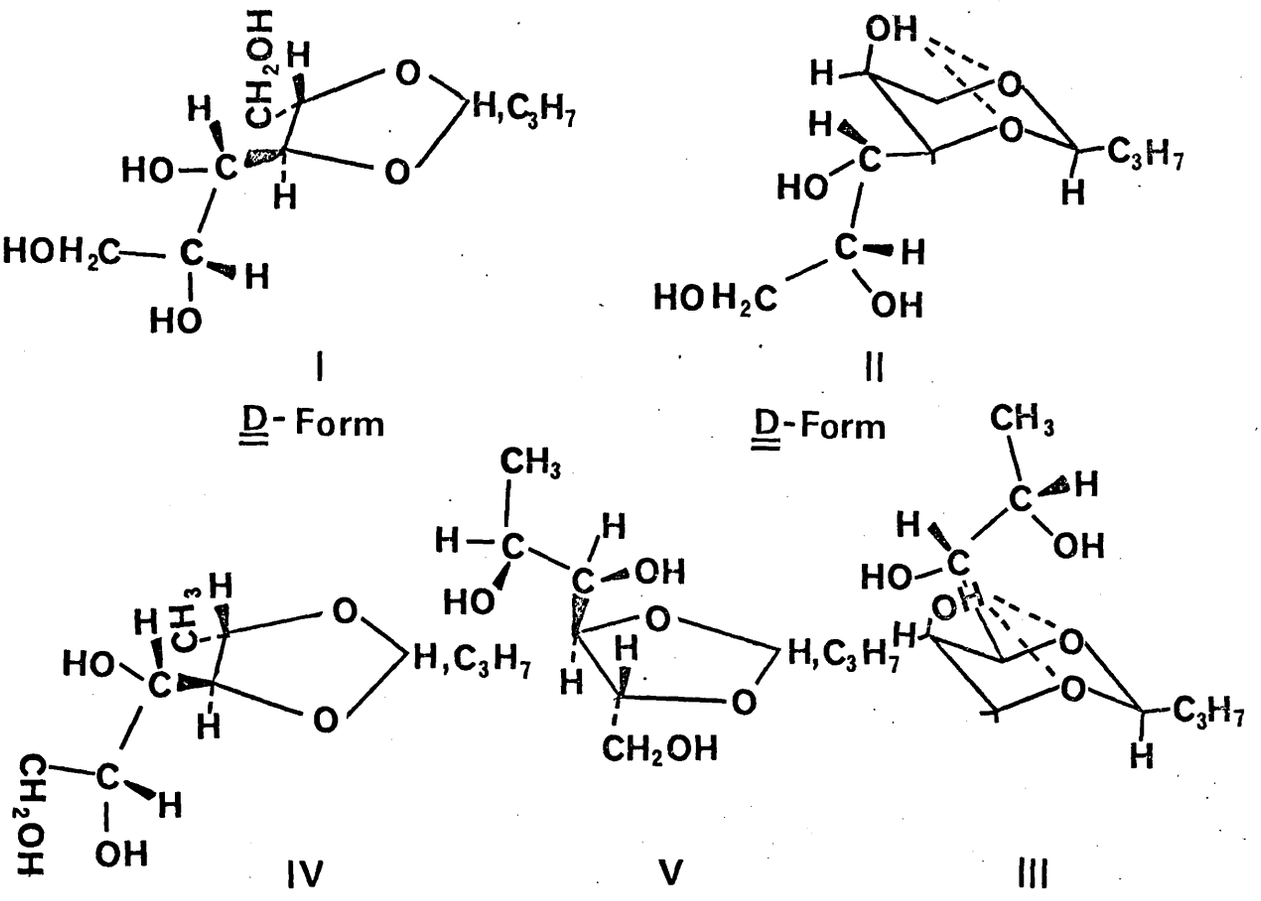


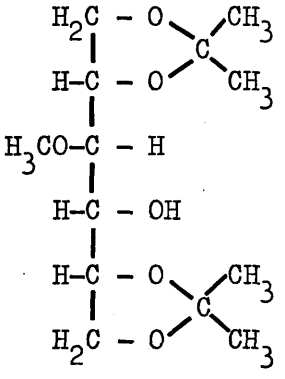
Fig. III-7

Generally, primary alcohol groups are more acidic than the secondary ones.[64] Also in compounds (II) and (III) the axial hydroxyl groups are involved in intramolecular hydrogen bonding with the ring oxygens, whereas in compound (I) the primary hydroxyl cannot form strong hydrogen bonding because of the free rotation. This makes the secondary hydroxyl group on the 1,3-dioxane ring (II) even less acidic. As expected, the greater acidity and steric availability of the primary hydroxyl group gives stronger interaction with the resin particles and hence the acetals carrying this group, namely 2,3-monoacetals of galactitol and 1-deoxy-D-galactitol (I and IV) and 4,5-monoacetal of 1-deoxy-D-galactitol (V), eluted last from the resin column.

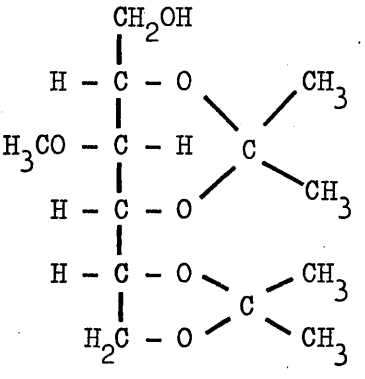
IV. Butylidene Acetals of 3-O-Methyl-D-glucitol

i) Introduction

The reaction of 3-O-methyl-D-glucitol with acetone yielded 1,2:5,6- and 2,4:5,6-di-isopropylidene derivatives[65] (Fig. IV-1). Benzylidenation of this polyol afforded two crystalline di-O-benzylidene derivatives of the same structure[65] namely the 2,4:5,6-dibenzylidene acetals, however, their n.m.r. spectra were different and the chemical shifts of the acetal proton signals indicated that two benzylidene acetals were diastereoisomers on the 5,6-benzylidene acetal carbon.



1,2:5,6-di-O-isopropylidene-3-O-methyl-D-glucitol



2,4:5,6-di-O-isopropylidene-3-O methyl-D-glucitol

Fig. IV -1

The reactions of 3-O-methyl-D-glucitol with several aldehydes were followed polarimetrically and it was shown that this polyol does not afford kinetically controlled intermediate products unlike D-glucitol.[1] The reaction with n-butyraldehyde afforded only one monoacetal in good

yield for which the structure, 2,4-O-butylidene-3-O-methyl-D-glucitol was assigned as a result of chemical methods.[1] It was mentioned in previous sections, that D-glucitol gave 2,3-monoacetal as an intermediate product. As this is not possible in the case of the 3-O-methyl derivative, it was not surprising that only one monoacetal (2,4-ring) was observed.

ii) Results and Discussion

The changes in the optical activities of the reaction mixtures of some polyols with n-butyraldehyde are shown in Fig. IV-2. 3-O-Methyl-D-glucitol is the only polyol which showed a smooth decrease in the optical activity of its reaction mixture, suggesting the formation of only one type of acetal. All the other curves showed minimums, indicating the formations of different products at different stages of the reactions. It is possible to obtain kinetically controlled products by stopping these reactions at the times corresponding minimums.

The reaction of 3-O-methyl-D-glucitol with n-butyraldehyde in 0.5N-hydrochloric acid was followed by g.l.c., and in agreement with previous work,[61] the main product was found to be the 2,4-monoacetal.

The 3-O-methyl-D-gluctiol, used in this work was prepared by the reduction of 3-O-methyl-D-glucopyranose, with sodium borohydride. Although 3-O-methyl-D-glucopyranose was available commercially, a synthesis of this sugar from D-glucose was also attempted.[66] The path of this reaction is shown below (Fig. IV-3).

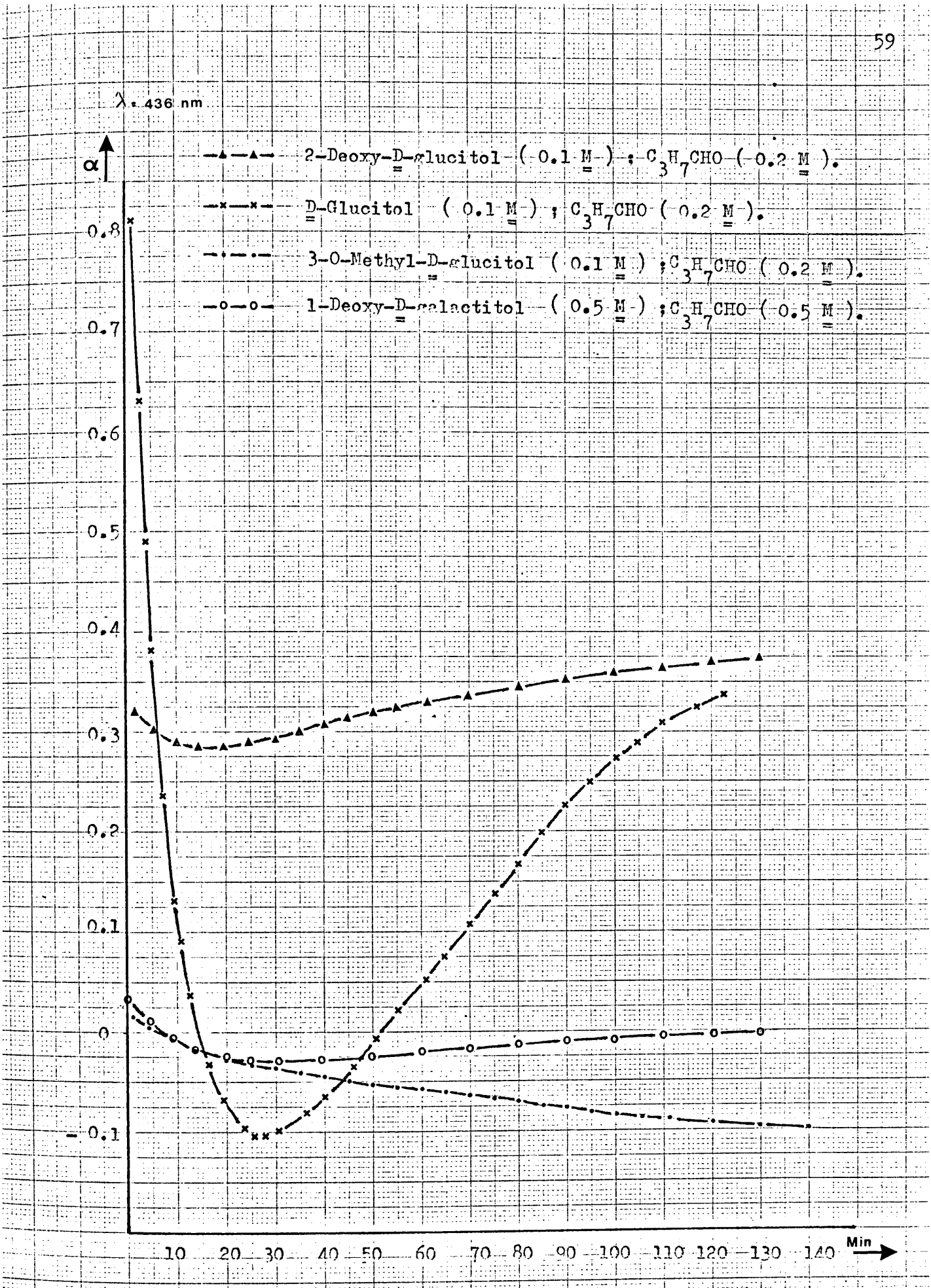
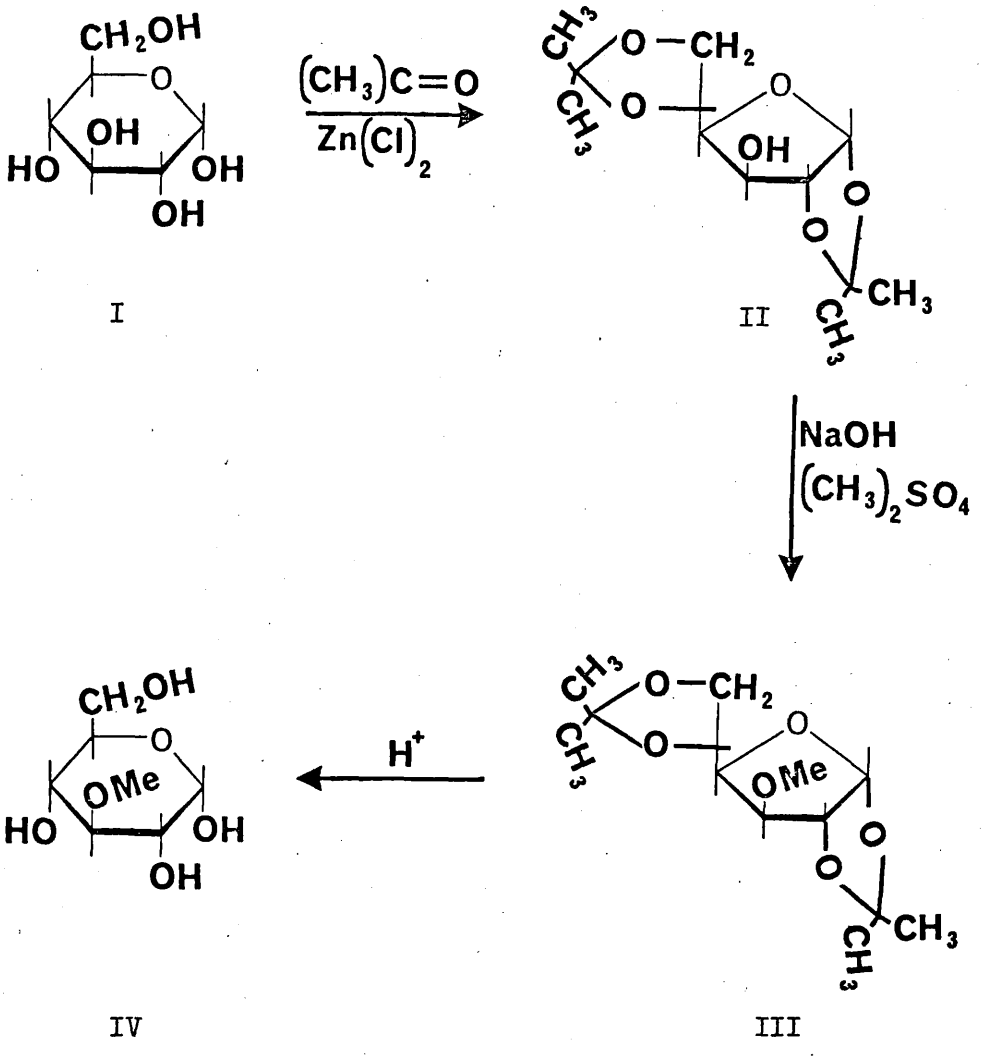


Fig. IV-2 Changes in the optical activities of the reaction mixtures of some polyols with n-butyraldehyde at 25°, in N-hydrochloric acid.



I II

IV III

Fig. IV-3

Thus, 3-O-methyl-D-glucose (IV) was obtained in moderate yield and reduced to 3-O-methyl-D-glucitol which was obtained as a pale yellow syrup. 3-O-Methyl-D-glucitol was characterised as its crystalline bis-phenylboronate. The polyol also gave the previously known diastereoisomeric 2,4:5,6-dibenzylidene acetals.[65]

The reaction of 3-O-methyl-D-glucitol with n-butyraldehyde, using 5N-hydrochloric acid or anhydrous zinc chloride gave a syrupy product which was very soluble in all the organic solvents. When the product was examined by t.l.c. in benzene-methanol (9:1), it behaved as a single compound. The g.l.c. analysis of the syrup as its t.m.s. (trimethylsilyl) derivative on Apiezon-K column at 180°, showed two very close peaks in approximately equal intensities. All the attempts to crystallise the product failed and the syrup showed no tendency to solidify on keeping at -5° for three months. The elemental analysis of the product supported the assumption that, the product was a dibutylidene acetal of 3-O-methyl-D-glucitol. The structure of this compound was shown to be the 2,4:5,6-di-O-butylidene-3-O-methyl-D-glucitol by chemical methods.

iii) Structural Analysis of 2,4:5,6-Di-O-butylidene-3-O-methyl-D-glucitol

The 100 MHz n.m.r. spectrum of the syrupy dibutylidene-3-O-methyl-D-glucitol showed that the acetal in fact was a mixture of diastereoisomers. The n.m.r. spectrum which will be discussed further in the section VIII, is shown in Fig. VIII-10. The triplet at τ 5.47 is characteristic for a six-membered acetal ring proton and triplets at τ 5.03 and τ 5.11 are due to the acetal protons of the diastereoisomeric five-membered rings. The attempts to separate these isomers failed, therefore the syrupy mixture was used as it stood for the structural investigations employing chemical methods.

The dibutylidene acetal (Fig. IV - 4, II; $R_1R_2 = C_3H_7$, $R'_2 = H$ and $R_1R'_2 = C_3H_7$, $R_2 = H$) was methylated with methyl iodide and silver oxide to give a syrupy methylated acetal (III, $R_1R_2 = C_3H_7$, $R'_2 = H$ and $R_1R'_2 = C_3H_7$, $R'_2 = H$) for which the n.m.r. spectrum showed two methoxyl signals.

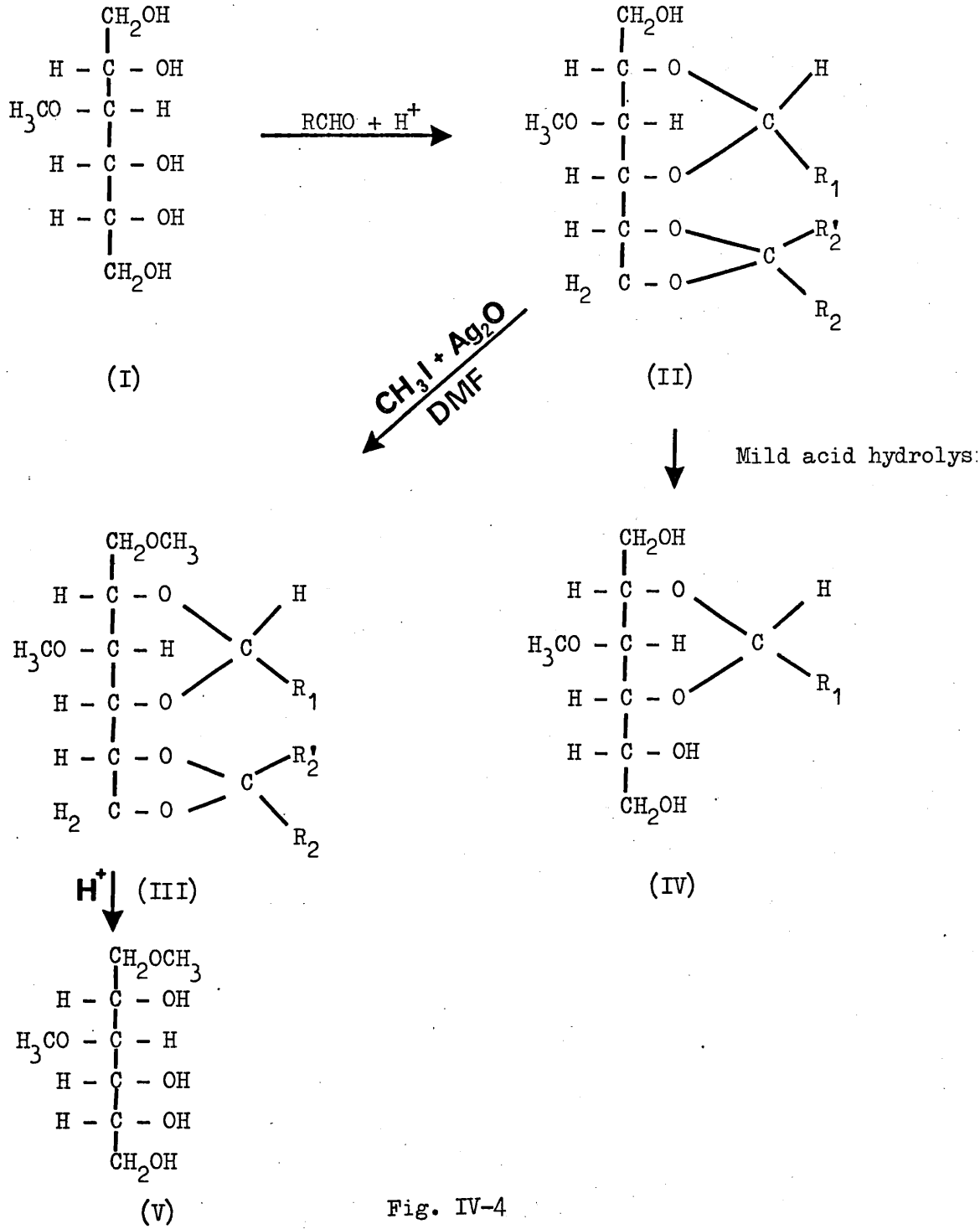


Fig. IV-4

The acetal-proton signals showed the ratio of the stereoisomers remained unchanged after methylation. The dibutylidene acetal dimethyl ether was refluxed as a solution in ethanol-water in the presence of acidic resin IR-120(H^+). This removed the butylidene groups completely giving the dimethyl-D-glucitol (Fig. IV-4, V). The dimethyl ether (V) consumed 2.15 mol periodate ion and released 1.08 mol of formaldehyde and 1.10 mol of formic acid, as expected from structure (V).

The presence of a primary hydroxyl group and hence evidence for structure (II) was obtained as follows. A tosyl derivative of the acetal (Fig. IV-5,I) was prepared which could not be crystallised but gave correct C, H analysis results. The tosylate (Fig. IV - 5,I) was reduced by lithium aluminium hydride to give a syrupy 1-deoxy derivative (Fig. IV-5,II). The 1-deoxy-dibutylidene acetal could not be obtained in a perfectly pure state, however, in the n.m.r. spectrum the appearance of a doublet for the deoxy group at τ 8.69 was good evidence for the formation of the 1-deoxy compound (II) from the dibutylidene-3-O-methyl-D-glucitol.

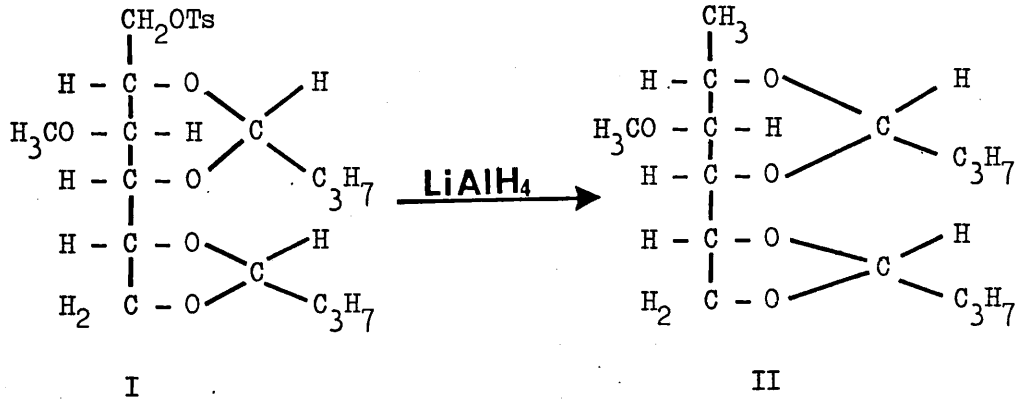


Fig. IV-5

Further evidence for the presence of the primary hydroxyl group was obtained by the infrared spectrum of the dibutylidene-3-O-methyl-D-glucitol. A 0.002 M carbon tetrachloride solution of the acetal showed absorptions at 3710 cm^{-1}, 3645 cm^{-1} and 3612 cm^{-1}. The band at 3645 cm^{-1} is characteristic for a free primary hydroxyl group and the band at 3612 cm^{-1} is characteristic for bonded primary hydroxyl group.[65] The spectrum showed no absorption bands for secondary hydroxyl groups.

The 1,3-di-O-methyl-D-glucitol was also synthesised from 2,4-O-benzylidene-5,6-O-isopropylidene-D-glucitol (Fig. IV-4,II; $R_1 = C_6H_5, R_2R_2' = CH_3$).[67] This compound was methylated using silver oxide and methyl iodide and the methylated compound was hydrolysed using trifluoroacetic acid,[48] to give 1,3-di-O-methyl-D-glucitol. The dimethylglucitol, thus obtained was found to show the same chromatographic behaviour as the one obtained from di-O-butylidene-3-O-methyl-D-glucitol.

iv) Synthesis of a Di-O-methylene-3-O-methyl-D-glucitol

The reaction of 3-O-methyl-D-glucitol with formalin in the presence of sulphuric or hydrochloric acid gave a crystalline dimethylene-3-O-methyl-D-glucitol in moderate yield. The compound gave a single peak on g.l.c. (Apiezon-K 180°) and a single spot on t.l.c. (m.e.k-water). The methylation of this compound afforded a crystalline methyl ether in slightly impure state therefore a satisfactory methoxyl analysis was not obtained. However the hydrolysis of this methylated acetal using N-hydrochloric acid and phloroglucinol as catalyst[69] gave a syrupy product which was chromatographically identical with the 1,3-di-O-methyl-D-glucitol. Therefore the structure of this compound was assumed to be

2,4:5,6-di-O-methylene-3-O-methyl-D-glucitol.

A dimethylene derivative of 3-O-methyl-D-glucitol was reported in 1935 but no structural information was available on this product.[68] The m.p. of the reported acetal was 135° and our acetal had m.p. 122°, but no evidence could be obtained with regard to the structural relationship.

Demethylation of dimethylene-3-O-methyl-D-glucitol was attempted, using a novel method which had not been applied in carbohydrate chemistry.[70] It was hoped that the method would yield, 2,4:5,6-di-O-methylene-D-glucitol. The reaction was carried out according to the equation

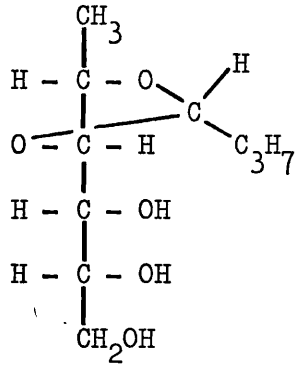
$$3RO\text{-}CH_3 + 2I_2 + NaBH_4 \longrightarrow B(OR)_3 + 3CH_3I + NaI + 2H_2$$

However, the end product was found to be a mixture of mainly 2,4-O-methylene-D-glucitol and D-glucitol as shown by g.l.c. and t.l.c., indicating that the 5,6-acetal ring had also been removed. With modifications, this reaction shows possibilities for effecting selective cleavage of some acetals as well as demethylation.

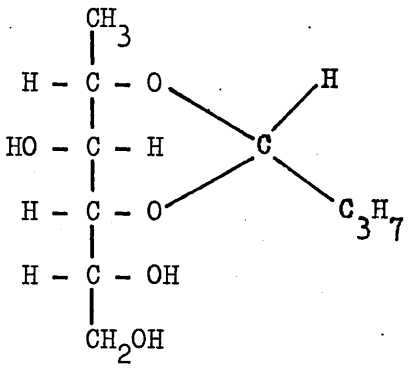
V. Butylidene Acetals of 1-Deoxy-D-glucitol

i) Introduction

1-Deoxy-D-glucitol is expected to behave very similarly to D-glucitol when its reactions with aldehydes are considered under conditions favouring the formation of monoacetals. In fact it was shown that this polyol also affords a 2,3-O-butylidene-1-deoxy-D-glucitol (Fig. V-1, I) under kinetically controlled conditions which is converted to the thermodynamically stable 2,4-O-butylidene-1-deoxy-D-glucitol (Fig. V-1, II).[61]



I



II

Fig. V-1, II

This similarity suggests that the hydroxyl group on C-2 is more reactive than the primary hydroxyl on C-6, towards acetalation. Also the formation of the 2,3-monoacetal and not the 3,4-monoacetal, indicates that the acidified aldehyde, $RCHOH^+$ (Fig. I-1), attacks the C-2 hydroxyl group and the 2,3-acetal is easily formed by ring closure. The "bent" conformation of D-glucitol and 1-deoxy-D-glucitol further increases the steric accessibility of the C-2 hydroxyl and shortens the distance between

the C-2 and C-3 hydroxyls thus making the ring closure easier. Under longer reaction conditions this acetal leads to the formation of the 2,4-monoacetal. The mechanism of this conversion was found to be dependent on the reaction conditions. G.l.c. studies suggested that the 2,3-monoacetal of D-glucitol first hydrolysed to polyol and then re-reacted to form the 2,4-monoacetal in the aqueous medium, but under non-aqueous conditions, using dimethylformamide containing hydrogen chloride, the 2,3-acetal rearranged to the 2,4-monoacetal.[61]

A dimethylene acetal of unknown structure obtained directly from 1-deoxy-D-glucitol has been reported.[71] Two diastereoisomeric 2,4:5,6-di-O-benzylidene-3-O-methyl-1-deoxy-D-glucitols were synthesised by the lithium aluminium hydride reduction of the 1-O-tosyl derivatives of the stereoisomeric 2,4:5,6-di-O-benzylidene-3-O-methyl-D-glucitols.[65]

The diacetals obtained by direct acetalisation of D-glucitol usually have the 1,3:2,4-structure,[3] however in the case of the 1-deoxy derivative, this structure is not possible, but a diacetal with a structure of 2,4:5,6-, may be expected to be preferred. This is only true if 1-deoxy-D-glucitol behaves comparatively to D-glucitol.

ii) Results and Discussion

1-Deoxy-D-glucitol in fact afforded the structure 2,4:5,6- with n-butyraldehyde although the yield was not as high as expected. In all stages of the reaction, products consisted of a complex mixture of structural and stereoisomers as shown by g.l.c and n.m.r spectroscopy.

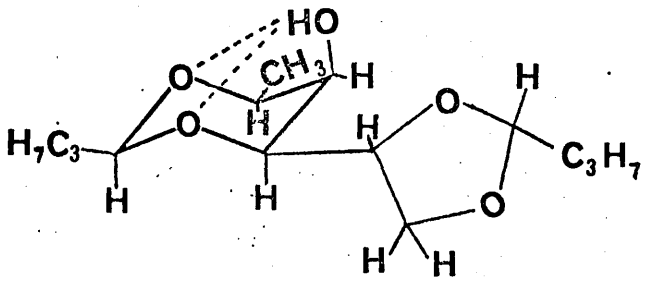


Fig. V-2

After two days, 2,4:5,6-diacetal which moved fastest on t.l.c. plate in benzene-methanol (9:1; v/v) was present in highest yield and this was the only acetal isolated in workable amounts (Fig.V-2). Although another crystalline product was obtained in extremely small yield, with elemental analysis for a dibutylidene-1-deoxy-hexitol, a mixture was indicated by n.m.r. spectroscopy.

The 2,4:5,6-diacetal was isolated by fractionation of the reaction mixture on neutral alumina, eluting with diethyl ether. The n.m.r. spectrum showed this product to be a mixture of stereoisomers which differed by the configuration of the acetal-proton on the five-membered ring (Section VIII, iii). A very small amount of pure cis isomer was also isolated. The structure of the diacetal was determined by chemical methods (details, Section V, iii).

The formation of several products from 1-deoxy-D-glucitol may be better understood, when the stereochemistry of some of its theoretically possible diacetals is considered. It is possible that the 2,4:3,5-diacetal of 1-deoxy-D-glucitol (Fig. V-3) is formed, due to the reasonable stability of the cis fused ring system with O-inside conformation. Although in this structure the $-CH_2OH$ group is axial to the 3,5-ring, the 2,4-ring has an equatorial methyl group which increases the stability of the molecule.

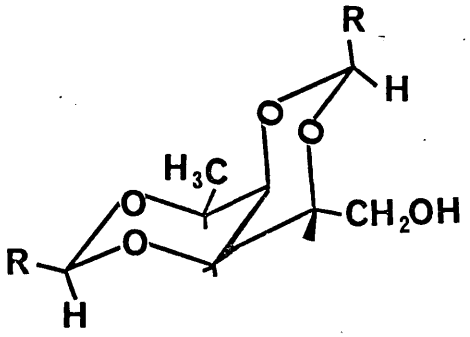


Fig. V-3

The other theoretically possible fused ring system with two six-membered rings is the 3,5:4,6-diacetal (Fig. V-4), however the formation of this structure is unlikely as it contains the less stable trans-fused system (Section I) as well as carrying the $(-CH(OH).CH_3)$ group axially to the 3,5-acetal ring. This destabilises the molecule.

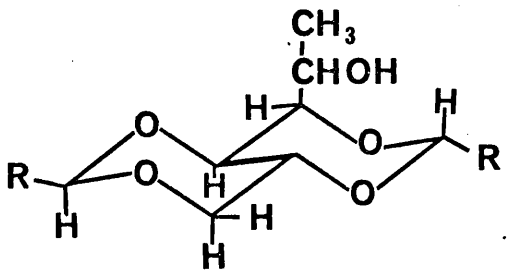


Fig. V-4

The other possible diacetals of 1-deoxy-D-glucitol can only have separated acetal rings, such as the 2,3:4,6- and 3,4:5,6-diacetals. The former is the more stable of the two since it contains a six-membered ring. The complexity of the actual reaction mixture suggests that some of these structures are probably formed during the reaction.

iii) Structural Analysis of 2,4:5,6-Di-O-butylidene-1-deoxy-D-glucitol

The diacetal was very soluble in all organic solvents, hence uncrystallisable, however its purity was assessed from its elemental analysis as well as g.l.c. and t.l.c. studies. On acetylation a syrupy monoacetate derivative was obtained. The diacetal (Fig. V-5,I) was also methylated to give the compound (II), which showed no hydroxyl absorption with i.r. spectroscopy. The acetal groups were removed from the compound (II) by hydrolysis with acidic resin IR-120(H^+). The monomethyl hexitol, thus obtained, consumed 2.13 mol periodate ion and released 1.10 mol of formaldehyde and 1.05 mol of formic acid, showing it to have the structure of 1-deoxy-3-O-methyl-D-glucitol (III).

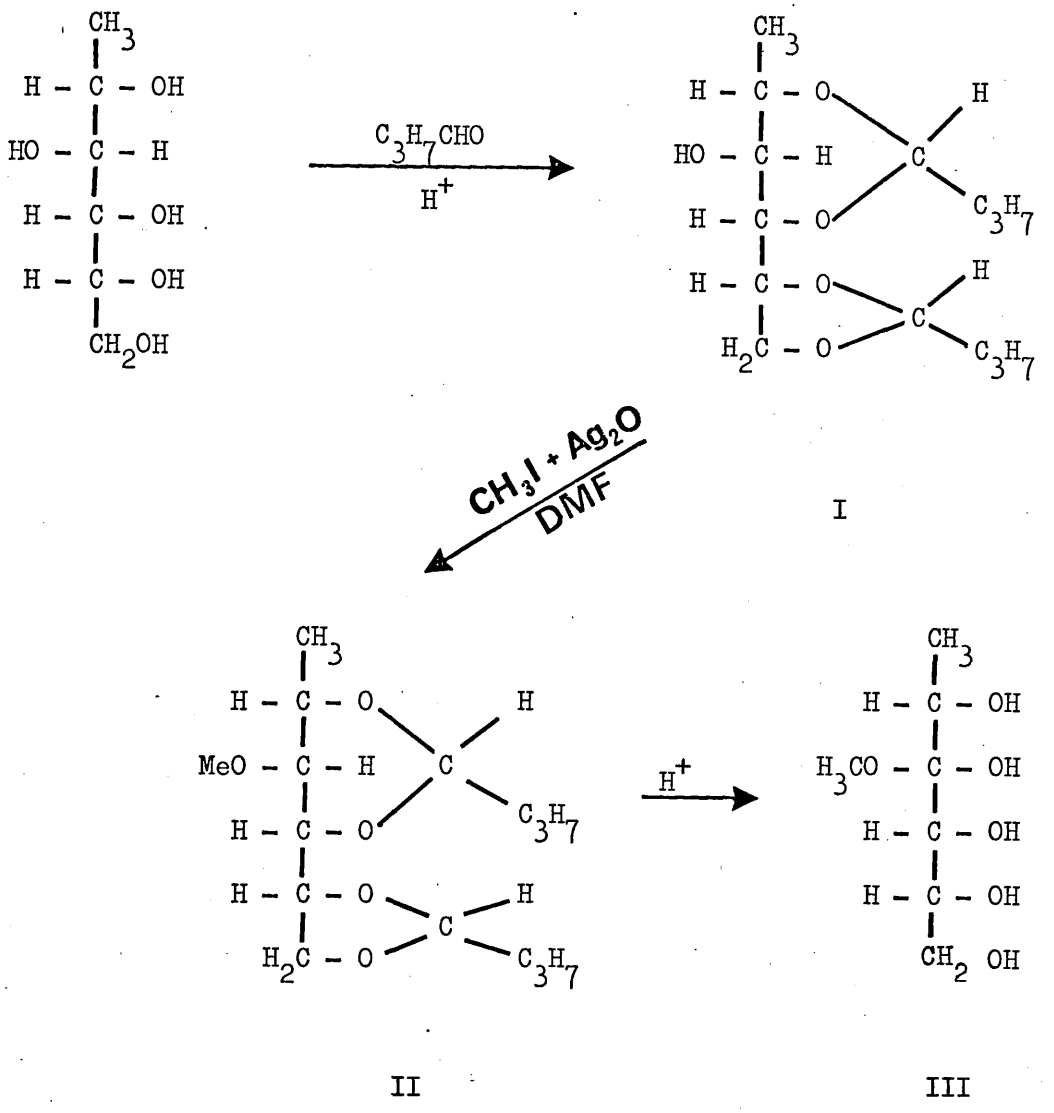


Fig. V-5

The diacetal (I), therefore must be the 2,4:5,6-di-O-butylidene-1-deoxy-D-glucitol. Further evidence for this structure was supplied by its n.m.r. spectrum, showing the presence of five and six-membered acetal rings, and its i.r. spectrum in carbon tetrachloride which showed a sharp absorption at 3580 cm^{-1} characteristic[72] of a secondary, intramolecularly hydrogen bonded hydroxyl group.

VI. Butylidene Acetals of 2-Deoxy-D-glucitol (2-deoxy-D-mannitol)

i) Introduction

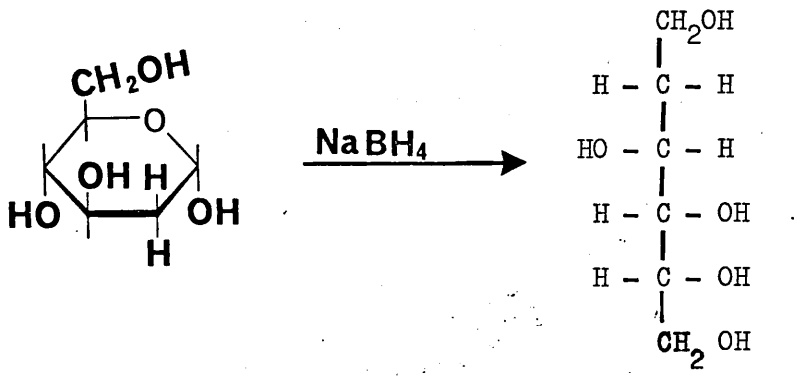
The known diacetals of 2-deoxy-D-glucitol consist of a dimethylene[73] and a di-(nitrobenzylidene)[74] derivative, both of unknown structure.

The only monoacetal obtained in a pure state is the 1,3-O-butylidene-2-deoxy-D-glucitol.[1] The presence of a 3,4-butylidene derivative in an unresolved mixture has also been reported.

2-Deoxy-D-glucitol most probably exists in the extended planar zig-zag conformation due to the absence of any 1,3-diaxial interactions.

ii) Results and Discussion

2-Deoxy-D-glucitol (Fig. VI-1, II) was obtained from commercially available 2-deoxy-D-glucose (I) by sodium borohydride reduction (Fig. VI-1).[2]



I II

Fig. VI-1

The reaction of 2-deoxy-D-glucitol with n-butyraldehyde under the thermodynamically controlled conditions, in the presence of hydrobromic acid gave the 1,3:4,6-diacetal which is favoured by the Barker and Bourne rules. This reaction was monitored by g.l.c. on Apiezon-K column. The chromatograms obtained at certain time intervals are shown in Figure VI-2. As the g.l.c. results suggested, the reaction was very fast and resulted in the formation of the 1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol as the main product. When the reaction was stopped after 2 h, the diacetal was isolated as a syrup which was then crystallised from light petroleum.

However, the g.l.c. analysis of the reaction (Fig. VI-2) suggested that, a considerable amount of another, obviously less stable product was formed at the early stages of the reaction. The reaction was stopped after $\frac{1}{2}$ min in order to obtain this kinetically controlled product, which was isolated as a syrupy mixture in good yield. T.l.c. in benzene-methanol (9:1, v/v), showed that the mixture contained 1,3:4,6-diacetal as well as the uncharacterised kinetically controlled acetal. The n.m.r. spectroscopy showed overlapping triplets at about τ4.95 suggesting the presence of five-membered acetal rings. The complexity of the acetal-proton region implied that the unidentified product was a mixture, most probably of the stereoisomeric forms.

Attempts were made to separate the kinetically controlled diacetals of 2-deoxy-D-glucitol on neutral and basic alumina and silica gel using several solvent systems as eluent. The resin Dowex-1 x 8 (OH^-) was also tried, with methanol-water as eluent, without success.

I – 2-Deoxy-D-glucitol
II – 1,3-O-Butylidene acetal
III – 3,4-O-Butylidene acetal
IV – 1,3:4,6-Di-O-butylidene acetal
V – Unknown acetal

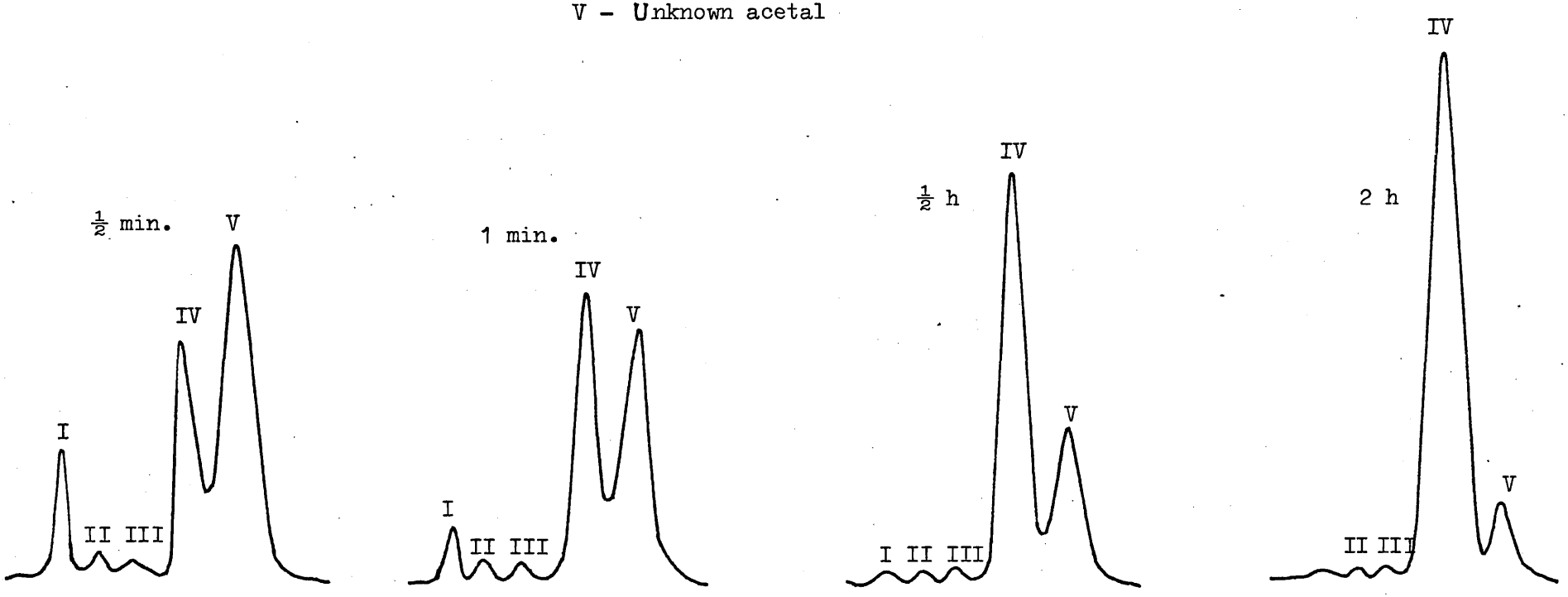


Fig. VI-2 The reaction of 2-deoxy-D-glucitol with n-butyraldehyde in conc. hydrobromic acid, monitored by g.l.c. (P.E. F-11; Apiezon K; temperature 180°).

The syrupy mixture of the diacetals was stored at -5°, after a separation attempt on a silica gel column. After several days, a partial crystallisation was observed and about a month later solidification was complete. The recrystallised solid gave the 1,3:4,6-diacetal in pure state. It was assumed that a trace of acid, possibly from the silica gel column or from the solvents used, catalysed the conversion of the unstable acetal to the stable 1,3:4,6-diacetal.

The reaction of 2-deoxy-D-glucitol with n-butyraldehyde proved to be very different from the similar reactions of D-glucitol and its 1-deoxy derivative. In 2-deoxy derivative the absence of the C-2 hydroxyl group eliminates the possibility of formation of the 2,4-acetal ring which is characteristic for D-glucitol, nor is it possible to obtain the 2,3-acetal ring which is also obtained from D-glucitol under kinetically controlled conditions.

It is clear from the results obtained that 2-deoxy-D-glucitol behaves as D-mannitol derivative rather than a derivative of D-glucitol towards acetalation. D-Mannitol also afforded the 1,3:4,6-dibutylideneacetal under thermodynamically controlled conditions together with some 1,3:2,5:4,6-triacetal, but direct formation of 1,3- and 4,6-mono or 1,3:4,6-diacetals from D-glucitol is not known.

iii) Structural Analysis of 1,3:4,6-Di-O-butylidene-2-deoxy-D-glucitol

The n.m.r. spectrum of the title acetal indicated the presence of two six-membered acetal rings, which limited the possible structures to the 1,3:4,6- and 3,5:4,6-. Theoretically the latter would be unstable as the trans-fused system (Fig. VI-3) contains the ($-CH_2-CH_2OH$) group axial to the 3,5-ring (analogous to 3,5:4,6-diacetal of 1-deoxy-D-glucitol, Fig. V-4).

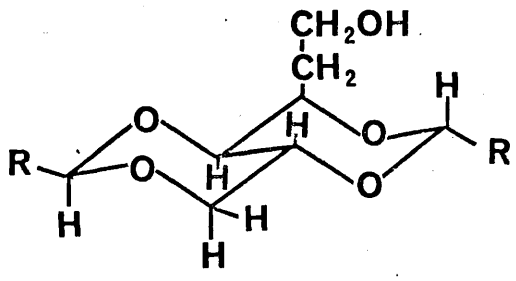
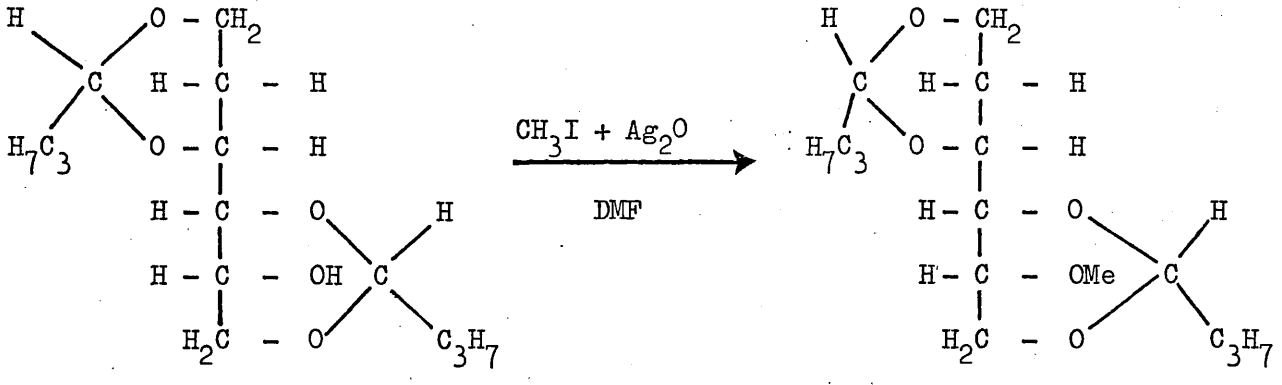
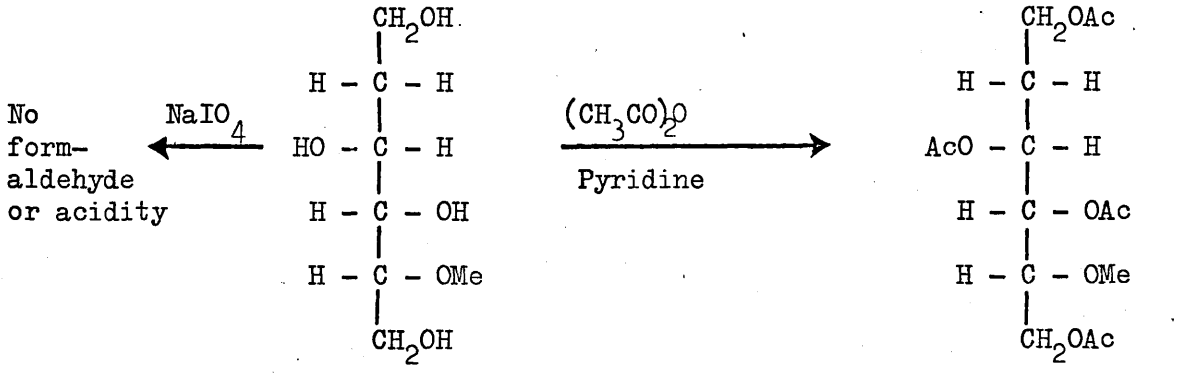


Fig. VI-3

The diacetal was methylated to give (II) which was obtained as a syrup and purified by vacuum distillation.



I II



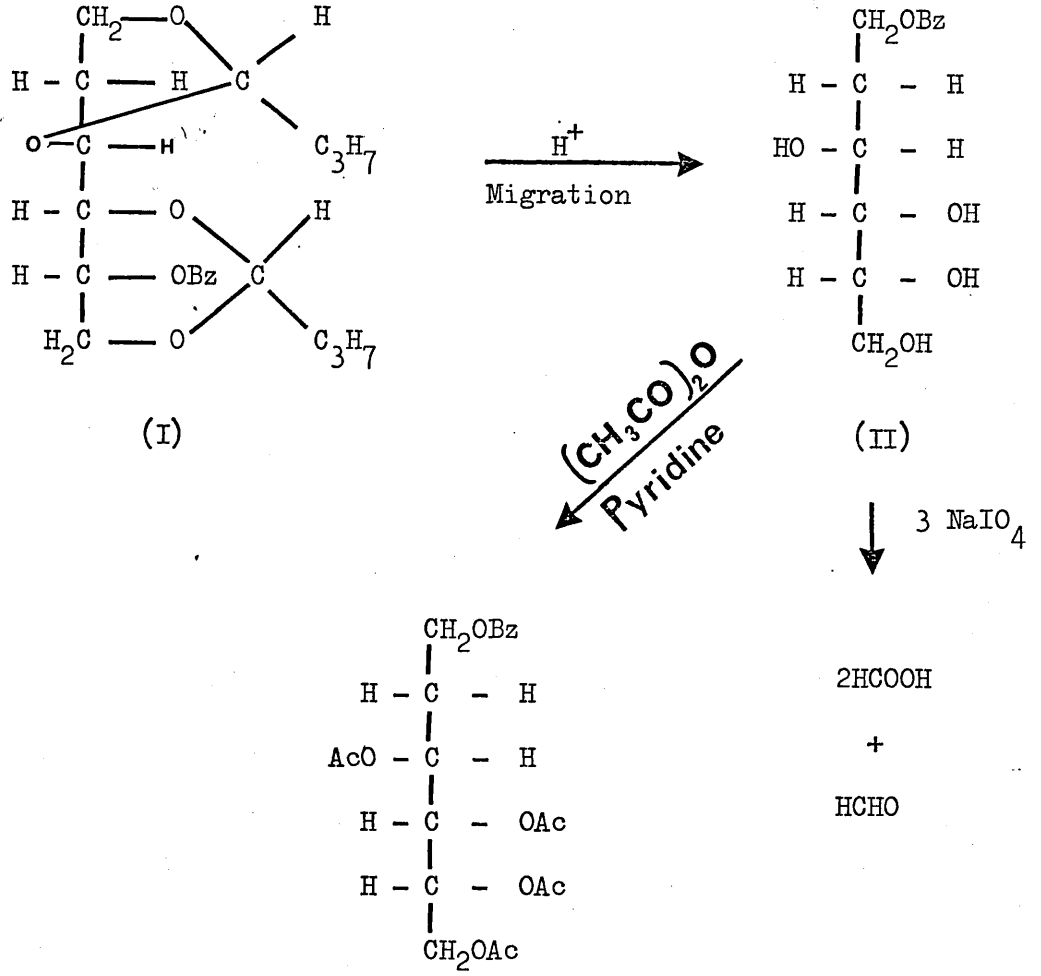
III IV

Fig. VI-4

The methyl ether of the acetal (II) was hydrolysed by refluxing it in the presence of acidic resin Amberlite IR-120(H^+). Thus a chromatographically pure, 2-deoxy-D-glucitol monomethyl ether was obtained. The periodate oxidation of this compound did not produce any formic acid and formaldehyde but it consumed 1.1 mol of periodate ion, proving the structure of this compound to be 2-deoxy-5-O-methyl-D-glucitol (III). The methyl ether (III) also gave a syrupy tetra-acetate derivative (IV), the mass spectrum of which will be discussed in a later section.

These results showed the presence of a free hydroxyl group on C-5 of the diacetal (I). Considering both chemical and spectroscopic evidence the most reasonable structure is 1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol.

The monobenzoate derivative of the 1,3:4,6-diacetal (Fig. VI-5, I) was also subjected to acid hydrolysis in order to find out if benzoyl migration took place and compare the results obtained from methylation and hydrolysis studies. Because of the possibility of benzoyl migration, hydrolysis could not be used in the structural analysis of the cyclic acetal. The acid hydrolysis of the benzoylated acetal (Fig. VI-5, I) afforded the crystalline monobenzoate derivative which was also characterised as its crystalline tetra-acetate derivative (III).



(I) (II) (III)

Fig. VI- 5

After periodate oxidation, the monobenzoate (II) produced 1.2 mol formaldehyde, eliminating the possibility of any substituent on C-6 and C-5, and 2.1 mol of formic acid thus showing the structure of this compound as 1-O-benzoyl-2-deoxy-D-glucitol.

VII The Synthesis of 4,6-O-Butylidene-D-galactose

The reactions of aldehydes with galactose usually afford the 4,6-monoacetals in good yield.[42, 73, 75] Synthesis of 4,6-O-butylidene-D-galactose was achieved using hydrobromic acid as catalyst in aqueous medium (Exp. 59). The product was obtained as a syrup and freeze-dried to a powder. The product contained mainly 4,6-monoacetal, although some unidentified acetals and galactose were also present. The galactose was removed by fractionation on a cellulose column eluting with ethyl methyl ketone saturated with water and the galactose free product was crystallised from dry acetone. The monoacetal was characterised as its triacetate derivative, the n.m.r. spectrum of which is discussed in Section VIII-ix. The 60 MHz spectrum of the free acetal clearly showed it to be an anomeric mixture (two anomeric doublets were observed), but acetylation in pyridine with acetic anhydride gave only the β-anomer. Same result was obtained from the acetylation of 4,6-O-butylidene-D-glucose which gave only the β-anomer. The impure 4,6-O-butylidene-D-galactose was reduced with sodium borohydride to give some 4,6-O-butylidene-D-galactitol in pure state. This acetal was not distinguishable from 1,3-butylidene-DL-galactitol by chromatography, and had the same m.p. and mixed m.p. 72 - 74°.

VIII Applications of N.m.r. Spectroscopy to Structural Investigations of Cyclic Acetals

i) Introduction

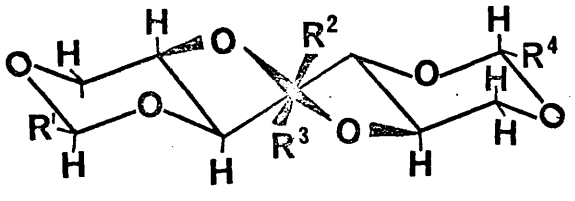
N.m.r. spectroscopy has proved to be one of the most useful techniques in structural studies of carbohydrate derivatives.[76,80] Many applications of this technique to structural problems confronted in the study of the cyclic acetal derivatives of carbohydrates,[76] as well as to simple diols[77] and polyols, have appeared in the literature. In 1963 R.U. Lemieux et al. were able to show that, 1,3:2,4-dimethylene-L-threitol existed in the O-inside conformation with the use of n.m.r. data.[78]

N.m.r. spectroscopy can be successfully applied to structural determinations, where the classical methods fail. For example, the mild acid hydrolysis methods used in the structural investigations of fully substituted acetal derivatives of some polyols, are not always successful due to the possibility of acetal ring migration. However, the structures of 1,3:2,4:5,6-tri-O-benzylidenegalactitols were successfully determined by interpretation of their n.m.r. spectra.[32]

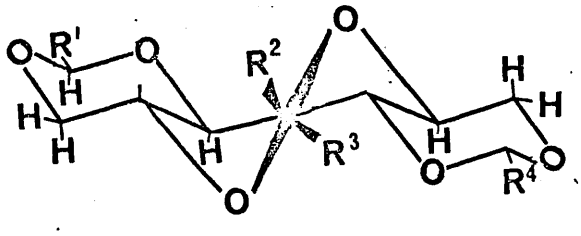
Further advantages of the technique were illustrated when n.m.r. spectra of a wide range of cyclic acetals were interpreted to show that assignments of the absolute configurations on the acetal-carbon atoms, as well as determinations of the ring sizes were possible. For example, several 2-phenyl-1,3-dioxane derivatives with equatorial substituents at positions 4 and 6 showed a single acetal-proton signal in the range of τ 4.82 - 5.02.[79] The acetal signals of several 4-alkyl-2-phenyl 1,3-dioxolane derivatives were in the ranges τ 4.62 - 4.67 and

τ 4.46 - 4.52 and these were assigned to the cis and trans isomers respectively.[79] Using these n.m.r. data the authors were able to assign the configurations at the acetal-carbon atoms of many benzylidene acetals of more complex carbohydrates.[32, 79]

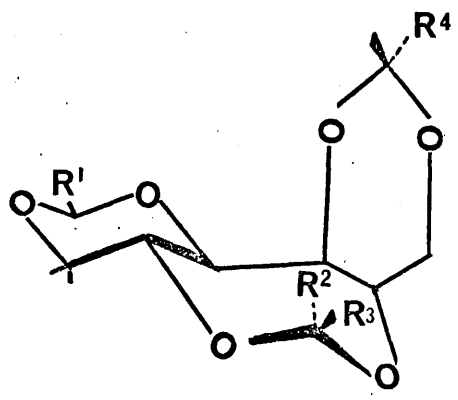
More recently n.m.r. studies on seven-membered acetals showed that the 2,5-methylene protons of 1,3:2,5:4,6-tri-O-methylene-D-mannitol and 1,3:4,6-di-O-benzylidene-2,5-O-methylene-D-mannitol were isochronous (equivalent nuclei which exhibit the same chemical shift).[12] This suggested that the acetals were either undergoing a fast ring inversion process between two degenerate chair forms (Fig. VIII-1) or that they existed in the conformationally stable twist chair conformation (Fig. VIII-1).



Twist boat



Twist chair



Chair

Fig. V III-1

Similar arguments and n.m.r. data were used to show that 1,3:2,5:4,6-tri-O-ethylidene-D-mannitol and 2,5-O-ethylidene-1,3:4,6-di-O-methylene-D-mannitol existed in the stable twist chair form (Fig. VIII-1), but in some bicyclic derivatives where 1,3-dioxolane rings are trans fused to 1,3-dioxepane rings at C-3 and C-4, the seven-membered ring may assume a twist-boat conformation.[81, 82]

Investigations on conformational equilibrium in 1,3-dioxane derivatives were also made using n.m.r. spectroscopy. For example, the n.m.r. spectrum of 5-methyl-5-isobutyl-1,3-dioxane (100 MHz in CS_2) at 86° (where a slow equilibration process occurs) gave two separate AB systems for the protons H_2, H_4 and H_6, showing the existence of two conformations at equilibrium (Fig. VIII-2).[83]

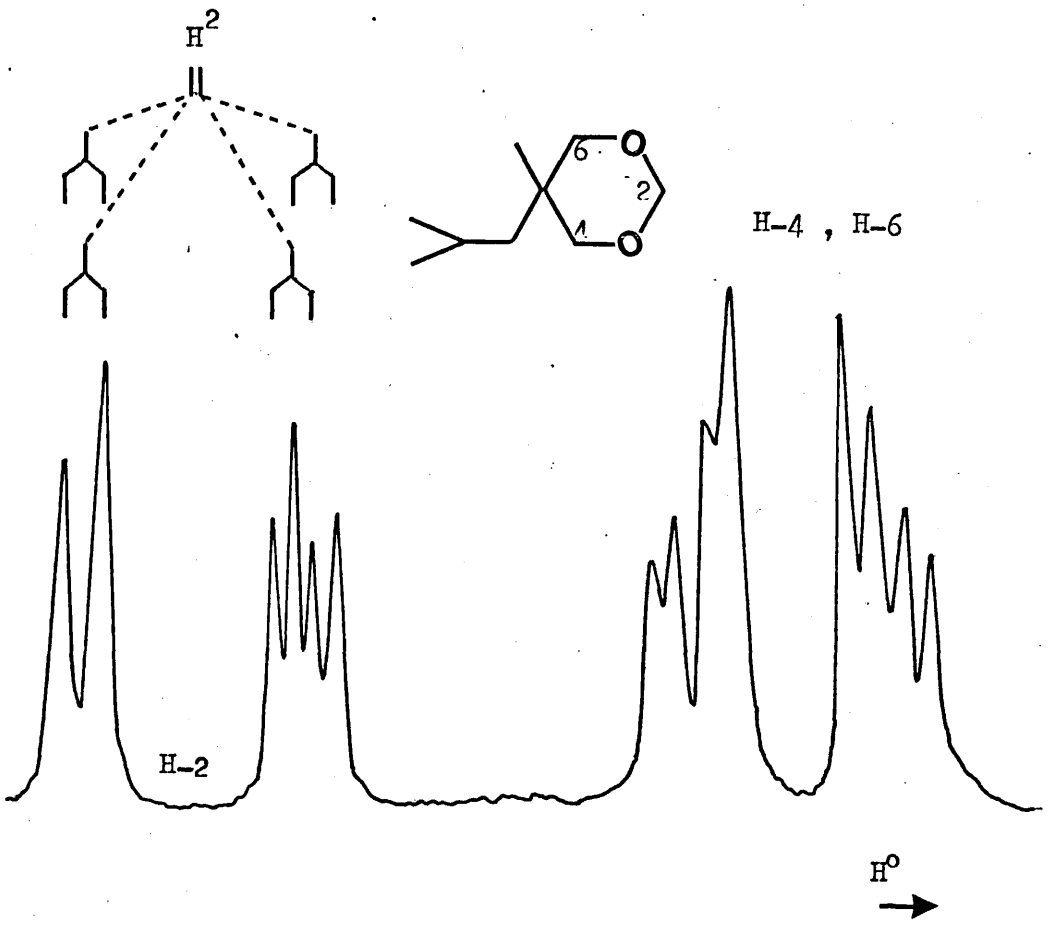


Fig. VIII-2

The application of n.m.r. spectroscopy in the cyclic acetal field remained limited because of the complex appearance of the spectra. In recent years, the availability of high field n.m.r. instruments, made it possible to derive first order or approximately first order information from complex molecules.[84] In this thesis it is shown that using high field n.m.r. spectroscopy, it is possible to obtain complete structural information about some cyclic acetal derivatives of hexitols. However, due to insufficient data in the literature on this subject, the structural assignments are made with caution in the cases where chemical evidence is not very strong. In many cases both 100 M Hz

and 220 MHz spectra are necessary for complete interpretation. The double resonance technique is also used to assign the signals. The spectra obtained during this work will be discussed after some aspects of n.m.r. spectroscopy are considered.

ii) Aspects of High Resolution Proton Magnetic Resonance Spectroscopy[85, 86, 87]

The basic principle of nuclear magnetic resonance spectroscopy is that the nuclei of the same species, protons in this case, but in different chemical environments absorb energy at different radio frequencies, when placed in a given magnetic field, due to the differing screening effects of the electrons. The separation between the absorption lines is called the chemical shift, when expressed in dimensionless field independent units. The absolute measurements of the screening constant at a nucleus is not possible; therefore it is necessary to compare the absorption line positions with the position of a resonance in a suitable reference compound. Tetramethyl silane is usually used as a reference compound since it gives a single, sharp n.m.r. signal and at a position where not many organic molecules give n.m.r. signals. However, tetramethyl silane (T.M.S.) is not soluble in water; therefore for the measurements in D_2O, 2,2-dimethyl-2-silapentane-5-sulphonate is usually used.

Chemical shifts are normally defined in the dimensionless parameter δ (p.p.m.) according to the equation (a).

$$\delta = \frac{\nu_{sample} - \nu_{ref.}}{\nu_{ref.}} \cdot 10^6 \qquad (a)$$

Most of the p.m.r. signals of organic compounds fall between δ 0 and δ 10. Another scale, often used, is the τ scale. The relation between τ and δ is given by $\tau = 10 - \delta$. In this thesis usually δ scale is used, but the τ scale is used for the acetal-proton signals for reasons of existing familiarity in the associations of ring sizes with τ values.

Spin-spin coupling.- Although the low resolution n.m.r. spectrum of ethanol gives three n.m.r. signals as shown in figure VIII-3, under high resolution fine structure can be observed on each line (Fig. VIII-3). The n.m.r. signals of methylene and methyl protons thus give a quartet and triplet respectively. Further splittings may be observed on the hydroxyl and methylene resonances when the exchange of the hydroxyl proton is sufficiently suppressed.[85]

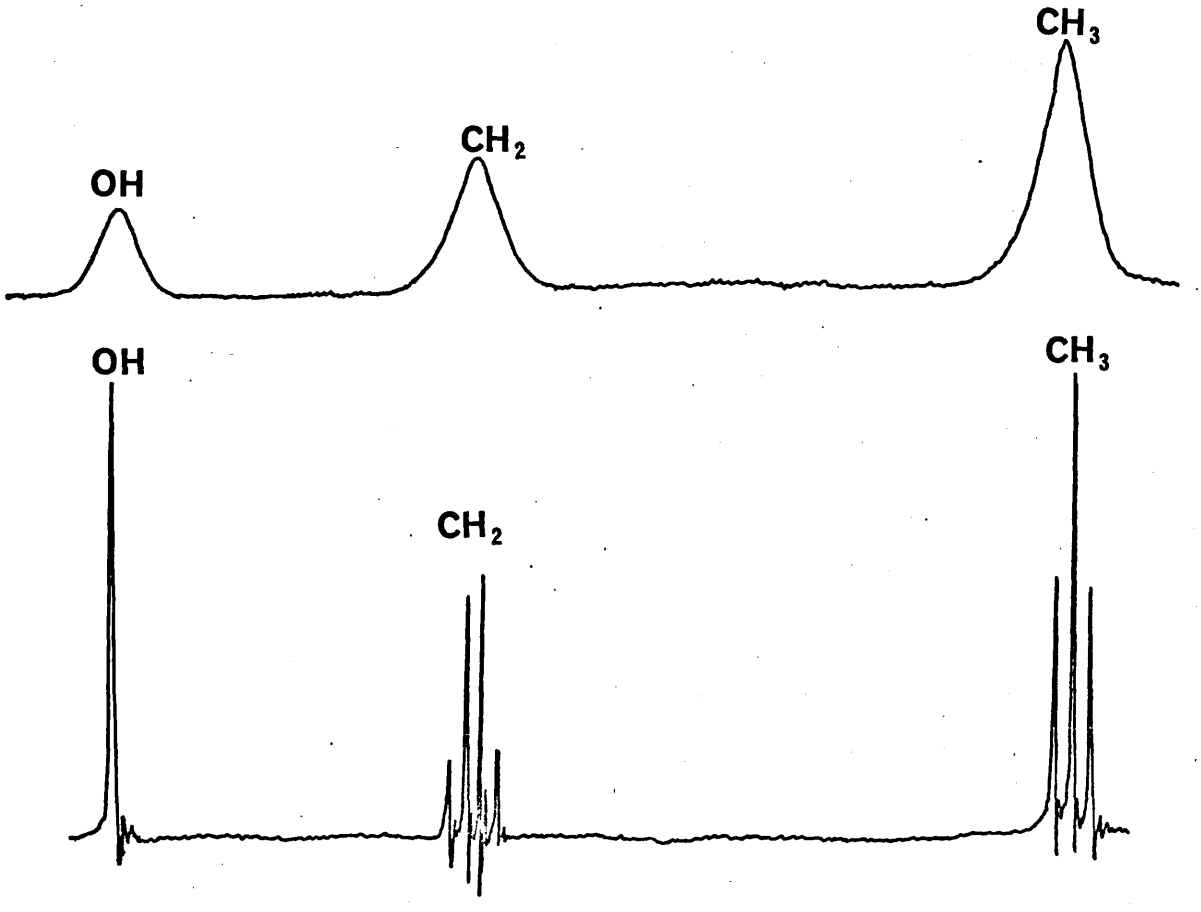


Fig.VIII-3

This fine structure is caused by so-called spin-spin interactions between different nuclei. This magnetic coupling is independent of the applied field and transmitted by electrons through the chemical bonds. In so-called first order spectra the magnitude of the coupling constant J (measured in Hz) may be deduced directly from splittings in the observed multiplets.

First order analysis can be applied under the following conditions.[86]

a) The difference between the chemical shifts of the two coupled protons (in Hz) must be more than six times the coupling constant.

b) Each proton in one group must be coupled equally to each and every proton in the second group.

In a first order spectrum the following characteristics are observed:

a) There is no manifestation of coupling between magnetically equivalent protons.

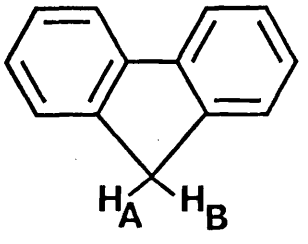
b) The multiplicity of a proton or a group of equivalent protons is dependent on the number of coupled protons, and the number of observed peaks is equal to the number of coupled protons plus one.

c) The peaks are symmetrical about the position of the line that would be observed in the absence of coupling; the separation within the multiplet is equal to J and the intensity distribution is binomial i.e. 1:1, 1:2:1, 1:3:3:1, etc.

Geminal coupling.- Spin-spin interactions of the geminal protons are called "geminal couplings". Usually the magnitude of this type of

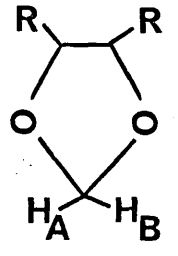
coupling is quite large (12 to 18 Hz), and usually negative in sign.[85]

The magnitude of the geminal coupling is dependent on the nature and electronegativity of the substituents on the neighbouring carbon atoms. For example in fluorene (Fig. VIII-4, I), a large negative value for $\underline{J}_{AB}$ was observed whereas in (II) the geminal coupling is only (0 ∓ 2 Hz). Thus the inductive effect of an electron withdrawing group usually causes a positive increment.[85, 88]



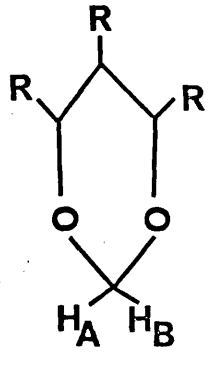
$\underline{J}_{AB}$ -22.3 Hz

I



$\underline{J}_{AB}$ = 0 ∓ 2 Hz

II

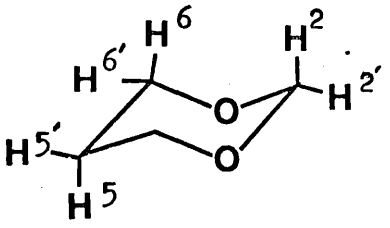


ca. $\underline{J}_{AB}$ - 6 Hz

III

Fig. VIII-4

The values of geminal coupling decrease down to ca.- 6 Hz as the angle between the geminal protons increases e.g. as in III compared to II. In 1,3-dioxane derivatives, the magnitude of the geminal coupling constants are usually in the range of -6 to -14 Hz. Figure VIII-5 shows some $J_{geminal}$ values in 1,3-dioxane.[85]



$J_{H^2H^{2'}}$	- 6.0 to - 6.2
$J_{H^6H^{6'}}$	-10.9 to -11.5
$J_{H^5H^{5'}}$	-12.6 to -13.5

Fig. VIII-5

Vicinal coupling.- The spin-spin interactions between the protons on the adjacent carbon atoms are called "vicinal coupling". An extremely useful rule was established by Karplus for predicting the dependence of vicinal coupling on the dihedral angle (ϕ) as given by

$$J = J^0 \cos^2\phi - C \quad \text{for } 0^\circ \leq \phi \leq 90^\circ$$

$$J = J^{180} \cos^2\phi - C \text{ for } 90^\circ \leq \phi \leq 180^\circ$$

In these equations, J^0, J^{180}, and C are constants. However the vicinal coupling constants are effected by factors other than the dihedral angle such as the electronegativities and orientations of substituents, hybridisation of the carbon atom, bond angles and bond lengths. These must be taken into account in applications of the

Karplus equation. The angular relationship of the vicinal coupling constant is shown in figure VIII-6.

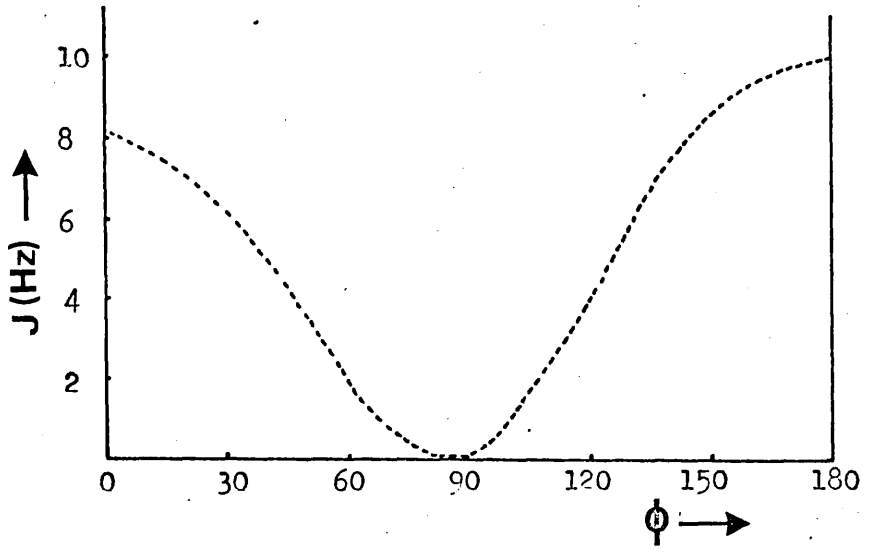


Fig. VIII-6

Long range coupling.- Spin-spin couplings, which sometimes occur over four bonds are called long range coupling. Usually protons in a planar zig-zag conformation separated by four bonds along a W path couple considerably.[85,88] The protons may be separated by hetero atoms or double bonds since this type of coupling is independent of the nature or hybridisation of the intervening atoms. The magnitude of the coupling is usually in the range of 0 - 2.5 Hz. The long range coupling can give valuable information in structural determinations. For example, the n.m.r. spectrum of 2,5-isopropylidene-1,3:4,6-di-O-methylene-D-mannitol showed broadening of the equatorial protons of O-methylene groups in the 1,3-dioxane rings, which is caused by long range coupling between the equatorial acetal-protons and equatorial geminal protons

suggesting that these protons are positioned on a W path.[81]

The presence or absence of long range coupling may also be used in eliminating one or more of the possible structures proposed for a compound, for example one of the conformations proposed for the acetal, methyl 2,3-O-methyl-4,6-O-benzylidene-D-glucopyranoside in which the phenyl group occupies the axial position on the acetal-carbon (Fig. I-20, page 15), should show a broadening of the acetal-proton signal due to W coupling with the equatorial proton on C-6.

iii) The General Characteristics of the N.m.r. Spectra of Acetals

The n.m.r. spectra of butylidene acetals are easily recognised by their low field acetal-proton triplets, which usually appear in the range τ 4.5 - 5.6, and the high field propyl group signals. In 100 MHz spectra the propyl groups give two separate group of signals, a multiplet for the $CH_2 \cdot CH_2$ group in the region δ 1-2, and a non-symmetrical triplet for the CH_3 group near δ 1. In the 220 MHz spectrum the (CH_2) multiplet is separated into two groups, the low field one being assigned to the (CH_2) nearest the ring oxygens. The methyl group of the propyl side chain appears as a symmetrical triplet which is now part of a first order spectrum.

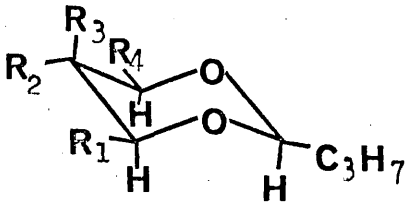
The chemical shifts of the acetal-proton triplets are dependent on the ring sizes, thus providing a means for distinguishing the five and six-membered butylidene acetal rings.[29] The five-membered ring acetal-protons usually appear at or below τ 5.10 and the six-membered butylidene acetal-proton triplets appear at or above τ 5.40.

The chemical shifts of acetal-proton signals of several six-membered butylidene acetals are shown in Table VIII-1. It is seen that the substituents on the 1,3-dioxane ring influence the chemical shifts only slightly. The available data is not sufficient to make generalised structural assignments possible, however it is reasonably safe to use the chemical shifts of butylidene acetal-proton triplets in determining the ring sizes of the acetals.

The acetal-proton signal of 1,3:4,6-di-O-butylidenegalactitol (contains cis-1,3-dioxane ring) at τ 5.38 resonates at lower field than the acetal-proton of 1,3:4,6-dibutylidene-D-mannitol at τ 5.51 (contains trans-1,3-dioxane ring). This is in agreement with the observation that the benzyl proton signal of cis-5-hydroxy-2-phenyl-1,3-dioxane (τ 4.90) appears at lower field than the trans isomer (τ 5.02).

Separate acetal-proton triplets are usually observed for the stereoisomers, with differing configuration on the acetal-carbon atoms of the 1,3-dioxolane derivatives. Configurational assignments are only possible in the cases where both the triplets are observed.

The 100 MHz spectrum of 2,3-O-butylidene-1-deoxy-D-galactitol (Fig. VIII-8) in D_2O for example, showed two overlapping acetal-proton triplets at τ 4.96 and τ 4.85, indicating a stereoisomeric mixture. Two configurational isomers are possible (Fig. VIII-7).



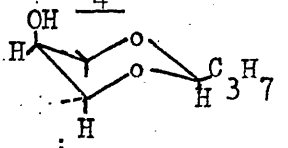
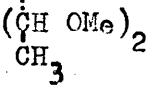
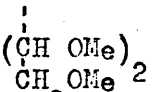
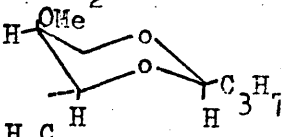
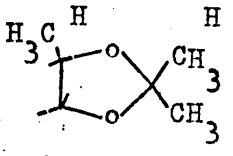
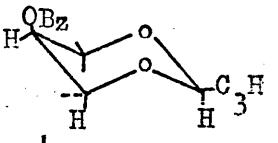
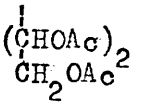
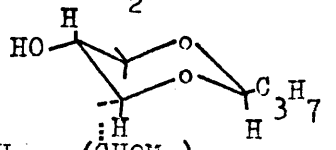
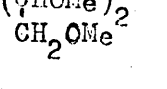
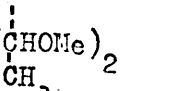
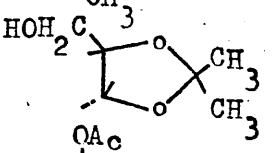
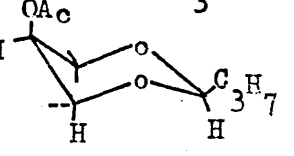
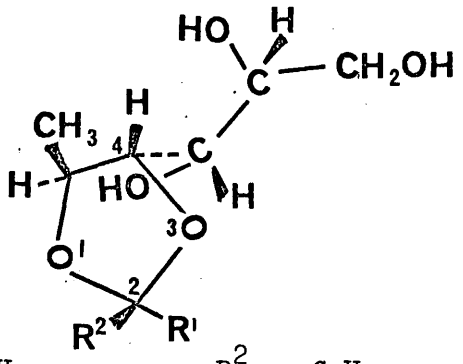
	τ	R_1	R_2	R_3	R_4
1,3:4,6-Di-O-butylidene galactitol	5.37	H	H	OH	
4,6-O-Butylidene-1-deoxy-2,3,5-tri-O-methyl-D-galactitol	5.38	H	H	OMe	
1,3-O-Butylidene-2,3,5,6-tetra-O-methylgalactitol	5.41	H	H	OMe	
1,3:4,6-Di-O-butylidene-2,5-di-O-methylgalactitol	5.42	H	H	OMe	
4,6-O-Butylidene-1-deoxy-2,3-isopropylidenegalactitol	5.43	H	H	OH	
1,3:4,6-Di-O-butylidene-2,4-di-O-benzoylgalactitol	5.54	H	H	$OCOC_6H_5$	
4,6-O-Butylidene-1,2,3,5-tetra-O-acetyl-D-glucitol	5.51	H	$OCOCH_3$	H	
1,3:4,6-Di-O-butylidene-D-mannitol	5.51	H	OH	H	
4,6-O-Butylidene-1,2,3,5-tetra-O-acetylgalactitol	5.49	H	H	$OCOCH_3$	
4,6-O-Butylidene-1-deoxy-2,3,5-tri-O-acetyl-D-galactitol	5.49	H	H	$OCOCH_3$	
4,6-O-Butylidene-2,3-isopropylidene-galactitol	5.49	H	H	OH	
1,3:4,6-Di-O-butylidene-2,5-di-O-acetylgalactitol	5.48	H	H	$OCOCH_3$	

Table VIII-1



(I) $R^1 = H$ $R^2 = -C_3H_7$

(II) $R^1 = -C_3H_7$ $R^2 = H$

Fig. VIII-7

The acetal-proton in isomer (I) is expected to be more deshielded since it is on the same side of the 1,3-dioxolane ring as the 4-substituent. Deshielding arises from the expansion of the electron clouds of the acetal-proton and the close proximity of the 4-substituent. In isomer (II), deshielding of the acetal-proton is also expected because of the effect of the methyl group which is now cis to the acetal-proton however the effect of this group is less than that of the larger 4-substituent. The lower field triplet was therefore assigned to isomer (I).

The signal of the methyl groups (deoxy) appears at high field as doublets in the spectra of the acetals of 1-deoxy-hexitols. The spectrum of 2,3-O-butylidene-1-deoxy-D-galactitol (Fig. VIII-8) showed two partially overlapping doublets at δ 1.36 and δ 1.43. The low field doublet was assigned to the 5-methyl group of isomer (I) which is deshielded by the cis n-propyl group.

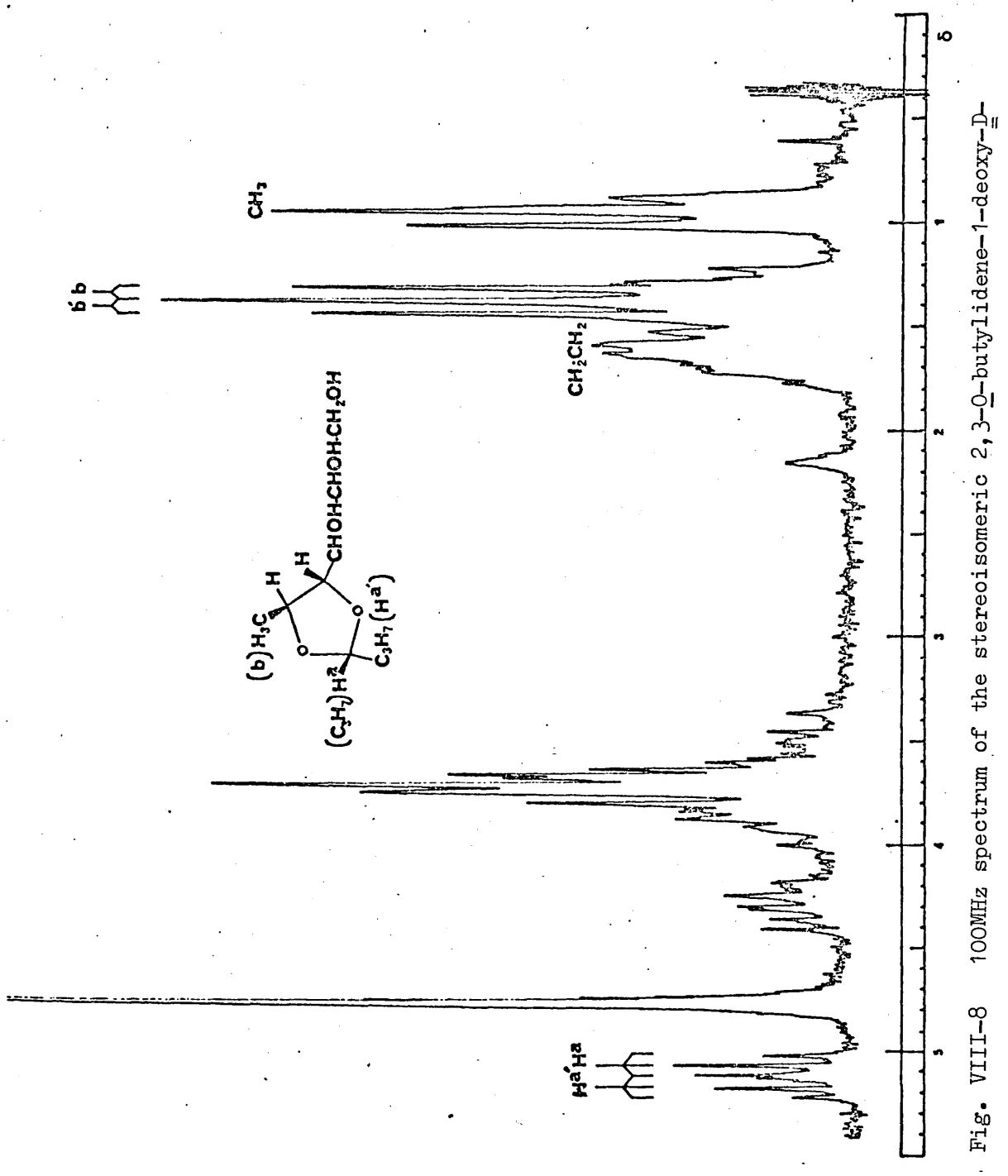


Fig. VIII-8 100MHz spectrum of the stereoisomeric 2,3-O-butylidene-1-deoxy-D-galactitol in D_2O.

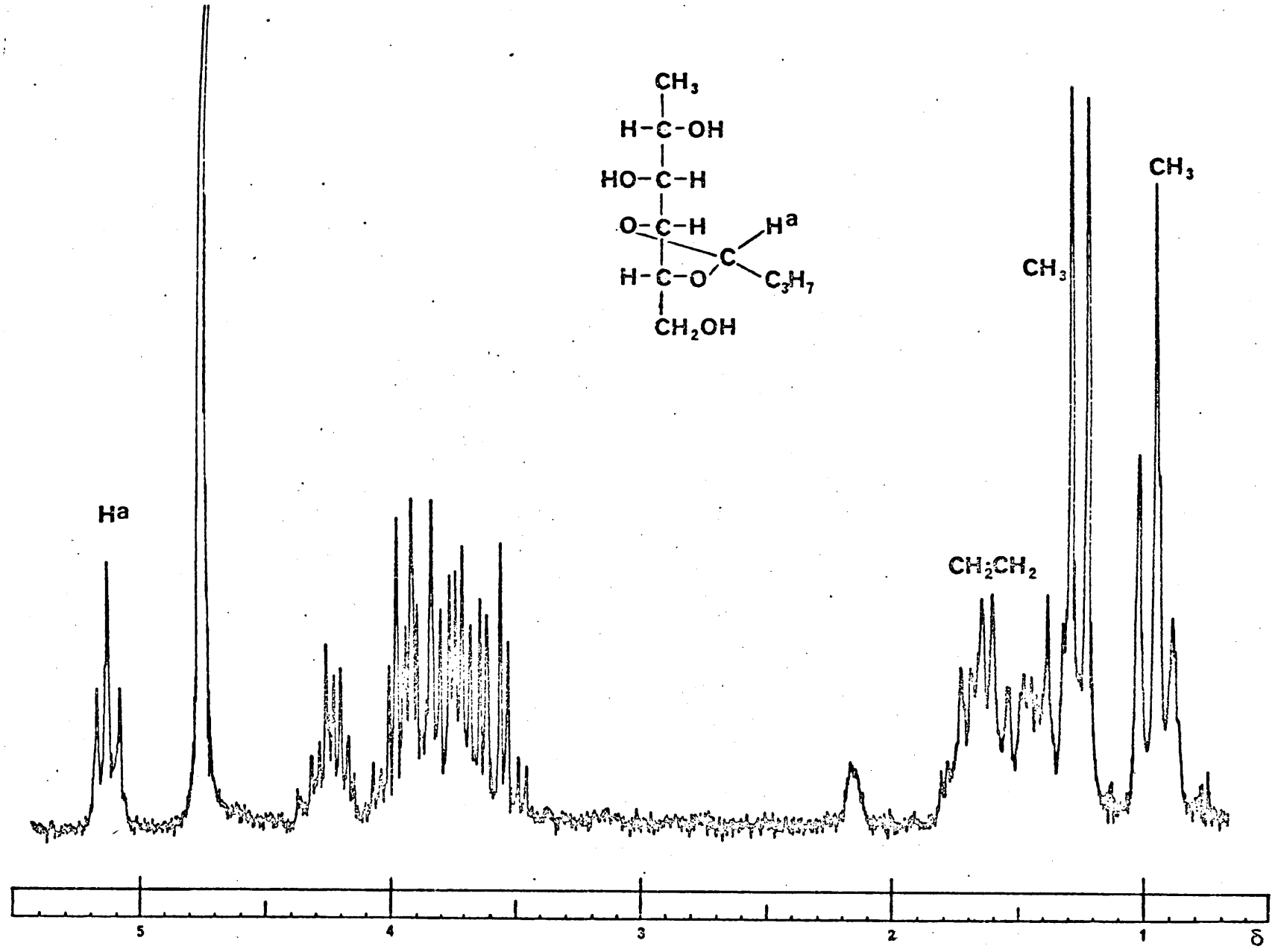


Fig. VIII-9 100 MHz spectrum of 4,5-O-butylidene-1-deoxy-D-galactitol (D_2O).

In the spectrum of 4,5-O-butylidene-1-deoxy-D-galactitol (Fig. VIII-9) only one acetal-proton was observed at τ 4.89, therefore this product was assumed to be a pure stereoisomer, but it was not possible to assign the configuration on the acetal-carbon.

The configuration of the acetal-proton of 2,3-O-butylidene-DL-galactitol also could not be determined, since the n.m.r. spectrum of the fully methylated compound showed only one acetal-proton triplet at τ 4.95. Interconversion of configurational isomers is not likely during methylation, therefore the product is either the thermodynamically preferred one or the acetal-proton signals of both stereoisomers are superimposed.

The 100 MHz spectrum of 2,4:5,6-di-O-butylidene-3-O-methyl-D-glucitol shows a triplet at τ 5.42 for the 1,3-dioxane ring acetal-proton (Fig. VIII-10) and two overlapping triplets at τ 5.11 and τ 5.04 for the five-membered ring acetal-proton, suggesting the presence of stereoisomers only for the 5,6-acetal ring. The low field triplet at τ 5.04 was assigned to the trans isomer (Fig. VIII-11,II) and the triplet at τ 5.11 to the cis isomer (Fig. VIII-11,I); as in the former case, the acetal-proton is deshielded by the large substituent (2,4-ring), on the same side.

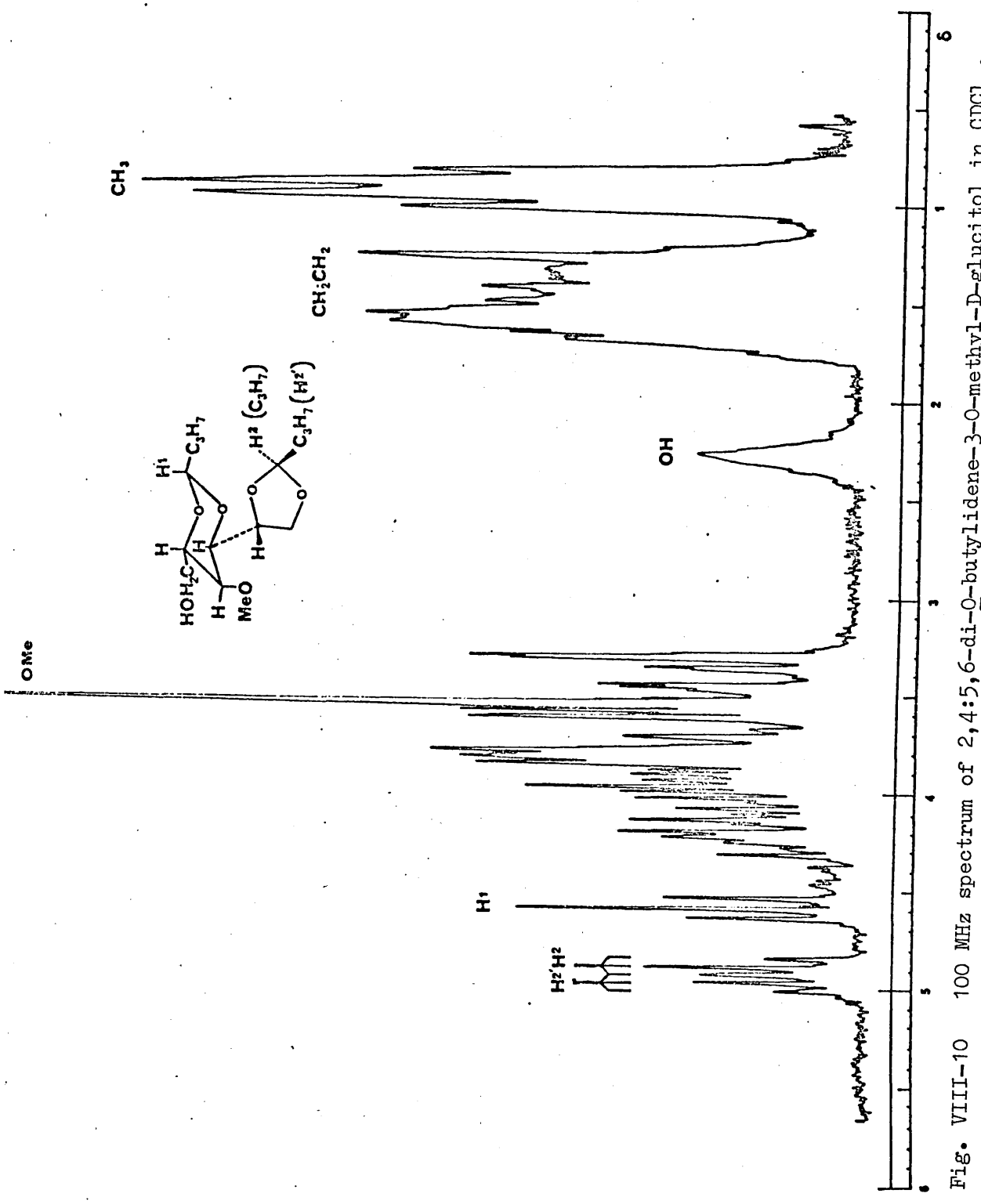
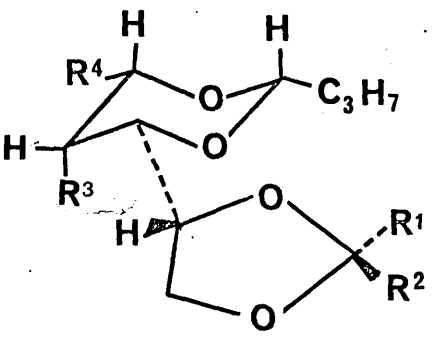


Fig. VIII-10 100 MHz spectrum of 2,4:5,6-di-O-butylidene-3-O-methyl-D-glucitol in $CDCl_3$.



(I)	$R^1 = C_3H_7$;	$R^2 = H$;	$R^3 = OMe$;	$R^4 = CH_2OH$
(II)	$R^1 = H$;	$R^2 = C_3H_7$;	$R^3 = OMe$;	$R^4 = CH_2OH$
(III)	$R^1 = C_3H_7$;	$R^2 = H$;	$R^3 = OH$;	$R^4 = CH_3$
(IV)	$R^1 = H$;	$R^2 = C_3H_7$;	$R^3 = OH$;	$R^4 = CH_3$
(V)	$R^1 = C_3H_7$;	$R^2 = H$;	$R^3 = OMe$;	$R^4 = CH_3$
(VI)	$R^1 = H$;	$R^2 = C_3H_7$;	$R^3 = OMe$;	$R^4 = CH_3$
(VII)	$R^1 = C_3H_7$;	$R^2 = H$;	$R^3 = OMe$;	$R^4 = CH_2OMe$
(VIII)	$R^1 = H$;	$R^2 = C_3H_7$;	$R^3 = OMe$;	$R^4 = CH_2OMe$

Fig. VIII-11

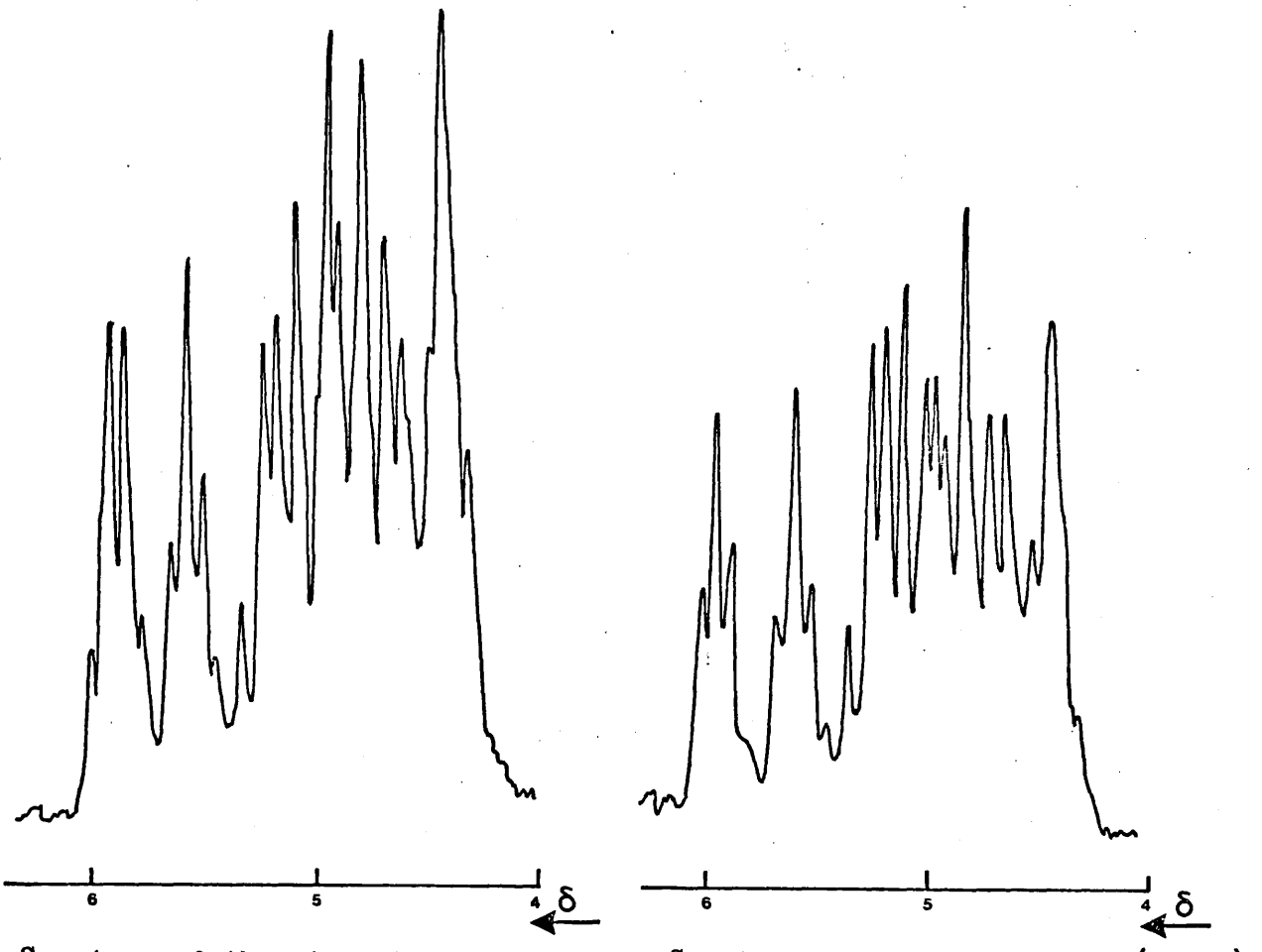
Similar assignments were made for the other stereoisomeric 2,4:5,6-butylidene acetals of D-glucitol derivatives (Table VIII-2) from their 100 MHz spectra.

	Compound	2,4-ring	5,6-ring	
		(τ)	cis (τ)	trans (τ)
Fig. VIII-11	I	5.42	5.11	
"	II	5.42		5.04
"	III*	5.40	5.12	
"	IV*	5.40		5.05
"	V	5.47	5.11	
"	VI	5.47		5.03
"	VII	5.43	5.11	
"	VIII	5.43		5.06

* 60 MHz spectrum

Table VIII-2

All the above compounds were obtained as the mixtures of stereoisomers which could not be resolved. However, fractionation of 2,4:5,6-di-O-butylidene-1-deoxy-D-glucitol on alumina gave some pure trans isomer in extremely low yield. The 60 MHz spectrum (the low field part) of the pure isomer and the mixture is shown in figure VIII-12.



Spectrum of the stereoisomeric mixture.

Spectrum of the pure isomer (Trans).

Fig.VIII-12

The methoxyl group proton signals which appear as sharp singlets are easily detectable even in complex spectra.The spectrum of 1,3:4,6-dibutylidenegalactitol dimethyl ether showed a methoxyl signal at τ 6.57 (integrated for six protons).The fully methylated 1,3-monoacetal had methoxyl signals at τ 6.54,6.56(two methoxyl groups)and at τ 6.62. The tri-O-methyl-1,3-monoacetal had methoxyl signals at τ 6.50,6.51 and 6.54.The 2,3-monoacetal tetramethyl ether showed methoxyl signals at τ 6.50 6.52,6.60.and 6.61.The 2,4,5,6-tetra-O-methylgalactitol and 1,4,5,6-tetra-O-methylgalactitol gave methoxyl signals at τ 6.49,6.50,6.54,6.61 and at τ 6.50,6.51,6.60,6.61 respectively.These results are in agreement with the results of E.B.Rathbone et al.[89,90,91]

iv) Utilisation of the (-OH) Proton Signals in Structural Analysis

A coupling between a hydroxyl group proton and a proton on the same carbon can sometimes be observed in the n.m.r. spectra of certain hydroxy compounds, which may be used to obtain additional structural information.[92, 93] This type of coupling is not always observed due to the fast exchange rate of the labile hydroxyl proton. Normally at room temperature the rate of exchange of hydroxy proton is considerably faster than the n.m.r. time scale, unless this process is slowed down by other effects.[88] Hydrogen bonding may be one of the reasons for slowing the exchange of the hydroxyl protons.[85] The $\underset{HO-C-H}{J}$ couplings are usually observed in solvents, such as DMSO which provide a strong intermolecular hydrogen bond with the hydroxyl groups as shown in figure VIII-13.[85, 92, 94]

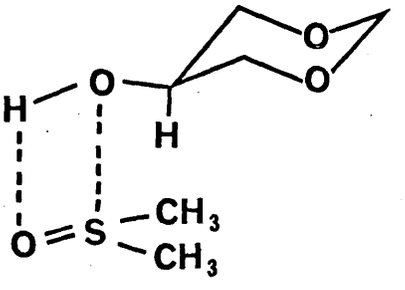


Fig. VIII-13

The chemical shifts of hydroxyl group protons are concentration and temperature dependent. In complex molecules, these properties may be useful in determination of the hydroxyl group signals.

Figure VIII-14 shows the 60 MHz n.m.r. spectra of 1,4:3,6-dianhydromannitol. Identification of the hydroxyl proton signal is difficult in the spectrum of the concentrated solution (I), but on dilution (II), a

doublet due to the hydroxyl group proton moves to higher field. The identification of the signal is confirmed by addition of a trace of trifluoroacetic acid (III), which increases the rate of exchange of the hydroxyl proton thus removing the observed splitting of the signal.

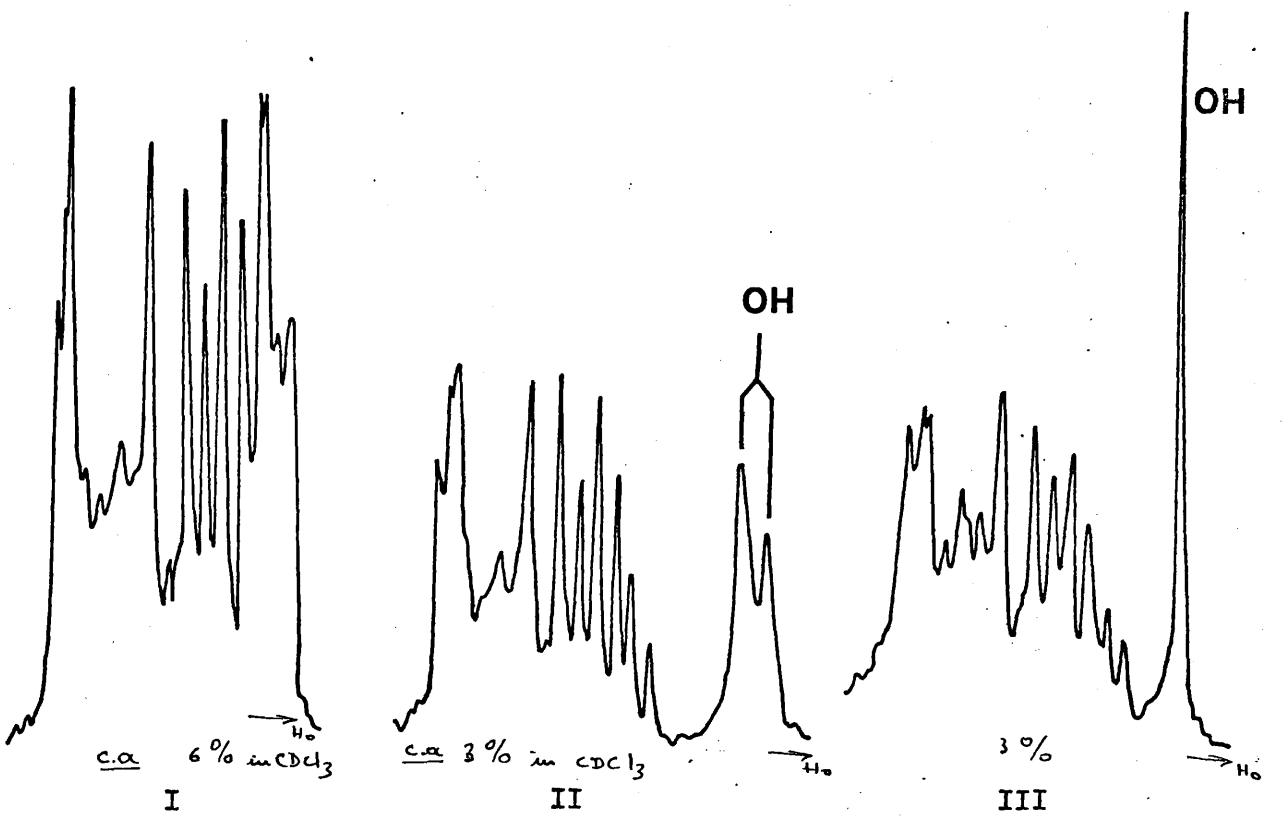


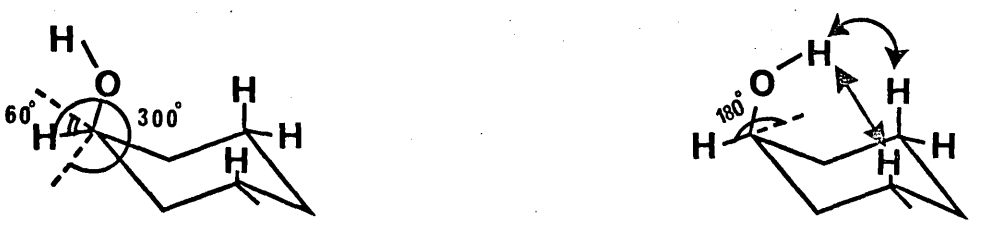
Fig. VIII-14

Experimental difficulties are encountered in observation of the $\underset{HO-C-H}{\underline{J}}$ couplings in cases where it is not possible to obtain the organic compounds in sufficiently pure state. Hence it was not possible to observe any $\underset{HO-C-H}{\underline{J}}$ couplings in any of the syrupy acetals obtained.

The 1,3:4,6-dibutylidene acetal of 2-deoxy-D-glucitol only gave a broadened hydroxyl signal even after several crystallisations, possibly due to the presence of a trace of acid.

A considerable amount of data on alcohols, available in the literature, show, that almost certainly the J_{HO-C-H} coupling constants are dependent on the dihedral angles, analogous to the Karplus rules.[88] The values usually are, $J_{synclinal}$ ca. 2-4 Hz, and $J_{antiperiplanar}$ ca. 12 Hz.

In cyclohexanol derivatives, it was suggested that the observed J_{HO-C-H} coupling constants are the average values of all of the rotameric conformations which are obtained by the rotation of O-H/C-H bonds.[95, 96] An equatorial hydroxyl group has three preferred rotameric conformations, where the dihedral angle (ϕ) can be 60°, 180° and 300°. An axial hydroxyl group has only two important rotameric conformations which are mirror images of each other (I) with ϕ = 60° and 300°. The third rotamer (II) with ϕ = 180° is probably less favoured due to hydroxyl hydrogen axial hydrogen interactions (Fig. VIII-15).[95]



I II

Fig. VIII-15

In agreement with these arguments, larger coupling constants (ca. J 5 Hz) were observed for the equatorial hydroxyl protons of some cyclohexanol derivatives.

In 1,3-dioxane derivatives an opposite situation is expected, because interactions between the hydroxyl hydrogens and axial hydrogens do not exist. On the contrary the ring oxygens provide a source of donatable electrons for intramolecular hydrogen bonding (Fig. VIII-16), which facilitates the retention of the preferred rotameric conformation of the hydroxyl group with a dihedral angle of ca. 180°.

In the 100 MHz spectra of benzylidene, chloroethylidene and butylidene 1,3:4,6-diacetals of galactitol, hydroxyl protons showed large coupling constants ($\underset{HO-\underline{C}-H}{J}$ 12 Hz), suggesting that the conformations of the hydroxyl group protons and protons on the same carbons are antiperiplanar (Fig. VIII-16).

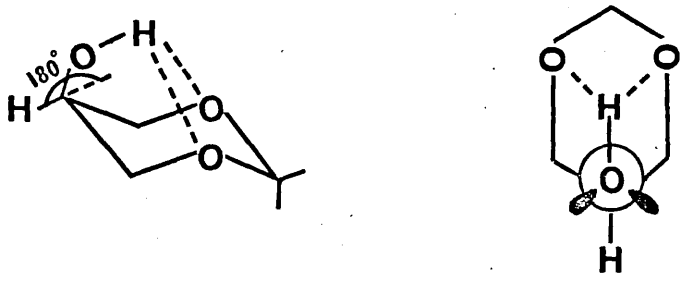


Fig VIII-16

In 1,3-dioxane derivatives, an equatorial hydroxyl proton is expected to show similar coupling constant values as in cyclohexanol derivatives, since it also has three preferred rotameric conformations with $\phi = 60°$, 180°, 300°. The largest coupling constant observed for these compounds is ca. 5 Hz. Thus it is possible to distinguish between axial and equatorial hydroxyl substituents whenever the observation of the $\underset{HO-\underline{C}-H}{J}$ coupling is possible.

The 100 MHz spectrum of 1,3:4,6-dibutylidene-D-mannitol showed a doublet for the hydroxyl proton with J_{HO-C-H} 1.5 Hz. The small value of the coupling constant suggested that the hydroxyl occupies an equatorial position and the dihedral angle between the hydroxyl proton and the axial proton is about 60-80° (Fig. VIII-17).

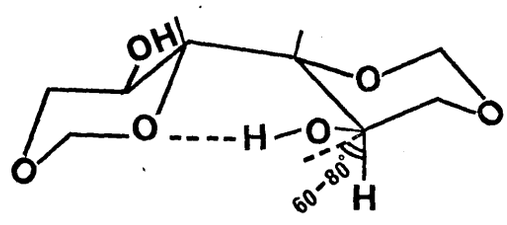


Fig. VIII-17

In other words, the contribution of the other theoretically possible rotamer ($\phi = 180°$) of the equatorial hydroxyl to the average value of the coupling constant is very small. Similar observations could not be made in the case of 1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol where a broad hydroxyl proton signal was obtained (Fig. VIII 38). The 1,3:5,6-dibutylidene-D-mannitol gave one doublet for each of the hydroxyl group protons, with coupling constants of 6 Hz and 4 Hz.

The signal with the larger coupling constant can be attributed to the 4-OH, if the carbon skeleton is assumed to exist in the zig-zag conformation (Fig. VIII-18). In this case the hydroxyl on C-4 has less rotameric freedom than the hydroxyl on C-2, due to possible hydrogen

bonding with one of the ring oxygens, which could increase the population of the rotameric conformation with a large dihedral angle ca. $\Phi = 180^{\circ}$, giving a large coupling constant (Fig. VIII-18).

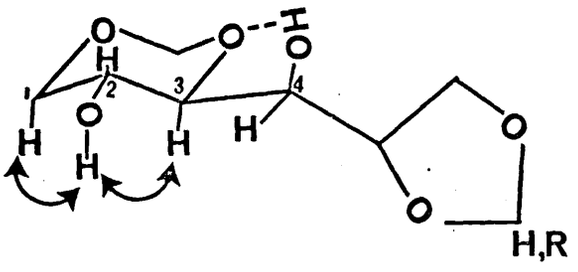


Fig. VIII-18

In the 100 MHz spectrum of 1,4:3,6-dianhydro-D-glucitol, as expected, two doublets for hydroxyl groups were observed. The signal with larger coupling constant (J 6 Hz), can be assigned to the C-5 hydroxyl proton, because its rotameric freedom is almost locked by the intramolecular hydrogen bonding (Fig. VIII-19), and the dihedral angle at this conformation is about 120°. The C-2 hydroxyl group, although not in an exact

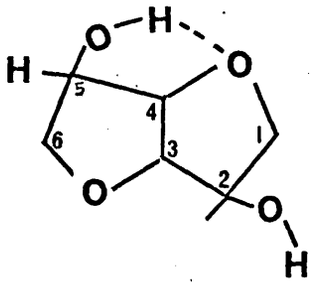


Fig. VIII-19

equatorial situation, can however have similar rotameric conformations. It is on this basis that the observed average coupling constant of 4 Hz is expected.

In the spectrum of 1,4:3,6-dianhydromannitol, only one doublet for the hydroxyl groups was observed with a coupling constant of 8 Hz. In this molecule both hydroxyl groups are involved in intramolecular hydrogen bonding (Fig. VIII-20).

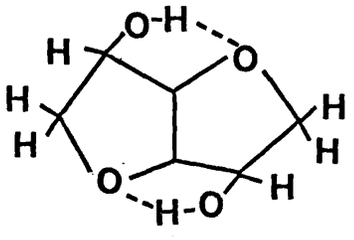


Fig. VIII-20

The observation of a large coupling in this case, also confirms the accuracy of the assignments in the D-glucitol compound. However in dianhydromannitol, probably both rings are puckered, thus causing larger dihedral angles between the hydroxyl protons and protons on the same carbon atom and therefore showing larger $\underset{HO-C-H}{J}$ value of 8 Hz than the analogous D-glucitol derivative.

The hydroxyl group proton signals can also give information about the degree of substitution of an alcohol,[93] the primary hydroxyl proton couples to two protons thus giving a triplet; whereas a secondary alcohol only gives a doublet. In the case of a tertiary alcohol a singlet is expected,

however a singlet is usually observed for any type of alcoholic protons in the presence of trace acid, therefore assignments of tertiary alcohols need extra caution.

In all the spectra considered, the chemical shifts of hydroxyl protons were found to be concentration dependent. This is due to the existence of an equilibrium in the solution in which protons are present in various molecular species, such as the intermolecularly hydrogen bonded dimeric, trimeric or polymeric forms as well as the non-bonded monomer and the intramolecularly hydrogen bonded monomeric species. The observed chemical shift is an average of all the species present. The equilibrium therefore is dependent on the concentration, temperature and the nature of the solvent. In pyridine and dimethyl sulphoxide, the hydroxyl chemical shifts change only by insignificant amounts, possibly due to hydrogen bonding of these solvents with the compounds considered. In fact, in these solvents the hydroxyl proton resonances move to very low field due to hydrogen bonding.

A preliminary experiment carried out on the change of chemical shifts with dilution of the hydroxyl protons of certain cyclic acetal derivatives are shown in figure VIII-21.

In all the spectra, the signals move to higher field by dilution. The explanation is that, in moderate concentrations, the intermolecularly hydrogen bonded species dominate the equilibrium but are reduced in number by the addition of more solvent. The best solvent for this type of investigation is carbon tetrachloride, however due to the low solubility of the compounds studied in this solvent, deuterated chloroform was used.

At infinite dilution, only the monomeric species is expected to be present in the solution, and hence the position of the signal gives the true chemical shift of the hydroxyl proton. In other words, the chemical shift of the hydroxy proton at infinite dilution is only dependent on its magnetic environment. This can be useful in determining the nature of the hydroxyl groups. Investigations on the behaviour of hydroxyl proton chemical shifts of alcohols and phenols have appeared in the literature.[97,98,99] In some cases, the equilibrium constants for monomer-dimer formation were evaluated and the results were explained in terms of the equilibrium between the hydrogen bonded species.[97] Quellette and Booth[98] found that the slope of the dilution curve (chemical shift vs mole fraction) at low concentrations (e.g. 0.020 to 0.002 mole fraction range) in carbon tetrachloride was directly related to the steric environment of the hydroxyl proton.

So far no work on the application of this phenomenon to carbohydrate derivatives has been reported. In this thesis, some preliminary experiments carried out with cyclic acetals are shown in figure VIII-21. It was not possible to observe the hydroxyl signals at very low concentrations and therefore the results are only interpreted qualitatively. However with the use of digital signal averages (C.A.T.) it should be possible to work at very low concentrations, to provide valuable information in the carbohydrate field.

In figure VIII-21 it is seen that, for dilutions between 0.4M and 0.05M, there is only a small change in the hydroxyl chemical shifts of 1,3:4,6-di-O-butylidene-D-mannitol and 1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol. This situation can be an indication of the presence of predominant intramolecular hydrogen bonding in these compounds, since intramolecular hydrogen bonding is not expected to be concentration dependent.

In the case of 1,4:3,6-dianhydroglucitol, the curve for $-OH^2$ is similar to that of 1,4:3,6-dianhydro mannitol, but the curve for $-OH^1$ shows a faster change in chemical shift. The latter hydroxyl (OH^1), therefore, must be positioned on C-5 where it cannot form intramolecular hydrogen bonding, and the former (OH^2) on C-2 where intramolecular hydrogen bonding is possible.

The dilution curve for OH^1 of the 1,3:5,6-di-O-butylidene-D-mannitol is almost parallel to the curve of 1,3:4,6-di-O-butylidene-D-mannitol but the curve for OH^2 shows a faster shift to high field on dilution, which indicates that OH^2 cannot form intramolecular hydrogen bonding and this limits its position to C-2 (Fig. VIII-18).

-●-●- 1,3:5,6-Di-O-butylidene-D-mannitol (OH^2)
-×-×- 1,3:4,6-Di-O-butylidene-D-mannitol
-△-△- 1,3:4,6-Di-O-butylidene-2-deoxy-D-glucitol
-▲-▲- 1,4:3,6-Dianhydromannitol
-■-■- 1,4:3,6-Dianhydroglucitol(OH^2)
-+-+- 1,3:4,6-Di-O-butylidenegalactitol
-o-o- 1,3:5,6-Di-O-butylidene-D-mannitol (OH^1)
-•-•- 1,4:3,6-Dianhydroglucitol (OH^1)

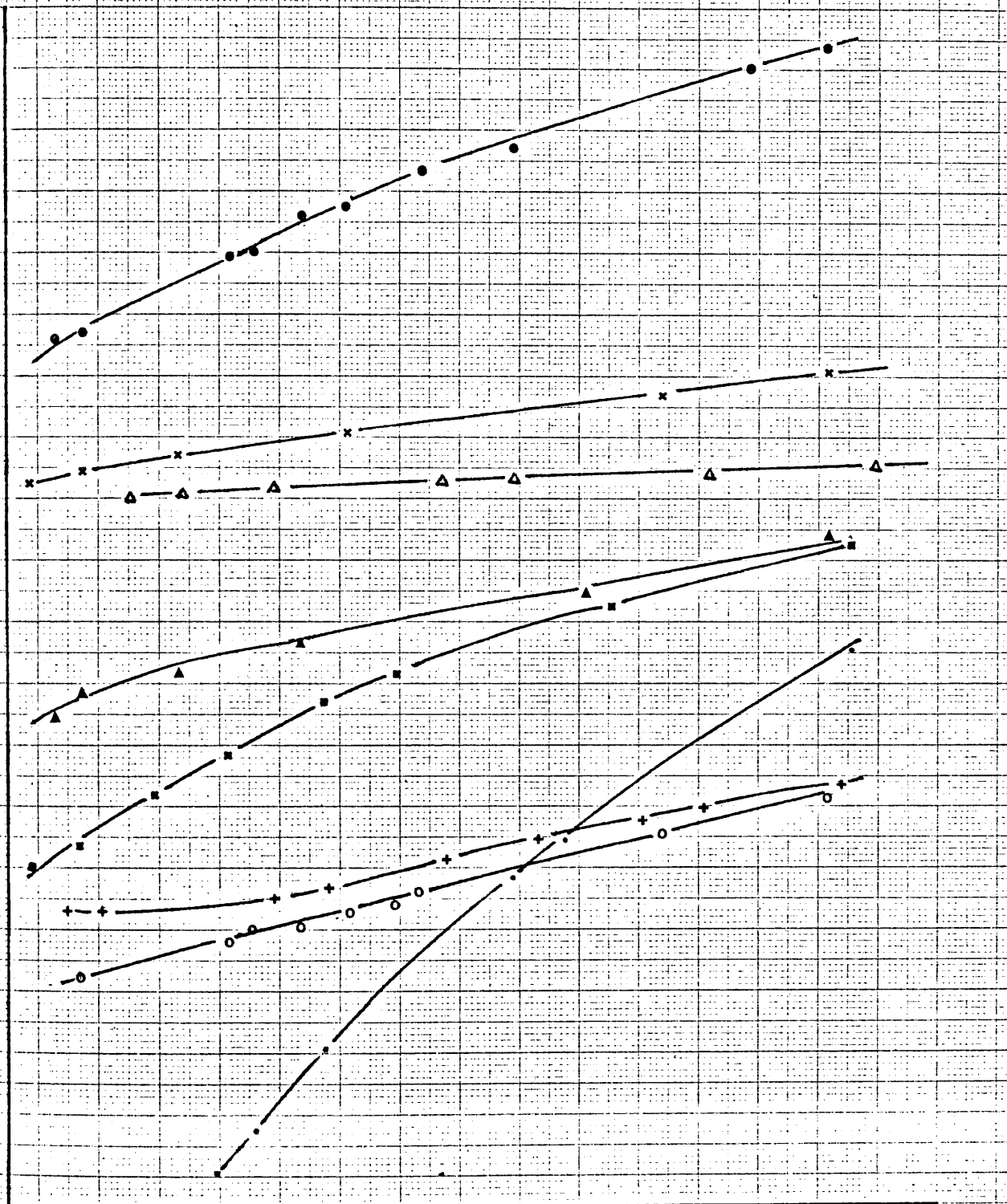


Fig.VIII-21 Concentration dependence of hydroxyl proton signals.
(Probe temperature 31°, solvent:chloroform-d.)

v) Spectroscopic Evidence for the Structures of 2,4:5,6- and 2,3:4,5-Dibutylidenegalactitols

The presence of free primary hydroxyl groups in 2,3:4,5-dibutylidenegalactitol was indicated by the hydroxyl group proton signal which appeared as a triplet (integrating for two protons), in the 60 MHz n.m.r. spectrum. The signal collapsed to a single line on addition of a trace of trifluoroacetic acid. The overall spectrum was too complex for assignments of the other signals, but the superimposed acetal-proton triplets at τ 4.92 in the 60 MHz spectrum was a good indication for the presence of a five-membered ring. The observation of only a low field triplet, precludes the presence of a six-membered ring.

Mass spectroscopy also provided additional information for the structure of this compound as shown in the next section.

The 100 and 220 MHz spectra of 2,4:5,6-di-O-butylidene-DL-galactitol are shown in figures VIII-22 and 23. Even the 220 MHz spectrum was too complicated for complete interpretation but the acetal-proton signals were easily detectable. The high field acetal-proton triplet at τ 5.42 can be assigned to the butylidene acetal-proton of the 1,3-dioxane ring and the triplet at τ 4.94 to the 1,3-dioxolane ring.

In the 100 MHz spectrum, two separate hydroxyl signals were observed (Fig. VIII-22). The hydroxyl signals in the 220 MHz spectrum broadened due to the presence of trace of water in the solvent (Fig. VIII-23).

The assignments of the signals were confirmed by the addition of a trace of trifluoroacetic acid to the solution whereupon the hydroxyl signals converged to a single, sharp line (Fig. VIII-22).

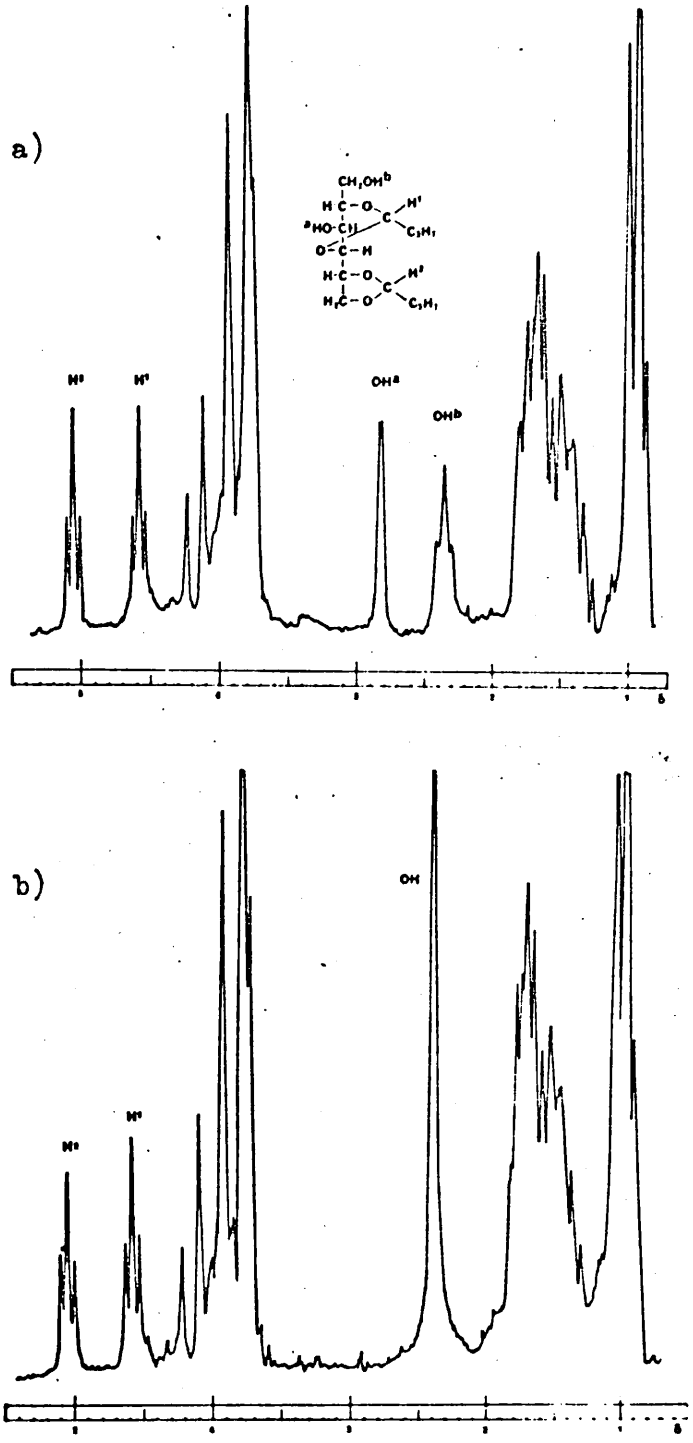


Fig. VIII-22 100 MHz spectrum of 2,4:5,6-di-O-butylidene-DL-galactitol
a) in $CDCl_3$
b) with trace of CF_3COOH.

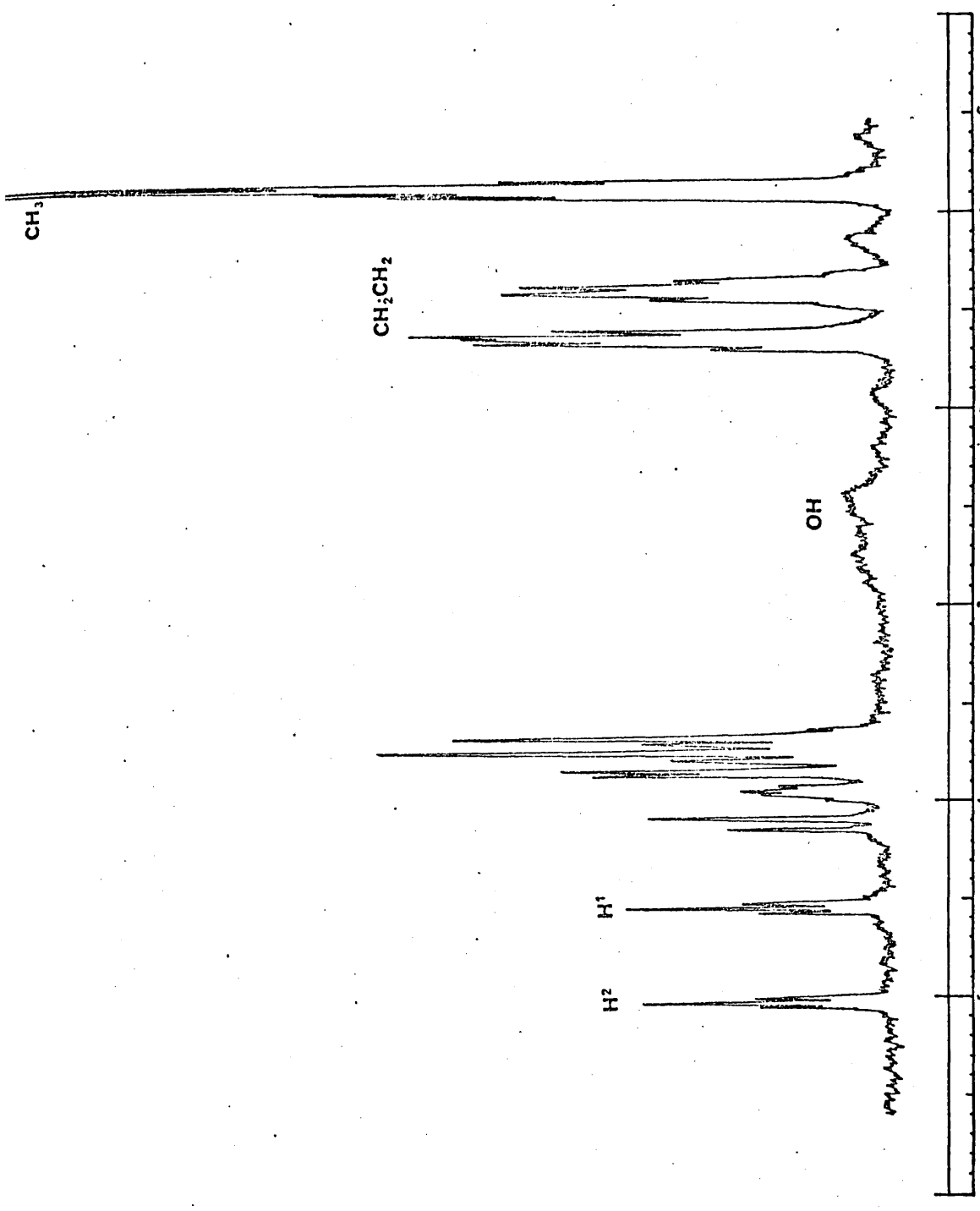
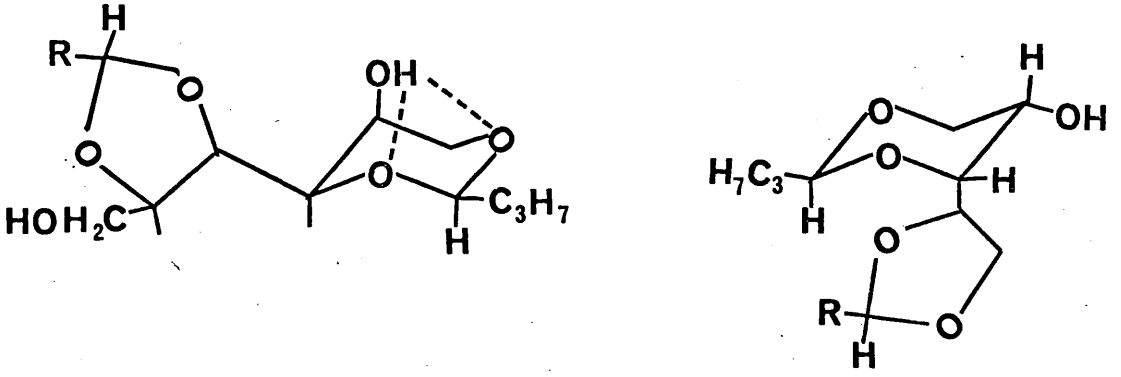


Fig. VIII-23 220 MHz spectrum of 2,4:5,6-di-O-butylidene-DL-galactitol in $CDCl_3$.

A triplet and a doublet (the coupling constant can be measured easily on the expanded spectrum, although this could not be seen in the normal spectrum) for the hydroxyl group protons indicated that a primary and secondary hydroxyl groups were present. The above findings limit the possible structures to 1,3:4,5-di-O-butylidene-DL-galactitol and 2,4:5,6-di-O-butylidene-DL-galactitol. Two of the possible conformational formulae for the former are (I) and (II) (Fig. VIII-24).



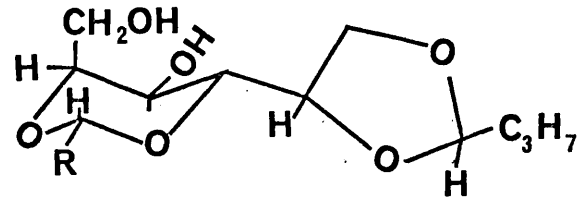
I (D-form) $R = C_3H_7$ II (D-form)

Fig. VIII-24

The conformation (I) is a reasonably stable one in which the 1,3-dioxane ring has two equatorial substituents and an axial hydroxyl group which is capable of forming intramolecular hydrogen bonding. Therefore a large J_{HO-C-H} type coupling is expected, but the observed coupling is only 2 Hz, indicating that the hydroxyl group is more likely an equatorial one. The conformation (II) is also a configurational isomer of

(I), (differing in configuration on the 1,3-dioxane ring acetal-carbon) although it contains the secondary hydroxyl in the equatorial position, the 4,5-ring is axial, thus causing instability.

For the other possible structure, namely 2,4:5,6-di-O-butylidene-DL-galactitol, the most probable conformation is shown in figure VIII-25,



(D-form)

Fig. VIII-25

which fits best to the observed spectrum. The mass spectroscopic evidence also supported this structure.

vi) The N.m.r. Spectra of 1,3:2,4:5,6-Tri-O-butylidene-DL-galactitol.

The 100 MHz spectrum of 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol was very complicated but the acetal-proton triplets were easily detectable at τ 5.40, 5.25 and 4.78. These signals were confirmed by a double resonance experiment, by irradiating the $-CH_2-CH_2-$ multiplet at δ 1.5, (Fig. VIII-26) which converged the triplets to singlets. The chemical shifts of these acetal-protons are also in accordance with the assumed structure. The signals at τ 5.25 and 5.40 are too high for five-membered ring acetal-protons but the triplet at τ 4.78 can only be due to a five-membered ring acetal-proton which must be deshielded by the oxygens of 2,4-ring.

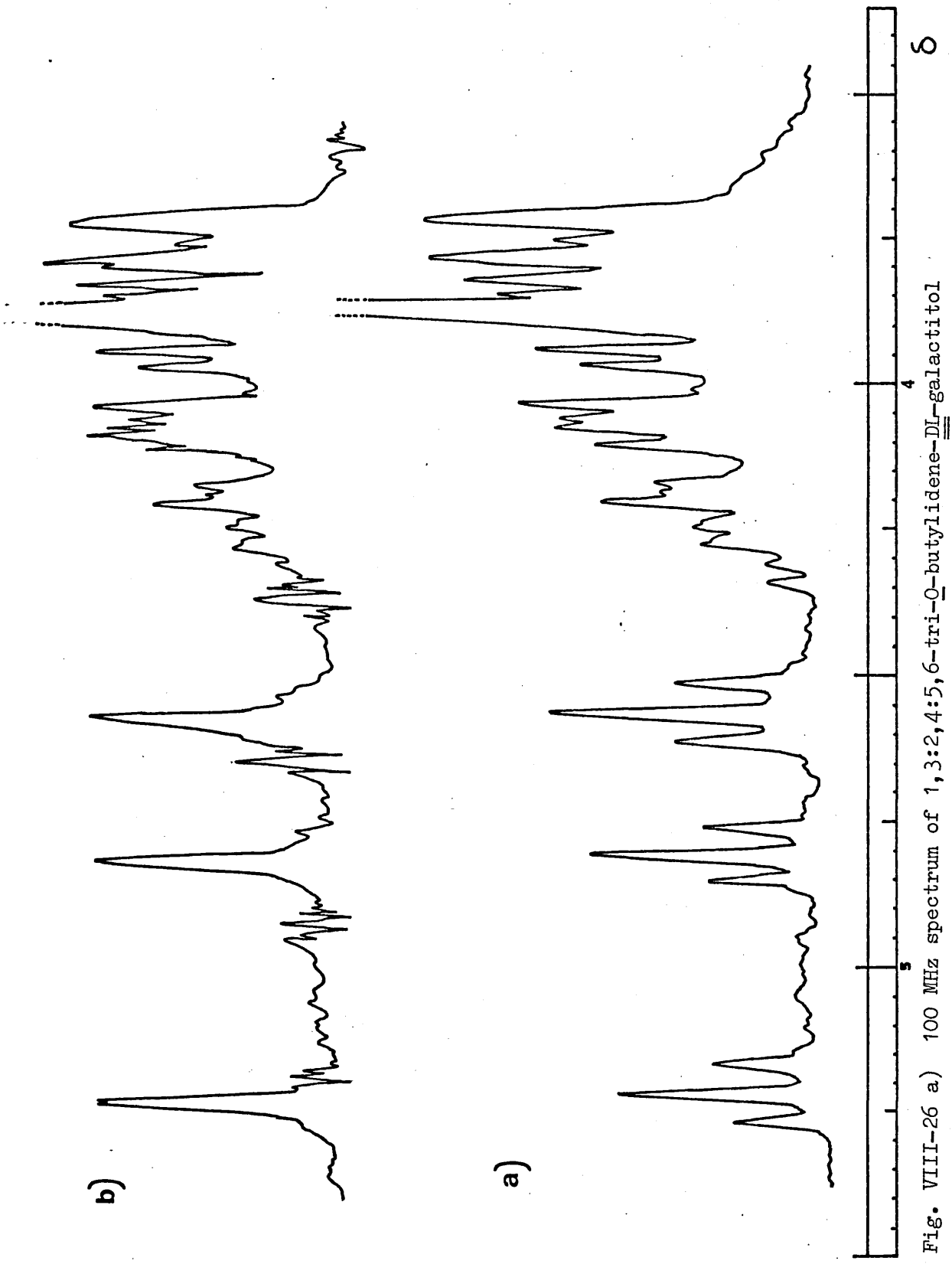
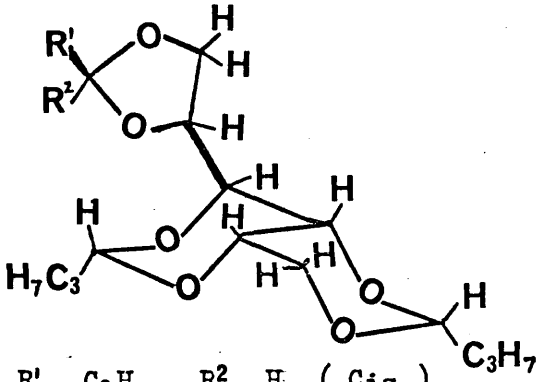


Fig. VIII-26 a) 100 MHz spectrum of 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol (low field part) in $CDCl_3$. b) Double resonance experiment.

The only triacetal obtained was stereoisomerically pure, therefore the configuration on the 5,6-ring acetal-carbon could not be assigned, however after crystallisation of this product, the mother liquor yielded a syrupy product whose n.m.r. spectrum showed several triplets but none at lower field than τ 4.78. This syrupy product was assumed to be a mixture of the other stereoisomer of 1,3:2,4:5,6-triacetal and possibly some other triacetals of different structure, and some polymerised butyraldehyde. It appears that the triplet at τ 4.78 is due to the trans isomer of the two possible 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol (Fig. VIII-27), in which the acetal-proton of the 5,6-ring is closer to the 2,4-ring.



$R' = C_3H_7$, $R^2 = H$ (Cis)
$R' = H$, $R^2 = C_3H_7$ (Trans)
Fig. VIII-27

The same conformation also explains the shift of the 2,4-ring acetal-proton triplet to low field (τ 5.25) due to deshielding effect of the oxygens of the 5,6-ring. The 220 MHz spectrum of the triacetal was better resolved. The low field part of the expanded spectrum with the possible assignments is shown in figure VIII-28.

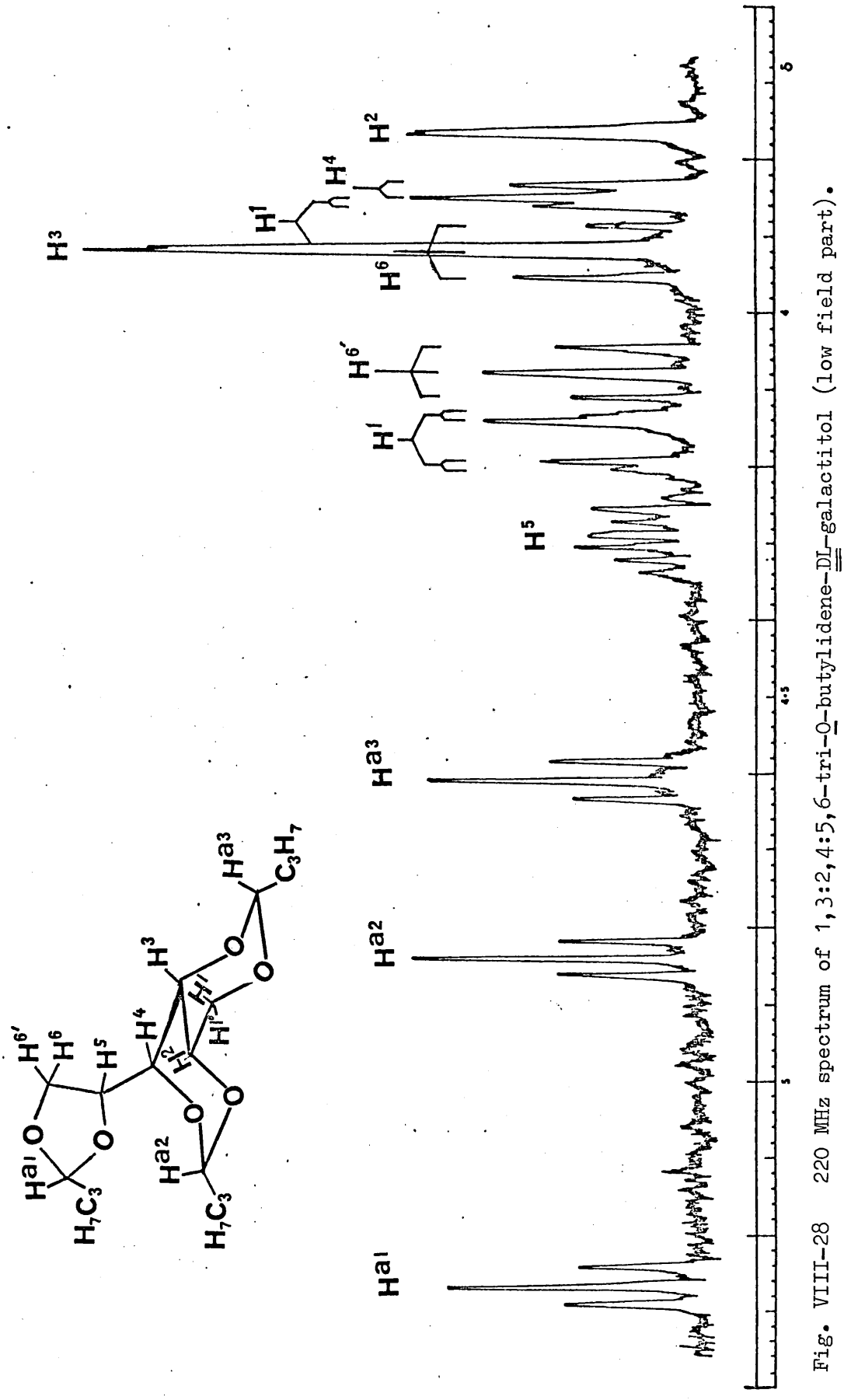
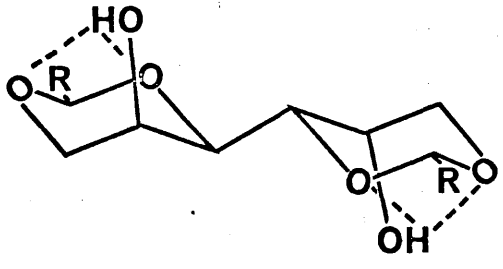


Fig. VIII-28 220 MHz spectrum of 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol (low field part).

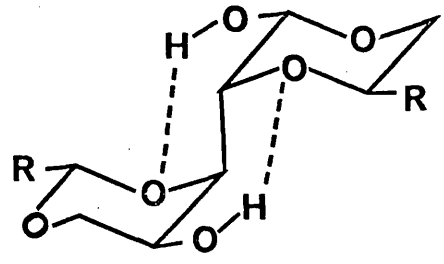
vii) N.m.r. Spectra of some 1,3:4,6-Diacetals of Galactitol and Their Derivatives

In this section, the 100 MHz n.m.r. spectra of 1,3:4,6-dibutylidene, 1,3:4,6-dichloroethylidene and 1,3:4,6-dibenzylidene acetals of galactitol and some derivatives of these acetals are considered. The structure of the 1,3:4,6-dibutylidene acetal was derived by synthetic methods in section II-B. The 1,3:4,6-di-O-chloroethylidenegalactitol was prepared according to the method of H.B. Sinclair[100] who also determined its structure by synthetic methods. The 1,3:4,6-di-O-benzylidenegalactitol was prepared by the method of Hudson et al.[21] who also determined its structure.

The 60 MHz n.m.r. spectrum of the 1,3:4,6-dibenzylidenegalactitol in dioxane was described briefly and the benzylidene acetal signal at τ 4.78 was used as evidence for the suggested conformation (Fig. VIII-29, I), in which two 1,3-dioxane rings have one axial and two equatorial substituents.[79]



I



II

Fig. VIII-29

Some years later H.B. Sinclair[100] et al. suggested a different conformation for the 1,3:4,6-dichloroethylidenegalactitol, based on theoretical considerations, in which the 1,3-dioxane rings were axial to each other and the equatorially disposed hydroxy groups could form hydrogen bonds with the neighbouring ring oxygens (Fig. VIII-29, II).[100] It was suggested that the energy lowering of these hydrogen bonds was sufficient to overcome the axial interactions. However, detailed examination of 100 MHz n.m.r. spectra in this thesis revealed that, all three acetals and their derivatives existed in the conformation (I).

The n.m.r. spectrum of 1,3:4,6-di-O-butylidenegalactitol is shown in figure VIII-30. Identical chemical shifts were observed for the equivalent protons of the two 1,3-dioxane rings due to the symmetrical disposition of two rings. The same phenomenon was also observed for the other 1,3:4,6-diacetals and their derivatives. The spin-spin couplings and chemical shifts (table VIII-3) were obtained by approximate first order measurements. The similarities of the n.m.r. spectra of 1,3:4,6-diacetals pointed strongly to a common structure. The 100 MHz spectrum of 1,3:4,6-di-O-butylidenegalactitol is presented as a model in assigning the signals of other acetals.

The geminal protons were easily recognised in all the spectra. In figure VIII-30, the lower half of the signal for the axial geminal protons was superimposed onto the signal of H^3, which appeared as a sharp singlet in all the spectra, suggesting a zero or very small coupling between H^3 and H^2. The signal of H^2 was obtained as a broadened doublet at δ 3.61. Double resonance at the centre of this

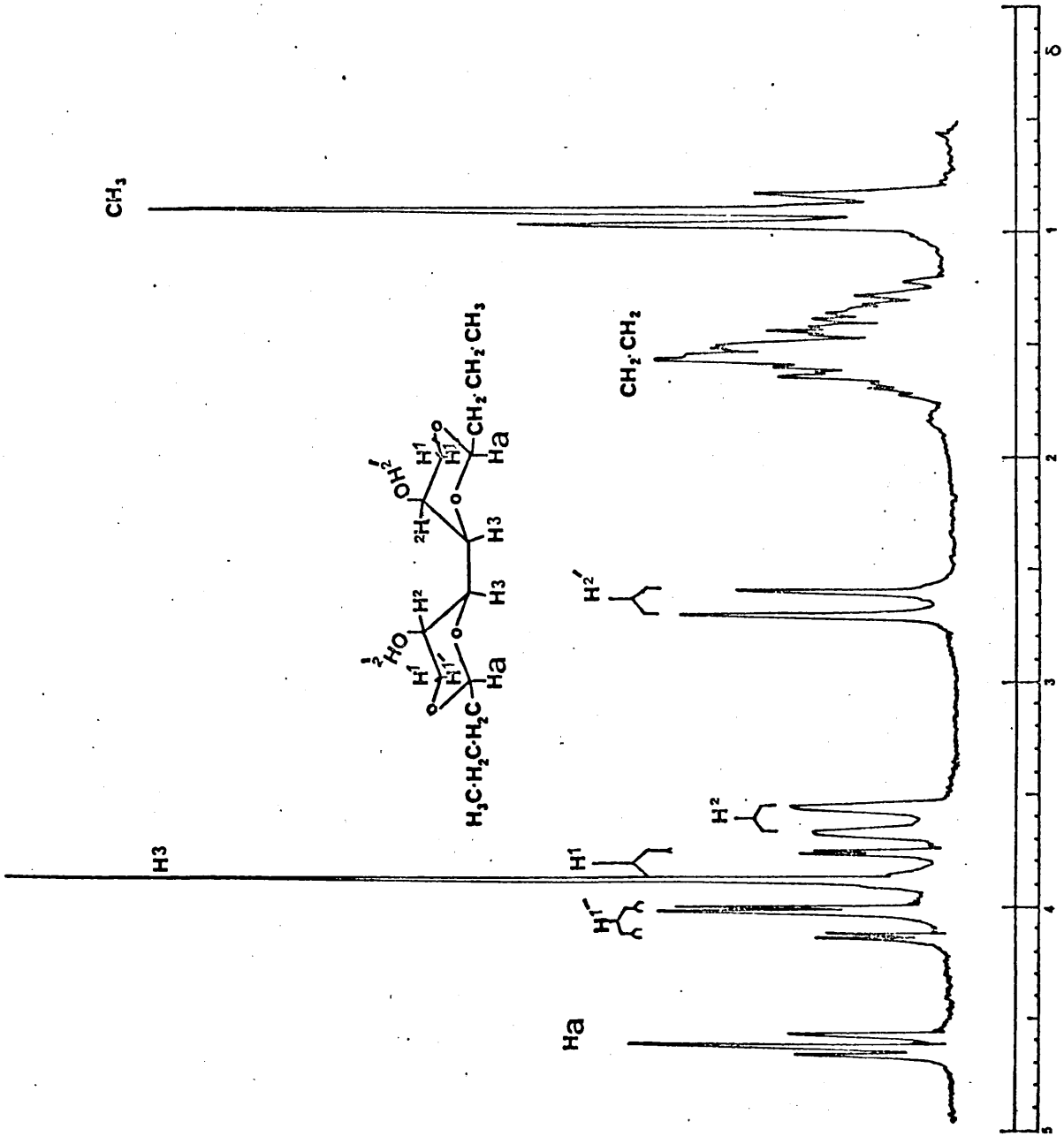


Fig. VII-30 100 MHz spectrum of 1,3:4,6-di-O-butylidenegalactitol in $CDCl_3$.

doublet caused the high field doublet of $H^{2'}$ to converge to a single line showing that, these protons were coupled. At the same time the small splittings on the geminal proton signals were removed showing that, they were also caused by the spin-spin interactions of H^2. The hydroxyl proton signal ($H^{2'}$) was easily recognised by its concentration dependence. The large coupling between H^2 and $H^{2'}$ is diagnostic for an axial hydroxyl group (Section VIII-iv).

Each line of the H^2 doublet in the same spectrum was in fact an unresolved triplet as confirmed by expansion to a 250 Hz scale (Fig. VIII-31). The computed spectrum of the compound (shown in the same figure) was obtained by the use of the computer programme[101] "U.E.A. n.m.r. basic non-iterative" which gave a reasonably good agreement with the observed spectrum.

In the n.m.r. spectrum of the dimethyl ether of 1,3:4,6-dibutylidenegalactitol, the low field part of which is represented in figure VIII-32, the H^2 signal appeared as a broad line, or a slightly resolved triplet, depending on the resolving power of the spectrometer. The eight lines due to the geminal protons were well separated. The low field quartet centred at δ 4.29, was assigned to the equatorial geminal proton and the high field quartet centred at δ 3.72 was assigned to the axial one. Irradiation of the signal of H^2 (δ 3.22) collapsed the splittings on the geminal protons, thus simplifying the spectrum (upper spectrum, figure VIII-32) to a four-line AB pattern, which confirmed the accuracy of the interpretation. The computed spectrum of this compound (figure VIII-33) was obtained with the programme " U.E.A. n.m.r. basic".[101] The chemical shifts and coupling constants read directly from the observed spectrum were fed into computer and the

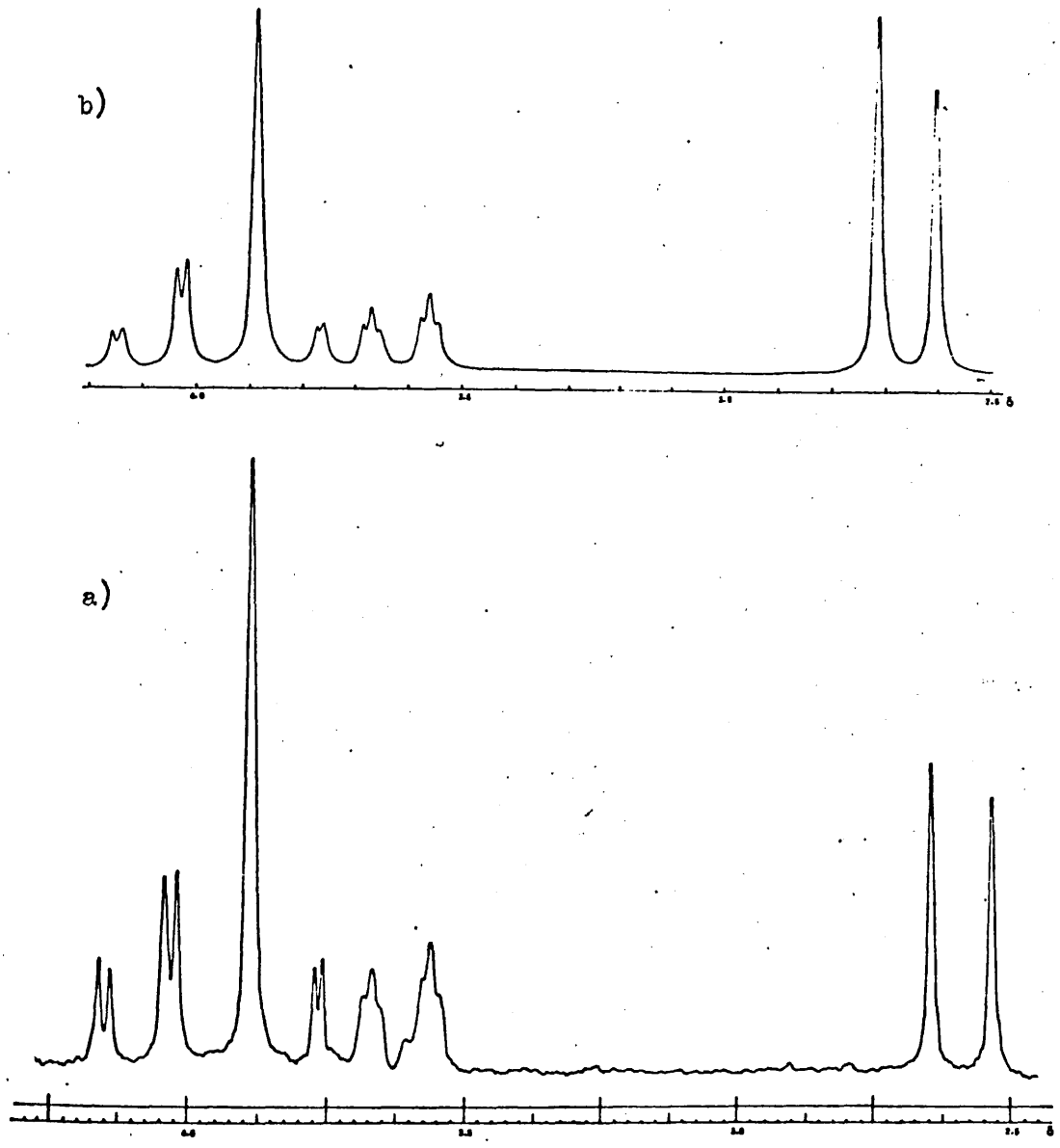


Fig. VIII-31 a) 100 MHz spectrum of 1,3:4,6-di-O-butylidenegalactitol in $CDCl_3$ (250 Hz sweep width) b) Computed spectrum.

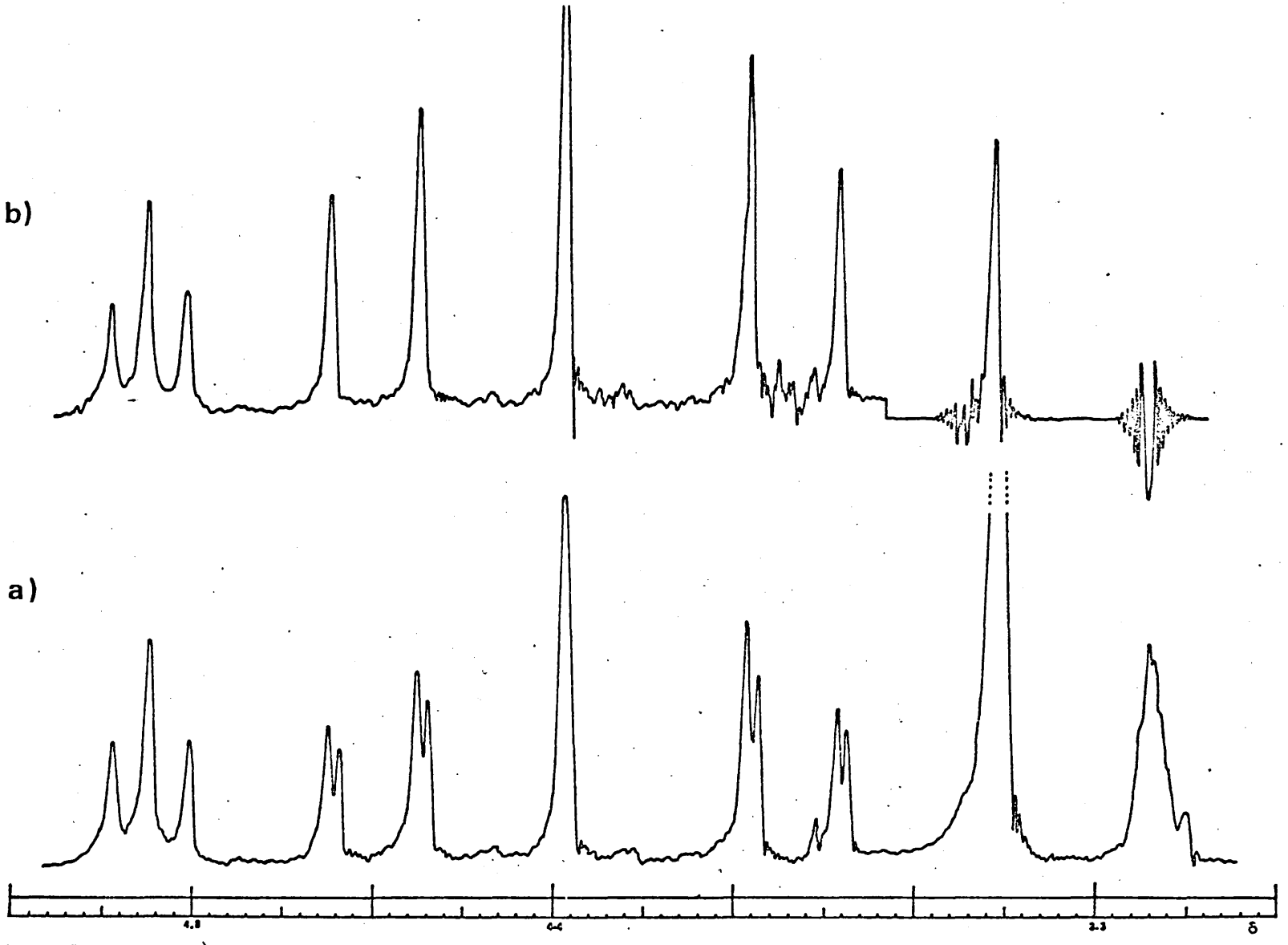


Fig. VIII-32 a) 100 MHz spectrum of 1,3:4,6-di-O-butylidenegalactitol dimethyl ether in $CDCl_3$ (250 Hz sweep width) b) Double resonance experiment.

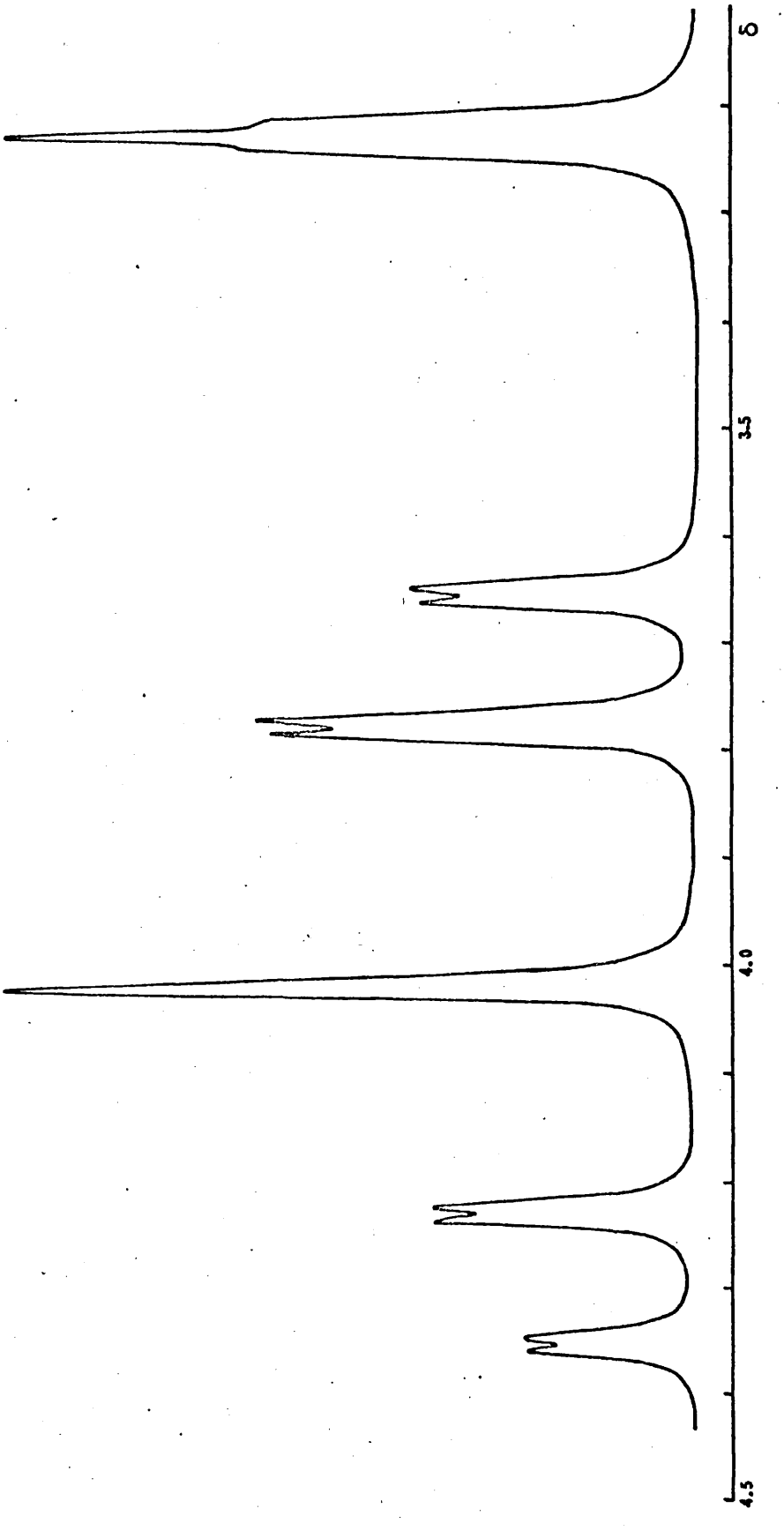


Fig. VIII-33 Computed spectrum of 1,3:4,6-di-O-butylidenegalactitol dimethyl ether.

values unobtainable from the spectrum were found by interpolation. The values taken from the observed and the computed spectrum are shown in table VIII-3.

The coupling constants (J_{H^2,H^3}) could not be measured from the spectra, as the fine splittings on the H_2 and H_3 signals were not observed due to insufficient resolving power of the instrument used. These values therefore, are given as smaller than 1 Hz in the tables.

viii) The N.m.r. Spectra and the Structures of Some Acetals of Hexitols and Deoxy-hexitols

In this part, the n.m.r. spectra of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-DL-galactitol (1), 4,6-O-butylidene-1,2,3,5-tetra-O-acetyl-D-glucitol (2), 4,6-O-butylidene-2,3,5-tri-O-acetyl-1-deoxy-D-galactitol (3), 1,3:4,6-di-O-butylidene-D-mannitol (4) and 1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol (5) are considered. The 100 MHz spectra of some of these compounds were interpretable but in some cases the 220 MHz spectra were necessary for unambiguous assignment of signals. In order to facilitate the comparison of the above compounds, the acetals (2), (3) and (5) are called 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-L-gulitol, 1,3-O-butylidene-2,4,5-tri-O-acetyl-6-deoxy-L-galactitol, 1,3:4,6-di-O-butylidene-5-deoxy-D-mannitol respectively.

The n.m.r. spectrum of 1,3:4,6-di-O-butylidene-D-mannitol indicated that the protons on either of the 1,3-dioxane rings have identical chemical shifts. The observation implied the following possibilities: (i) the protons of the two 1,3-dioxane rings are equivalent and therefore exhibit the same shift and (ii) the protons of the two 1,3-dioxane rings are not equivalent but have coincidental shifts.

The first possibility is the case found for the 1,3:2,5:4,6-trimethylene-D-mannitol in which the acetal-protons are equivalent due to the presence of an axis of symmetry in the twist-chair or twist-boat conformations (Fig. VIII-34).[12]

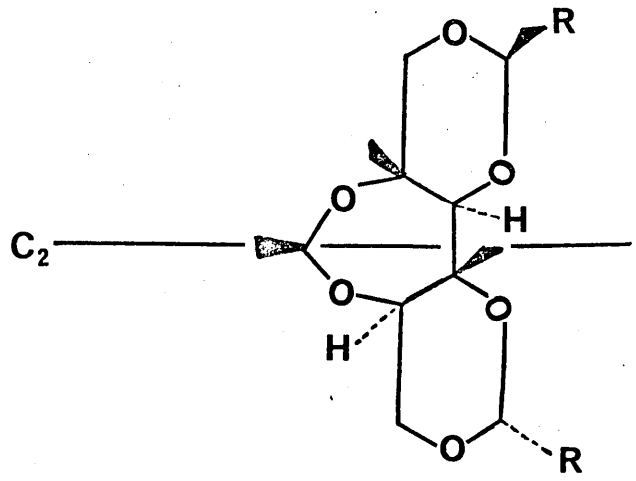


Fig. VIII-34

In the case of the 1,3:4,6-diacetals a similar conformation is not favourable due to the interactions of the hydroxyl groups on C-2 and C-5 (Fig. VIII-35, I).

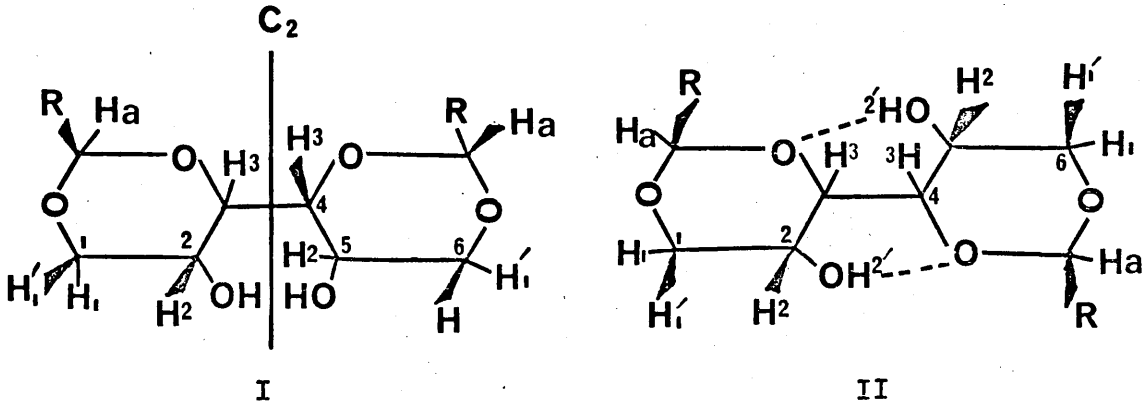


Fig. VIII-35

A more favourable conformation is (II), in which the interactions between the hydroxyl groups are minimised and possible intramolecular hydrogen bonding further increases the stability. The magnitude of the coupling constant $\overset{J}{HO-C-H}$ also supports this view as discussed in the section VIII-iv.

The conformation (II) also possesses a two-fold rotational symmetry axis perpendicular to the C-3, C-4 bond, of type D_2. Therefore the protons of both rings are equivalent.

Fig. VIII-36, shows the 220 MHz spectrum of the compound (4), (Fig. VIII-35, II). The signal of H^1 was found to be a triplet at δ 3.40, coupling to the equatorial H1' with a coupling constant of 10 Hz, also to the H^2 with the same coupling constant. The large vicinal coupling constant indicated that protons H^1 and H^2 were antiperiplanar and hence both axial. The equatorially positioned geminal proton H1' gave a quartet at δ 4.22 since it was strongly coupled to H^1 (geminal coupling, J 10 Hz) and to H^2 with a coupling constant of 4.7 Hz, which is characteristic of synclinal vicinal protons. In the 100 MHz spectrum, the quartet of H^1 and the doublet of H^3 overlapped with the signals of H^2 appearing as a complex multiplet. The splitting of the hydroxyl group proton signal was observed in the 100 MHz spectrum, whereas a singlet was obtained in the 220 MHz spectrum.
The large coupling constants J_{H^2, H^3} indicated that these protons were antiperiplanar (Table VIII-4).

The 100 MHz spectrum of the compound (5) (Fig. VIII-37) was too complicated for complete interpretation (Fig. VIII-38), but the 220 MHz

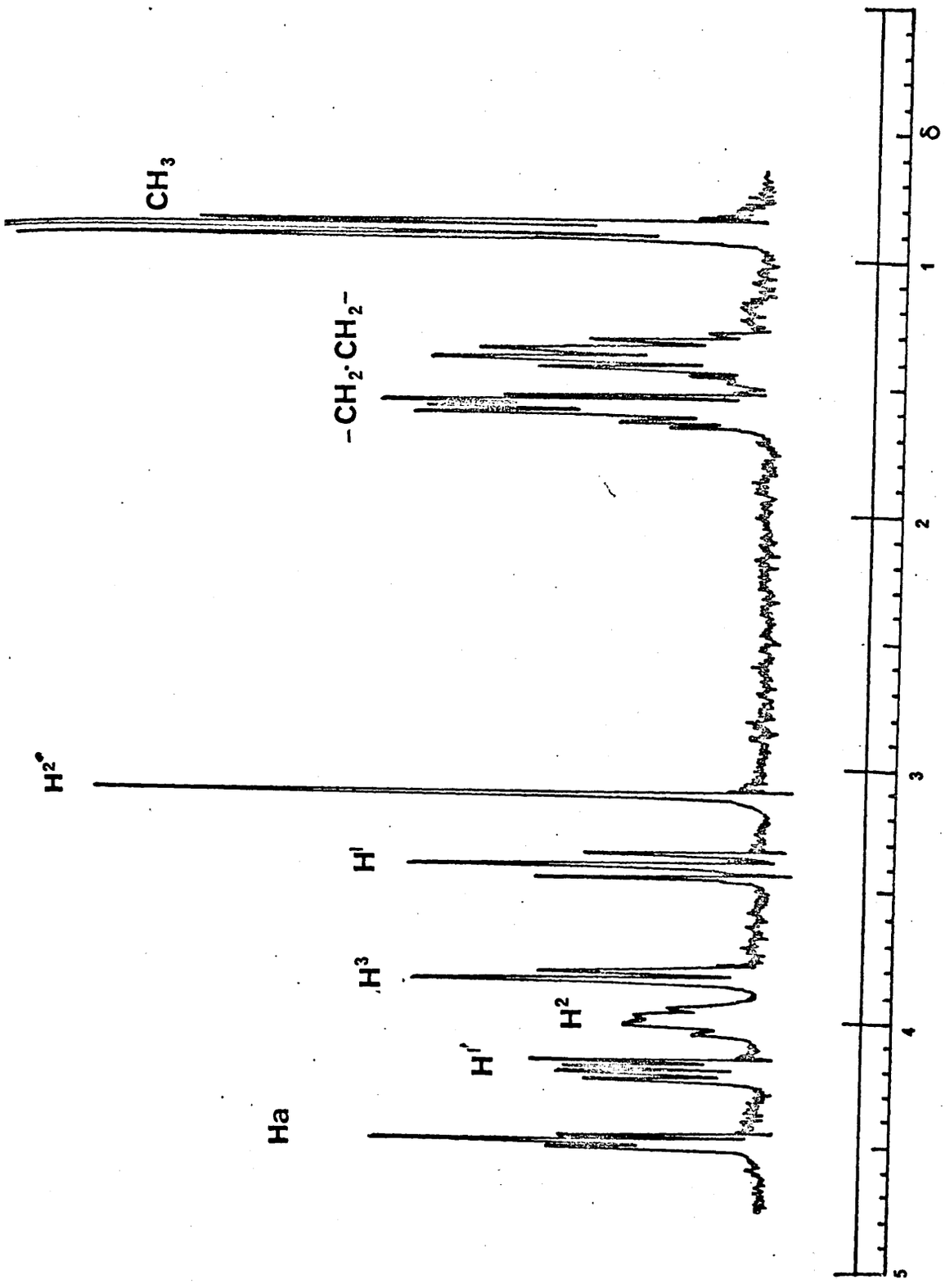
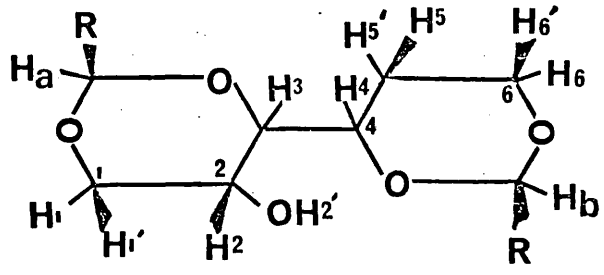


Fig. VIII-36 220 MHz spectrum of 1,3:4,6-di-O-butylidene-D-mannitol in $CDCl_3$.

spectrum (Fig. VIII-39) gave a good separation of the signals, thus providing evidence for the structure (III) (Fig. VIII-37). 1,3-O-Butylidene ring of this compound is probably identical with the 1,3-ring of the compound (4). In the spectra of these two compounds, the similarities of the H^1, $H^{1'}$ signals for the 1,3-rings supported this view. A triplet for H^1 and a quartet for $H^{1'}$ showed similar coupling constants and chemical shifts in both spectra (Table VIII-4 and 5). The H^3 of the compound (5) appeared as a quartet at δ 3.55 due to its coupling to both H^2 (J_{H^2,H^3} 10 Hz; large dihedral angle) and to H^4 (J_{H^3,H^4} 4 Hz; small dihedral angle). The multiplet of H^2 in the spectrum of the compound (5) overlapped with the quartet of H1'. The assignments of the other signals are shown in figure VIII-39.



III

Fig. VIII-37

In the 100 MHz (Fig. VIII-40) and 220 MHz (Fig. VIII-41) spectra of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-L-gulitol, the H^1 appeared as a triplet at δ 3.37 ($J_{H^1,H^{1'}} = J_{H^1,H^2}$ 10 Hz) and the equatorial proton H1' as a quartet at δ 4.20 ($J_{H^1,H^{1'}}$ 10 Hz; $J_{H^{1'},H^2}$ 5.5 Hz). In the 100 MHz

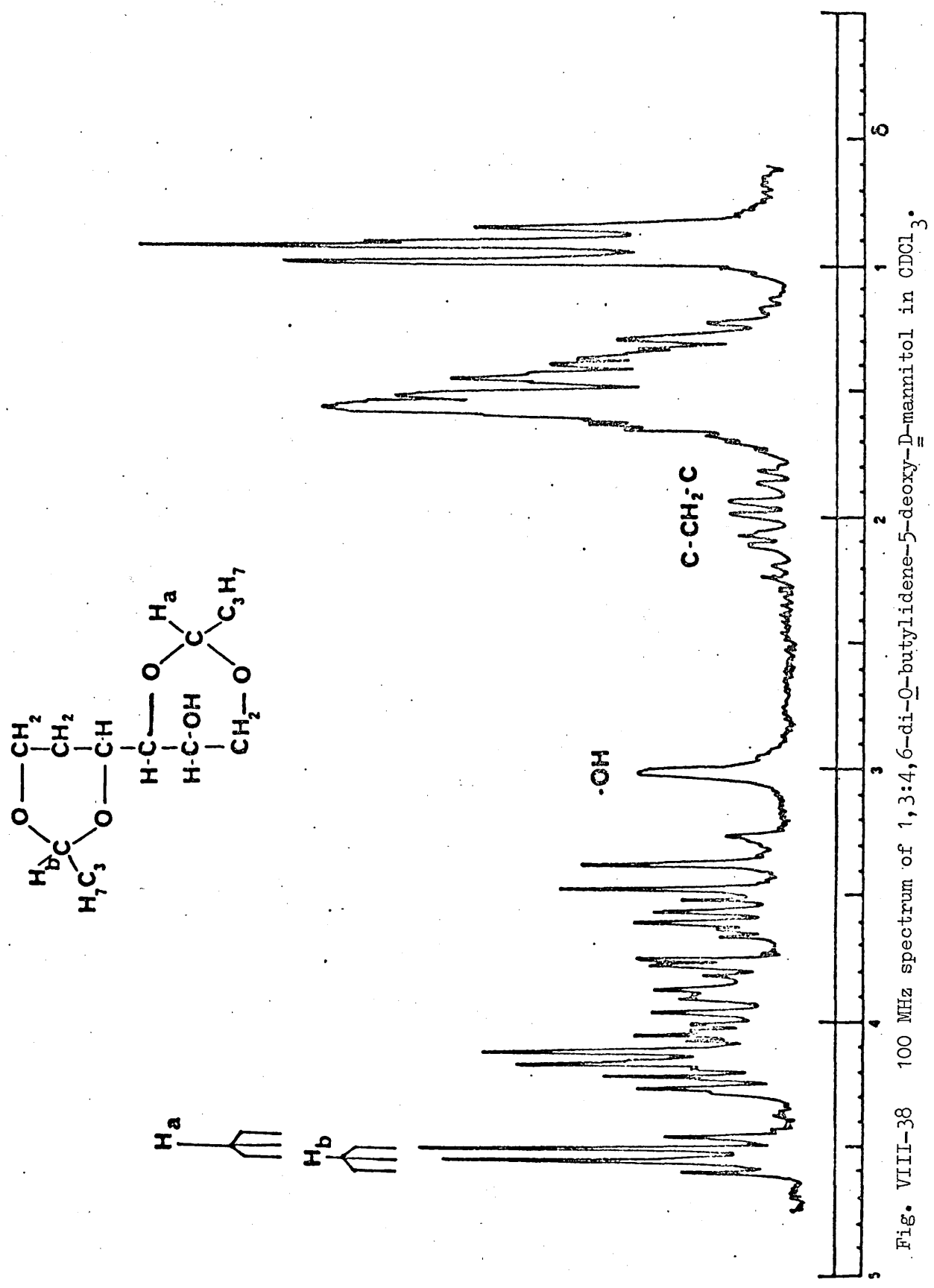


Fig. VIII-38 100 MHz spectrum of 1,3:4,6-di-O-butylidene-5-deoxy-D-mannitol in $CDCl_3$.

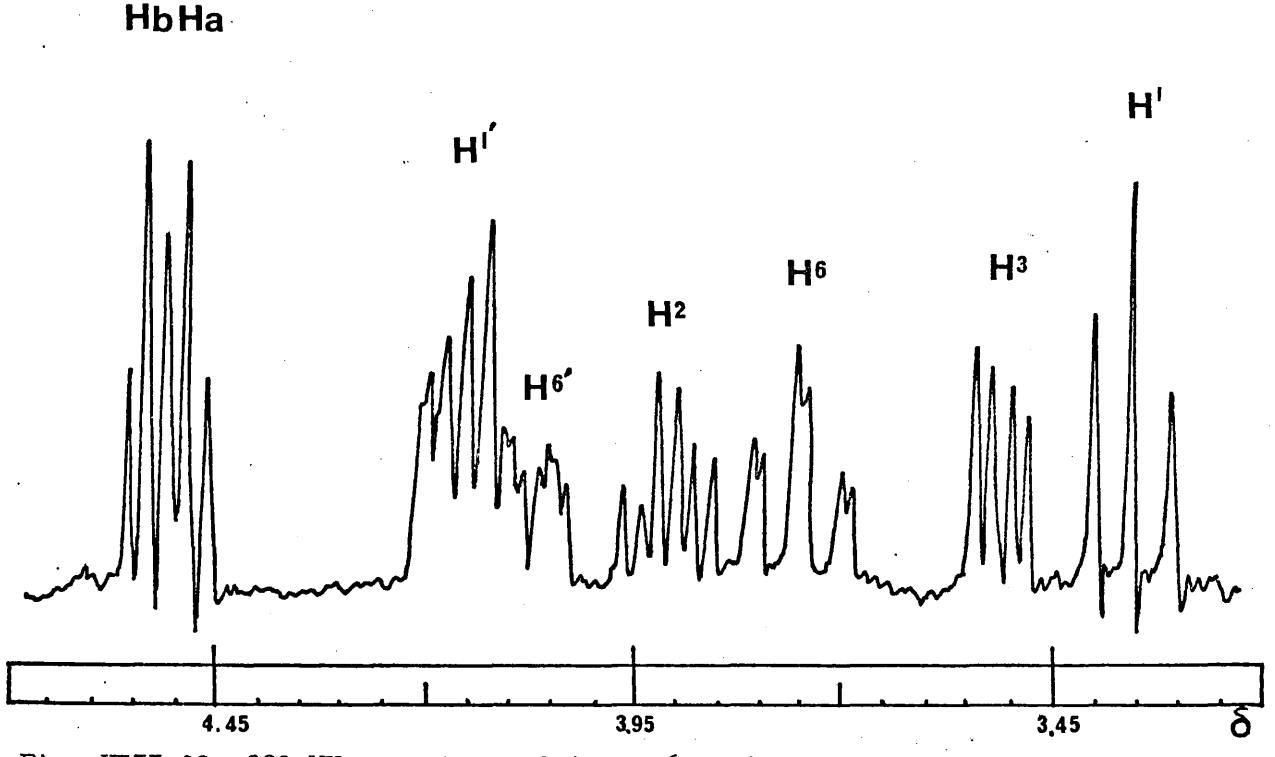


Fig. VIII-39 220 MHz spectrum of 1,3:4,6-di-O-butylidene-5-deoxy-D-mannitol (low field part) in $CDCl_3$.

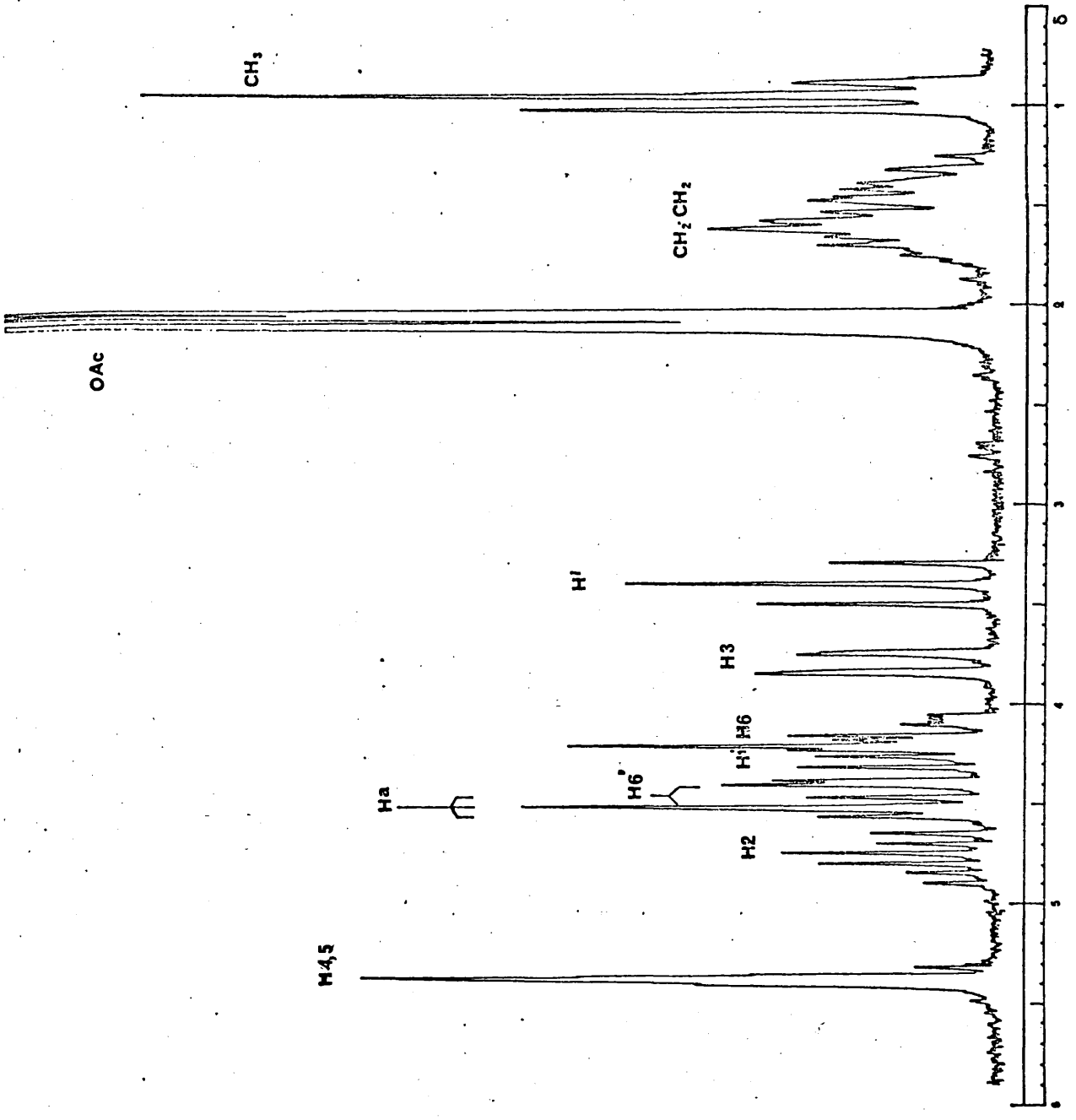


Fig. VIII-40 100 MHz spectrum of 1,3-O-butylidene-L-gulitol tetra-acetate in $CDCl_3$.

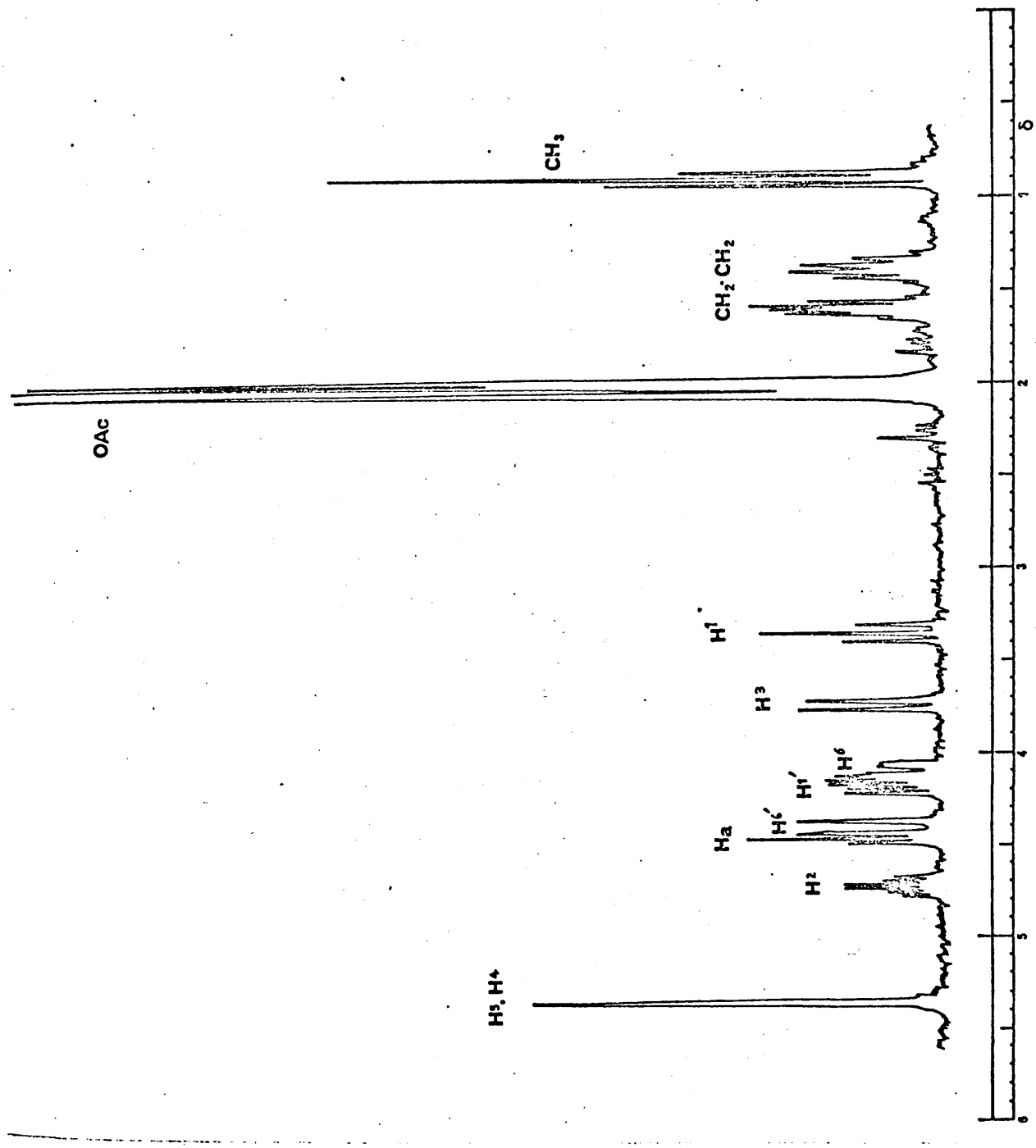


Fig. VIII-41 220 MHz spectrum of 1,3-O-butylidene-L-gulitol tetra-acetate in $CDCl_3$.

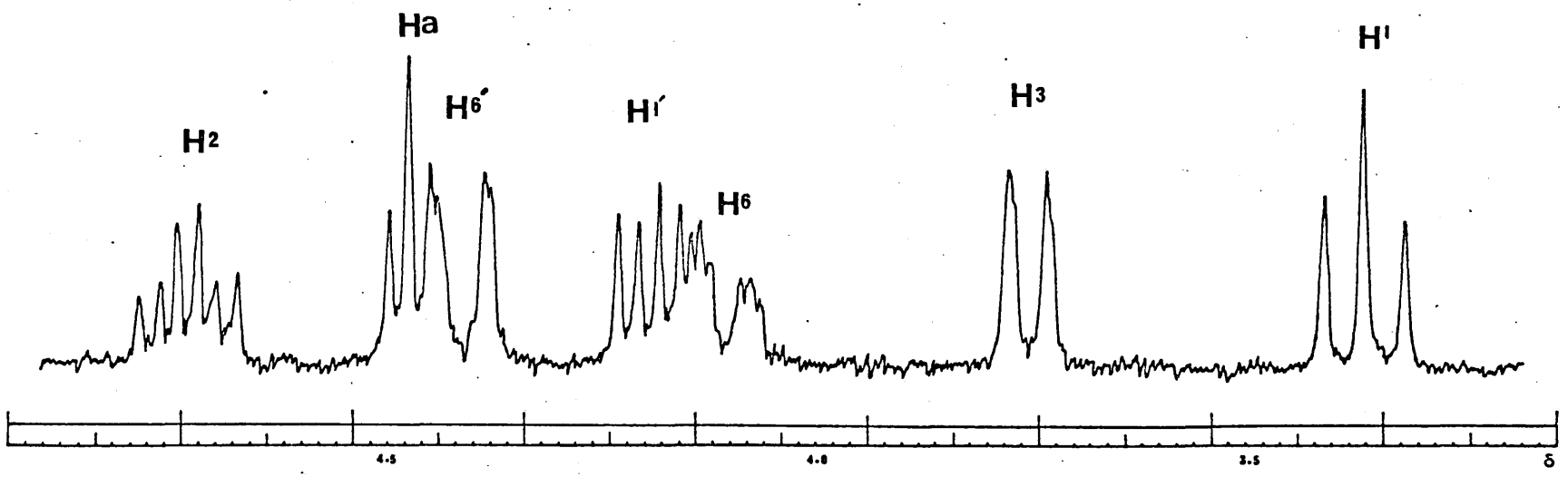


Fig. VIII-42 The low field part of the 220 MHz spectrum of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-L-gulitol in $CDCl_3$ (500 Hz sweep width).

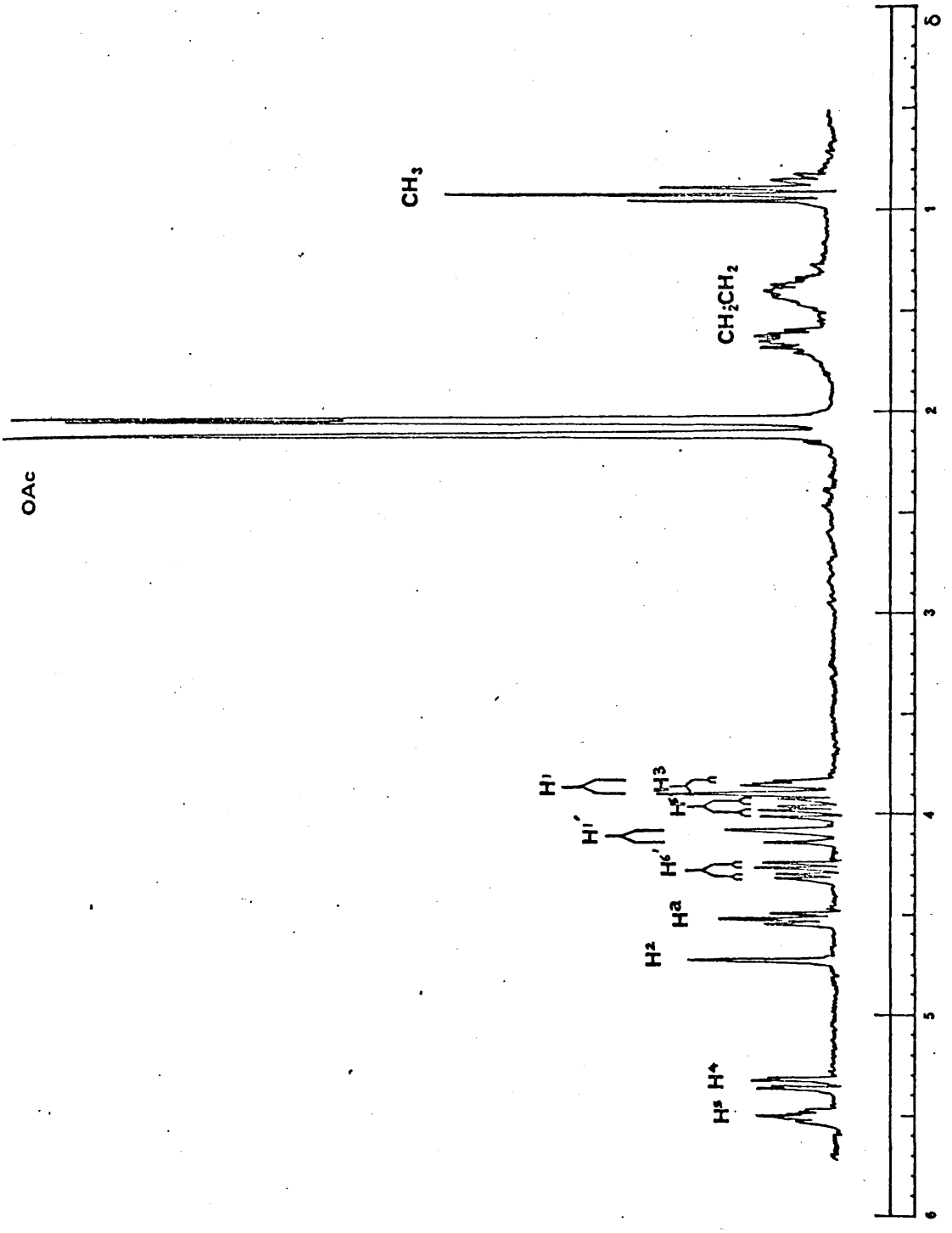


Fig. VIII-43 220 MHz spectrum of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-DL-galactitol in $CDCl_3$.

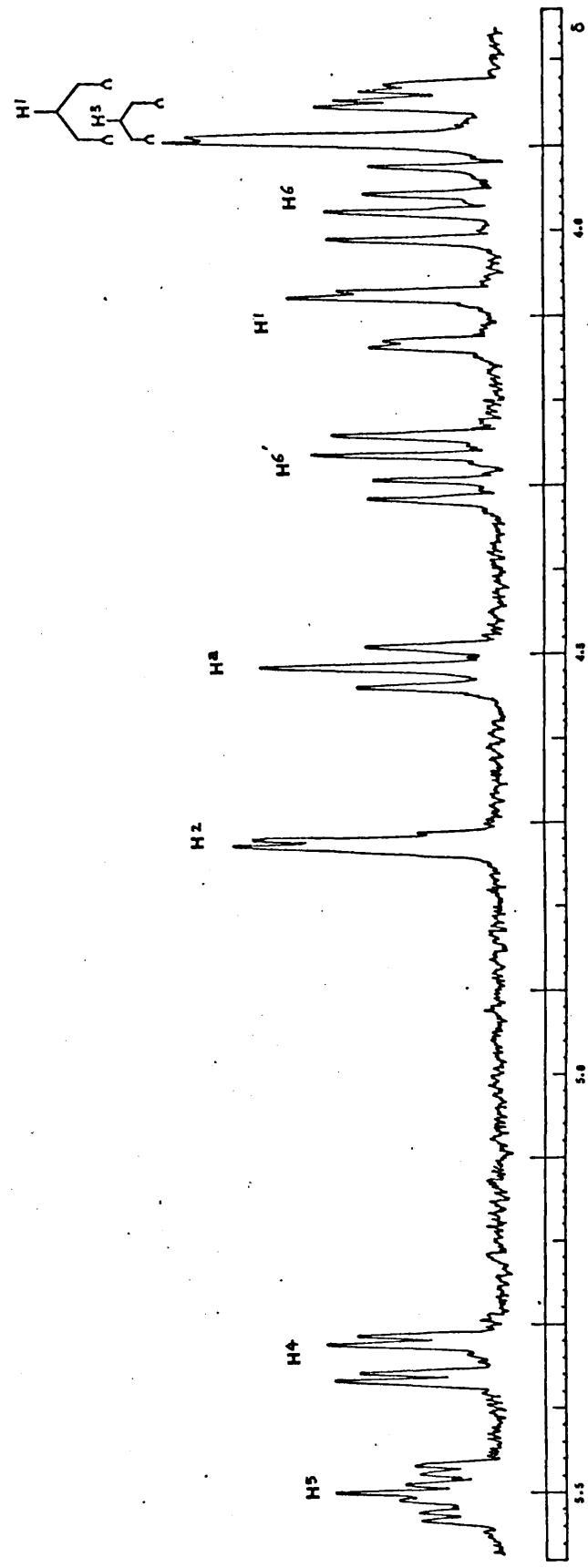


Fig. VIII-44 The low field part of the 220 MHz spectrum of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl DL-galactitol in $CDCl_3$. (500 Hz sweep width).

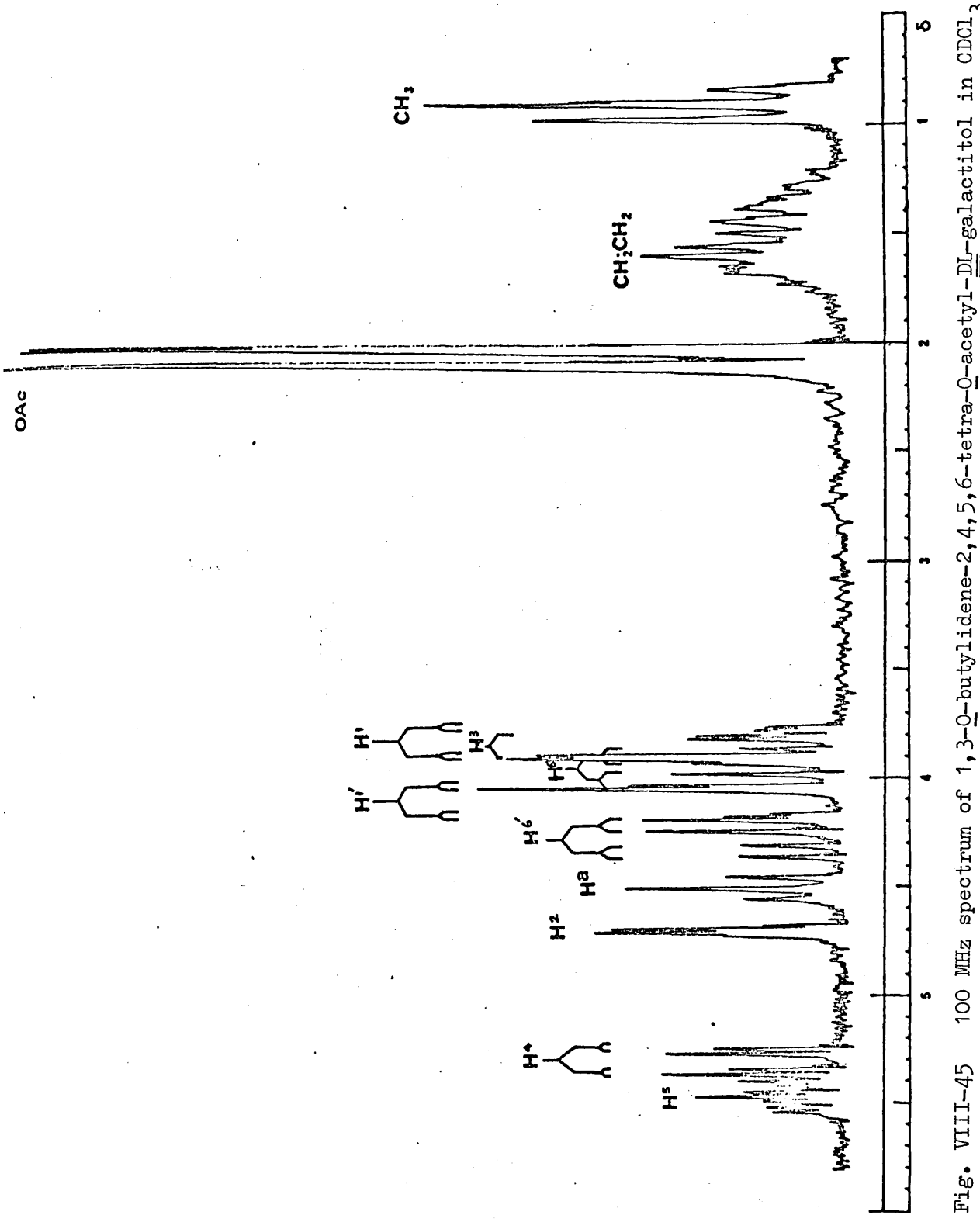


Fig. VIII-45 100 MHz spectrum of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-DL-galactitol in $CDCl_3$.

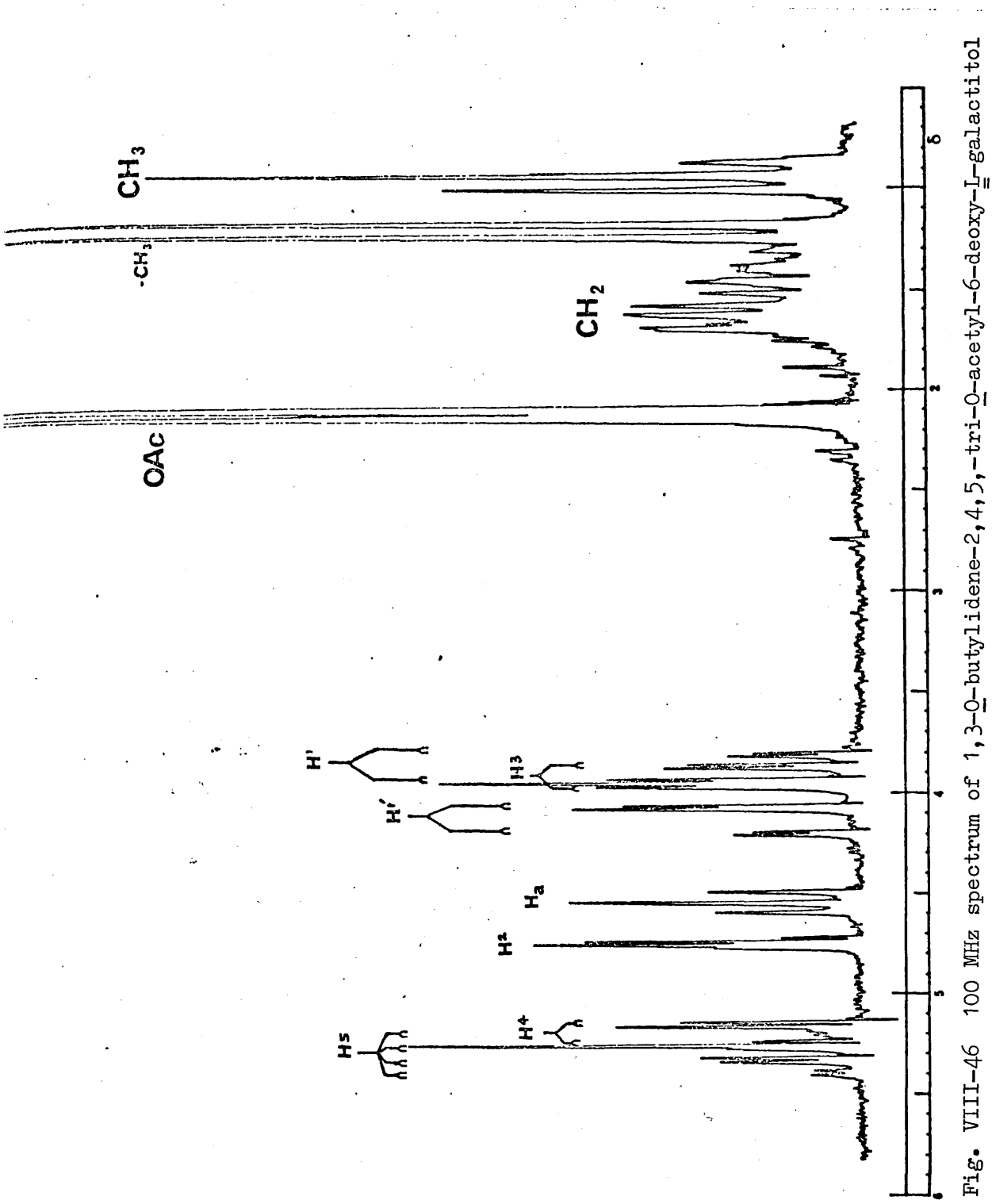


Fig. VIII-46 100 MHz spectrum of 1,3-O-butylidene-2,4,5,-tri-O-acetyl-6-deoxy-L-galactitol in $CDCl_3$.

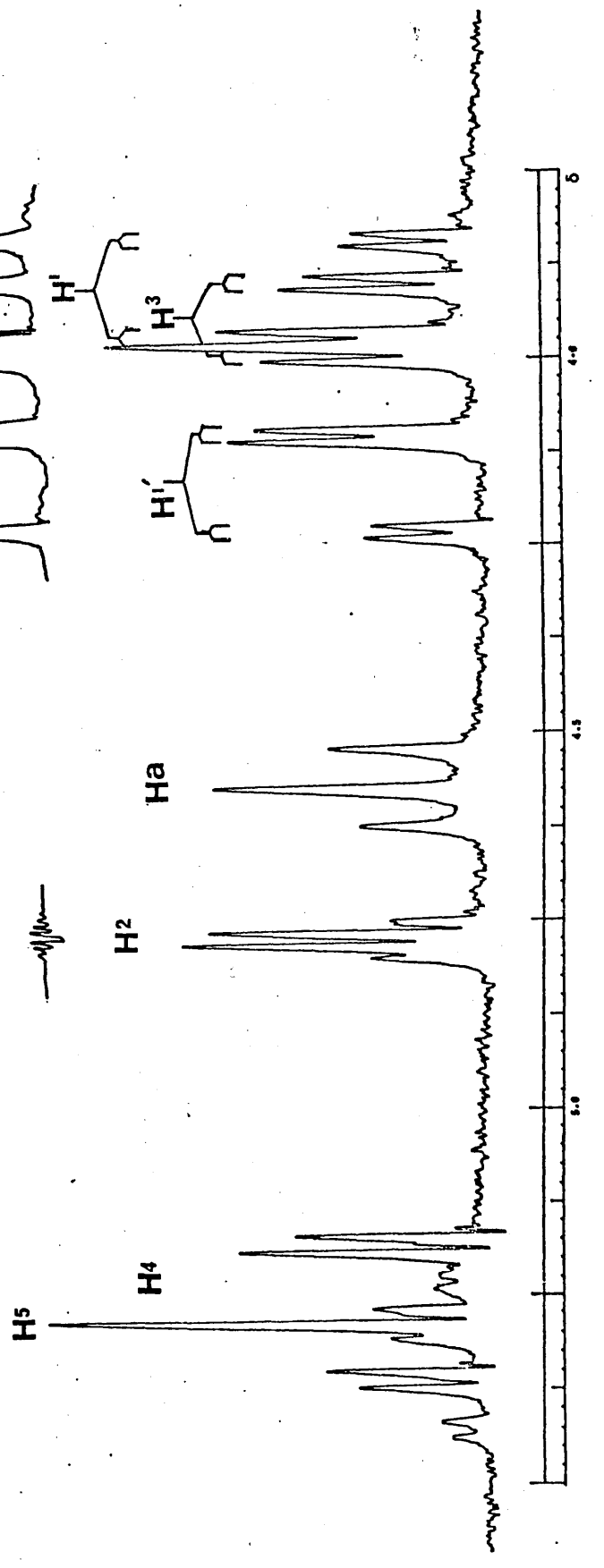


Fig. VIII-47 The low field part of the 100 MHz spectrum of 1,3-O-butylidene-6-deoxy-2,4,5-tri-O-acetyl-L-galactitol in $CDCl_3$ (250 Hz sweep width).

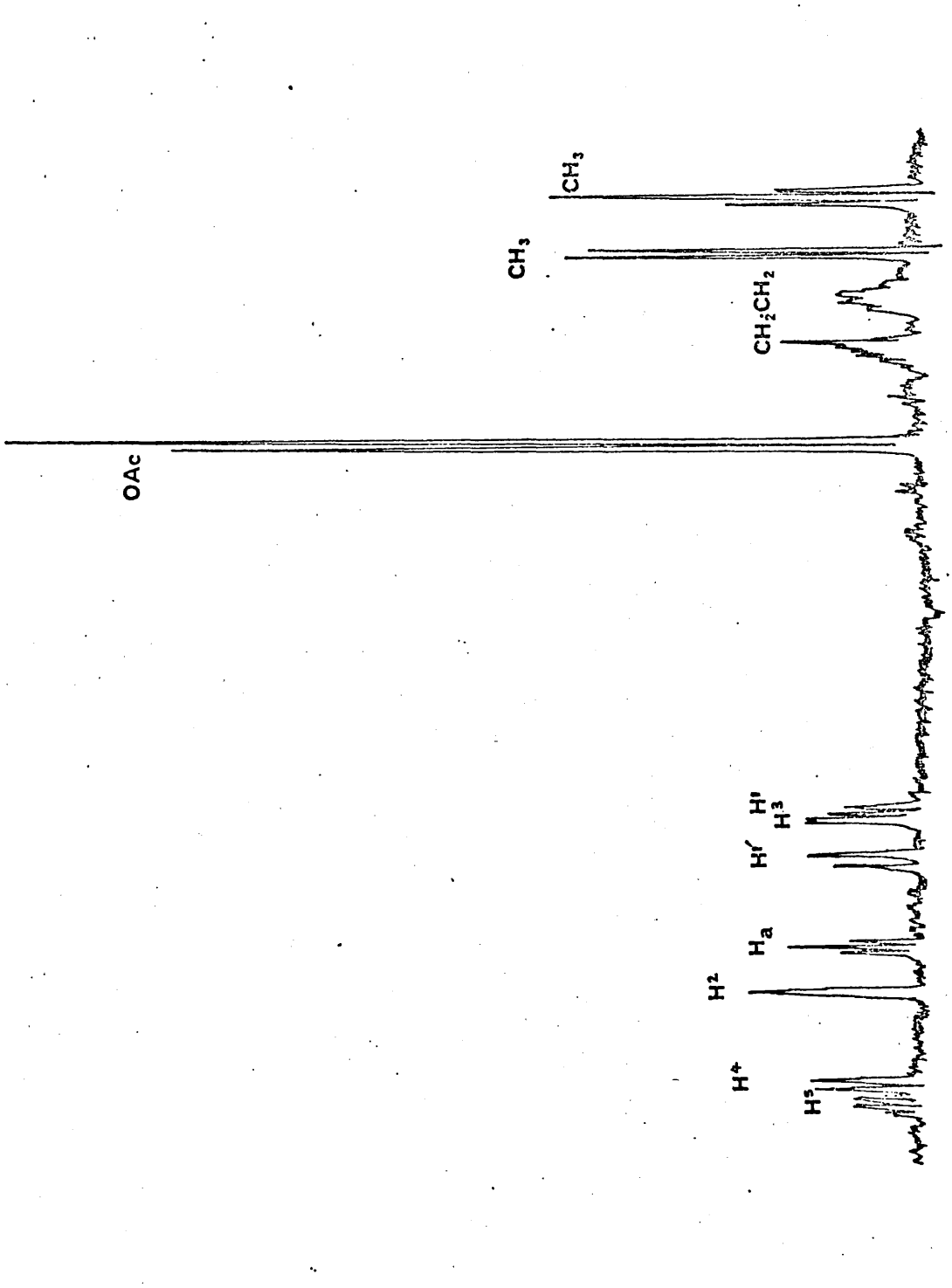


Fig. VIII-48 220 MHz spectrum of 1,3-O-butylidene-2,4,5-tri-O-acetyl-6-deoxy-L-galactitol in $CDCl_3$.

spectrum, the signals of $H1'$ were obscured due to overlapping of other signals in the region δ 4-4.5, but in the 220 MHz spectrum and its expansion (Fig. VIII-42), these signals and those of H^6 (a sextet) could be seen clearly. The signal of H^3 was observed in both spectra as six lines. The analogy in chemical shifts and coupling constants of the 1,3-ring protons of the three above mentioned acetals, indicated the similarities of these rings. In the 100 and 220 MHz spectra of compound (4) the signal of H^2 was a complicated multiplet due to the extra couplings to the hydroxyl group proton.

On the other hand, galactitol derivatives showed considerably different n.m.r. parameters. The vicinal coupling constants of the 1,3-ring protons were invariably small (also exhibited by the 1,3:4,6-derivatives), indicating that the conformations are synclinal. The proton H^2 occupies the equatorial position in these compounds hence the dihedral angles of the vicinal protons are about 60°.

The geminal protons (H^1,$H^{1'}$) in galactitol derivatives appeared as a pair of quartets. The magnitude of the geminal coupling constants was ~ 13 Hz in the 220 MHz spectrum(Fig. VIII-43).

The signal for H^2 appeared as a quartet at ca. δ 4.7 in all the spectra (Figs. VIII-44, 45, 46, 47) except in the 220 MHz spectra (Figs. VIII-43 and 48) where a broad line was obtained (poor resolution). However on the expanded scale some splittings were observed (Fig. VIII-44). The spin-decoupling experiments (irradiation of the signal of H^2) confirmed the assignments of the geminal proton signals and also the signal of H^3. In the 100 MHz spectra of both the galactitol derivatives

the signal of H^3 was a quartet partially overlapped by the signals of geminal protons. This quartet was collapsed to a doublet by the irradiation of the signal of H^2. This experiment is represented in the spectrum of 1,3-O-butylidene-2,4,5-tri-O-acetyl-6-deoxy-L-galactitol (Fig. VIII-47). In the case of the compound (1) more complex results were obtained as the signals of H^6 and $H^{6'}$ partially overlap the signals of H^1, $H^{1'}$ and H^3, however it was still possible to make assignments.

Conformational information was also supplied by the signals due to the side chain part of the monoacetals. In the galactitol derivatives the coupling constants J_{H^3,H^4} 9.0 Hz indicated an antiperiplanar conformation for these protons, whereas in the compound (2) the value of J_{H^3,H^4} was only 1.0 Hz suggesting that in this case the conformation is synclinal. The coupling constants J_{H^4,H^5} in the spectra of the compounds (3) and (2) were also small indicating the synclinal conformation of these protons. These results are in agreement with the planar zig-zag conformation of the polyols.

The signals of H^4 and H^5 in the spectra of the monoacetals appear at lowest field. The signal of H^4 in the spectra of the galactitol derivatives appeared as a quartet and the assignment was confirmed by double resonance at the centre of the quartet due to H^3, whereupon the coupling between H^3 and H^4 was not observed. The signal of H^5 was a multiplet of seven or eight lines. These signals were better separated in the 220 MHz spectra (Figs. VIII-44 and 48).

In the spectrum of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-L-gulitol in $CDCl_3$, the signals of H^4 and H^5 had coincidental shifts and therefore appeared as a broad singlet (Figs. VIII-40 and 41). Hence, in this case,

it was not possible to measure the magnitude of the J_{H^4,H^5}. Another interesting aspect of the spectrum was the extra splittings shown by the signal of H^6. Under the first order considerations, the maximum multiplicity expected from these signals is four lines, caused by a large geminal coupling and a second coupling to the vicinal proton H^5. However the signal of H^6 appeared as a pair of quartets (centred at δ 4.11) partially overlapping the quartet of $H^{1'}$, which implied that H^6 coupled to H^4 as well as H^5. The signal of $H^{6'}$ was a quartet as expected which partially overlapped the acetal-proton triplet. These signals were better separated in the 220 MHz spectrum (Fig. VIII-42), with chemical shifts δ 4.42 and 4.13.

A double resonance experiment (Fig. VIII-49) confirmed the above assignments. The irradiation of the signal of H^4 and H^5 at δ 5.36 simplified the signals of H^6 and $H^{6'}$ to doublets showing that the small splittings were due to the coupling of the geminal H^6 and $H^{6'}$ to H^4 and H^5. The existence of a long range coupling between H^6 and H^4 implied that these protons were either on a W path as in conformation (I) (Fig. VIII-50) or that they possessed the conditions for "Virtual Coupling".

A virtual coupling is possible when the coupling between H^4 and H^5 is large.[76] (Similarly the anomeric proton signal of β-D-galactopyranose penta-acetate appeared as a quartet due to virtual long range coupling to H^3, since the protons H^2 and H^3 possessed coincidental chemical shifts and also coupled strongly)[76]. In the extended planar zig-zag conformation (III) and in the conformation (I), the dihedral angle between H^4 and H^5 is small. But in the bent conformation (II), the dihedral angle is large.

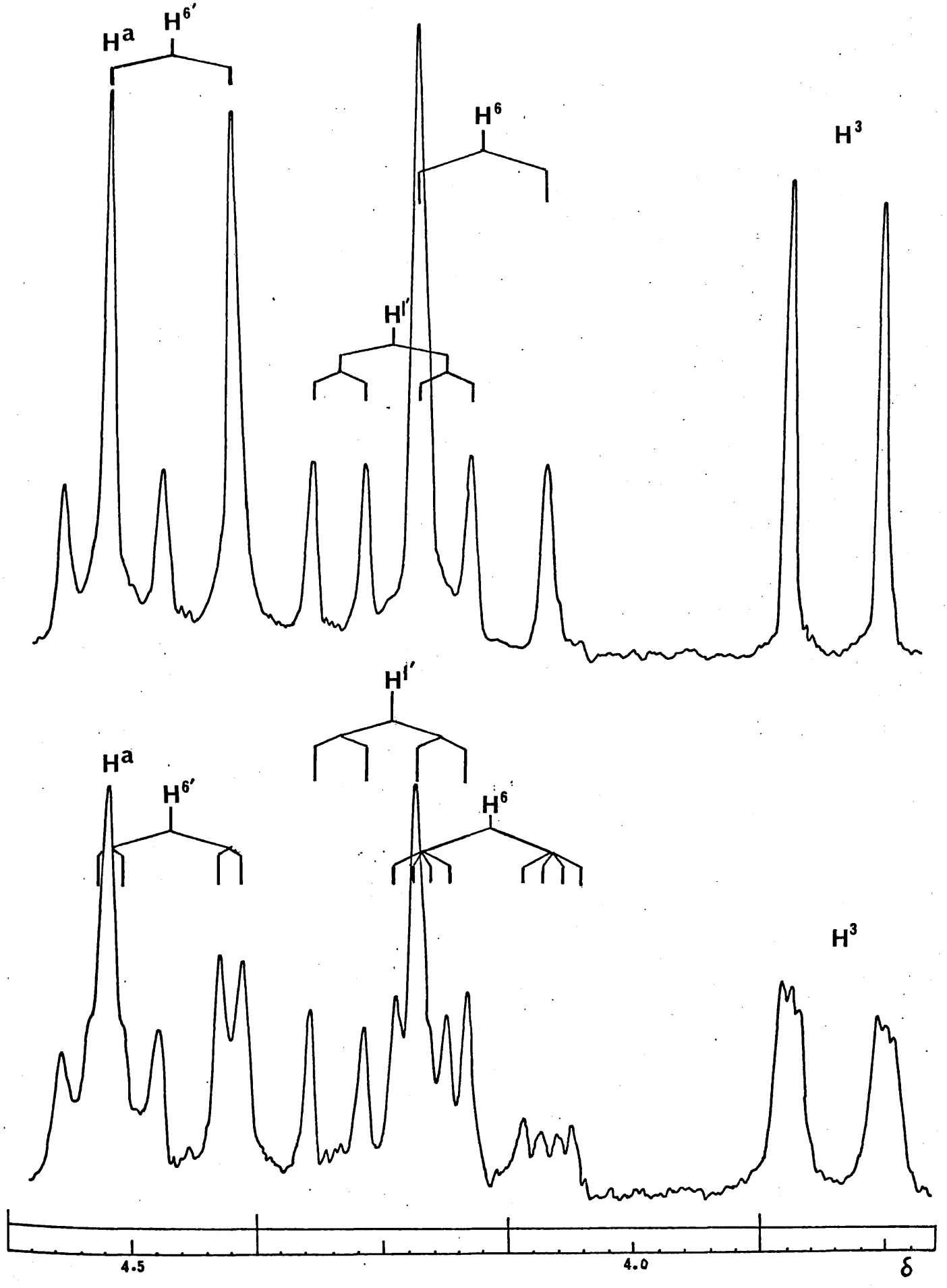


Fig. VIII-49

In the 100 MHz spectrum of the same compound in deutero benzene, the signals of H^4 and H^5 were partially separated. The signal of H^4 appeared as a quartet partially overlapping the multiplet of H^5 (Fig. VIII-51). In this case, by means of a double resonance experiment, it was possible to measure the coupling between H^4 and H^5.

The small splittings of the H^4 quartet were removed on irradiation of the signal of H^3 at δ 3.73, leaving a doublet with a large coupling constant of 8.0Hz, which was obviously due to the coupling of H^4 to H^5. The large coupling constant J_{H^4,H^5} suggested that these protons were almost antiperiplanar, which excluded the extended planar zig-zag conformation (III) (Fig. VIII-50) of the carbon chain and also the conformation (I), in which the protons H^4 and H^5 are synclinal. The most suitable conformation for the observed n.m.r. data was that of (II).

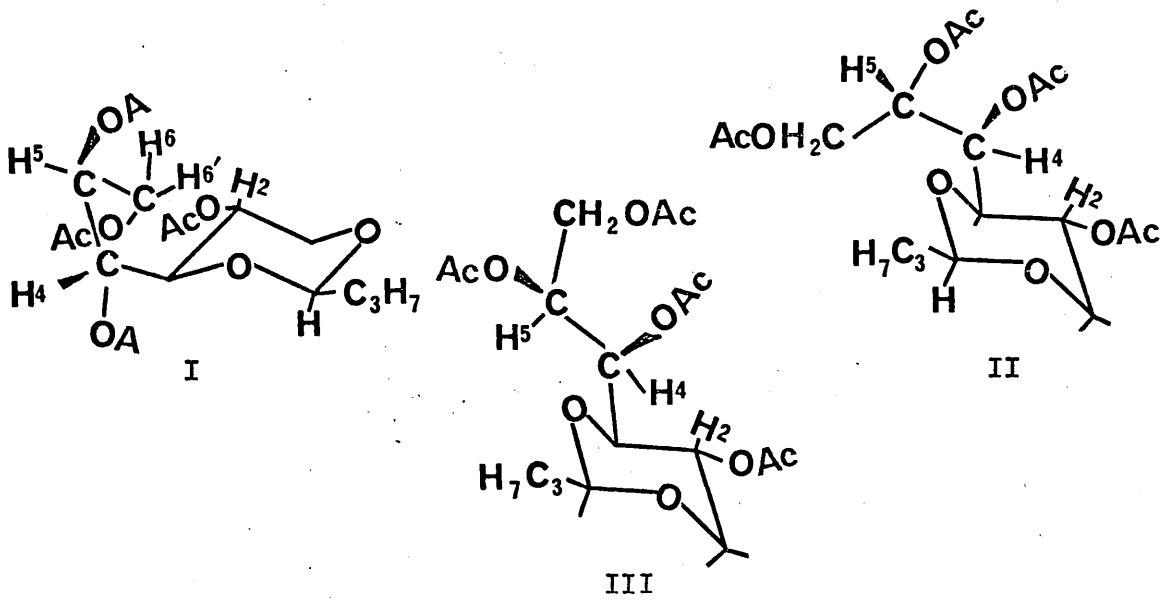


Fig. VIII-50

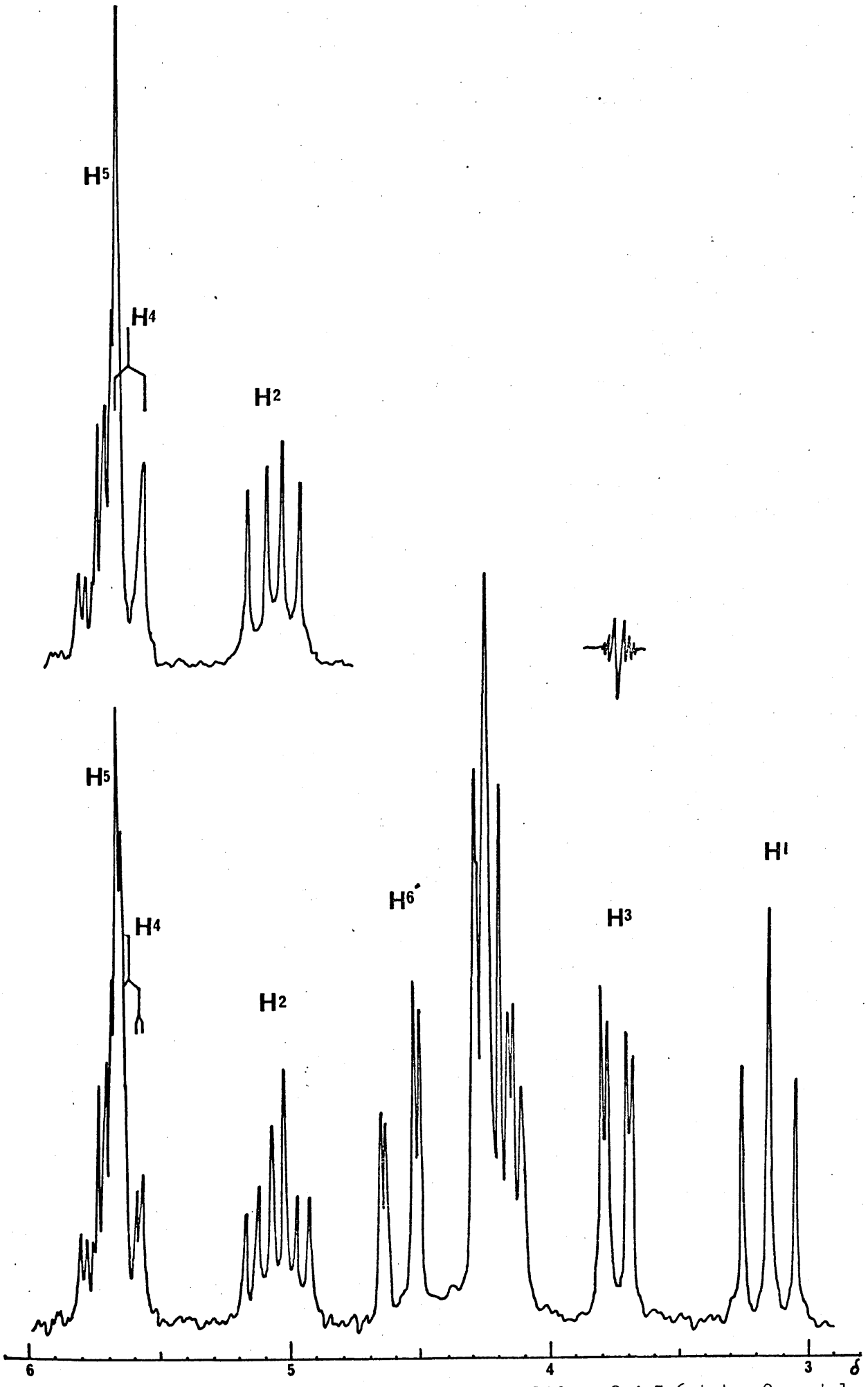


Fig. VIII-51 100 MHz spectrum of 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-L-gulitol in C_6D_6 (low field part).

ix) The Spectra of the Fully Acetylated 4,6-O-Butylidene Acetals of D-Galactose and D-Glucose

The 100 MHz spectrum of 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-galactopyranose was fully interpreted to show the existence of a cis fused ring system. The signals of H^6 and $H^{6'}$ appeared as pairs of symmetrical quartets. The signal of H^5 appeared as a quartet, very similar to the signal of H^2 in the galactitol derivatives (section VIII-viii), but at higher field. The assignments of the signals were confirmed by double resonance experiments. The signal of H^4 was located by the irradiation of the signal of H^3 (Fig. VIII-52), and the irradiation of H^5 confirmed the assignments of H^4, H^6 and $H^{6'}$ (Fig. VIII-53). In the 100 MHz spectrum, the signal of H^1 and H^2 were partially overlapped but 220 MHz spectrum provided a good separation (Fig. VIII-54). The magnitude of the J_{H^1,H^2} was found to be characteristic for a β-galactopyranose derivative (Table VIII-9). The coupling constants obtained are in agreement with the assumed cis fused ring conformation of this compound.

A complex 100 MHz spectrum was obtained for the 4,6-O-butylidene-β-D-glucopyranose tri-acetate in which the signal of $H^{6'}$ showed extra splittings, probably due to the "virtual coupling" of H^4 to $H^{6'}$ (Fig. VIII-55). The 220 MHz spectrum provided a better separation for the signals of H^1, H^2, H^3 and $H^{6'}$ but the signals of H^4, H^5 and H^6 remained unchanged (Fig. VIII-56). The magnitude of the J_{H^1,H^2} was characteristic for a β-glucopyranose derivative, and the values of J_{H^1,H^2}, and J_{H^2,H^3} were in agreement with the data obtained from the galactose acetals since the configurations of protons up to C-3 are the same in both compounds (Table VIII-10) but J_{H^3,H^4} was smaller in the spectrum of the galactose acetal. The coupling constant J_{H^3,H^4} was found to be large in the D-glucose acetal due to the trans diaxial relationship of the protons H^3 and H^4 in the trans fused ring system (Fig. VIII-56).

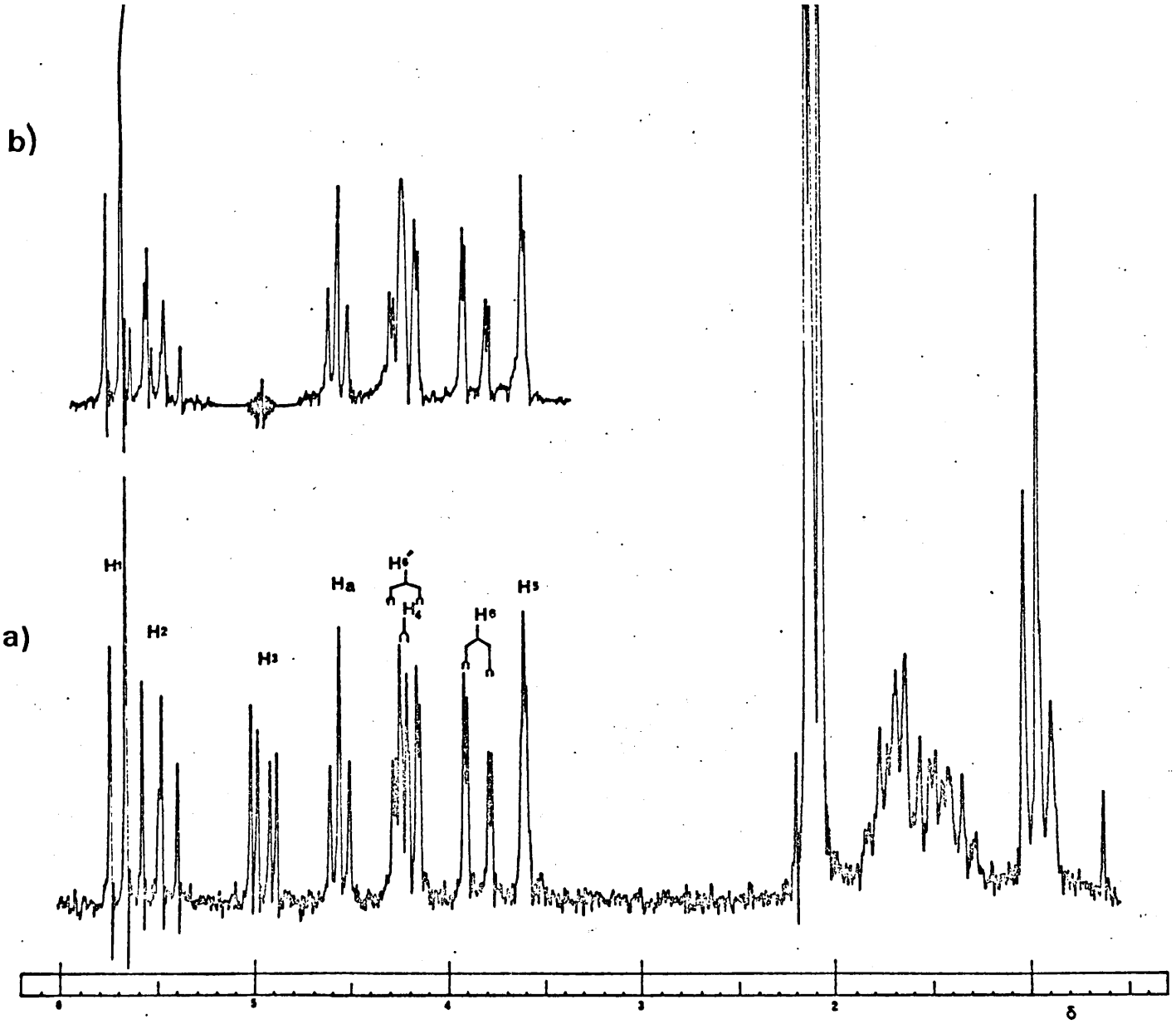


Fig. VIII-52 (a) 100 MHz spectrum of 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-galactopyranose in $CDCl_3$. (b) Double resonance experiment.

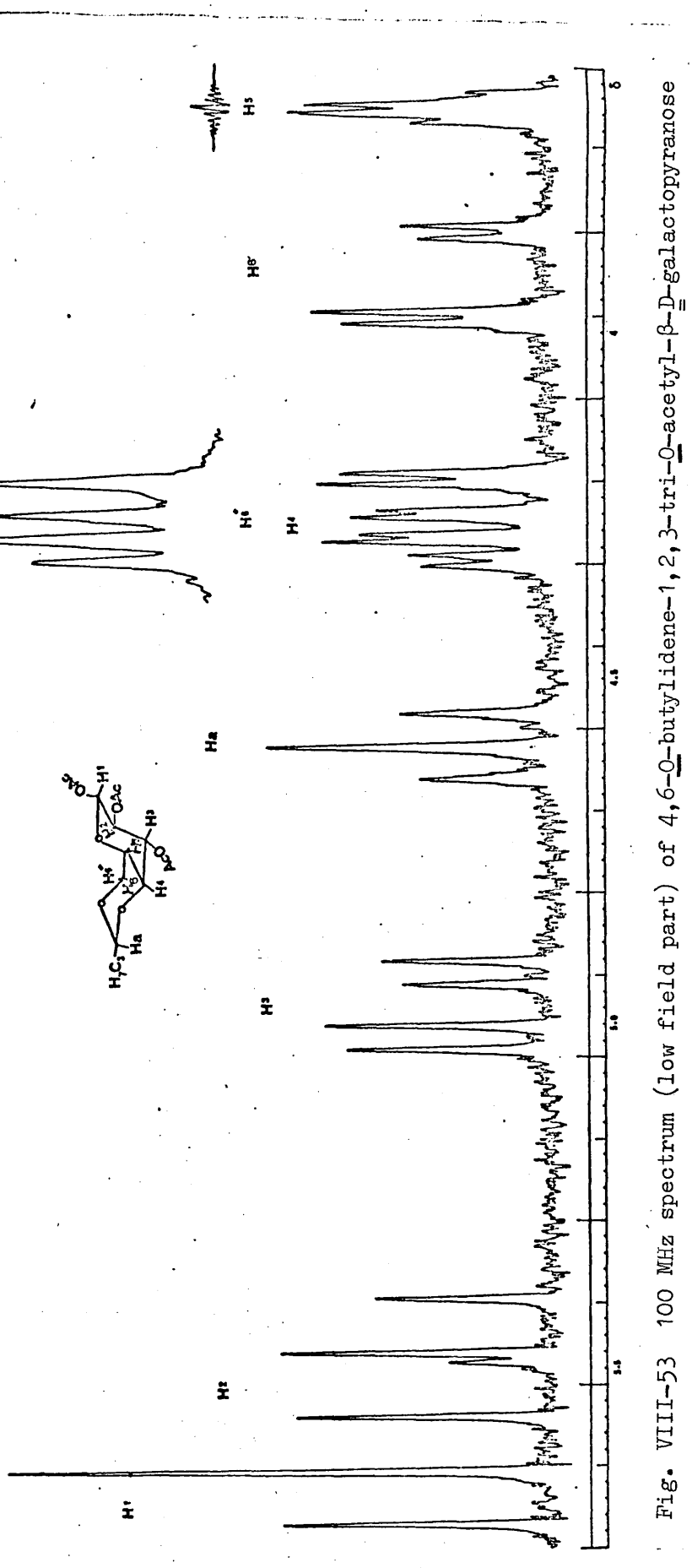


Fig. VIII-53 100 MHz spectrum (low field part) of 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-galactopyranose in $CDCl_3$ and the double resonance experiment.

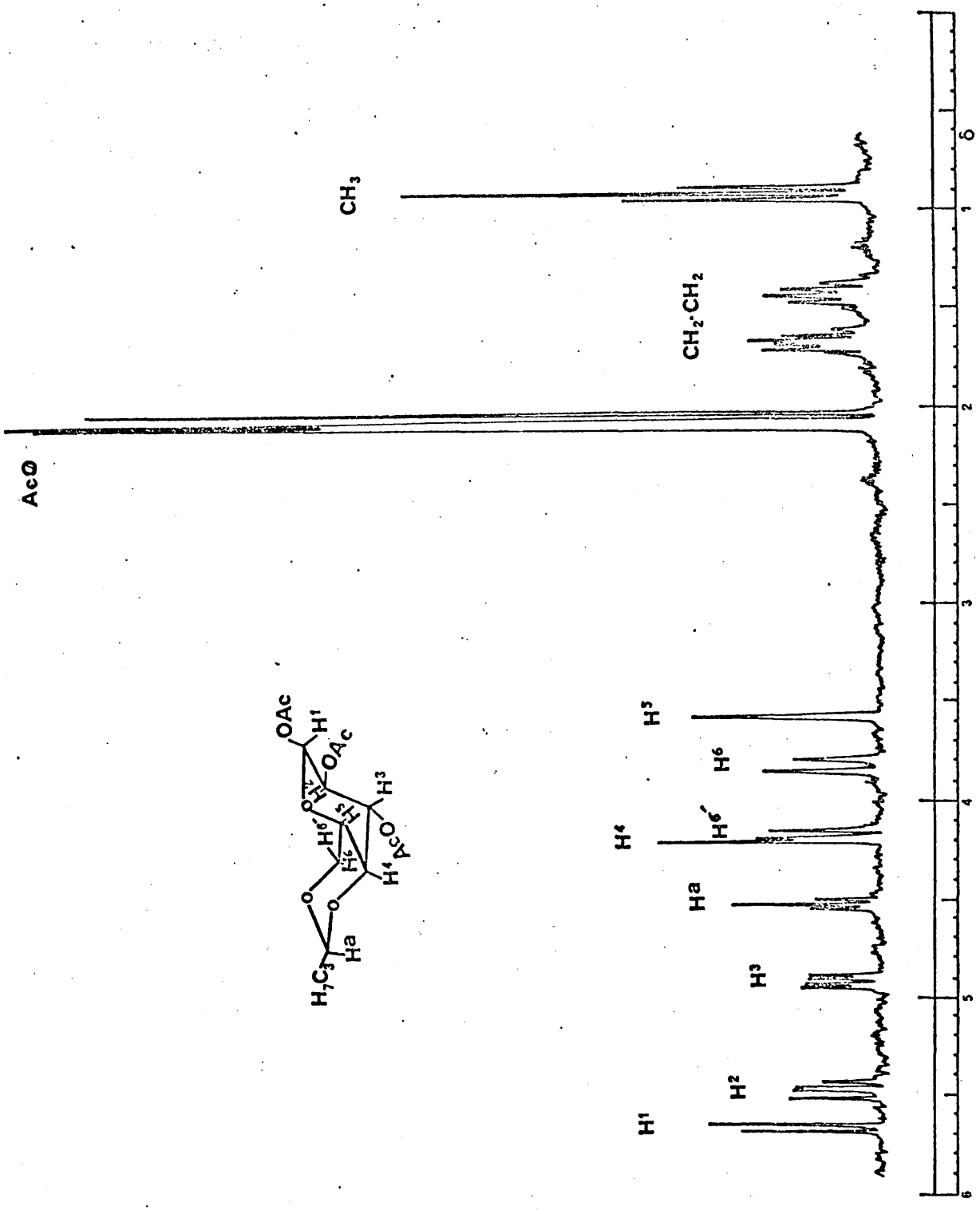


Fig. VIII-54 220 MHz spectrum of 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-galactopyranose in $CDCl_3$.

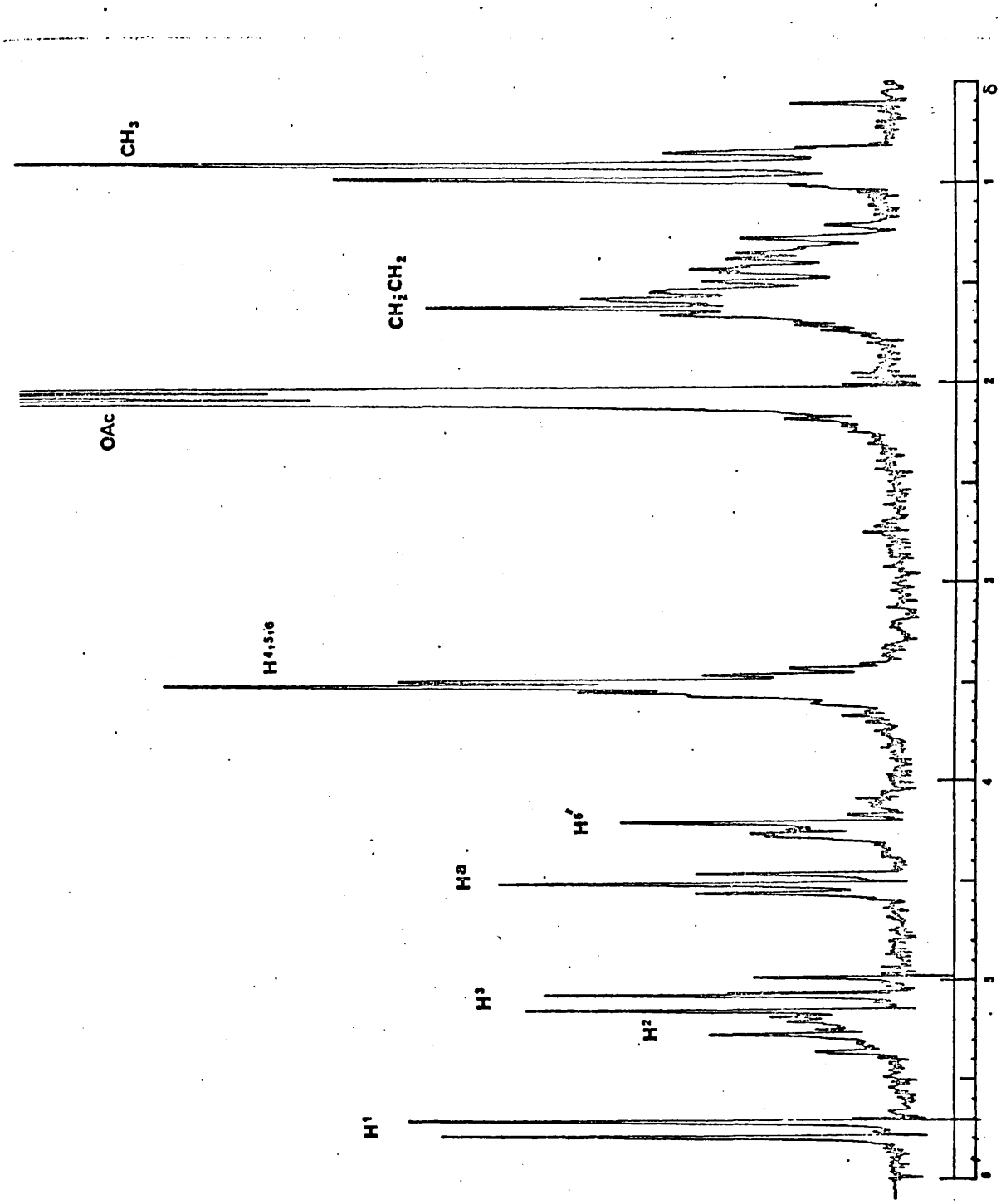


Fig. VIII-55 100 MHz spectrum of 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-glucopyranose in $CDCl_3$.

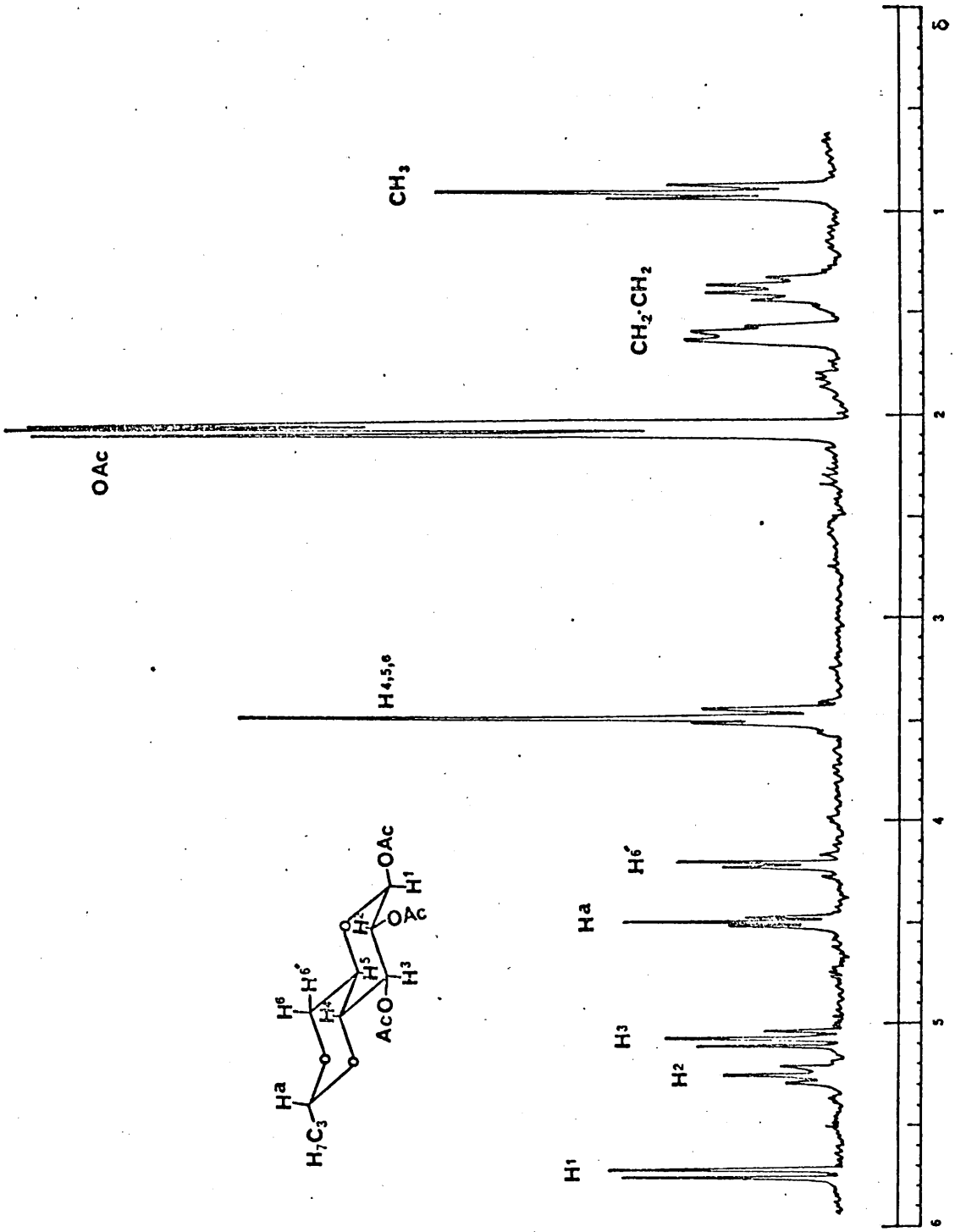
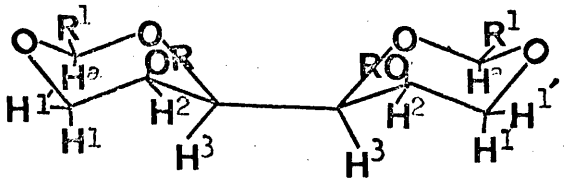


Fig. VIII-56 220 MHz spectrum of 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-glucopyranose in $CDCl_3$.



R	R_1	H_a		$H_{1'}$		H_1		H_2		H_3	
H	C_3H_7	463	407	407.0*	384	382.5*	361	361.0*	388	388.0*	
H	CH_2Cl	485	417		392		369		401		
Me	C_3H_7	460	429	429.0*	372	371.5*	322	322.0*	402	402.5*	
Ac	C_3H_7	451	421		386		483		396		
Bz	C_3H_7	441	427		389		511		410		
Me	C_6H_5	563	448		396		339		440		

Chemical shifts in Hz.

R	R_1	$J_{H_1H_{1'}}$		$J_{H_{1'},H_2}$		J_{H_1,H_2}		$J_{H_2H_3}$	
H	C_3H_7	-12.0	-12.0*	2.0	2.0*	1.5	1.5*	<1	<1*
H	CH_2Cl	-11.0		2.0		1.5		"	
Me	C_3H_7	-12.5	-12.0*	1.5	1.5*	1.5	1.5*	"	"
Ac	C_3H_7	-13.0		1.5		1.5		"	
Bz	C_3H_7	-13.0		1.0		1.0		"	
Me	C_6H_5	-12.0		1.0		1.0		"	

Coupling constants in Hz.

* Values obtained from the computed spectra.

Table VIII-3 Chemical shift and coupling constant data for some 1,3:4,6-diacetals of galactitol and their derivatives in chloroform-d.

	CHEMICAL SHIFTS					COUPLING CONSTANTS IN HZ	
	Hz 100 MHz	δ	Hz 220 MHz	δ		100 MHz	220 MHz
H_1	340	3.40	748.5	3.40	$J_{H}^{1,H1'}$	9.0	10.0
$H^{1'}$	422	4.22	927.5	4.22			
H^2	394	3.94	883.0	4.01	$J_{H}^{1, H2}$	9.0	10.0
H^3	381	3.81	844.5	3.83			
Ha	444	4.44			$J_{H}^{1', H2}$	4.7	5.5
CH_2			395	1.79	$J_{H}^{2,H3}$	8.0	8.5
CH_2			305	1.39			
CH_3			195	0.89	J_{HO-C-H}	1.5	-

Table VIII-4 Chemical shift and coupling constant data for 1,3:4,6-di-O-butylidene-D-mannitol in chloroform-d.

CHEMICAL SHIFTS	(220 MHz spectrum) Hz	δ
H^1	748	3.40
$H^{1'}$	925	4.20
H^2	869	3.95
H^3	783	3.55
H^4	—	—
$H^{5'}$	442	2.00
H^5	—	—
$H^{6'}$	899	4.09
H^6	829	3.75
Ha	988;999	4.49;4.54

COUPLING CONSTANTS	(220 MHz spectrum)
$J_{H^1H^{1'}}$	-10.0
$J_{H^1H^2}$	10.0
$J_{H^1H^{2'}}$	5.0
$J_{H^2H^3}$	10.0
$J_{H^3H^4}$	4.0
$J_{H^4H^5}$	—
$J_{H^4H^{5'}}$	—
$J_{H^5H^6}$	12.0
$J_{H^5H^{6'}}$	3.0
$J_{H^{5'}H^6}$	3.0
$J_{H^5H^{6'}}$	—
$J_{H^6H^{6'}}$	-12.0

Table VIII-5 Chemical shift and coupling constant data for 1,3:4,6-di-O-butylidene-5-deoxy-D-mannitol in chloroform-d.

	CHEMICAL SHIFTS					COUPLING CONSTANTS IN HZ	
	100 MHz Hz	δ	220 MHz Hz	δ		100 MHz	220 MHz
H^1	384	3.84	850.0	3.86	$J_{H^1,H^{1'}}$	-13.0	-13.0
$H^{1'}$	411	4.11	903.0	4.10	J_{H^1,H^2}	1.7	1.5
H^2	471	4.71	1039.5	4.73	$J_{H^{1'},H^2}$	1.5	1.5
H^3	388	3.88	851.5	3.87	J_{H^2,H^3}	1.5	1.5
H^4	531	5.31	1174.8	5.34	J_{H^3,H^4}	9.0	9.5
H^5	547	5.47	1210.0	5.50	J_{H^4,H^5}	2.2	2.5
H^6	396	3.96	872.5	3.97	J_{H^5,H^6}	7.0	8.5
$H^{6'}$	428	4.28	941.0	4.28	$J_{H^5,H^{6'}}$	5.2	5.5
Ha	451	4.51	993.5	4.52	$J_{H^6,H^{6'}}$	-11.7	-12.0
CH_2			370.0; 320.0	1.67; 1.45			
CH_3			200.0	0.91			
OAc			477.5	2.17			
			475.0	2.16			
			390.0	1.77			
			395.0	1.79			

Table VIII-6 Chemical shift and coupling constant data for 1,3-O-butylidene-2,4:5,6-tetra-O-acetyl-DL-galactitol in chloroform-d.

	CHEMICAL SHIFTS					COUPLING CONSTANTS IN HZ	
	100 MHz		220 MHz				
	Hz	δ	Hz	δ		100 MHz	220 MHz
H^1	384	3.84	850.5	3.87	$J_{H^1,H^{1'}}$	-13.0	-13.0
$H^{1'}$	410	4.10	900.5	4.09	J_{H^1,H^2}	1.7	1.5
H^2	471	4.71	1039.0	4.72	$J_{H^{1'},H^2}$	1.5	1.0
H^3	388	3.88	854.5	3.88	J_{H^2,H^3}	2.0	1.5
H^4	518	5.18	1139.5	5.18	J_{H^3,H^4}	9.0	9.5
H^5	528	5.28	1160.0	5.27			
H_{deoxy}	118	1.18	210.0	0.95	J_{H^4,H^5}	2.2	2.0
Ha	451	4.51					
CH_2			355.0;305.0	1.61;1.38	$J_{H^5,H^{deoxy}}$	6.5	7.0
CH_3			190	0.86			
OAc			475.0;455.0	2.16;2.07			

Table VIII-7 Chemical shift and coupling constant data for 1,3-O-butylidene-2,4,5-tri-O-acetyl-6-deoxy-L-galactitol in chloroform-d.

	CHEMICAL SHIFTS				COUPLING CONSTANTS IN HZ		
	100 MHz		220 MHz				
	Hz		Hz			100 MHz	220 MHz
H^1	337.0	3.37	742.5	3.37	$J_{H^1,H^{1'}}$	-10.0	-10.5
$H^{1'}$	436.5	4.36	925.0	4.20	J_{H^1,H^2}	10.0	10.5
H^2	475.0	4.75	1145.0	5.20	$J_{H^{1'},H^2}$	5.2	5.5
H^3	377.0	3.77	827.5	3.77	J_{H^2,H^3}	10.0	9.5
H^4	536.5	5.36	1182.5	5.38	J_{H^3,H^4}	1.0	<1
H^5	536.5	5.36	1182.5	5.38			
H^6	411.0	4.11	907.5	4.42	J_{H^4,H^5}	-	-
$H^{6'}$	443.0	4.43	972.5	4.13	J_{H^5,H^6}	2.2	
Ha	449.0	4.49					
CH_2			357.5;310.0	1.63;1.41	$J_{H^5,H^{6'}}$		
CH_3			202.5	0.92			
OAc			460.0;450.0	2.09;2.05	$J_{H^6,H^{6'}}$	-12.5	-13.5
			445.0	2.02			

Table VIII-8 Chemical shift and coupling constant data for 1,3-O-butylidene-2,4,5,6-tetra-O-acetyl-L-gulitol in chloroform-d.

	CHEMICAL SHIFTS					COUPLING CONSTANTS IN HZ	
	100 MHz		220 MHz			100 MHz	220 MHz
	Hz	δ	Hz	δ			
H^1	566	5.66	1242	5.64	J_{H^1,H^2}	8.0	8.0
H^2	548	5.48	1199	5.45	J_{H^2,H^3}	8.0	8.0
H^3	492	4.92	1078	4.90	J_{H^3,H^4}	4.0	3.5
H^4	418	4.18	918	4.17			
H^5	357	3.57	781	3.55	J_{H^4,H^5}	1.0	-
H^6	380	3.80	836	3.80	J_{H^5,H^6}	2.0	1.0
$H^{6'}$	417	4.17	908	4.12	$J_{H^5,H^{6'}}$	3.0	1.0
Ha	452	4.52	991	4.50			
CH_2	-	-	363; 308	1.65; 1.40	$J_{H^6,H^{6'}}$	12.5	-13.0
CH_3	-	-	199	0.90			
OAc	-	-	461; 458; 447	2.09; 2.08; 2.03			

Table VIII-9 Chemical shift and coupling constant data for 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-galactopyranose in chloroform-d.

	CHEMICAL SHIFTS					COUPLING CONSTANTS IN HZ	
	100 MHz		220 MHz				
	Hz	δ	Hz	δ		100MHz	220 MHz
H^1	573	5 73	1258	5.71	J_{H^1,H^2}	–	10.0
H^2	–	–	1151	5.23			
H^3	–	–	1110	5.04	J_{H^2,H^3}	–	10.0
H^4	–	–	765	3.47	J_{H^3,H^4}	–	10.0
H^5	–	–	"	"			
H^6	–	–	765	3.47	J_{H^4,H^5}	–	–
$H^{6'}$	419	4.19	922	4.19	J_{H^5,H^6}	–	–
Ha	450	4.50	983	4.46	$J_{H^5,H^{6'}}$	–	–
CH_2	–	–	350;298	1.59;1.35			
CH_3	–	–	195	0.88	$J_{H^6,H^{6'}}$	–	-7.0
OAc	–	–	460,452	2.09;2.05			
			447	2.03			

Table VIII-10 Chemical shift and coupling constant data for 4,6-O-butylidene-1,2,3-tri-O-acetyl-β-D-glucopyranose in chloroform-d.

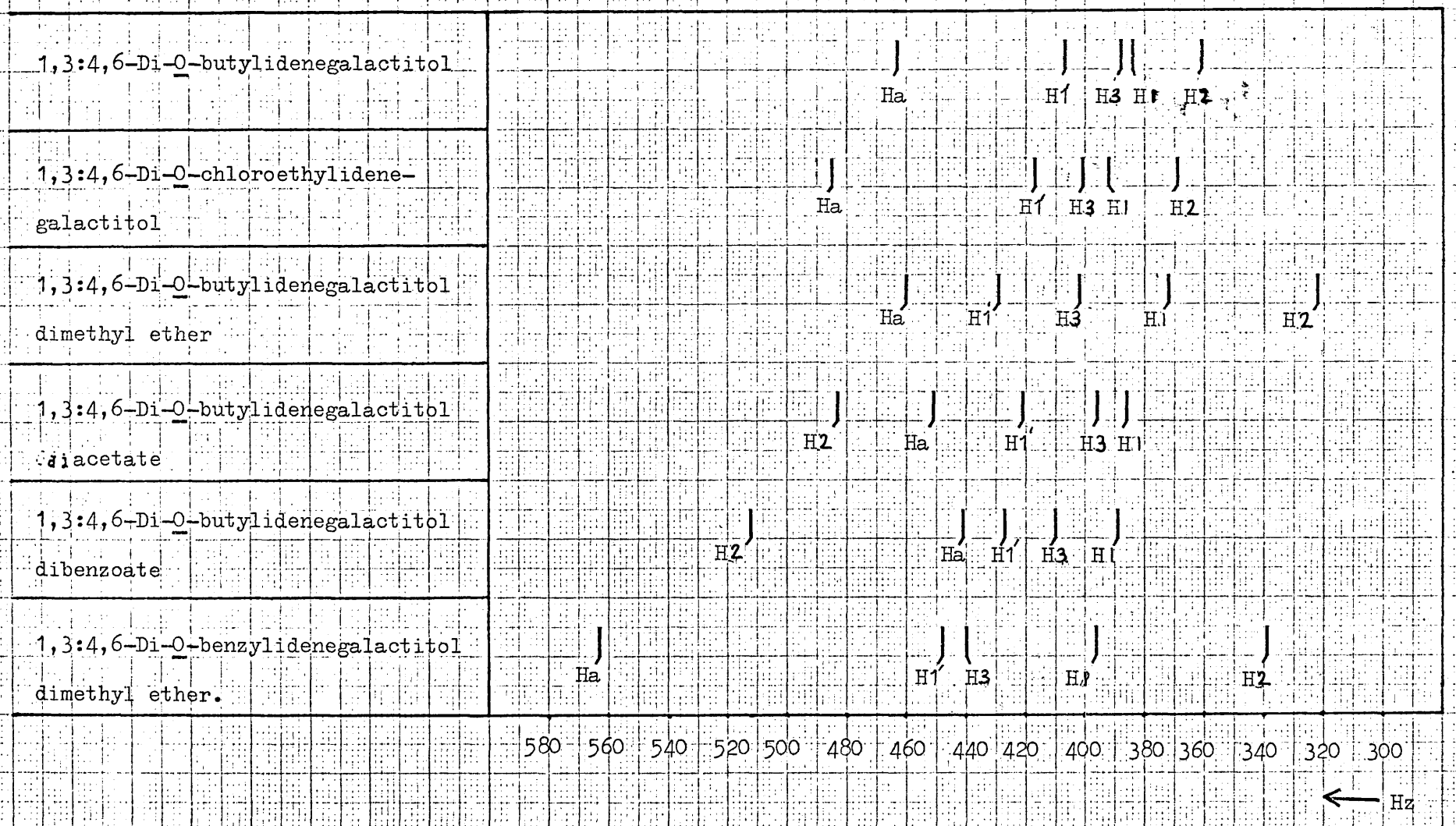


Fig. VIII-57 Chemical shifts of some 1,3:4,6-diacetals of galactitol

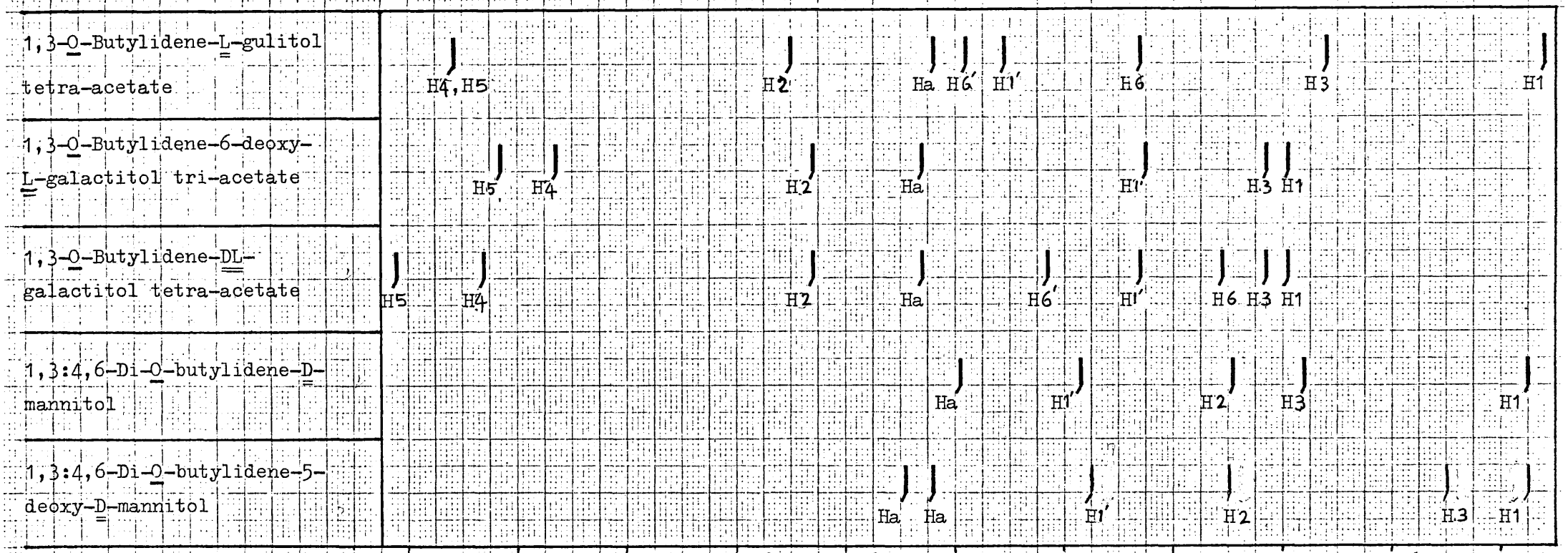


Fig. VIII-58 Chemical shifts of some butylidene acetals.

x) ^{13}C Spectra of Some Butylidene Acetals

The ^{13}C n.m.r. spectra of some butylidene acetals suggested that this technique could be applied to the investigations of cyclic acetals. The figure VIII-59 shows the ^{13}C spectrum of 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol; the acetal-carbon signals appear at lowest field and well separated from the ring protons. The high field signals are due to the propyl group carbons, and also well separated from the ring protons. There is no data on the ^{13}C spectra of cyclic acetals in the literature although some polyols have been studied.[102] It is known that the number of the signals, in the spectra of symmetrical polyols are equal to the half of the number of carbon atoms in the molecule.[102] The same situation was observed for the symmetrical cyclic acetal derivatives, such as the 1,3:4,6-di-O-butylidenegalactitol which showed only seven signals. However in the ^{13}C spectrum of the unsymmetrical acetal, 1,3-O-butylidene-DL-galactitol, one signal for each carbon atom was observed.

	Acetal carbons	Ring protons	Propyl groups
1,3:2,4:5,6-Tri-O-butylidene-DL-galactitol	105.3	78.4	37.2
	101.5	74.2	36.9
	98.2	71.8	35.9
		69.4	17.7
		68.3	17.4
		65.6	14.1
			13.9
1,3-O-Butylidene-DL-galactitol	103.4	78.4	43.5
		72.9	18.0
		71.1	14.3
		69.1	
		64.2	
		63.6	
1,3:4,6-Di-O-butylidene-2-deoxy-D-glucitol	102.6	80.2	37.1
	102.0	77.0	36.4
		70.5	17.5
		66.5	17.2
		61.5	14.0
1,3:4,6-Di-O-butylidene-DL-galactitol	102.6	76.3	36.7
		72.1	17.2
		62.6	10.0

Table VIII- 11 ^{13}C Chemical shifts (δ) of some butylidene acetals relative to tetramethyl silane.

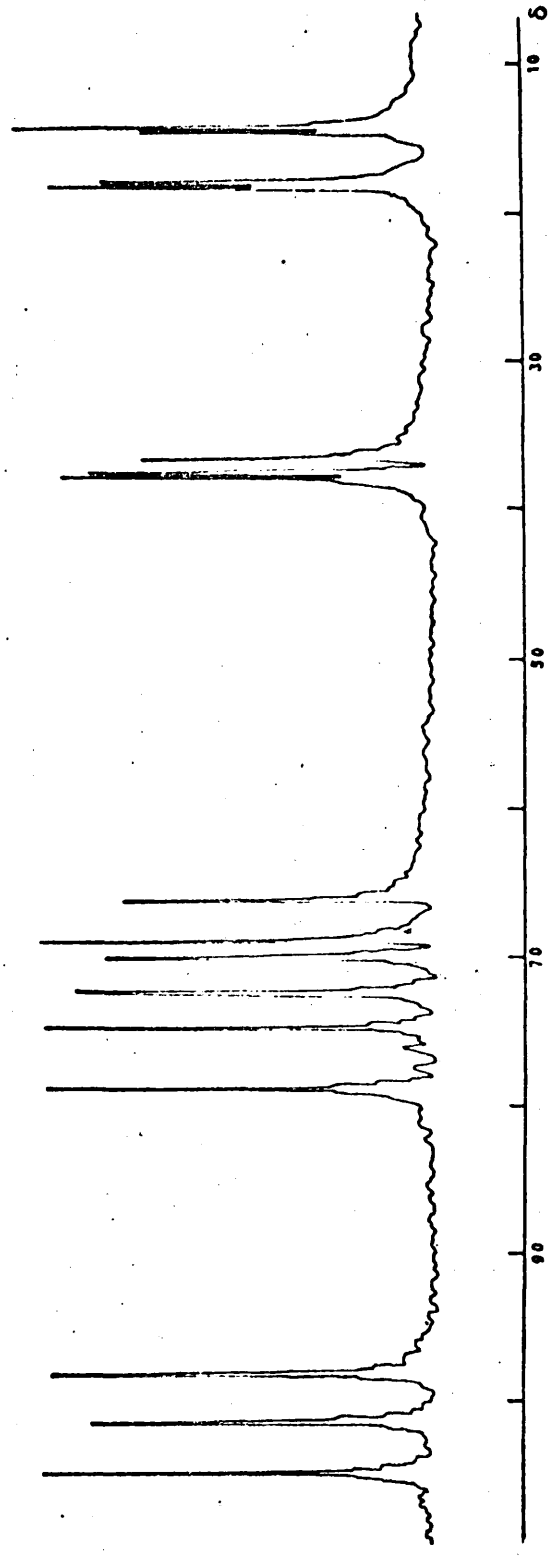


Fig. VIII-59 ^{13}C N.m.r. spectrum of 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol (solvent $CDCl_3$).

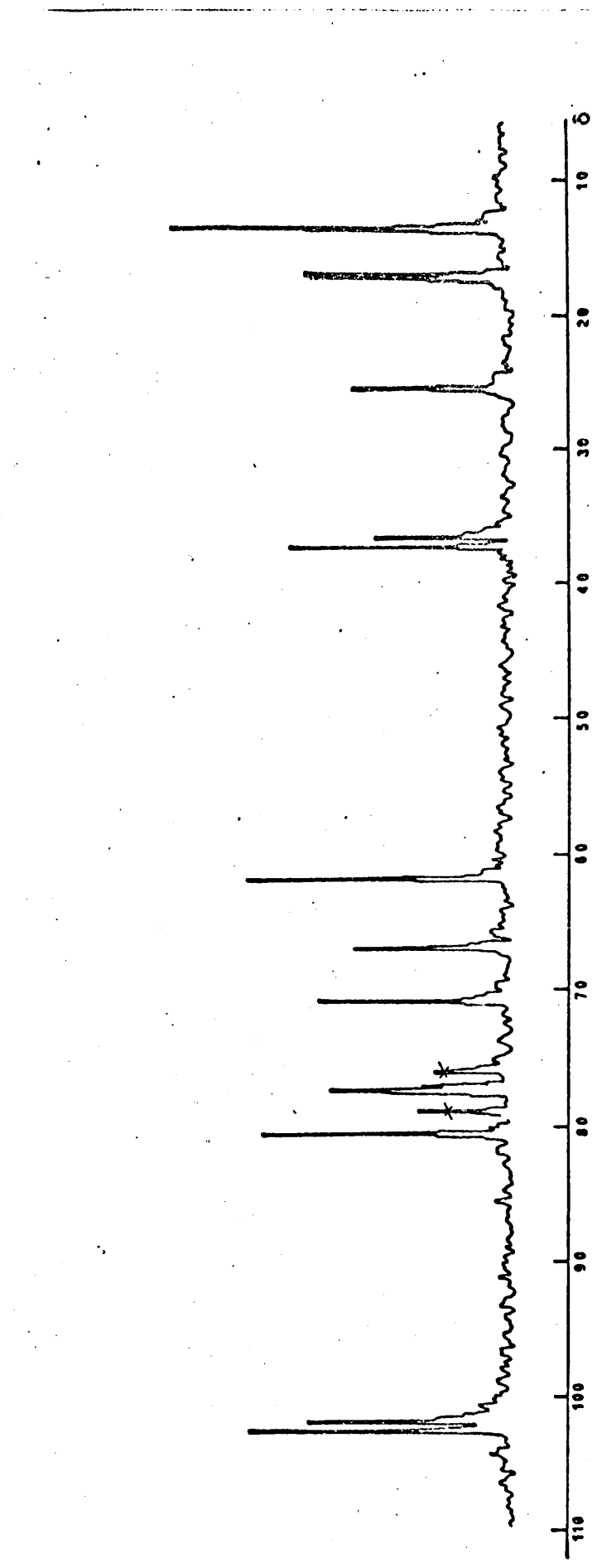


Fig. VIII-60 ^{13}C N.m.r. spectrum of 1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol (solvent $CDCl_3$).

IX The Application of Infrared and Mass Spectroscopy to the Structural Investigations

i) Infrared Spectroscopy

The characteristic -OH stretching frequency (3500-3700 cm^{-1}) in the infrared spectra of hydroxy compounds may be a valuable tool in obtaining structural information. However, the formation of hydrogen bonding, alters the appearance of the spectrum, therefore reliable information can only be obtained in non-polar solvents, such as carbon tetrachloride, as very dilute solutions. Concentrations of 0.005M in carbon tetrachloride are considered to be free from intermolecular hydrogen bonding.

The intramolecularly bonded hydroxyl groups absorb at lower frequencies than the free hydroxyl groups. In a wide range of 5-hydroxy-1,3-dioxane derivatives, the free hydroxyl groups were found to be in the range 3633 - 3644 cm^{-1} and the bonded hydroxyl groups in the range 3592 - 3604 cm^{-1}. [103]

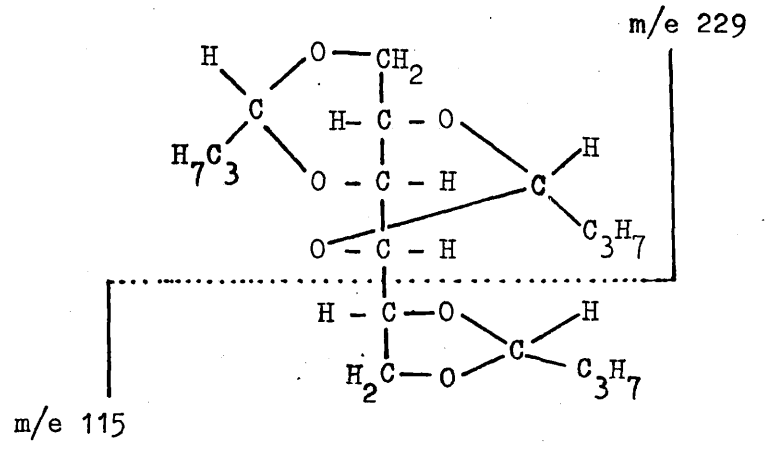
The i.r. spectra of 1,3:4,6-di-O-butylidenegalactitol and 2,4:5,6-di-O-butylidene-1-deoxy-D-glucitol in carbon tetrachloride at concentrations lower than 0.005M, showed sharp absorption bands at 3580 cm^{-1}, which suggested that the hydroxyl groups of these compounds had similar conformations. The band at 3580 cm^{-1} is characteristic for intramolecularly bonded secondary hydroxyl groups.[72] The i.r. spectra of 1,3:4,6-di-O-butylidene-D-mannitol and 1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol, showed slightly broader absorption bands at 3550 cm^{-1} and 3540 cm^{-1} respectively. Similarities of the absorption bands again suggested similar conformations for the hydroxyl groups.

The absorption lines in the i.r. spectrum of the 2,4:5,6-di-O-butylidene-3-O- methyl-D-glucitol were at 3708, 3645 and 3612 cm^{-1}. The absorptions at 3612 and 3648 cm^{-1} were repeated for 2,4:5,6-di-O-isopropylidene-3-O-methyl-D-glucitol. The line at 3612 cm^{-1} was claimed[65] to be characteristic for primary hydroxyl groups.

ii) The Mass Spectra of Some Butylidene Acetals

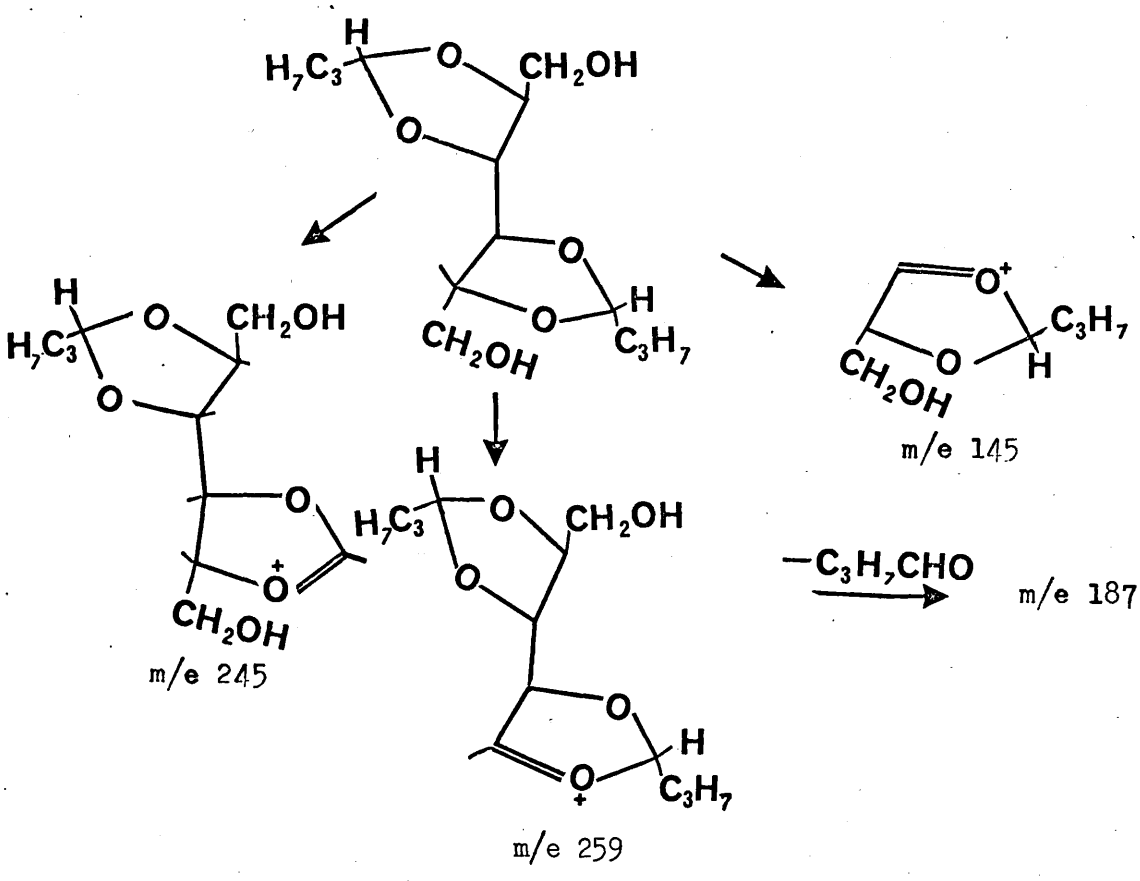
In the mass spectra of the butylidene acetals, the molecular ion $(M)^+$ and the ion for $(M-1)^+$ are always observed,[104] the ion $(M-1)^+$ being found in higher abundance. The other characteristic ion is the $(M-43)^+$, formed by the loss of n-propyl group, which is especially intense in the spectra of 2,3:4,5-dibutylidenegalactitol and 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol. The "half-ions" observed in the spectra of the cyclic acetals are formed by the "h-rupture" mechanism,[105] which involves the fission of the bond separating the two rings. The mass number of the half-ions are equal to the half of the molecular weight in the symmetrical molecules. In non-symmetrical molecules more than one h-ion can be observed and sum of the mass number of these signals give the molecular weight. The fused ring systems also give h-ions by a different mechanism.[105,106]

In the mass spectrum of the 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol the intense peaks at m/e 229 and m/e 115 are formed by the h-rupture mechanism as shown below.



The spectrum of 1,3:4,6-di-O-butylidenegalactitol dimethyl ether contained an intense peak at m/e 275 and half-ion at m/e 159 (table IX-1).

The most abundant peak in the spectrum of 2,3:4,5-di-O-butylidene-galactitol was m/e 247. The other characteristic peak was the h-ion at m/e 145. The peak, m/e 259 formed by the loss of ($-CH_2OH$) group from the molecule, gave the m/e 187 by further loss of butyraldehyde. Some fragmentation of this compound is shown below.



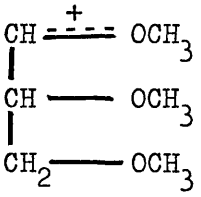
In the mass spectrum of the 2,4:5,6-di-O-butylidene-DL-galactitol, the absence of the peak at m/e 145 supported the n.m.r. evidence in favour of the assumed structure (section VIII-v_) and discarded the structure 1,3:4,5-di-O-butylidene-DL-galactitol, from which the ion m/e 145 could have arisen as the h-ion. The h-ions m/e 175 and m/e 115 expected from the 2,4:5,6-diacetal were in fact observed. However these peaks also exist in the spectra of other galactitol acetals and therefore they cannot be regarded as structural evidence.

	M	M-1	M-C_3H_7	h-ions
1,3:4,6-Di-O-butylidenegalactitol dimethyl ether	318	317	275	159
1,3:2,4:5,6-Tri-O-butylidene-DL-galactitol	344	343	301	229, 115
2,4:5,6-Di-O-butylidene-DL-galactitol	290	289	247	175, 115
2,3:4,5-Di-O-butylidenegalactitol	290	289	247	145
2,4:5,6-Di-O-butylidene-D-glucitol dimethyl ether	318	317	275	203, 115
2,4:5,6-Di-O-butylidene-1-deoxy-3-O-methyl-D-glucitol	288	287	245	173, 115

Table IX-1 Some characteristic peaks in the spectra of certain butylidene acetals

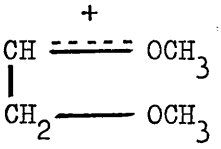
iii) The Mass Spectra of the Partially Methylated Alditol Acetates Obtained from the Cyclic Acetals

The fragments m/e 133 (A) and m/e 89 (B) were observed in the mass spectra of the 2,4,5,6-tetra-O-methyl-DL-galactitol diacetate and 1,4,5,6-tetra-O-methyl-DL-galactitol diacetate. The secondary fragments derived from (A) by the loss of methoxyl groups and methanol appeared at m/e 102, m/e 71, and m/e 101.[107]



m/e 133

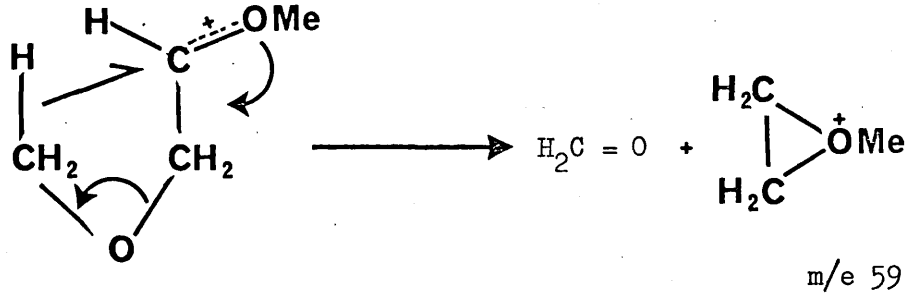
A



m/e 89

B

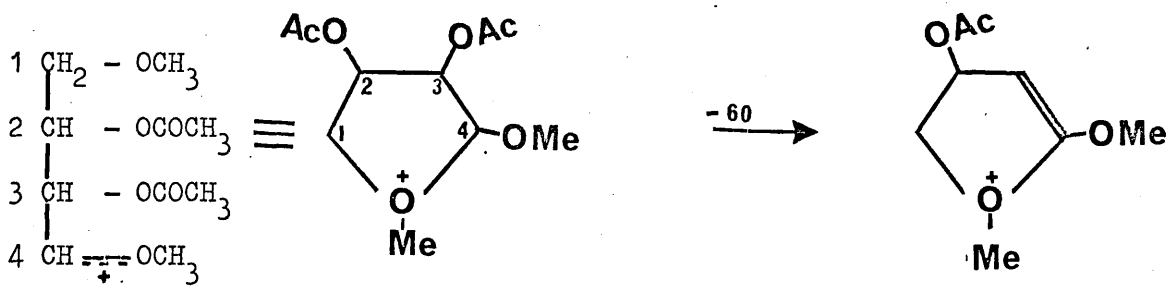
The fragment m/e 59 (C) was formed by formaldehyde elimination from B.[108]



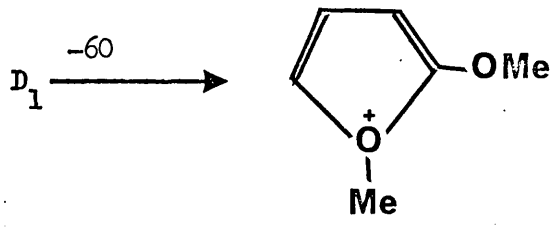
m/e 59

B C

The characteristic peaks in the spectrum of 1,4,5,6-tetra-O-methyl-galactitol diacetate were the primary fragment (D), m/e 233 and the secondary fragment (E) m/e 113, derived from (D) by the elimination of acetic acid.[109]



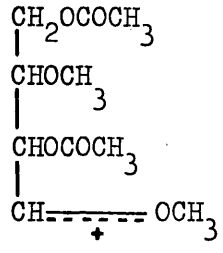
D m/e 233 D_1



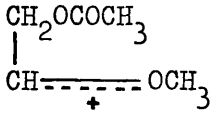
m/e 113

E

The spectrum of 2,4,5,6-tetra-O-methylgalactitol diacetate also contained a fragment at m/e 233 with the probable structure of (F). This compound also gave a peak at m/e 117 (G) which is characteristic for molecules containing a primary acetoxy group and an adjacent methoxyl group.[107]



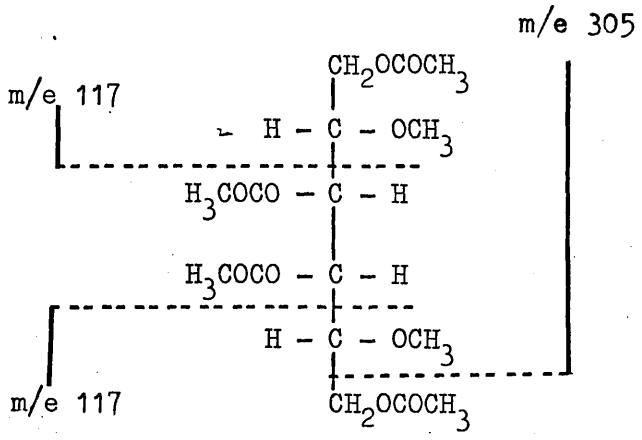
F



G

The peak at m/e 277 shown by the spectra of both the tetra-O-methyl diacetates may have formed by the loss of a ($-CH_2OCH_3$) group from the molecules.[107]

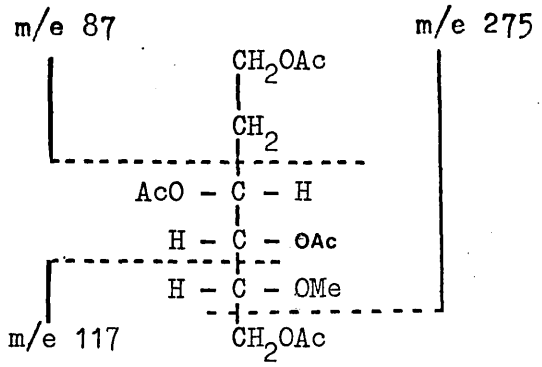
The primary fragment with the highest mass number in the spectrum of 2,5-di-O-methylgalactitol tetra-acetate (H) was m/e 305, which was formed by the loss of an acetoxymethyl group from the molecule.



H

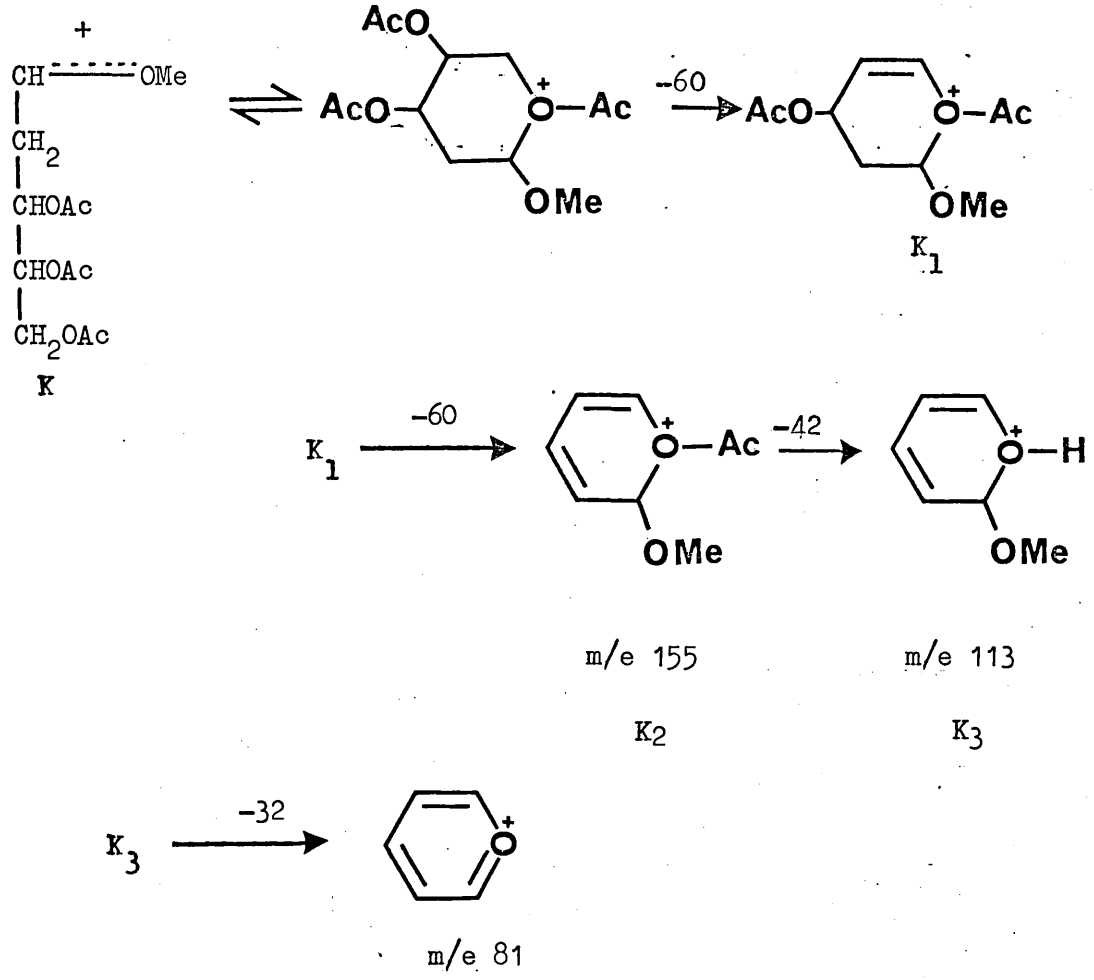
The most intense signal in the spectrum of 2,5-di-O-methylgalactitol tetra-acetate (H) was m/e 117.

The presence of the ion, m/e 275 in the spectrum of 2-deoxy-5-O-methyl-1,3,4,6-tetra-O-acetyl-D-glucitol (2-deoxy-5-O-methyl-D-arabino-hexitol acetate) indicated the presence of a primary acetoxyl group. A very intense peak at m/e 117 indicated the presence of a ($\begin{matrix} CH\text{–}OMe \\ | \\ CH_2OAc \end{matrix}$) group which suggested carbon-5 as the position of the methoxyl group in (J).

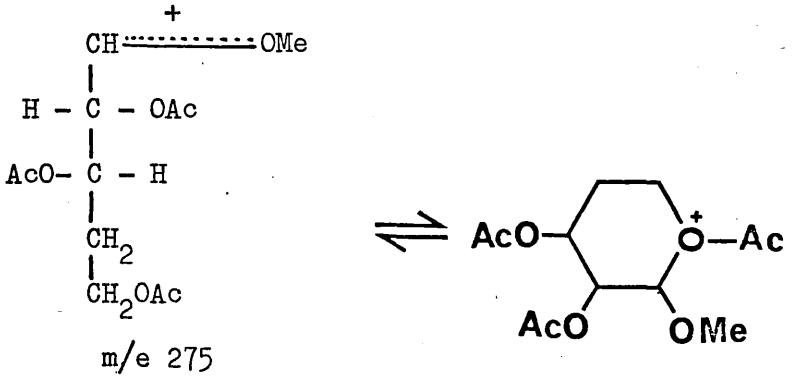


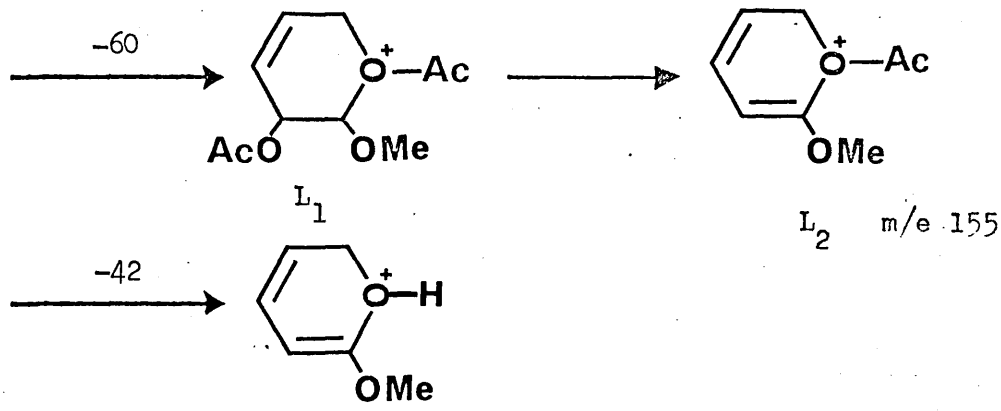
J

It has been shown that[109] the primary fragment (K), obtained from 3-deoxy-2-O-methyl-D-arabino-hexitol acetate by the elimination of $-CH_2-OAc$, undergoes the following fragmentation sequence. (Only the fragments which carry C-6 acetoxyl group can undergo these reactions).



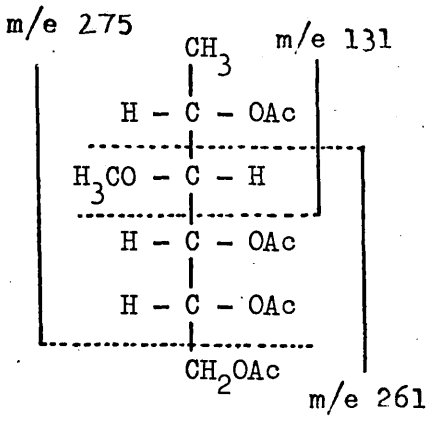
The fragment (L) obtained from (J) can also undergo similar fragmentations.



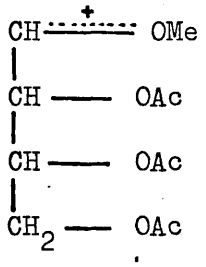


The fragment (L_3) cannot eliminate methanol as easily as (K_3), therefore an intense peak at m/e 113 was observed.

The characteristic peaks in the spectrum of 1-deoxy-3-O-methyl-D-glucitol tetra-acetate (M) were the m/e 131 and m/e 217 formed by the fission of $C_{(3)} - C_{(4)}$ bond.[107] The primary peak with the highest mass number, m/e 261 (N) was observed in a relatively high intensity, which is characteristic for alditol acetates methylated at position 3 and acetylated at positions 4, 5 and 6. This fragment was also observed in the spectrum



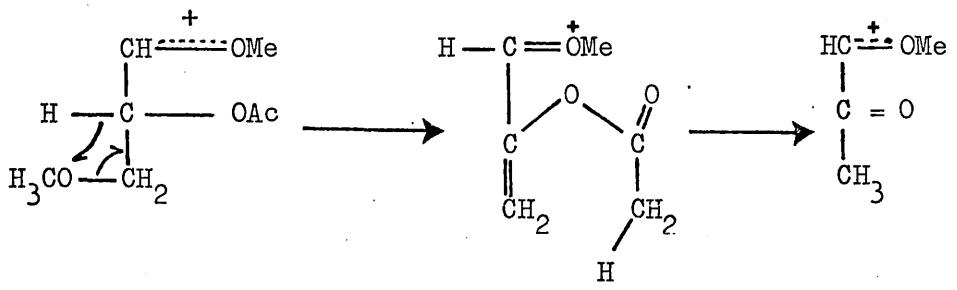
M



m/e 261

N

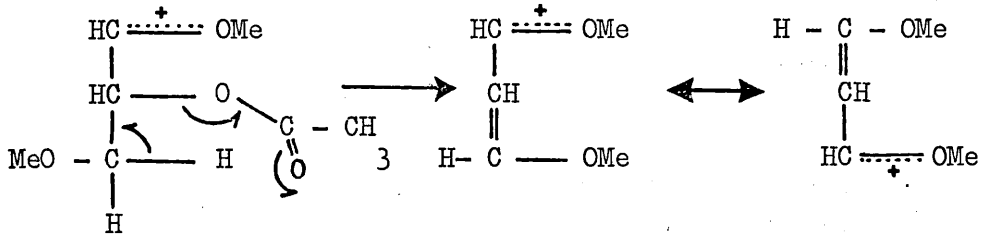
of 1,3-di-O-methyl-D-glucitol tetra-acetate which also showed another characteristic primary fragment (P) at m/e 161. The secondary fragments formed from (P) were as follows.



m/e 161 m/e 129 m/e 87

P

The ion m/e 101 also forms from (P) as follows:



m/e 101

P

X. General Techniques and Materials

The 60 MHz n.m.r. spectra, recorded on a Varian E.M. 360 instrument, were used for routine control analysis of the products and in monitoring some of the reactions. The 100 MHz spectra were run on a Varian HA-100 instrument and the 220 MHz spectra were recorded by P.C.M.U., Harwell, using a Varian HR-220 spectrometer. All spectra were obtained at ambient temperature with internal references, except in the case of spin decoupling experiments, where the high field propyl group signals were irradiated, an external reference was used. The reference compound was sodium 4,4-dimethyl-4-silapentane-1-sulphonate for the D_2O solution and tetramethylsilane (T.M.S.) for all others.

The mass spectra were recorded by the University of London Intercollegiate Research Service on an A.E.I. MS-902, using direct insertion mode with an ionization potential of 70 eV , in temperature range 200-220°.

Gas-liquid chromatography (g.l.c.) was carried out on a modified Perkin-Elmer F-11 and a Pye-104 instrument, both equipped with flame ionisation detectors. The stationary phases used, were Apiezon-K (7.5%), OV-17(7.5%) and P.P.E. (5%) on Celite. The liquid phase Apiezon-K was found to be the best, for the separation of the cyclic butylidene acetals. With the exception of some fully methylated derivatives, all samples were gas chromatographed as their trimethylsilyl ethers.[110] A solution of the sample ca. 10 mg in dry pyridine (0.5 ml) was treated with hexamethyl-disilazane (0.2 ml) and trimethylchloro silane (0.1 ml) for 10 min. at room temperature. The precipitate was removed by centrifugation and the solution rotary evaporated to dryness at 40°. The residue was taken up in dry diethyl ether (0.5 ml) and used for injection into the chromatograph. The $\underline{\underline{R}}_V$ values are relative to $\underline{\underline{D}}$-glucitol in the case of the $\underline{\underline{D}}$-glucitol acetals, and to galactitol in the case of the galactitol acetals.

The infrared spectra were recorded on a Perkin-Elmer 257 instrument. The samples were examined as their sodium chloride discs, nujol mulls or as neat syrups. The examinations of the hydroxyl stretching regions were carried out on a Perkin-Elmer 325spectrophotometer. The samples were used as their dilute solutions in carbon tetrachloride.

The optical rotation measurements were carried out with the Perkin-Elmer-141 polarimeter, using 1 dm. glass or quartz cells.

Silica gel coated glass or precoated plastic plates were used for thin layer chromatography. The solvent system (A) (ethyl methyl ketone, saturated with water), was used for the separations of mono and diacetals and for the separations of polyols from acetals. The solvent (B) (benzene-methanol: 9:1; v/v) was used for the separations of di- and triacetals and partially methylated polyols and their acetate derivatives. The detection of the chromatograms was achieved with 5% ethanolic sulphuric acid at 120°.

Paper chromatography was carried out on Whatman No.1 paper. The solvent mixture A (m.e.k. - H_2O) was used for the separation of the five and six-membered monoacetals. For the separation of polyols and partially methylated polyols, the solvent system, butanol-ethanol-water (40:11:19) was used.

The chromatograms were detected by dipping the dried papers in a solution of silver nitrate (2.5 g) in acetone (490 ml) and water (10 ml) and then into an ethanolic sodium hydroxide solution (sodium hydroxide: 2 g, ethanol: 98 ml, water:2 ml) to produce brown spots. Aqueous sodium thiosulphate solution (2.5%) was used as a fixer.

Optical densities were measured using Unicam S.P. 500 and Unican SP 1800 spectrophotometers.

Materials: Pyridine was distilled over sodium hydroxide pellets at 115-117° and stored over sodium hydroxide. N,N-Dimethyl formamide (DMF) was distilled at atmospheric pressure and dried over molecular sieve (type 4A). The n-butyraldehyde was freshly distilled for each experiment. D-Glucose, D-galactose, 2-deoxy-D-glucose and galactitol were obtained from Koch-Light Laboratories Ltd., The acetals, 1,3:4,6-di-O-butylidene-D-mannitol, 1,3:5,6-di-O-butylidene-D-mannitol and 4,6-O-butylidene-D-glucitol tetra-acetate were kindly supplied by Dr. D. Lewis and a sample of 4,6-O-butylidene-D-glucose was supplied by Mr. T.J. Julnes. A sample of L-fucose was kindly supplied by Dr. E. Percival.

XI. Experiments

Experiment 1 Reaction of Galactitol with Butyraldehyde

A solution of galactitol (15 g; 1 mol) in 0.5 N-hydrochloric acid (500 ml) was shaken with n-butyraldehyde (6 ml; 0.9 mol) and the solution was left at room temperature for 48 h, then neutralised with N-sodium hydroxide (250 ml) and evaporated under vacuum to 150 ml. Some crystals of 1,3:4,6-di-O-butylidenegalactitol (I) which formed during concentration, were filtered off and washed with water. The filtrate was extracted with chloroform (2 x 75 ml), dried and evaporated to dryness. Crystallisation of the residue from ether gave a further crop of the diacetal, m.p. 131-133°, total yield 1.8 g, R_V = 2.20; R_F = 0.70 (solvent A). The recrystallised diacetal (I) had a m.p. 133-135°. (Found: C, 57.99; H, 8.84. $C_{14}H_{26}O_6$ requires: C, 57.91; H, 9.03%).

The aqueous layer gave a solid on evaporation which was extracted with ethanol (3 x 75 ml). Removal of the solvent resulted in a syrup (12.5g), t.l.c. of which in solvent A showed two spots, R_F = 0.27 and R_F = 0.38.

A column of Dowex-1 X8, 200-400 mesh (chloride form; 300 g), was washed with M-sodium hydroxide (3 l) and then with deionised and CO_2-free water (3 l).

The mixture of the monoacetals in water (5 ml) was applied to the column and eluted with deionised and CO_2-free water. The fractions collected (25 ml) were analysed by t.l.c. The syrupy 1,3-O-butylidene-DL-galactitol (II) was eluted first, which crystallised on standing at 5° overnight (2.4 g). Recrystallised acetal (from ethanol-ether, 5:1; v/v),

had m.p. 73-75°. (Found: C, 50.94; H, 8.62. $C_{10}H_{20}O_6$ requires: C, 50.83; H, 8.53%). R_F = 0.27 (solvent A).

Later fractions on concentration gave syrupy 2,3-O-butylidene-DL-galactitol (III) which crystallised on standing (1.3 g). The recrystallised acetal (ethanol-ether, 5:1; v/v) had m.p. 83-85°. (Found: C, 50.66; H, 8.57. $C_{10}H_{20}O_6$ requires: C, 50.83; H, 8.53%). R_F = 0.38 (solvent A).

Experiment 2 Derivatives of the Acetals Obtained from Experiment 1.

A solution of 1,3-O-butylidene-DL-galactitol (II) (0.20 g) was acetylated with acetic anhydride (1.5 ml) in pyridine (4 ml) to give the tetra-acetate (0.35 g), (100%). The recrystallised compound (from ethanol) had m.p. 111-112° (Found: C, 53.56; H, 6.85. $C_{18}H_{28}O_{10}$ requires: C, 53.46; H, 6.98%).

A solution of (II) (0.25 g) was benzoylated with benzoyl chloride (1.5 ml) in pyridine (10 ml), to give the tetra-benzoate (0.40 g) (57%), m.p. 89-91° after recrystallisation from ethanol. (Found: C, 70.07; H, 5.52. $C_{38}H_{36}O_{10}$ requires: C, 69.93; H, 5.55%).

The acetal (III) (50 mg) was acetylated with acetic anhydride (1 ml) in pyridine (3 ml). The resulting 1,4,5,6-tetra-O-acetyl-2,3-O-butylidene-DL-galactitol (83 mg) had m.p. 46-48° when recrystallised from ethanol-light petroleum. (Found: C, 53.33; H, 6.77. $C_{18}H_{28}O_{10}$ requires: C, 53.46; H, 6.98%).

The acetal (I) (0.30 g) was acetylated with acetic anhydride (2 ml) in pyridine (10 ml). The resulting 2,5-di-O-acetyl-1,3:4,6-di-O-butylidenegalactitol (0.26 g) (67%) crystallised from carbon tetrachloride.

M.p. 200-202°. (Found: C, 57.58; H, 7.92. $C_{18}H_{30}O_8$ requires: C, 57.74; H, 8.08%).

The acetal (I) (1 g) was benzoylated in pyridine (15 ml) with benzoyl chloride (1 ml) to give 2,5-di-O-benzoyl-1,3:4,6-di-O-butylidene-galactitol in quantitative yield (1.70 g). M.p. 154-156°. Recrystallisation from boiling ethanol gave m.p. 157-159°. (Found: C, 67.58; H, 6.83. $C_{28}H_{34}O_8$ requires: C, 67.45; H, 6.87%).

Experiment 3 Methylation of 1,3-O-Butylidene-DL-galactitol.

A solution of the acetal (II) (3 g) in N,N-dimethylformamide (25 ml) was stirred with silver oxide (10 g) and methyl iodide (10 ml) for 24 h at room temperature. The solids were filtered off and washed with N,N-dimethylformamide. The filtrate and the washings were evaporated and remethylated. The suspension was filtered and the filtrate was evaporated completely under vacuum leaving a white solid which was extracted with light petroleum. The concentrated extract deposited a syrup overnight at -5°. The supernatant liquor was decanted and the syrup was crystallised from ethanol-light petroleum. The infrared spectrum (nujol mull) showed absorptions in the hydroxyl stretching range. The n.m.r. spectrum and elemental analysis indicated the compound to be the 1,3-O-butylidene-tri-O-methyl-DL-galactitol, m.p. 91-93°, yield 0.16 g, R_F = 0.24 (solvent B). (Found: C, 56.53; H, 9.21; OMe, 33.18. $C_{13}H_{26}O_6$ requires: C, 56.10; H, 9.42; OMe, 33.45%).

The t.l.c. of the supernatant liquor showed one spot in solvent B (R_F = 0.49). Evaporation of the solvent gave a colourless syrup which crystallised on standing at -5°, m.p. 22-24°, yield 2.6 g (69%). The

tetramethyl ether gave a single peak on g.l.c. and its infrared spectrum showed no hydroxyl absorption. (Found: C, 57.73; H, 9.71; OMe, 42.21. $C_{14}H_{28}O_6$ requires: C, 57.51; H, 9.65; OMe, 42.46%).

Experiment 4 2,4,5,6-Tetra-O-methyl-DL-galactitol

A solution of the fully methylated 1,3-monoacetal (2.1 g) in ethanol-water (7:3; 50 ml) was refluxed and stirred for 3 h with Amberlite IR-120 (H^+) resin (50 ml) and then concentrated to a syrup.

T.l.c. in solvent B, showed this to contain a product with R_F = 0.16 and a small amount of unhydrolysed acetal (R_F = 0.49) which was removed by extraction with light petroleum (b.p. 40-60°). The remaining syrup crystallised from ether-light petroleum to give 2,4,5,6-tetra-O-methyl-DL-galactitol, m.p. 72-74°, yield 0.74 g (43.5%). (Found: C, 50.31; H, 9.12; OMe, 51.73. $C_{10}H_{22}O_6$ requires: C, 50.41; H, 9.31; OMe, 52.10%).

A solution of this compound (150 mg) in pyridine was treated with acetic anhydride to yield the syrupy 1,3-di-O-acetyl-2,4,5,6-tetra-O-methyl-DL-galactitol (74%) whose infrared spectrum showed no hydroxyl absorption. (Found: C, 51.81; H, 8.20. $C_{14}H_{26}O_8$ requires: C, 52.16; H, 8.13%).

Experiment 5 Demethylation[111] of 2,4,5,6-Tetra-O-methyl-DL-galactitol

The foregoing methyl ether (40 mg), in dichloromethane (3 ml) was treated with boron trichloride (4 ml) at -75° for 1 h, then left at room temperature for 24 h. Methanol (10 ml) containing water (1 ml) was added to the reaction. The solvent was evaporated off after ½ h. Successive addition and evaporation of methanol left a white solid which was recrystallised from ethanol-water to give galactitol (78%), m.p. and mixed m.p. 187-188°.

Experiment 6 2,4,5,6-Tetra-O-methyl-1-O-triphenylmethyl-DL-galactitol

A solution of the foregoing methyl ether (100 mg) in pyridine (3 ml) was treated with trityl chloride (200 mg) for 5 days at room temperature. A solid separated on pouring into water which was filtered and dried and recrystallised from ethanol to give the title compound (55%), m.p. 134-136°. (Found: C, 72.36; H, 7.37; OMe, 25.50. $C_{29}H_{36}O_6$ requires: C, 72.47; H, 7.55; OMe, 25.83%).

Experiment 7 Methylation of 2,3,-O-Butylidene-DL-galactitol

The solution of the acetal (III) (3 g) in N,N-dimethylformamide (20 ml) was treated with silver oxide (10 g) and methyl iodide (10 ml) for 24 h. After the removal of the solid the filtrate was remethylated. The suspension was filtered and the filtrate was evaporated. The residue was extracted with light petroleum to give the syrupy 1,4,5,6-tetra-O-methyl-2,3,-O-butylidene-DL-galactitol, with R_F = 0.42 in solvent B. Yield 2.7 g (71%), b.p. 113-116°/0.4 mm Hg. (Found: C, 57.35; H, 9.49; OMe, 42.16. $C_{14}H_{28}O_6$ requires: C, 57.51; H, 9.65; OMe, 42.46%).

Experiment 8 1,4,5,6-Tetra-O-methyl-DL-galactitol

A solution of the fully methylated 2,3-monoacetal (2.5 g) in ethanol-water (7:3; v/v) (25 ml) was refluxed with stirring in the presence of Amberlite IR-120 (H^+) resin (25 ml) for 3 h, then filtered and evaporated to give a syrup for which the t.l.c. in solvent B showed one main product (R_F = 0.19) with a small amount of unhydrolysed acetal. The product was resolved chromatographically over silica gel, eluting with benzene-methanol (9:1; v/v), to yield the tetramethyl ether (1.5 g; 74%). (Found: C, 50.57; H, 9.10; OMe, 51.88. $C_{10}H_{22}O_6$ requires: C, 50.41; H, 9.31; OMe, 52.10%).

The tetramethyl ether (50 mg) was acetylated with acetic anhydride (1 ml) in pyridine, to give a syrupy diacetate (92%). T.l.c. (in solvent B) indicated a single product (R_F = 0.47), for which i.r. spectroscopy showed no hydroxyl absorption. (Found: C, 51.96; H, 8.23; OMe, 38.17. $C_{14}H_{26}O_8$ requires: C, 52.16; H, 8.13; OMe, 38.50%).

Experiment 9 Demethylation of 1,4,5,6-Tetra-O-methyl-DL-galactitol

The tetramethyl ether (26 mg) was demethylated with boron trichloride (2 ml) as in Experiment 5, to yield galactitol (70%), m.p. and mixed m.p. 187-189°.

Experiment 10 Periodate oxidation of 1,4,5,6-Tetra-O-methyl-DL-galactitol

A mixture of tetra-O-methylgalactitol (250 mg) and aqueous solution of sodium metaperiodate (0.25 g in 5 ml) was left at room temperature for 1.5 h. The reaction mixture was distilled after addition of more water (3 ml) and the distillate (3 ml) was treated with a warm solution of p-nitrophenylhydrazine. Crystallisation of the precipitate from aqueous ethanol gave orange needles of methoxyacetaldehyde p-nitrophenylhydrazone (0.16 g, 75%), m.p. and mixed m.p. 113-116°.

The residual solution was extracted with chloroform (10 x 15 ml), which on evaporation gave a chromatographically pure syrupy tri-O-methyl-DL-threose (R_F = 0.26 in solvent B). The presence of three methoxyl groups were deduced from its n.m.r. spectrum. Yield 0.15 g (88%). (Found: C, 51.57; H, 8.64; OMe, 57.01. $C_7H_{14}O_4$ requires: C, 51.84; H, 8.70; OMe 57.40%).

Experiment 11 1,3:4,6-Di-O-butylidene-2,5-di-O-methylgalactitol

A solution of the diacetal (I) (1.1 g) in N,N-dimethylformamide (20 ml) was stirred with silver oxide (5 g) and methyl iodide (5 ml) at room temperature for 23 h. The solids were filtered off and the filtrate was evaporated to dryness. The residue was extracted with hot diethyl ether which on cooling gave the crystalline dimethyl ether. Its i.r. spectrum showed the absence of free hydroxyl groups and t.l.c. gave a single spot R_F = 0.55 in solvent B. Yield 0.95 g (79%). After recrystallisation from ether or methanol the compound had m.p. 162-164°. (Found: C, 60.25; H, 9.33; OMe, 19.41. $C_{16}H_{30}O_6$ requires: C, 60.35; H, 9.50; OMe, 19.50%).

Experiment 12 2,5-Di-O-methylgalactitol

A solution of the foregoing dimethyl ether (0.7 g) in ethanol-water (7:3, v/v; 25 ml) was refluxed with Amberlite IR-120 (H^+) resin (25 ml) for 2 h. The resin was filtered off and filtrate was evaporated down to a solid which after several recrystallisations from ethanol gave the pure dimethyl ether, m.p. 176-177.5°, yield 0.2 g (43.5%). R_F = 0.03 in solvent B and R_F = 0.12 in benzene-methanol (9:2). (Found: C, 45.54; H, 8.52; OMe, 29.78. $C_8H_{18}O_6$ calc.: C, 45.70; H, 8.63; OMe, 29.52%).

The dimethyl ether (40 mg) was acetylated in pyridine (3 ml) and acetic anhydride (4 ml), to give a tetra-acetate (90%) m.p. 148°, which gave a single spot on t.l.c., R_F = 0.42 in solvent B. (Found: C, 50.81; H, 6.79; OMe, 16.33. $C_{16}H_{26}O_{10}$ calc.: C, 50.79; H, 6.93; OMe, 16.40%).

Experiment 13 Demethylation of 2,5-Di-O-methylgalactitol

The dimethyl ether (28 mg) was demethylated in dichloromethane (2 ml) with boron trichloride (2 ml) as in Experiment 5 to give galactitol (70%), m.p. and mixed m.p. 187-188°.

Experiment 14 2,5-Di-O-methyl-1,6-di-O-triphenylmethylgalactitol

A solution of the foregoing dimethyl ether (50 mg) in pyridine (5 ml) was treated with trityl chloride (150 mg) for 5 days. A gummy product separated which solidified on cooling, when the reaction mixture was poured into water. The recrystallised (from ethanol) ditrityl derivative (42%) had m.p. 202-204°. (Found: C, 79.54; H, 6.56; OMe, 9.07. $C_{46}H_{46}O_6$ requires: C, 79.51; H, 6.67; OMe, 8.93%).

Experiment 15 Periodate oxidation of 2,5-Di-O-methylgalactitol

A solution of the dimethyl ether (62 mg) was prepared in 0.015 M sodium periodate (200 ml), a portion (2 ml) of which was used in determination of the periodate ion consumption after 2 h. The remaining solution was extracted with chloroform and evaporated down to give a syrup (58 mg), which on borohydride reduction, yielded 2-O-methylglycerol (57 mg). This was converted to its di-p-nitrobenzoate, m.p. 158-160° (lit.[44] m.p. 159.5-160.5).

Experiment 16 General Method for Periodate Oxidations

A. Periodate ion uptake determination.[112]- Separate solutions (0.015 M) of sodium metaperiodate (0.321 g) and potassium iodate (0.321 g) in water (100 ml) were prepared. An aliquot (1 ml) of each solution was diluted 250 times and its optical density measured at 223nm using water as reference.

A linear calibration graph, relating optical density to the per cent ion composition of the solution, was obtained by assuming that the periodate solution contained 0% IO_3^- and 100% IO_4^- and that the iodate solution contained 100% IO_3^- and 0% IO_4^- ions.

The sample under investigation (ca. 0.01 g) was accurately weighed and dissolved in the 0.015 M-sodium metaperiodate solution (10 ml). The optical densities of aliquots (1 ml) taken at certain time intervals (e.g. after 2 h and 16 h) and diluted 250 times, were measured. The calibration graph was used to deduce the corresponding IO_3^- contents and hence the IO_4^-% reduced by the test samples. The data gave the number of mol. of periodate ion required to oxidise one mol. of the sample, 2,5-O-methylene — D-mannitol was used as a standard compound to check the accuracy of the method. Periodate oxidation results for compounds investigated are given in the appropriate discussion sections.

B. Estimation of formaldehyde.[113]- The formaldehyde was estimated spectrophotometrically by its colour reaction with chromotropic acid reagent (chromotropic acid sodium salt (0.2 g) in H_2O: conc. H_2SO_4; 20 ml: 80 ml). Periodate oxidation was carried out on the reference compound, 2,5-O-methylene-D-mannitol, and the test sample as described in A. After 20 h, aliquots (1 ml), from the standard solution, were diluted accurately to 10 ml., 20 ml., and 50 ml and an aliquot (1 ml) from the test sample was diluted to 20 ml. A portion (1 ml) from each diluted solution, was mixed with an accurately measured amount of 20% aqueous sodium sulphite solution (0.1 ml) and chromotropic acid reagent (8.4 ml). A blank sample of water (1 ml) was treated in the same way. The samples were heated for 1 h in a boiling water bath to develop the characteristic violet colour.

After cooling, 0.4% aqueous thio urea solution (0.5 ml) was added to the solutions bringing the total volume to 10 ml. The optical densities of the samples were measured at 570 nm using the blank solution as reference sample. A linear calibration graph was prepared by plotting the optical densities obtained for the standard, 2,5-O-methylene-D-mannitol, against the calculated formaldehyde concentration of the samples. The formaldehyde liberated from the test samples was deduced from this graph.

C. Estimation of formic acid.[114]- A solution of the test sample (ca. 0.01 g) in 0.015 M-sodium metaperiodate solution (10 ml) was prepared and after 16 h, an accurately measured portion (5 ml) was treated with two drops of ethylene glycol, to reduce the excess periodate, and then titrated against standard 10^{-2} N-sodium hydroxide solution, with methyl red as indicator. A titration was also carried out on a "blank" sample of sodium periodate solution similarly treated. The difference in the titres was used to deduce the formic acid produced by periodate oxidation of the test sample.

Experiment 17 The Reaction of Galactitol with n-Butyraldehyde in 5 N-Hydrochloric Acid

A. Kinetically controlled Reaction.- Galactitol (7.5 g) and n-butyraldehyde (12 ml) were shaken in 5 N-hydrochloric acid (10 ml) for 17 h at room temperature. The reaction mixture was extracted with chloroform (3 x 100 ml), washed with sodium bicarbonate solution, dried (Na_2SO_4) and evaporated to a syrup (7.3 g) which deposited some crystals of 1,3:4,6-di-O-butylidenegalactitol on treatment with light petroleum

(150 ml). The product was recrystallised from methanol to give m.p. and mixed m.p. 133-135° and yield 1.5 g.

The light petroleum solution also deposited a syrup on storing at -5° overnight, which was shown by t.l.c. to be a mixture of acetals other than the 1,3:4,6-diacetal. The acetal mixture (2.5 g) was fractionated on a column of neutral alumina (300 g) eluting with diethyl ether. The fractions (10 ml) were monitored by n.m.r. spectrometer. Rotary evaporation of fractions 90-110 yielded a solid (70 mg) which melted at 124-126° after several crystallisations from carbon tetrachloride. N.m.r. spectroscopy presented evidence in favour of the structure 2,4:5,6-di-O-butylidenegalactitol. (Found: C, 58.05; H, 9.01. $C_{14}H_{26}O_6$ requires: C, 57.91; H, 9.03%).

The next 30 fractions also gave a solid (150 mg) on evaporation, which melted at 83°, after several recrystallisations from carbon tetrachloride. N.m.r. spectroscopy presented evidence in favour of the structure 2,3:4,5-di-O-butylidengalactitol (stereoisomeric mixture). (Found: C, 57.60; H, 8.79. $C_{14}H_{26}O_6$ requires: C, 57.91; H, 9.03%).

On evaporation, the remaining supernatant light petroleum solution gave a syrup (3 g) for which t.l.c. showed a single spot (R_F = 0.63) in solvent B. Colourless crystals of 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol was obtained when the light petroleum solution of the syrup was kept at -5°. Crystallisation was also achieved from methanol solution by addition of water. The recrystallised acetal (2 g) had m.p. 80-83°. (Found: C, 62.70; H, 9.26. $C_{18}H_{32}O_6$ requires: C, 62.76; H, 9.36%).

B. The Reaction under Thermodynamic Conditions.- Galactitol (7.5 g) and n-butyraldehyde (12 ml) were shaken with 5 N-hydrochloric acid (20 ml) at room temperature, for 5 days. The reaction mixture was extracted with chloroform, washed with sodium bicarbonate solution and water, then dried and evaporated. The syrup obtained, deposited crystals of the 1,3:4,6-diacetal on addition of light petroleum, which were filtered, washed with light petroleum and recrystallised. Yield 4.5 g, m.p. and mixed m.p. 133-135°.

The concentrated filtrate and washings next deposited crystals of 1,3:2,4:5,6-tri-O-butylidene-DL-galactitol (3.7 g) on storing at -5°, with m.p. 78-80°. The recrystallised compound had m.p. and mixed m.p. 80-83°.

Experiment 18 Some Reactions of 1,3:2,4:5,6-Tri-O-butylidene-DL-galactitol

A. A solution of the triacetal (0.1 g) in trifluoroacetic acid-water (9:1; v/v) (1 ml), was left at room temperature for 15 min and rotary evaporated to give a syrup, for which t.l.c. in solvent B, showed several spots R_F = 0.0 (monoacetals), R_F = 0.26, R_F = 0.33, R_F = 0.43 (1,3:4,6-diacetal). G.l.c. analysis indicated a more complicated reaction mixture.

B. A solution of the triacetal (100 mg) in glacial acetic acid (5 ml) was left at room temperature, overnight. The solvent was evaporated under vacuum and the triacetal was recovered unchanged.

C. The triacetal (5 g) was shaken with n-butyraldehyde (2 ml) in 5 N-hydrochloric acid (50 ml) for four days. The 1,3:4,6-di-O-butylidenegalactitol (1.5 g) was isolated as in experiment 17-B, m.p. and mixed m.p. 133-135°.

Experiment 19 Attempted Synthesis of 1,3:4,6-Di-O-butylidene-2,5-O-isopropylidenegalactitol

The 1,3:4,6-dibutylidenegalactitol (3 g) was shaken in 2,2-dimethoxypropane (20 ml) in the presence of toluene-p-sulphonic acid (0.5 g) at room temperature for 4 h. The starting material was recovered unchanged.

Experiment 20 1,3:4,6-Di-O-chloroethylidenegalactitol

The compound was prepared from galactitol (16 g) and chloroacetaldehyde diethyl acetal (30 g), according to the method of H.B. Sinclair.[100] The product was separated as a gum, which solidified on standing (3 g). The recrystallised acetal (90% ethanol), had m.p. 217-220°, lit. m.p. 214-219°.

Experiment 21 1,3:4,6-Di-O-benzylidene-2,5-di-O-methylgalactitol

A solution of 1,3:4,6-di-O-benzylidenegalactitol (1 g) (prepared according to Hudson's method[21]) in DMF was stirred with silver oxide (5 g) and methyl iodide (5 ml), at room temperature for 24 h. The usual working up procedure as in Experiment 7 gave the dimethyl ether (0.1 g), m.p. 225-227° (decomp.). (Found: C, 68.19; H, 6.66; OMe, 15.88. $C_{22}H_{26}O_6$ requires: C, 68.37; H, 6.78; OMe, 16.06%).

Experiment 22 The Reaction of 1,3-O-Butylidene-DL-galactitol with Acetone

The monoacetal (0.3 g) was stirred in acetone (25 ml) containing sulphuric acid (1 drop) and anhydrous copper sulphate (0.5 g) for 14 h. After removal of the solids, the reaction mixture was concentrated to a

syrup and extracted with hot light petroleum. The t.l.c. of the extract in solvent B, showed some impurities, $\underline{R}_F$ = 0.20 (main product), $\underline{R}_F$ = 0.17 (impurity), $\underline{R}_F$ = 0.14 (impurity), $\underline{R}_F$ = 0.00 (impurity). The syrupy product was not purified further.

Experiment 23 1-Deoxy-D-galactitol (L-fucitol)

A. D-Galactose diethyl thioacetal.[115]

A solution of D-galactose (50 g) in concentrated hydrochloric acid (75 ml) in a wide-necked bottle with a glass stopper was shaken vigorously with ethanethiol (50 ml), releasing the pressure occasionally. After 5 min, heat evolved and some ice was added, whereupon the reaction mixture solidified. The white solid was recrystallised twice from boiling water giving the diethyl thioacetal(50 g), m.p. 140-142°, lit. m.p. 140-142°.

B. Raney nickel

Nickel-aluminium alloy (90 g) was added gradually with stirring to a solution of 6 N-sodium hydroxide (500 ml) in a 2 l beaker kept in ice. The solution was then allowed to come to room temperature and then heated at 70° for 2 h. After cooling, the Raney nickel was washed thoroughly with water until completely free of alkali.

C. Partial Desulphurisation of D-Galactose diethyl thioacetal

D-Galactose diethyl thioacetal (1 g) in 70% ethanol (50 ml) was refluxed with Raney nickel (6 ml) for 1½ h. The used nickel was filtered through Celite containing a top layer of charcoal and washed well with water-ethanol. Paper chromatography showed that the main product was not the expected 1-deoxy-D-galactitol (R_F = 0.46, butanol-ethanol-H_2O; 40:11:19). Evaporation of the ethanol and recrystallisation of the residue (ethanol) gave pure 1-deoxy-1-S-ethyl-D-galactitol (R_F = 0.66, butanol ethanol H_2O; 40:11:19), m.p. 150-152°, lit.[58] m.p. 149-151°.

D. Complete Desulphurisation of D-galactose diethyl thioacetal

A solution of the foregoing diethyl mercaptal (30 g) in 80% ethanol (600 ml) was mixed with freshly prepared Raney nickel (500 ml) and stirred under reflux for 1½ h. The nickel was filtered through Celite with a top layer of charcoal and washed well with ethanol–water. The filtrate gave a solid on evaporation, which was crystallised from ethanol to give 1-deoxy-D-galactitol (L-fucitol) (12 g), m.p. 153°, lit.[57] m.p. 153°. The mixed m.p. with the authentic compound, obtained as described in Experiment 24, showed no depression. Paper chromatography in solvent (butanol, ethanol H_2O; 40:11:19) gave R_F = 0.46 in agreement with the reported[58] values.

Experiment 24 1-Deoxy-D-galactitol from L-Fucose

A solution of L-fucose (0.5 g) in water (15 ml) was treated with sodium borohydride (0.15 g) for 2 days at room temperature and then shaken with Amberlite IR-120 (H^+) resin (30 ml). The resin was filtered off and the filtrate was evaporated to a syrup, from which the borate ions were removed as the volatile methyl borate by rotary evaporation after addition of methanol, leaving a white solid, which was recrystallised from ethanol to give L-fucitol (0.4 g), m.p. 153–154°.

Experiment 25 Investigation of the Reaction of L-Fucitol with n-Butyraldehyde.

A. By G.l.c.

L-Fucitol (3.5 g) as a solution in N-hydrochloric acid (200 ml) was mixed with n-butyraldehyde (1.7 ml). The samples (2 ml) were withdrawn at certain time intervals and neutralised with N-sodium hydroxide (2 ml).

The solvent was removed by rotary evaporation at 40° and the resiude was extracted with dry pyridine (1 ml) and centrifuged to remove the solids. The t.m.s. derivatives were prepared as explained in general techniques. The pyridine was removed by rotary evaporation and the residue was extracted with dry diethyl ether, centrifuging where necessary, and injected (2 µl) to the fractometer.

B. By Polarimeter

A solution of L-fucitol (0.5 M) in N-hydrochloric acid was mixed with n-butyraldehyde (0.5 M) and the change in optical activity was followed using a polarimeter. The change of optical activity with time was plotted as shown in page 59.

Experiment 26 4,5-O-Butylidene-1-deoxy-D-galactitol

A part of the remaining reaction mixture (150 ml) from the Experiment 25 - A was neutralised after 48 h, evaporated to dryness and the residue was extracted with ethanol. The solution deposited the crystals of L-fucitol (0.15 g), which were filtered off. The filtrate was evaporated and the residue was extracted with chloroform which deposited some crystals of 4,5-O-butylidene-1-deoxy-D-galactitol (0.1 g), from the concentrated solution on standing at -5° for 2 days, m.p. 103-105°. Several recrystallisations gave m.p. 105-108° (R_m=0.67, S-A). $(\alpha)_D^{25}$ = +18.7° (C, 0.49 in methanol); (Found: C, 54.35; H, 9.02. $C_{10}H_{20}O_5$ requires: C, 54.5; H, 9.1%).

Experiment 27 Reaction of 1-Deoxy-D-galactitol with n-Butyraldehyde

A solution of 1-deoxy-D-galactitol (7 g) in N-hydrochloric acid (400 ml) was shaken with n-butyraldehyde (5 ml) and left at room temperature

for 2 days. Some water insoluble oily material was extracted with light petroleum and the water layer was neutralised with 4N-sodium hydroxide and rotary evaporated to a syrup. T.l.c. of the syrup in the solvent A showed three spots, R_{F1} = 0.09, (L-fucitol), R_{F2} = 0.65 (4,6-mono-acetal), R_{F3} = 0.67 (five-membered ring monoacetals).

The syrup was extracted with ethanol which deposited some unreacted polyol from the concentrated solution on standing at 0 - 5° overnight. The solid was filtered off and the filtrate (containing only a trace of L-fucitol) was rotary evaporated to syrupy mixture of acetals (4.0 g), which was fractionated on a Dowex-1 (OH^-) resin (250 g) column, eluting with deionised and CO_2-free water. The fractions were examined by t.l.c.. The 4,6-O-butylidene-1-deoxy-D-galactitol eluted first, giving 1.7 g of syrupy chromatographically pure acetal (R_F = 0.65 in solvent A). $[\alpha]_D^{25}$ = -9.64° (c, 0.56 in methanol); (Found: C, 54.01; H, 8.93. $C_{10}H_{20}O_5$ requires: C, 54.50; H, 9.1%).

The fractions containing the five-membered acetals (R_F = 0.67, solvent A) were combined and evaporated to give a syrupy mixture (2.0 g) which solidified on keeping at -5° and gave the crystals of 4,5-O-butylidene-1-deoxy-D-glucitol (0.4 g), from ethanol-diethylether solution (1:1, v/v), m.p. 105 - 108°.

The mother liquor from the above reaction was evaporated to a syrup which gave more crystals from ether-light petroleum solution (light petroleum added to a turbidity) on keeping at -5°, yield 0.8 g. Several recrystallisations gave crystals of 2,3-O-butylidene-1-deoxy-D-galactitol (0.6 g, stereoisomeric mixture), m.p. 66-68°, $[\alpha]_D^{25}$ = -12.8° (c, 1.09 in

methanol); (Found: C, 54.78; H, 8.97. $C_{10}H_{20}O_5$ requires: C, 54.50; H, 9.1%).

Experiment 28 4,6-O-Butylidene-1-deoxy-2,3,5-tri-O-methyl-D-galactitol

A solution of the 4,6-butylidene-1-deoxy acetal (0.9 g) in DMF (20 ml), was stirred with silver oxide (5 g) and methyl iodide (5 ml), for 24 h. The methylated product was isolated as in Experiment 7 and crystallised from the concentrated solution of light petroleum. The yield was small (0.25 g) and the product contained some impurity which was removed after several recrystallisations from light petroleum, m.p. 61 - 63°. (Found: C, 59.63; H, 9.64. $C_{13}H_{26}O_5$ requires: C, 59.50; H, 9.90%).

Experiment 29 2,3,5-Tri-O-acetyl-4,6-O-butylidene-1-deoxy-D-galactitol

A solution of the 4,6-butylidene-1-deoxy acetal (0.10 g) in pyridine was acetylated with acetic anhydride (1 ml) at room temperature overnight. A solid was separated on pouring into ice-water which was crystallised from ethanol-water, yield 0.12 g, m.p. 153-156°. (Found: C, 55.81; H, 7.32. $C_{16}H_{26}O_8$ requires: C, 55.48; H, 7.56%).

Experiment 30 Periodate Oxidation of 4,6-O-Butylidene-1-deoxy-D-galactitol

The title acetal (0.25 g) was dissolved in sodium periodate (0.2 g) solution in water (5 ml) and kept at room temperature for 3 h. The reaction mixture was neutralised with sodium bicarbonate solution and after addition of more water (5 ml), it was distilled. The distillate (3 ml) was collected and treated with the 2,4-dinitrophenyl hydrazine

reagent (0.14 g in 2 ml methanol, H_2SO_4 added to dissolution). The 2,4-dinitrophenylhydrazone of acetaldehyde (0.18 mg) immediately precipitated and gave orange needles after crystallisation from ethanol-water m.p. 140-145°.

Experiment 31 3-O-Methyl-D-glucopyranose[66]

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (78 g), acetone (75 ml) and pulverised sodium hydroxide (32 g) were mechanically stirred in a three-necked flask equipped with a condenser, and a dropping funnel. The mixture was warmed under reflux to 45° and dimethyl sulphate (42.6 ml) was added dropwise from the funnel during 90 min, after which the temperature was raised to 60° for a further 90 min. and then lowered to 50° for 3 h. The cooled contents of the flask were diluted with water and extracted with chloroform (3 x 150 ml). The extracts, after washing with water and drying over sodium sulphate, were concentrated and the 1,2:5,6-di-O-isopropylidene-3-O-methyl-α-D-glucofuranose was freed from acetone condensation products by heating on a steam bath at 1 - 3 mm Hg. Yield 83 g.

This product in ethanol-water was boiled with resin Amberlite IR-120(H^+) with stirring for 3 h and then filtered. The filtrate was evaporated to a syrup which was crystallised from ethanol to give the 3-O-methyl-D-glucopyranose, m.p. 168°, lit. m.p. 168°, yield 10 g.

Experiment 32 3-O-Methyl-D-glucitol

3-O-Methyl-α-D-glucopyranose (2 g) and sodium borohydride (0.3 g) were dissolved in water (20 ml) and kept at room temperature overnight.

The usual procedure as in Experiment 24 gave the syrupy 3-O-methyl-D-glucitol (1.9 g), R_f = 0.29 (butanol-ethanol-H_2O; 30:11:19).

Experiment 33 Bis-phenylboronate of 3-O-methyl-D-glucitol

3-O-Methyl-D-glucitol (80 mg) was dissolved in dry methanol (2 ml) and treated with phenyl boronic acid (53 mg) for 5 min. The removal of the solvent under vacuum deposited a solid, which was crystallised from carbon tetrachloride, m.p. 142-146°. The compound on recrystallisation, gave the pure bis-phenylboronate of 3-O-methyl-D-glucitol (68 mg), m.p. and mixed m.p. 147 - 148°. (Found: C, 60.91; H, 5.82; B, 5.93. $C_{19}H_{22}B_2O_6$ calc.: C, 62.01; H, 6.00; B, 5.87%).

Experiment 34 Di-O-methylene-3-O-methyl-D-glucitol

3-O-Methyl-D-glucitol (0.5 g) was mixed with formalin (0.7 ml) and treated with concentrated hydrochloric acid (2 ml). The mixture was refluxed for $2\frac{1}{2}$ h on a water bath and the water present was removed on a rotary evaporator to give a thick syrup which was triturated with boiling light petroleum until all the diacetal was extracted. The yield was 0.2 g, m.p. 117-122°. The extracted diacetal on recrystallisation from carbon tetrachloride gave the pure title compound (0.15 g), m.p. 120-123° $[\alpha]_D^{24}$ = -7.6° (c, 1.0 in methanol). (Found: C, 49.00; H, 7.24. $C_9H_{16}O_6$ requires: C, 49.08; H, 7.32%).

Experiment 35 Attempted Demethylation[70] of Dimethylene-3-O-methyl-D-glucitol

A solution of the foregoing dimethylene acetal (0.1 g) in dry carbon tetrachloride (5 ml) was stirred with iodine (0.4 g) and sodium borohydride (0.03 g) for 2 h at 40°, whilst a stream of nitrogen was passed through the

solution. Methanol (20 ml) was added to the reaction mixture refluxed for further 2 h. The concentrated solution was poured into water and the iodine destroyed with sodium thiosulphate. After removal of all the solvents, the residue was taken up in pyridine and silylated. G.l.c. showed the presence of 2,4-O-methylene-D-glucitol and D-glucitol. Mixed t.m.s. derivatives of the product and the standards gave identical chromatograms at various temperatures.

Experiment 36 Methylation of Di-O-methylene-3-O-methyl-D-glucitol

Dimethylene-3-O-methyl-D-glucitol (0.2 g), methyl iodide (2 ml) and silver oxide (1.5 g) were warmed at 70° for ½ h, after cooling more methyl iodide (2 ml) was added and the mixture was stirred for a further 24 h at room temperature. The solid was filtered off, washing with dimethylformamide. The filtrate was rotary evaporated to remove the solvent. The residue was extracted with carbon tetrachloride which deposited the crystalline title compound (70 mg), m.p. 65-67° which was slightly impure (off white crystals). (Found: C, 50.66; H, 7.90; OMe, 24.26. $C_{10}H_{18}O_6$ requires: C, 51.27; H, 7.74; OMe, 26.49%).

Experiment 37 Hydrolysis of Di-O-methyl-di-O-methylene-D-glucitol

The title compound (40 mg) was refluxed with phloroglucinol (25 mg) in 0.5 N-hydrochloric acid for 4½ h. The polymeric material was filtered and washed with a little methanol. After evaporation, the filtrate gave a syrupy product which co-chromatographed with 1,3-di-O-methyl-D-glucitol (R_f = 0.49 in butanol-ethanol-H_2O; 40:11:19).

Experiment 38 2,4:5,6-Di-O-butylidene-3-O-methyl-D-glucitol

A solution of 3-O-methyl-D-glucitol (3 g) in 5 N-hydrochloric acid was mixed with freshly distilled n-butyraldehyde (5 ml) and shaken vigorously for 6 h at room temperature. The reaction mixture was then extracted with light petroleum. The extract was washed with sodium bicarbonate solution and water, dried and evaporated down to a syrup. The polymeric n-butyraldehyde products were removed on a neutral alumina column and the syrupy acetal (3 g) thus purified, behaved as a single substance on t.l.c. in solvents A and B, but gave two very close peaks on g.l.c. using Apiezon-K as the liquid phase (stereoisomeric mixture). Attempts to crystallise this product failed. $[\alpha]_D^{25} = -2.9^\circ$ (c, 0.85 in carbon tetrachloride), (Found: C, 60.07; H, 9.29; OMe, 10.11. $C_{15}H_{28}O_6$ requires: C, 59.18; H, 9.27; OMe, 10.19%).

Experiment 39 Methylation of the 2,4:5,6-Di-O-butylidene-3-O-methyl-D-glucitol

The stereoisomeric title acetal (1.3 g) in N,N-dimethylformamide (25 ml) was mixed with methyl iodide (5 ml) and silver oxide (5 g) and stirred for 22 h at room temperature. The 2,4:5,6-di-O-butylidene-1,3-di-O-methyl-D-glucitol was obtained as in Experiment 7 as a pale yellow syrup (0.8 g), $R_F = 0.51$ (solvent B). (Found: C, 61.62; H, 9.59; OMe, 18.81. $C_{16}H_{30}O_6$ requires: C, 60.35; H, 9.49; OMe, 19.49%).

Experiment 40 Hydrolysis of 1,3:4,6-di-O-butylidene-3-O-methyl-D-glucitol

The syrupy diacetal dimethyl ether (0.7 g) in ethanol (20 ml) was treated with Amberlite IR-120 (H^+) resin (30 ml) containing water (20 ml)

and refluxed for 2 h. The resin was then filtered off washing well with hot methanol, and the filtrate was rotary evaporated to give a syrup, which was extracted with diethyl ether, and evaporated down to a syrup (0.2 g). Paper chromatography showed some impurity, therefore the product was purified by preparative paper chromatography in butanol-ethanol-water (40:11:19; v/v).

The purified compound (20 mg) was acetylated in pyridine with acetic anhydride overnight at room temperature to give the syrupy tetra-acetate derivative which was chromatographically pure, t.l.c. R_{F} = 0.41 in solvent B.

Experiment 41 Partial Hydrolysis of 2,4:5,6-Di-O-butylidene-3-O-methyl-D-glucitol

The title compound (0.3 g) in aqueous hydrobromic acid (ca. 24%, 10 ml) was refluxed for 30 min. After neutralisation with sodium hydroxide, the water was removed by rotary evaporation and the residue was extracted with hot light petroleum. The crystals of 2,4-O-butylidene-3-O-methyl-D-glucitol (0.1 g) were obtained from the light petroleum solution on cooling. M.p. and mixed m.p. 155-156°.

Experiment 42. Phenyl boronate of 2,4-O-butylidene-3-O-methyl-D-glucitol

2,4-O-butylidene-3-O-methyl-D-glucitol (70 mg) from the previous experiment was dissolved in dry methanol (2 ml) and treated with phenyl boronic anhydride (90 mg) for 10 min. Evaporation of methanol left a syrup which was extracted with carbon tetrachloride and filtered. The clean solution gave the crystals of the phenyl boronate (70 mg), m.p. 105 - 107°.

Experiment 43 1-Deoxy-D-glucitol [61]

A suspension of D-glucose toluene-p-sulphonylhydrazone (25.0 g) in methanol (700 ml) was gradually treated with potassium borohydride (15.0 g) and then refluxed for 12 h. Methanol was removed by rotary evaporator and the residue taken in water (500 ml). Potassium ions were removed from the solution by treating with Amberlite IR-120 (H^+) resin and then taken to dryness by evaporation under reduced pressure. The residue was repeatedly dissolved in methanol and evaporated to remove boric acid as the volatile methyl borate. The residual syrup contained 1-deoxy-D-glucitol and D-glucitol as shown by paper chromatography in solvent (butanol:ethanol:water; 40:11:19). The syrup was fractionated on a cellulose column (7.5 x 80 cm), eluting with n-butanol saturated with water. Fractions containing the 1-deoxy-D-glucitol were combined and concentrated to a white solid which on recrystallisation from ethanol had m.p. 128 - 129°, lit.[61] m.p. 128 - 129°, yield 2.5 g.

Experiment 44 1-Deoxy-D-glucitol

A - Glucose diethyl thioacetal

A solution of D-glucose (50 g) in concentrated hydrochloric acid (75 ml) was treated with ethane thiol as in Experiment 23-A. The solidified product was crystallised from boiling water to give diethyl mercaptal (50 g), m.p. 128°.

B - Desulphurisation of D-Glucose diethyl thioacetal

A solution of the title compound (30 g) in 80% ethanol (500 ml) was mixed with freshly prepared Raney Nickel (500 ml). The reaction was carried out as in Experiment 23-D to give the pure 1-deoxy-D-glucitol (12 g) (crystallised from ethanol), m.p. and mixed m.p. 129 - 130°.

Experiment 45 2,4:5,6-Di-O-butylidene-1-deoxy-D-glucitol

A mixture of 1-deoxy-D-glucitol (3 g), n-butyraldehyde (3 ml) and concentrated hydrobromic acid (1 ml) was shaken overnight at room temperature and then extracted with petroleum ether (60 - 80°). The extract was neutralised with sodium bicarbonate, washed and dried over sodium sulphate. Removal of the solvent under reduced pressure gave a syrup (3.5 g), for which t.l.c. in solvent B showed a major fast moving product and several minor products. The mixture of the acetals (3.5 g) was fractionated on neutral alumina column (200 g), eluting with diethyl ether. First 30 fractions (10 ml each) contained polymeric products of butyraldehyde and the next 100 fractions contained the 2,4:5,6-diacetal which behaved as a single substance on t.l.c. (solvent B and solvent A). Yield 1 g. (Found: C, 61.34; H, 9.44. $C_{14}H_{26}O_5$ requires: C, 61.28; H, 9.55%).

Experiment 46 The Unknown dibutylidene-1-deoxy-D-glucitols

1-deoxy-D-glucitol (0.5 g) was dissolved in concentrated hydrobromic acid (0.2 ml) and mixed with n-butyraldehyde (0.4 ml). The reaction was stoppped after 2.5 h, by neutralising with sodium hydroxide solution, and rotary evaporated down to give a syrupy residue, which was extracted with light petroleum. The concentrated extract gave a crystalline mixture of diacetals on standing at -5° for 2 days, m.p. 67-69°, yield 30 mg. (Found: C, 61.49; H, 9.54).

Experiment 47 3-O-Acetyl-2,4:5,6-di-O-butylidene-1-deoxy-D-glucitol

A solution of di-O-butylidene-1-deoxy-D-glucitol (0.2 g) in pyridine (5 ml) was treated with acetic anhydride (1 ml) and kept at room

temperature for 15 h, then poured into ice-water. A syrup separated out which was extracted with chloroform. Evaporation of the solvent gave a syrup (0.25 g) which failed to crystallise. (Found: C, 60.58; H, 8.76. $C_{16}H_{28}O_6$ requires: C, 60.73; H, 8.92%).

Experiment 48 Methylation of 2,4:5,6-di-O-butylidene-1-deoxy-D-glucitol

A solution of the diacetal (0.4 g) in dry dimethyl formamide (10 ml) was stirred at room temperature with silver oxide (6 g) and methyl iodide (6 ml) for 15 h. The syrupy methylated diacetal (0.3 g) was obtained as in Experiment 7. (Found: C, 63.51; H, 9.93; OMe, 12.09. $C_{15}H_{28}O_5$ requires: C, 62.47; H, 9.78; OMe, 10.76%).

Experiment 49 Hydrolysis of 2,4:5,6-di-O-butylidene-3-O-methyl-1-deoxy-D-glucitol

The methylated acetal (0.25 g) was refluxed with 0.1 N-hydrochloric acid (10 ml) for 5 h. The cooled reaction mixture was poured into water (25 ml), whereupon a brown oil separated, which was removed by extraction with a little chloroform. The water layer, on evaporation gave the pure syrupy monomethyl ether of 1-deoxy-D-glucitol (0.15 g). (Found: C, 46.99; H, 8.84; OMe, 17.02. $C_7H_{16}O_5$ requires: C, 46.14; H, 8.85; OMe, 17.03%).

Experiment 50 2,4-O-Butylidene-5,6-O-isopropylidene-1-deoxy-D-glucitol

2,4-O-Butylidene-1-deoxy-D-glucitol (0.2 g) (prepared according to the method of P.J.V. Cleare[61]) dissolved in dry acetone (25 ml) was stirred with anhydrous copper sulphate (2 g) and concentrated sulphuric acid

(1 drop), at room temperature for 5 h and then the solid was filtered off. The solvent was removed from the filtrate and the residue was extracted with light petroleum, which on evaporation yielded a syrup (0.1 g) for which t.l.c. in solvent B, showed one spot R_F = 0.38. (Found: C, 60.35; H, 9.26. $C_{13}H_{24}O_5$ requires: C, 59.97; H, 9.29%).

Experiment 51 Preparation of 2-deoxy-D-glucitol

2-Deoxy-D-glucose (1 g) and sodium borohydride (0.2 g) were dissolved in water (10 ml), and kept at room temperature for 24 h. 2-Deoxy-D-glucitol was obtained as in Experiment 24 and crystallised from ethanol, yield 0.9 g (86%) m.p. 105 - 106°, lit.[61] m.p. 105 - 106°.

Experiment 52 1,3:4,6-Di-O-butylidene-2-deoxy-D-glucitol

2-Deoxy-D-glucitol (3 g) was dissolved in concentrated hydrobromic acid (2 ml) and mixed with freshly distilled n-butyraldehyde (3.2 ml) by vigorous shaking. An exothermic reaction started soon after the addition of the aldehyde. The reaction flask was cooled by dipping into cold water for a few minutes and then left at room temperature for 3 h. The reaction mixture was neutralised by the addition of sodium hydroxide solution and rotary evaporated to dryness. The residue was extracted with light petroleum, which on concentration and keeping at -5°, gave the crystals of 1,3:4,6-diacetal (1.8 g) R_F = 0.42 (solvent B), $[\alpha]_D^{25}$ = +16° (c,1 in carbon tetrachloride) m.p. 61 - 63° after recrystallisation. (Found: C, 61.13; H, 9.38. $C_{14}H_{26}O_5$ requires: C, 61.28; H, 9.55%).

The diacetal (0.1 g) was acetylated with acetic anhydride in pyridine to give a syrupy monoacetate derivative, for which i.r. showed no absorptions in the hydroxyl stretching region.

Experiment 53 5-O-Benzoyl-1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol

A solution of the 1,3:4,6-dibutylidene acetal (2 g) in pyridine (20 ml) was treated with benzoyl chloride (4 ml) at room temperature for 14 h and then poured into water. A syrup separated which was extracted into chloroform and dried. Removal of the solvent under vacuum gave the syrupy monobenzoate which did not crystallise. Yield 2 g. I.r. spectroscopy did not show any absorptions in the hydroxyl stretching range. (Found: C, 66.64; H, 7.15. $C_{21}H_{30}O_6$ requires: C, 66.64; H, 7.99%).

Experiment 54 Acid hydrolysis of 5-O-benzoyl-1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol

The foregoing benzoate (1.9 g) was dissolved in ethanol (70%, 30 ml), and boiled with stirring in the presence of Amberlite I.R. 120(H^+) resin (25 ml) for 3 h. The resin was filtered and washed well with hot ethanol. The concentrated ethanol solution gave crystals on standing overnight in a cool place. Recrystallised monobenzoyl-2-deoxy-D-glucitol had m.p. 160 - 162°. I.r. spectrum showed carbonyl absorption, n.m.r. spectrum gave aromatic signals (integrated for 5 protons). (Found: C, 57.41; H, 6.75. $C_{13}H_{18}O_6$ requires: C, 57.76; H, 6.71%).

Experiment 55 3,4,5,6-Tetra-O-acetyl-1-O-benzoyl-2-deoxy-D-glucitol

The monobenzoyl-2-deoxy-D-glucitol (50 mg) (from the Experiment 54) was dissolved in pyridine and treated with acetic anhydride (1 ml), at room temperature for 2 days and then poured into water. The crystals (50 mg) which separated on cooling at 0°, were filtered, washed with

water and dried, m.p. 69 - 71°. (Found: C, 58.11; H, 5.66. $C_{21}H_{26}O_{10}$ requires: C, 57.52; H, 5.97%).

Experiment 56 5-O-Methyl-1,3:4,6-di-O-butylidene-2-deoxy-D-glucitol

A solution of the 1,3:4,6-diacetal (0.9 g) in dry dimethyl formamide (15 ml) was stirred at room temperature with silver oxide (2.5 g) and methyl iodide (3 ml) for 24 h. The monomethyl derivative was obtained as in Experiment 7, as a liquid which was distilled under reduced pressure, b.p. 172 - 178°/8 mm Hg, yield 0.5 g. (Found: C, 62.33; H, 9.97; OMe, 10.52. $C_{15}H_{28}O_5$ requires: C, 62.47; H, 9.78; OMe, 10.76%).

Experiment 57 Kinetically Controlled Reaction of 2-Deoxy-D-Glucitol with n-butyraldehyde

2-Deoxy-D-glucitol (2 g) was dissolved in concentrated hydrobromic acid (1 ml) and mixed with n-butyraldehyde (2.5 ml). The exothermic reaction was stopped exactly after $\frac{1}{2}$ min. by neutralising with sodium hydroxide solution. The reaction mixture was rotary evaporated to dryness and extracted with light petroleum. Removal of the solvent gave a syrup (3.5 g). T.l.c. in solvent B showed 2 spots R_F = 0.42 (1,3:4,6-diacetal), R_F = 0.50 (kinetically controlled unknown diacetal).

Experiment 58 Acid hydrolysis of 5-O-methyl-1,3:4,6-di-O-butylidene--2-deoxy-D-glucitol

A solution of the title compound (0.45 g) in aqueous ethanol (70%) was refluxed with the resin Amberlite IR-120 (H^+) (25 ml) for 3 h with stirring. The resin was then filtered off and washed well with hot ethanol. Removal of the solvent left a syrup, which was dissolved in

ethyl acetate (t.l.c. showed three spots) and kept at -5° overnight, whereupon syrupy 5-O-methyl-2-deoxy-D-glucitol (0.1 g) separated, t.l.c. of which showed one spot R_F = 0.03 in solvent B.

The above monomethyl ether (60 mg) was acetylated in pyridine (2 ml) with acetic anhydride (1 ml) at room temperature for 14 h, to give the 1,3,4,6-tetra-O-acetyl-5-O-methyl-2-deoxy-D-glucitol as a pale yellow syrup (75 mg). (Found: C, 51.56; H, 6.85; OMe, 8.93. $C_{15}H_{24}O_9$ requires: C, 51.71; H, 6.94; OMe, 8.90%).

Experiment 59 4,6-O-Butylidene-D-galactopyranose

D-Galactose (10 g) in hydrobromic acid solution (5 ml; 48% in 100 ml water) was mixed with n-butyraldehyde (8 ml) and shaken well. The reaction mixture was left at room temperature for 2 days and then neutralised with N-sodium hydroxide. The water was removed under reduced pressure, to leave a syrup which was extracted with ethanol-ethyl acetate (250 ml; 1:1, v/v). Evaporation of the solvent left a hygroscopic solid (15 g) which showed some unreacted D-galactose on t.l.c. in solvent A.

Part of the product (5 g) was fractionated on a silica gel column, eluting with solvent A, to give the galactose free 4,6-O-butylidene acetal, which was crystallised and recrystallised from dry acetone, yield 3.4 g, m.p. 119.5-121.5°. (Found: C, 51.17; H, 7.57. $C_{10}H_{17}O_6$ requires: C, 51.49; H, 7.34%).

Experiment 60 4,6-O-butylidene-1,2,3-Tri-O-acetyl-β-D-galactopyranose

4,6-O-Butylidene-D-galactose (0.3 g) was acetylated in pyridine (5 ml) with acetic anhydride (2 ml) at room temperature for 16 h. The reaction mixture was concentrated under vacuum and poured into water whereupon a syrup separated, which was crystallised from methanol-water, to give the title

compound (0.3 g), m.p. 94-97° (Found: C, 53.39; H, 6.75. $C_{16}H_{24}O_9$ requires: C, 53.32; H, 6.71%).

Experiment 61 4,6-O-Butylidene-1,2,3-tri-O-acetyl-β-D-glucopyranose

4,6-O-Butylidene-D-glucose (0.5 g) was acetylated in pyridine (10 ml) with acetic anhydride (2 ml) as in Experiment 60 to give the title compound (0.3 g), m.p. and lit. m.p. 162-164°.

Experiment 62 4,6-O-Butylidene-D-galactitol

The crude 4,6-O-butylidene-D-galactose (2g) was reduced with sodium borohydride (0.3 g) as in experiment 51, to give 4,6-O-butylidene-D-galactitol (1,3 g), m.p. 72-74°, R_F=0.27 (solvent A).

Experiment 63 Convertion of 2,4:5,6-Di-O-butylidene-3-O-methyl-D-glucitol into 1-Deoxy-derivative

A solution of 2,4:5,6-di-O-butylidene-3-O-methyl-D-glucitol (0.5 g) and toluene-p-sulphonyl chloride (0.36 g) in pyridine (5 ml) was stored overnight at room temperature. A small amount of water was added and the mixture was poured into a solution of sodium bicarbonate. The syrup which separated was extracted with chloroform. Evaporation of the solvent gave the syrupy tosyl derivative (0.4 g). (Found: C, 57.82; H, 7.98. $C_{22}H_{34}O_8S$ requires: C, 57.62; H, 7.47%).

Lithium aluminium hydride (0.3 g) was added to a solution of the foregoing toluene-p-sulphonate (0.3 g) in ether (30 ml) and refluxed for 12 h. Excess reductant was destroyed with ethyl acetate and the alcoholates with water. Evaporation of the ether gave the syrupy (0.2 g) 1-deoxy derivative. The n.m.r. spectrum of the product confirmed the presence of deoxy group in the molecule.

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